A Simple and Efficient Route to Chaetomellic Anhydride A: A Potent Natural Ras Farnesyl-Protein Transferase Inhibitor

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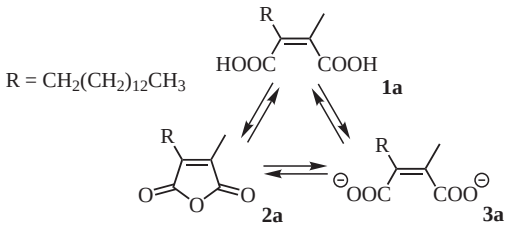
Abstract: A new and efficient approach to chaetomellic anhydride A has been devised starting from 2,2-dichloropalmitic acid. This involves the atom transfer radical cyclization of an *N*-alkyl-*N*-(3-chloro-2-propenyl)amide followed by rearrangement of the resulting trichloro-pyrrolidin-2-one.

Key words: amides, cyclisations, halogenation, pyrrolidinones, radical reactