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A new synthetic route to tyromycin A and its analogue from renewable resources

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ABSTRACT

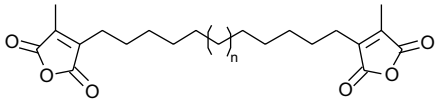
The synthesis of tyromycin A and that of the non-natural lower homologue, involving as featuring steps a transition metal catalyzed atom transfer radical cyclization and a functional rearrangement of the polyhalogenated 2-pyrrolidinones thus obtained, are described. Both routes use 10-undecenoic acid, a renewable source from castor oil, as starting material for the preparation of the pivotal intermediates α,α,α′,α′-tetrachlorodicarboxylic acids.

1. Introduction

Exopeptidases are proteolytic enzymes that catalyze the hydrolytic removal of amino acids from the termini of peptides and proteins. Two major classes of exopeptidases exist: aminopeptidases (APs), which cleave N-terminal amino acids, and carboxypeptidases, which cleave *C*-terminal ones.[1] APs occur in both soluble and membrane bound forms and mainly consist of metalloproteins. Historically, APs were considered as a ubiquitous set of enzymes with routinary roles in cell homeostasis, controlling mainly the final events of the journey of a polypeptide through a cell. Instead, in recent years, new evidence showed how APs carry out important functions in cell growth and development, and defence.[2] Hence APs are emerging as novel and exciting potential targets to treat diverse diseases, like hypertension, cancer, or immuno-disregulation,[3] among others.

Tyromycin A (**10**, Fig. 1) is a naturally occurring metabolite that holds two 3-methyl maleic (citraconic) anhydride moieties,[4] and was originally isolated from cultures of the wood basidiomycete *Tyromyces lacteus* (Fr.) Murr.[5] At non-cytotoxic levels, **10** strongly inhibits both leucine and cysteine mammalian APs bound to outer surface of HeLa S3 cells, holding in such way, promising potential as immunomodulating drug.[5] These properties, together with the scarce availability from natural origin, make **10** and analogous structures precious targets to be prepared, in order to investigate further the said biological activity. To the best of our knowledge, only a couple of synthetic approaches to **10** appeared in the literature.[6]

In this paper a new synthesis of **10**, based on a known strategy, developed by us for the attainment of mono methylmaleic anhydride structures,[7] is reported. The starting point is α,α,α′,α′-tetrachlorodicarboxylic acid **6**, an interesting bio-based building block recently prepared by us through an acyloin condensation (via the methylester) of 10-undecenoic acid (**1**), a renewable resource from castor oil (Scheme 1, route a).[8] An alternative manipulation of **1**, here illustrated (Scheme 1, route b), led to the one carbon atom fewer analogue **14**. From this molecule, the non-natural analogue **20** (Fig. 1) was prepared, following a modified approach we have recently worked out for the synthesis of disubstituted maleic anhydrides.[9] Both the syntheses of **6** and **14** were designed to be suitable for large scale, aiming to direct some effort into the production of bio-based chemicals.



10 (n=6,Tyromycin A)
20 (n=5)

Figure 1. Tyromycin A and its analogue.

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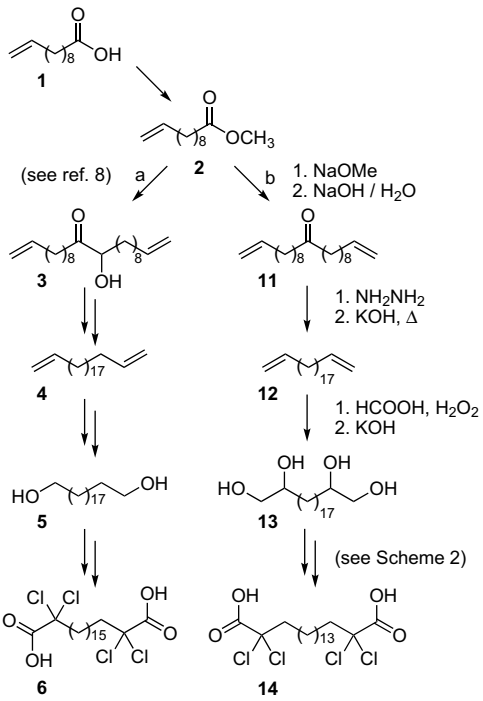


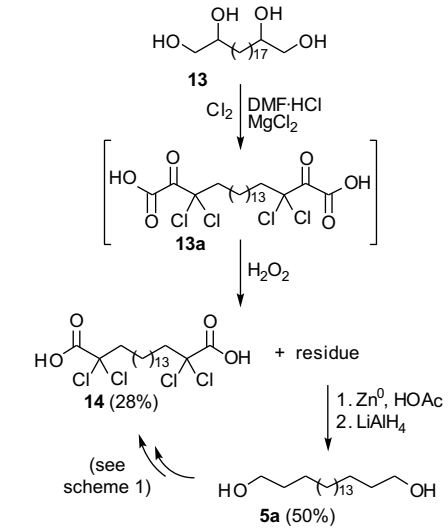
Scheme 1. Preparation of the intermediates from 10-undecylenic acid.

2. Results and discussion

2.1. Preparation of tetrachlorodiacid 14

For the construction of **14**, a Claisen condensation/decarboxylation of methylester **2** was developed (Scheme 1, route b) by which one carbon atom was lost. This coupling process furnished ketone **11**, isolated through crystallization in 64% yield, together with some unreacted starting material recovered as **1** from the aqueous phase (23%). Subsequent Wolff–Kishner reduction proceeded smoothly and gave diene **12** in 85% yield.

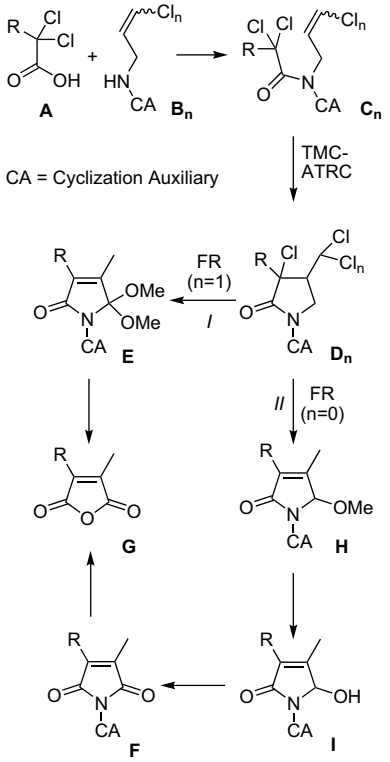
Dihydroxylation of **12** with formic acid/hydrogen peroxide gave tetraol **13** directly, without isolation of the diepoxide,[10] in a 50% crystallized yield. The direct chlorination of **13**, using gaseous Cl_2 within the DMF/$CHCl_3$/$MgCl_2$ system (Scheme 2),[11] gave bis-(3,3-dichloro-2-oxoacid) **13a**, which, without isolation, was further subjected to an oxidative treatment with aqueous H_2O_2, resulting in the breaking of the α-oxoacid moieties.[12] A convenient work-up was developed by the addition of Et_2O and a little amount of Et_3N (10 mol % in respect to **13**), after which an easily filterable crystalline mass was obtained. Isolation of this mass, a complex composed by Et_3N/**14** 1:3, permitted us to largely recover the desired product by acidification and recrystallization from CCl_4. Curiously enough, tetrachlorodiacid **14** is almost insoluble in CCl_4, $CHCl_3$ and CH_2Cl_2, but very soluble in Et_2O at 20 °C, whereas the triethylammonium monocarboxylate complex is poorly soluble in cold Et_2O and dissolves readily in CH_2Cl_2. This procedure, although straightforward, gave only 28% of purified **14**, while around 10% of it was still detected in solution (by ^1H NMR) together with some over-chlorinated compounds and unreacted oxoacids. A practical way to recover this valuable material was then successfully attempted. Treating the mother liquors with an excess of Zn^0 powder and HOAc (for 4 h at 110 °C), the crystalline non-chlorinated C19 diacid was obtained. Subsequent reduction with $LiAlH_4$ afforded the crystallizable diol **5a**, analogue of **5** (in 50% yield from **13**), whose conversion to the desired halogenated diacid **14** was possible (in 40% yield from **5a**), following the same steps used to prepare **6** from **5** (Scheme 1, route a).[8]



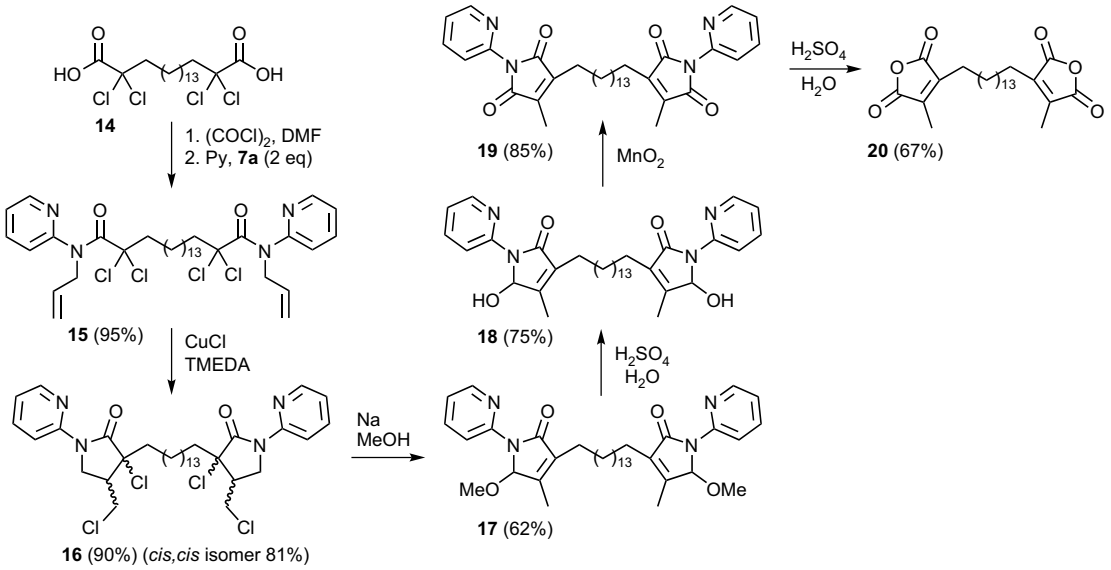
Scheme 2. Chlorination/oxidative breaking of tetraol **13**.

2.2. Preparation of tyromycin A and its analogue (20)

The condensation of α,α-dichlorocarboxylic acids **A** with *N*-3-chloroallyl secondary amine $\mathbf{B_1}$, followed by a Transition Metal Catalyzed-Atom Transfer Radical Cyclization (TMC-ATRC) promoted by the redox catalyst formed by CuCl and a polydentate nitrogen ligand, is a convenient route towards polychloro pyrrolidinones $\mathbf{D_1}$ (Scheme 3).[13] The ensuing functional rearrangement (FR) of $\mathbf{D_1}$ (route I), promoted by the methoxide ion in methanol, represents an elegant access to 5,5-dimethoxy-4-methyl-3-pyrrolin-2-ones **E**, good precursors towards the methylmaleic anhydride framework **G**.[7] Alternatively **G** can be approached from a non-chlorinated amine $\mathbf{B_0}$ (route II, Scheme 3). In this case the FR of $\mathbf{D_0}$



Scheme 3. Alternative routes (I or II) towards methylmaleic cores.



Scheme 4. Preparation of the tyromycin A analogue (**20**) following the route II.

affords the 5-methoxy-3-pyrrolin-2-one **H**, an intermediate that requires two steps to be converted into the maleimide precursor **F**: (i) hydrolysis to the 5-hydroxy-3-pyrrolin-2-one **I**, and (ii) oxidation of **I** to **F**.[9]

Notwithstanding route I is shorter, it is afflicted by an inefficient preparation of the starting amine.[7] On the contrary, way II, even if longer, appears more practical, since both the preparation of the starting material and of all the intermediates can be completed with simple, economic and high yielding procedures.[9]

With the aim to compare the two approaches, we scheduled the synthesis of **20** from **14** according to path II (Scheme 4), and that of **10** from **6** following the route I (Scheme 5), using *N*-allylamines **7a** and **7** (Fig. 2), respectively. The selected cyclization auxiliary, i.e., the 2-pyridyl group, not only helps the TMC-ATRC step, but is able to facilitate the FR and the final hydrolytic steps.[9]

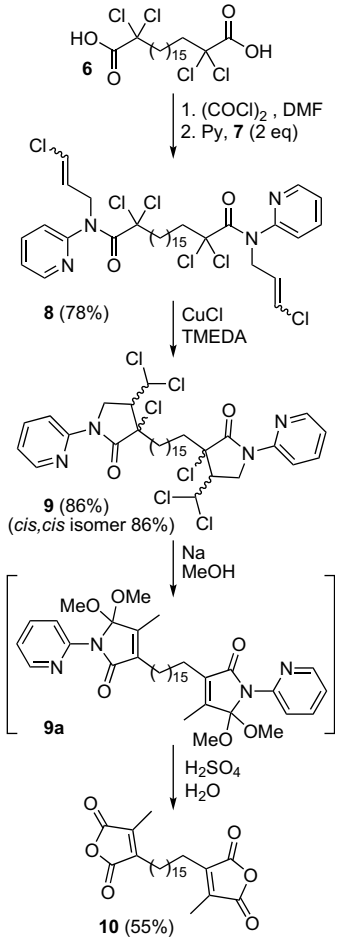
After the preparation of *N*-allyl-2-aminopyridine **7a** (as described in Ref. 9), its coupling with diacid **14** smoothly furnished bis-amide **15** (Scheme 4). TMC-ATRC of **15**, promoted by CuCl/TMEDA in CH_3CN and CH_2Cl_2 (as a co-solvent to improve the solubility), gave bis-2-pyrrolidinone **16**. The cyclization was conducted at 60 °C for 20 h (under thermodynamic control)[9] in order to obtain **16**, mainly in the cis,cis configuration (81%). The cis arrangement between the pyrrolidinones' substituents bound at the annular positions C(3) and C(4) is a need, since it is the only configuration that can give the functional rearrangement with sodium methoxide in methanol.[7,9]

In fact, after subjecting **16** to the FR in MeOH and Et_2O (as a solubility enhancer), bis-5-methoxy-3-pyrrolin-2-one **17** was isolated in 62% yield. The hydrolysis of **17** gave us 5,5′ dihydroxy-pyrrolinone **18** in 75% yield; **18** was then oxidized with MnO_2 affording imide **19** in good yield (85%). Finally, the hydrolysis of **19** secured the desired tyromycin A analogue **20** in 67% yield (23% from **14**).

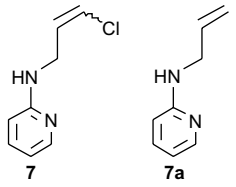
The preparation of *N*-(3-chloroallyl)-2-aminopyridine **7** (as described in Ref. 7), although not particularly effective (35% yield), gave us bis-amide **8** through its coupling with diacid **6** (prepared as in Ref. 8), in good yield (Scheme 5). TMC-ATRC of **8**, promoted by CuCl/TMEDA in CH_3CN and CH_2Cl_2 (to improve the solubility) at 60 °C for 20 h, gave bis-pyrrolidinone **9**, mainly in the cis,cis-relative configuration (86%).

Then, subjecting **9** to the one-pot FR-hydrolysis sequence,[7] crude tyromycin A (**10**) was obtained. For the purification of **10**, we observed that when the crude reaction residue was solubilized in hot ethanol, an insoluble brown impurity oiled-out during cooling. After its removal, a clean and easy crystallization, from the same solvent, afforded **10** in 55% yield (37% overall yield from **6**).

Although path II is more appropriate for large-scale preparation, owing to the easier preparation of the starting allylamine, it appears less efficient than route I, 23% overall yield against 37%, calculated from the intermediates α,α,α′,α′-tetrachlorodicarboxylic



Scheme 5. Tyromycin A synthesis according to route I.



7 7a

Figure 2. Amines used following route I (**7**) or II (**7a**).

acids **14** and **6**, respectively. Surely the main reason for this less appealing performance of II relates to the isolation–purification of every intermediate. This is not the case for route I where the FR and hydrolysis stages were integrated in a one-pot process. Since the hydrolytic steps of the intermediates **17** and **19** (path II) were carried out in acidic water, the identification of an environmental friendly oxidant able to work effectively in H_2O/H^+ will give the opportunity to integrate these three passages in a one-pot procedure with favourable effect on the process efficiency.

3. Conclusions

We have described the synthesis of tyromycin A (**10**) and that of its non-natural lower homologue **20**, comparing two different procedures for building of the maleic core. The pivotal intermediates to these target compounds, α,α,α′,α′-tetrachlorodicarboxylic acids **6** and **14**, were both obtained from undecylenic acid (**1**), a renewable resource from castor oil. While the preparation of **6** was illustrated in our previous article,[8] we now also report the transformation of **1** to get **14**.

4. Experimental part

4.1. General

Reagents and solvents were standard grade commercial products, purchased from: Aldrich, Acros, Fluka or RdH, and used without further purification, except for acetonitrile and CH_2Cl_2 that were dried over three batches of 3 Å sieves (5% w/v, 12 h). 2,2,19,19-Tetrachloroicosan-1,20-dioic acid (**6**), 10-undecylenic acid methylester (**2**), *N*-(2-pyridyl)-3-chloro-allylamine (**7**) and *N*-(2-pyridyl)-allylamine (**7a**) have been prepared according to the literature.[7–9] The silica gel used for flash chromatography was Silica Gel 60 Merck (0.040–0.063 mm). ^1H and ^{13}C NMR were recorded on a Jeol JNM-EX 300 NMR, a Bruker DPX 200 and a Bruker Avance 400 spectrometer. Chemical shift (δ) have been reported in parts per million (ppm) relative to the residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR; CD_3OD: 4.84 ppm for ^1H NMR and 49.05 ppm for ^{13}C NMR). Carbon spectra assignments are supported by DEPT analysis and ^1H–^{13}C correlations where necessary. The relative stereochemistry of structure **9** was assigned by comparison of its ^1H NMR spectrum with those of *cis*- and *trans*-*N*-(2-pyridyl)-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone, which relative configurations between C(3) and C(4) were determined through NOE techniques.[7] Particularly, the cis diastereomer shows a multiplet for the C(4)H proton and a doublet for the $CHCl_2$ at 3.02 and 6.11 ppm, respectively, while for the trans isomer, the same signals can be found at 3.41 and 5.99 ppm, respectively. Similarly, the ^1H NMR spectra of *cis*- and *trans*-*N*-(2-pyridyl)-3-chloro-4-chloromethyl-3-methyl-2-pyrrolidinone, previously analyzed through NOE techniques,[9] were compared with ^1H NMR spectra of **16**. The cis isomer shows a multiplet for the C(4)H proton at 2.67 ppm and an ABX system for the diastereotopic protons C(5)H_2 at 3.66 and 4.50 ppm. Instead, in the trans diastereomer the C(4)H multiplet is at 3.06 ppm, and the ABX system can be found at 4.00 and 4.38 ppm. Elemental analyses were performed through a Perkin Elmer CHNS/O 2400 (Series II) Analyzer, at Ghent University facility. Infrared spectra were recorded on a Perkin Elmer 1600 Series FTIR spectrophotometer. Mass spectra were acquired over an Agilent 1100 Series HPLC coupled with a VS (ES, 4000 V) MS (Agilent 1100 Series) or, alternatively, over a HP6890 GC coupled with an HP5973 MS quadrupole detector. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and are uncorrected.

4.2. Preparation of heneicosa-1,20-dien-11-one (11)

A solution of NaOMe was prepared by dissolving Na^0 (27 g, 1.27 mol) in dry methanol (250 mL) into a 1-L two-necked flask, fitted with a dropping funnel and a condenser connected at the top to a $CaCl_2$ tube. Methylester **2** (500 g, 2.52 mol) was then added to the (still) hot solution of NaOMe, with the help of a little amount of petroleum ether (bp 40–60 °C), and heater was turned on. Through a 40 cm Vigreux column (not insulated, to prevent the distillation of **2**), petroleum ether (bp. 40–60 °C) and methanol were distilled off. After 20 h, vacuum was applied to obtain 10 mmHg with a bath temperature of 150 °C. After cooling down the mixture, a solution of NaOH (60 g, 1.5 mol) in ethanol/water 8:2 (250 mL) was added and the mixture was refluxed for 4 h. Then, vacuum was applied in order to remove most of the ethanol and to ensure a complete hydrolysis. Dilution with water (250 mL) and extraction with CH_2Cl_2 (2×250 mL) gave the crude product (without much problem of emulsification). Evaporation of the solvent and recrystallization from petroleum ether (bp 40–60 °C) (or from ethanol) at 0 °C (or less) afforded the ketone **11** (247.4 g, 64%), as white solid. Some unreacted undecylenic acid **1** (106.8 g, 23%) was recovered from the aqueous phase by acidifying with concentrated $HCl_{(aq)}$ (until pH 2) and extracting with petroleum ether (bp. 40–60 °C).

Found: C, 82.2; H, 12.6. $C_{21}H_{38}O$ requires C, 82.29; H, 12.50. ^1H NMR (200 MHz, $CDCl_3$): δ 1.00–1.45 (20H, m, 10CH_2), 1.45–1.70 (4H, m, 2CH_2), 2.04 (4H, q, *J* 6.6 Hz, 2CH_2CH=), 2.38 (4H, t, *J* 7.4 Hz, 2C(O)CH_2), 4.85–5.08 (4H, m, 2=CH_2), 5.81 (2H, qt, *J* 17.0, 10.2, 6.6 Hz, 2C*H*=). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 23.9 (2CH_2CH$_2$C(O)), 28.9, 29.0, 29.2, 29.3, 29.3 (10CH_2), 33.8 (2CH_2CH=), 42.8 (2CH_2C(O)), 114.1 (2=CH_2), 139.2 (2C*H*=), 211.7 (*C*=O). IR (KBr): 915 (CH=CH_2), 994 (CH=CH_2), 1698 (C=O) cm^{-1}. MS (EI, *m*/*z*): 306 (5%, M^+), 249 (18), 167 (29), 149 (28), 83 (56), 69 (47), 55 (100). Mp=55–56 °C.

4.3. Preparation of heneicosa-1,20-diene (12) by Wolff–Kishner reduction

Ketone **11** (30.7 g, 0.10 mol) was dissolved in diethylene glycol (DEG) (300 mL) into a 1-L two-necked flask, fitted with a dropping funnel and a condenser. Then, hydrazine monohydrate 98% (64–65% NH_2NH_2) (50.1 mL, 10 equiv) was added and the reaction mixture was heated at 80 °C for 30 min. Afterwards, KOH (14 g, 2.5 mol), dissolved in DEG (150 mL), was added and the reaction mixture was heated at 140 °C using an oil bath for 1 h. Then, the reflux condenser was replaced by a Vigreux column (first a 20 cm Vigreux, then a 10 cm one and, at the end of the distillation, no Vigreux column) and water and the excess of hydrazine were distilled off. This took from 2.5 to 4 h. The temperature of the oil bath should reach 170–190 °C in order to break down the hydrazone intermediate, but higher temperatures lead to isomerisation reactions. The mixture was cooled down and extracted with hexane (200 mL). After washing three times with water, the organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. Distillation at reduced pressure afforded the diene **12** (25.0 g, 85%) (bp 145 °C at 0.11 mbar) as a colourless thick oil.

Found: C, 86.4; H, 13.9. $C_{21}H_{40}$ requires C, 86.22; H, 13.78. ^1H NMR (200 MHz, $CDCl_3$): δ 1.00–1.50 (30H, m, 15CH_2), 2.05 (4H, q, *J*

6.8 Hz, 2CH_2CH=), 4.88–5.08 (4H, m, 2=CH_2), 5.82 (2H, qt, *J* 17.0, 10.3, 6.8 Hz, 2C*H*=). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 29.0, 29.2, 29.5, 29.7, 29.7 (15CH_2), 33.8 (2CH_2CH=), 114.1 (2=CH_2), 139.2 (2CH=). IR (film): 909 (CH=CH_2) cm^{-1}; 992 (CH=CH_2) cm^{-1}. MS (EI, *m*/*z*): 292 (5%, M^+), 109 (32), 96 (83), 82 (93), 69 (68), 55 (100). Mp=27–29 °C.

4.4. Preparation of heneicosane-1,2,20,21-tetraol (13)

A mixture of the diene **12** (50.0 g, 0.17 mol), formic acid 99% (300 mL) and lauric acid (solubility enhancer) (0.6 g) was vigorously stirred at 25 °C in a 500-mL two-necked flask, fitted with a dropping funnel and a reflux condenser. $H_2O_{2(aq)}$ 50 wt % (28 g, 0.42 mol) was added and the reaction mixture was stirred for 18 h at 40 °C, then another amount of H_2O_2 (14 g, 0.21 mol) was carefully inserted and the reaction mixture was stirred again for 18 h at 40 °C. After, 3 mL of 5 N aqueous H_2SO_4 were added and the excess of formic acid was removed (and recovered) through distillation at reduced pressure. The residue was refluxed for 1 h with alcoholic KOH (3 N in EtOH, 165 mL, 0.495 mol). Most of the alcohol was then evaporated and water (200 mL) was added in order to precipitate the crude tetraol. After cooling to room temperature and removing the water, the crude product was washed again (2×100 mL H_2O) to remove the residual base. Recrystallization from ethanol/water 8:2 afforded tetraol **13** (30.81 g, 50%), as white solid.

Found: C, 70.3; H, 12.1. $C_{21}H_{44}O_4$ requires C, 69.95; H, 12.30. ^{1}H NMR (200 MHz, CD_3OD): δ 1.20–1.70 (34H, m, 17CH_2), 3.40 (2H, dd, *J* 10.9, 6.5 Hz, 2C*H*HOH), 3.47 (2H, dd, *J* 10.9, 4.3 Hz, 2C*H*HOH), 3.48–3.65 (2H, br m, 2C*H*OH). ^{13}C NMR (50.3 MHz, CD_3OD): δ 25.3 (2CH_2CH$_2$CHOH), 29.2, 29.3, 29.3, 29.4, 29.4 (13CH_2), 33.0 (2CH_2CHOH), 66.0 (2CH_2OH), 71.9 (2CHOH). IR (KBr): 3398 (O–H) cm^{-1}. ESI-MS (*m*/*z*): 361.5 $(M+H)^+$, 359.5 $(M-H)^-$. Mp=144–150 °C.

4.5. Preparation of 2,2,18,18-tetrachloro-nonadecane-1,19-dioic acid (14)

Tetraol **13** (70 g, 0.194 mol), DMF (300 mL), $CHCl_3$ (270 mL, from which EtOH (stabilizer) was removed by washing with concentrated H_2SO_4), CH_2Cl_2 (90 mL) and $MgCO_3$ (34.2 g, 0.4 mol) were added in a 2-L two-necked flask, equipped with a condenser connected at the top to a $CaCl_2$ tube. The mixture was stirred in the dark and was thermostated at 50 °C using an oil bath, then chlorine gas was flushed inside at ca. 3.1 g/min. An exotherm was rapidly detected (temperature rise to 73 °C), which finished after about 40 min (temperature down to 64 °C; ~25 mL of CH_2Cl_2 was added during this time to compensate for some evaporation). The chlorine flow was then gradually reduced and stopped after 2 h. The heating was stopped and the mixture was stirred overnight. The reaction mixture was extracted with a mixture of diethyl ether/petroleum ether (bp 40–60 °C) 2:1 (350 mL) and 50% $H_2SO_{4(aq)}$ (350 mL). The organic phase was washed with 50% $H_2SO_{4(aq)}$ (3×80 mL) and the aqueous phase was washed with diethyl ether/petroleum ether (bp 40–60 °C) 1:1 (2×125 mL). To the combined organic extracts, 35% $H_2O_{2(aq)}$ (130 mL) was added and the resulting mixture was stirred for 24 h at 30 °C, and at 40 °C for another 48 h. Vacuum evaporation of the solvent left a colourless crude product (85 g). The absence of a brownish colour during evaporation indicates a good conversion, otherwise re-dissolving the crude in CH_2Cl_2 and further treating with aqueous H_2O_2 are necessary. Dilution with diethyl ether (refrigerated at −5 °C, 500 mL) and treatment with Et_3N (2.8 mL, 20 mmol, i.e., around 1:10 of **13**) in Et_2O resulted in a filterable crystalline mass strongly enriched in the desired product **14** (around 90% as evidenced by ^{1}H NMR). After acid work-up, recrystallization from CCl_4 furnished the tetrachlorodiacid **19** as white crystals (25.32 g, 28%).

Found: C, 49.2; H, 7.0. $C_{19}H_{32}Cl_4O_4$ requires C, 48.94; H, 6.92. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.50 (22H, m, 11CH_2), 1.50–1.80 (4H, m, 2CH_2), 2.30–2.55 (4H, m, 2CH_2CCl$_2$), 8.56 (2H, br s, 2 O*H*). ^{13}C NMR (75.5 MHz, CD_3OD): δ 25.4 (2CH_2CH$_2$CCl$_2$), 28.7 (2CH_2CH$_2$CH$_2$CCl$_2$), 29.3, 29.4, 29.6 (9CH_2), 45.2 (2CH_2CCl$_2$), 86.9 (2CCl$_2$), 167.2 (2COOH). IR (KBr): 1740 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 463.3 $(M-H)^-$. Mp=99–102 °C.

4.6. Preparation of the N^1,N^{20}-di(3-chloroallyl)-N^1,N^{20}-di(2-pyridyl)-2,2,19,19-tetrachloro-icosane-diamide (8)

Tetrachlorodiacid **6** (8.00 g, 16.6 mmol) was weighed in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and equipped with a stirring bar. CH_2Cl_2 (17 mL) and a catalytic amount of dimethylformamide (56 μL) were added under nitrogen. Then, an excess of oxalyl chloride (4.46 mL, 50 mmol) was carefully added (evolution of CO!) and, leaving the screw cap slightly unlocked, the mixture was stirred for 2 h at room temperature (during this time, the complete dissolution of the chloride was observed). The solution was concentrated under vacuum with a membrane pump (equipped with a NaOH trap). The residual brownish oil was then cooled down with an ice bath and re-diluted with CH_2Cl_2 (8 mL). Pyridine (2.96 mL, 36.5 mmol), dissolved in CH_2Cl_2 (3.3 mL), and allylamine **7** (6.2 g, 36.5 mmol), dissolved in CH_2Cl_2 (5.5 mL), were slowly added under nitrogen. After locking the Schlenk cap and stopping the gas flow, the solution was stirred for 2.5 h at 0 °C. Afterwards, Na_2CO_3 (1.8 g, 16.7 mmol) was added, and the whole mixture was concentrated under vacuum. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether/CH_2Cl_2 gradient (from 9.5:0:0.5 to 5.5:4:0.5) as eluant, afforded **8** (10.21 g, 78%; mixture of two *E*/*Z* stereoisomers), as a yellow oil. R_f=0.44 (petroleum ether (bp 40–60 °C)/diethyl ether 50:50).

Found: C, 55.4; H, 6.2; N, 7.3. $C_{36}H_{48}Cl_6N_4O_2$ requires C, 55.33; H, 6.19; N, 7.17. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78–0.95 (4H, m, 2CH_2), 1.00–1.45 (20H, m, 10CH_2), 1.45–1.75 (4H, m, 2CH_2), 2.40–2.55 (4H, m, 2CH_2CCl$_2$), 4.70 (4H, d, *J* 6.3 Hz, 2E*CH*$_2$N), 4.86 (4H, dd, *J* 6.3, 1.4 Hz, 2Z*CH*$_2$N), 5.90–6.20 (4H, m, *E*+*Z*CH=C*H*), 7.26 (2H, ddd, *J* 7.7, 4.9, 0.8 Hz, 2H_{py}-5), 7.40 (2H, br dd, *J* 7.7, 2.9 Hz, 2H_{py}-3), 7.76 (2H, tt, *J* 7.7, 2.0 Hz, 2H_{py}-4), 8.54 (2H, br d, *J* 4.9 Hz, 2H_{py}-6). ^{13}C NMR (100.7 MHz, $CDCl_3$): *Z* δ 25.1 (2CH_2), 29.0, 29.3, 29.4, 29.5, 29.6 (12CH_2), 46.8 (2CH_2CCl$_2$), 48.2 (2CH_2N), 85.4 (2CCl$_2$), 121.1 (2=CHCl), 122.9 (2C$_{py}$-5), 123.7 (2C$_{py}$-3), 127.3 (2CH=), 137.9 (2C$_{py}$-4), 149.1 (2C$_{py}$-6), 154.2 (2C$_{py}$-2), 165.3 (2C=O); *E* δ 25.5 (2CH_2), 29.0, 29.3, 29.4, 29.5, 29.6 (12CH_2), 46.0 (2CH_2CCl$_2$), 50.6 (2CH_2N), 85.5 (2CCl$_2$), 121.5 (2=CHCl), 122.7 (2C$_{py}$-5), 123.3 (2C$_{py}$-3), 126.5 (2CH=), 137.8 (2C$_{py}$-4), 149.0 (2C$_{py}$-6), 153.8 (2C$_{py}$-2), 165.0 (2C=O). IR (film): 1667 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 779.0 $(M+H)^+$.

4.7. Preparation of 3,3′-(hexadecane-1,16-diyl)-bis(*N*-(2-pyridyl)-3-chloro-4-(dichloromethyl)-pyrrolidin-2-one) (9)

Diamide **8** (3.126 g, 4 mmol) and CuCl (79 mg, 0.8 mmol) were weighed in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and equipped with a magnetic stirring bar. CH_2Cl_2 (4 mL), acetonitrile (6 mL) and *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA) (242 μL, 1.6 mmol) were then added under nitrogen. The mixture was stirred at 60 °C for 20 h. Then it was diluted with $NaOH_{(aq)}$ 4% (16 mL) and extracted with CH_2Cl_2 (3×15 mL) and with toluene (3×12 mL). The combined organic layers were concentrated under vacuum and the crude product was purified by flash chromatography on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether/CH_2Cl_2 gradient (from 9:0:1 to 7:2:1) as eluant. The product **9** was recovered (2.70 g, 86%; mixture of cis,cis/cis,trans/trans,trans diastereomers 86:13:1; cis/trans 92:7 from ^{1}H

NMR spectrum) as a colourless oil. R_f=0.60 (petroleum ether (bp 40–60 °C)/diethyl ether 50:50).

Found: C, 55.7; H, 6.4; N, 7.3. $C_{36}H_{48}Cl_6N_4O_2$ requires C, 55.33; H, 6.19; N, 7.17. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75–0.97 (4H, m, 2CH_2), 1.00–1.80 (24H, m, 12CH_2), 2.42 (4H, m, 2C(3)CH_2), 3.26 (2H, td, *J* 9.2, 7.5 Hz, 2cisC(4)*H*), 3.37 (2H, br q, *J* 5.0 Hz, 2transC(4)*H*), 3.75 (2H, dd, *J* 11.5, 9.2 Hz, 2cisC(5)*H*), 4.40 (4H, d, *J* 5.5 Hz, 2transC(5)H_2), 4.52 (2H, dd, *J* 11.5, 7.5 Hz, 2cisC(5)*H*), 5.99 (2H, d, *J* 4.1 Hz, 2trans*C*HCl_2), 6.13 (2H, d, *J* 9.2 Hz, 2cis*C*HCl_2), 7.12 (2H, ddd, *J* 7.2, 5.2, 0.8 Hz, 2H_{py}-5), 7.74 (2H, ddd, *J* 8.6, 7.2, 1.8 Hz, 2H_{py}-4), 8.34–8.46 (4H, m, 2H_{py}-3+2H_{py}-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): cis δ 25.7, 29.3, 29.6, 29.7 (14CH_2), 37.3 (2C(3)CH_2), 47.2 (2*C*(5)H_2), 48.5 (2*C*(4)H), 71.7 (2*C*HCl_2), 73.4 (2*C*(3)), 115.2 (2C_{py}-3), 120.7 (2C_{py}-5), 138.1 (2C_{py}-4), 147.8 (2C_{py}-6), 150.8 (2C_{py}-2), 169.2 (2*C*=O); trans (signals not overlapped to the cis ones) δ 33.1 (2C(3)CH_2), 41.4 (2*C*(5)H_2), 53.3 (2*C*(4)H), 70.6 (2*C*HCl_2), 72.8 (2*C*(3)), 115.0 (2C_{py}-3), 120.5 (2C_{py}-5), 138.0 (2C_{py}-4). IR (film): 1723 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 779.0 (M+H)$^+$.

4.8. One-pot preparation of 3,3′-(hexadecane-1,16-diyl)-bis(4-methyl-furan-2,5-dione) (tyromycin A) (10) from 9

In a Schlenk tube, fitted with a Teflon septum (blocked by a screw cap), bis-pyrrolidinone **3** (2.20 g, 2.82 mmol) and diethyl ether (11.3 mL) were added, together with a stirring bar. The solution was thermostated at 25 °C. Apart, in a second Schlenk tube, metallic Na (0.52 g, 22.5 mmol) was carefully dissolved in CH_3OH (11.3 mL) and the resulting solution, thermostated at 25 °C, was poured into the first Schlenk tube. The reaction mixture was then stirred for 24 h. After aqueous H_2SO_4 2 M (1.4 mL) was added, the solvent was removed under vacuum and the residue was treated with H_2SO_4 2 M (4.2 mL) and water (1.4 mL). The mixture was heated at 130 °C for 3 h (under a stream of argon to remove the CH_3OH released from hydrolysis of the bis(5,5-dimethoxy 3-pyrrolin-2-one) intermediate **9a**, Scheme 5), then it was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were then concentrated under reduced pressure. Hence, a solid residue was collected (0.82 g). Recrystallization from ethanol (after quick separation of the insoluble impurities) afforded pure tyromycin A (**1**) (0.69 g, 55%), as a white solid. Characterizations were in agreement with those previously reported.[6]

4.9. Preparation of the N^1,N^{19}-diallyl-N^1,N^{19}-di(2-pyridyl)-2,2,18,18-tetrachloro-nonadecane-diamide (15)

Following the same procedure used for preparation of **8**, diacid **14** (4.90 g, 10.5 mmol) was coupled with allylamine **7a** (3.30 g, 22 mmol) affording the crude diamide **15**. Flash chromatography on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 10:0 to 6:4) as eluant, afforded **15** (6.99 g, 95%), as a yellow oil. Recrystallization at 0 °C from methanol was also possible, although the obtained white crystals of **15** melt to a yellow oil at room temperature. R_f=0.27 (petroleum ether (bp 40–60 °C)/diethyl ether 60:40).

Found: C, 60.2; H, 6.8; N, 7.8. $C_{35}H_{48}Cl_4N_4O_2$ requires C, 60.18; H, 6.93; N, 8.02. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14–1.45 (22H, m, 11CH_2), 1.62 (4H, m, 2CH_2), 2.49 (4H, m, 2CH_2CCl_2), 4.71 (4H, br d, *J* 6.0 Hz, 2CH_2N), 5.00–5.20 (4H, m, 2=CH_2), 4.88 (2H, qt, *J* 9.2, 6.0 Hz, 2–C*H*=), 7.23 (2H, ddd, *J* 7.4, 4.8, 0.9 Hz, 2H_{py}-5), 7.39 (2H, br dt, *J* 8.0, 0.9 Hz, 2H_{py}-3), 7.74 (2H, ddd, *J* 8.0, 7.4, 1.9 Hz, 2H_{py}-4), 8.54 (2H, ddd, *J* 4.8, 1.9, 0.7 Hz, 2H_{py}-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.3 (2CH_2), 29.2, 29.5, 29.6, 29.7 (11CH_2), 47.0 (2CH_2CCl_2), 53.7 (2CH_2N), 85.6 (2CCl_2), 118.7 (2=CH_2), 122.8 (2C_{py}-5), 123.9 (2C_{py}-3), 132.3 (2C*H*=), 137.8 (2C_{py}-4), 149.1 (2C_{py}-6), 154.4 (2C_{py}-2), 165.2 (2*C*=O). IR (film): 1668 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 697.0 (M+H)$^+$. Mp=10–12 °C.

4.10. Preparation of 3,3′-(pentadecane-1,15-diyl)-bis(*N*-(2-pyridyl)-3-chloro-4-(chloromethyl)-pyrrolidin-2-one) (16)

Following the same procedure used for the preparation of **9**, diamide **15** (5.31 g, 7.6 mmol) was transformed into the crude product **16**. Flash chromatography on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether/CH_2Cl_2 gradient (from 10:0:0 to 7:2:1) as eluant, afforded **16** (4.78 g, 90%; mixture of cis,cis/cis,trans/trans,trans diastereomers 81:18:1; cis/trans 90:10 from ^{1}H NMR spectrum) as a brownish-white solid. R_f=0.28 (petroleum ether (bp 40–60 °C)/diethyl ether 60:40). It was possible to purify **16** through crystallization from diethyl ether, but the preferential crystallization of the cis,cis isomer occurred.

Found: C, 60.1; H, 7.0; N, 7.8. $C_{35}H_{48}Cl_4N_4O_2$ requires C, 60.18; H, 6.93; N, 8.02. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.90 (26H, m, 13CH_2), 2.00–2.40 (4H, m, 2C(3)CH_2), 2.86 (2H, m, 2cisC(4)*H*), 3.03 (2H, m, 2transC(4)*H*), 3.51 (2H, t, *J* 10.4 Hz, 2trans*C*HCl), 3.70 (2H, dd, *J* 11.3, 9.3 Hz, 2cisC(5)*H*), 3.77 (2H, dd, *J* 11.2, 9.1 Hz, 2cis*C*HCl), 3.91 (2H, dd, *J* 11.2, 5.4 Hz, 2cis*C*HCl), 4.12 (2H, dd, *J* 11.6, 4.5 Hz, 2transC(5)*H*), 4.35 (2H, dd, *J* 11.6, 6.6 Hz, 2 transC(5)*H*), 4.52 (2H, dd, *J* 11.3, 7.3 Hz, 2cisC(5)*H*), 7.11 (2H, br ddd, *J* 7.3, 4.9, 1.0 Hz, 2H_{py}-5), 7.74 (2H, ddd, *J* 8.4, 7.3, 1.6 Hz, 2H_{py}-4), 8.30–8.50 (4H, m, 2H_{py}-3+2H_{py}-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): cis δ 25.3 (2CH_2), 29.4, 29.6, 29.7 (11CH_2), 37.6 (2C(3)CH_2), 42.6 (2*C*(4)H+2CH_2Cl), 47.8 (2*C*(5)H_2), 74.2 (2*C*(3)), 115.1 (2C_{py}-3), 120.5 (2C_{py}-5), 138.0 (2C_{py}-4), 147.8 (2C_{py}-6), 151.1 (2C_{py}-2), 170.1 (2*C*=O); trans (signals not overlapped to the cis ones) δ 24.2 (2CH_2), 33.8 (2C(3)CH_2), 42.2 (2CH_2Cl), 46.9 (2*C*(5)H_2), 47.5 (2*C*(4)H), 73.5 (2*C*(3)). IR (KBr): 1711 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 697.0 (M+H)$^+$. Mp=76–80 °C.

4.11. Preparation of 3,3′-(pentadecane-1,15-diyl)-bis(*N*-(2-pyridyl)-5-methoxy-4-methyl-3-pyrrolin-2-one) (17)

In a Schlenk tube, fitted with a Teflon septum (blocked by a screw cap), substrate **16** (3.97 g, 5.7 mmol) and Et_2O (9 mL) were added, together with a stirring bar. The solution was thermostated at 25 °C. Apart, in a second Schlenk tube, metallic Na (0.79 g, 34.2 mmol) was carefully dissolved in CH_3OH (9 mL) and the resulting solution, thermostated at 25 °C, was poured into the first Schlenk tube. The reaction mixture was stirred for 24 h. Then it was diluted with water (10 mL) and extracted with CH_2Cl_2 (2×10 mL) and toluene (2×10 mL). The combined organic layers were collected and concentrated under vacuum. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether/CH_2Cl_2 gradient (from 9.5:0:0.5 to 5:4.5:0.5) as eluant, afforded **17** (2.18 g, 62%), as a pale yellow oil. R_f=0.15 (petroleum ether (bp 40–60 °C)/diethyl ether 50:50).

Found: C, 71.9; H, 8.3; N, 8.9. $C_{37}H_{52}N_4O_4$ requires C, 72.05; H, 8.50; N, 9.08. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.40 (22H, m, 11CH_2), 1.40–1.70 (4H, m, 2CH_2), 2.01 (6H, s, 2C(4)CH_3), 2.33 (4H, t, *J* 7.7 Hz, 2C(3)CH_2), 3.11 (6H, s, 2OCH_3), 6.27 (2H, s, 2C(5)*H*), 7.03 (2H, ddd, *J* 7.1, 4.8, 0.9 Hz, 2H_{py}-5), 7.71 (2H, ddd, *J* 8.7, 7.1, 1.7 Hz, 2H_{py}-4), 8.16 (2H, br dt, *J* 7.1, 0.9 Hz, 2H_{py}-3), 8.42 (2H, ddd, *J* 4.8, 1.7, 0.9 Hz, 2H_{py}-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.7 (2C(4)CH_3), 23.5 (2C(3)CH_2), 28.5, 29.5, 29.6, 29.7 (13CH_2), 50.5 (2OCH_3), 87.3 (2*C*(5)H), 114.9 (2C_{py}-3), 119.4 (2C_{py}-5), 135.3 (2*C*(3)), 137.9 (2C_{py}-4), 147.9 (2*C*(4)), 148.1 (2C_{py}-6), 150.5 (2C_{py}-2), 170.1 (2C=O). IR (film): 1708 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 617.3 (M+H)$^+$.

4.12. Preparation of 3,3′-(pentadecane-1,15-diyl)-bis(*N*-(2-pyridyl)-5-hydroxy-4-methyl-3-pyrrolin-2-one) (18)

In a Schlenk tube, substrate **17** (0.617 g, 1 mmol), H_2SO_4 2 M (1 mL) and H_2O (1 mL) were added under nitrogen. The mixture, under vigorous stirring, was heated to 140 °C for 3 h. Then it was

neutralized with $NaOH_{(aq)}$ (1 M) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were concentrated under vacuum. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether/CH_2Cl_2 gradient (from 9.5:0:0.5 to 5:4.5:0.5) as eluant, afforded **18** (0.44 g, 75%), as a pale yellow oil. R_f=0.19 (petroleum ether (bp 40–60 °C)/diethyl ether 50:50).

Found: C, 71.3; H, 8.3; N, 9.7. $C_{35}H_{48}N_4O_4$ requires C, 71.40; H, 8.22; N, 9.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.40 (22H, m, 11CH_2), 1.40–1.70 (4H, m, 2CH_2), 2.07 (6H, s, 2C(4)CH_3), 2.30 (4H, t, *J* 7.4 Hz, 2C(3)CH_2), 5.70 (2H, br s, 2 O*H*), 5.97 (2H, s, 2C(5)*H*), 7.00 (2H, br dd, *J* 7.0, 5.3 Hz, 2H_{py}-5), 7.71 (2H, ddd, *J* 8.6, 7.0, 1.7 Hz, H_{py}-4), 8.26 (2H, br d, *J* 5.3 Hz, 2H_{py}-6), 8.37 (2H, d, *J* 8.6 Hz, 2H_{py}-3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.6 (2C(4)*C*H$_3$), 23.4 (2C(3)*C*H$_2$), 28.4, 29.1, 29.5, 29.7, 29.8 (13*C*H$_2$), 83.6 (2*C*(5)H), 113.1 (2C_{py}-3), 118.8 (2C_{py}-5), 134.5 (2*C*(3)), 138.7 (2C_{py}-4), 147.1 (2C_{py}-6), 149.5 (2*C*(4)), 151.8 (2C_{py}-2), 169.6 (2*C*=O). IR (film): 1699 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 589.3 (M+H)$^+$.

4.13. Preparation of 3,3′-(pentadecane-1,15-diyl)-bis(*N*-(2-pyridyl)-4-methyl-3-pyrrolin-2,5-dione) (19)

In a 100 mL round bottom flask, substrate **18** (1.93 g, 3.28 mmol), MnO_2 (13.12 g) and CH_2Cl_2 (65 mL) were added in sequence. The reaction mixture was vigorously stirred at room temperature. After 24 h (GC monitoring), the mixture was filtered on paper. The MnO_2 cake was washed with CH_2Cl_2 (3×15 mL) and the filtrate was concentrated under vacuum. In this way the crude product was recovered and further purified by recrystallization from methanol/diethyl ether. Pure **19** was obtained (1.56 g, 85%) as needle-shaped white crystals.

Found: C, 71.6; H, 7.6; N, 9.3. $C_{35}H_{44}N_4O_4$ requires C, 71.89; H, 7.58; N, 9.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.45 (22H, m, 11CH_2), 1.45–1.70 (4H, m, 2CH_2), 2.06 (6H, s, 2C(4)CH_3), 2.47 (4H, t, *J* 7.6 Hz, 2C(3)CH_2), 7.29 (2H, dddd, *J* 7.7, 4.9, 1.0 Hz, 2H_{py}-5), 7.34 (2H, br dt, *J* 7.7 Hz, 2H_{py}-3), 7.83 (2H, dt, *J* 7.7, 1.9 Hz, H_{py}-4), 8.62 (2H, ddd, *J* 4.9, 1.9, 0.7 Hz, 2H_{py}-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 9.0 (2C(4)*C*H$_3$), 23.9 (2C(3)*C*H$_2$), 28.3, 29.4, 29.6, 29.7 (13*C*H$_2$), 121.2 (2C_{py}-3), 122.9 (2C_{py}-5), 137.8 (2*C*(3)), 138.2 (2C_{py}-4), 141.9 (2*C*(4)), 146.4 (2C_{py}-2), 149.5 (2C_{py}-6), 170.1 (2*C*=O), 170.4 (2*C*=O). IR (KBr): 1711 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 585.3 (M+H)$^+$. Mp=76–77 °C.

4.14. Preparation of 3,3′-(pentadecane-1,15-diyl)-bis-(4-methyl-furan-2,5-dione) (20)

In a Schlenk tube, substrate **19** (0.89 g, 1.52 mmol), H_2SO_4 2 M (1.52 mL) and H_2O (1.52 mL) were added, together with a stirring bar. The mixture, under vigorous stirring, was heated to 130 °C for 3 h. Then it was diluted with H_2O (3.2 mL) and extracted with CH_2Cl_2 (4×5 mL). The combined organic layers were concentrated under vacuum. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether/CH_2Cl_2 gradient (from 9.5:0:0.5 to 6.5:3:0.5) as eluant, afforded **20** (0.44 g, 69%) as a beige solid. R_f=0.54 (petroleum ether (bp 40–60 °C)/diethyl ether 50:50). Then, the product was recrystallized from petroleum ether/diethyl ether as a white solid (0.43 g, 65%).

Found: C, 69.5; H, 8.6. $C_{25}H_{36}O_6$ requires C, 69.42; H, 8.39. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.45 (22H, m, 11CH_2), 1.45–1.70 (4H, m, 2CH_2), 2.07 (6H, s, 2C(4)CH_3), 2.45 (4H, t, *J* 7.6 Hz, 2C(3)CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 9.6 (2C(4)*C*H$_3$), 24.5 (2C(3)*C*H$_2$), 27.7, 29.3, 29.5, 29.6, 29.7 (13*C*H$_2$), 140.6 (2*C*(3)), 144.9 (2*C*(4)), 166.0 (2*C*=O), 166.4 (2*C*=O). IR (KBr): 1766 (C=O) cm^{-1}. ESI-MS (*m*/*z*): 433.3 (M+H)$^+$. Mp=53 °C.

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References and notes

1. Bradshaw, R.A. Aminopeptidases. In *Encyclopedia of Biological Chemistry*; Elsevier/Academic: Oxford, UK, 2004; Vol. 1, pp 96-98.
2. (a) Matsui, M.; Fowler, J. H.; Walling, L. L. *Biol. Chem.* **2006**, *387*, 1535–1544; (b) Taylor, A. *FASEB J.* **1993**, *7*, 290–298.
3. (a) Vazeux, G.; Wang, J.; Corvol, P.; Llorens-Cortès, C. *J. Biol. Chem.* **1996**, *271*, 9069–9074; (b) Sin, N.; Meng, L.; Wang, M. Q. W.; Wen, J. J.; Bornmann, W. J.; Crews, C. M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 6099–6103; (c) Wu, Q.; Lahti, J. M.; Air, G. M.; Burrows, P. D.; Cooper, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 993–997.
4. Chen, X.; Zheng, Y.; Shen, Y. *Chem. Rev.* **2007**, *107*, 1777–1830.
5. Weber, W.; Semar, M.; Anke, T.; Bross, M.; Steglich, W. *Planta Med.* **1992**, *58*, 56–59.
6. (a) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 1342–1343; (b) Mangaleswaran, S.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 5259–5261.
7. Bellesia, F.; Danieli, C.; De Buyck, L.; Galeazzi, R.; Ghelfi, F.; Mucci, A.; Orena, M.; Pagnoni, U. M.; Parsons, A. F.; Roncaglia, F. *Tetrahedron* **2006**, *62*, 746–757.
8. Van der Steen, M.; Stevens, C. V.; Eeckhout, Y.; De Buyck, L.; Ghelfi, F.; Roncaglia, F. *Eur. J. Lipid Sci. Technol.* **2008**, *110*, 846–852.
9. Ghelfi, F.; Pattarozzi, M.; Roncaglia, F.; Parsons, A. F.; Felluga, F.; Pagnoni, U. M.; Valentin, E.; Mucci, A.; Bellesia, F. *Synthesis* **2008**, *19*, 3131–3141.
10. Swern, D.; Billen, G. N.; Scanlan, J. T. *J. Am. Chem. Soc.* **1946**, *68*, 1504–1507.
11. De Buyck, L.; Casaert, F.; De Lepeleire, C.; Schamp, N. *Bull. Soc. Chim. Belg.* **1988**, *97*, 525–533.
12. De Buyck, L.; Vanslembrouck, J.; De Kimpe, N.; Verhè, R.; Schamp, N. *Bull. Soc. Chim. Belg.* **1984**, *93*, 913–917.
13. (a) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11; (b) Ghelfi, F.; Stevens, C. V.; Laureyn, I.; Van Meenen, E.; Rogge, T. M.; De Buyck, L.; Nikitin, K. V.; Grandi, R.; Libertini, E.; Pagnoni, U. M.; Schenetti, L. *Tetrahedron* **2003**, *59*, 1147–1157.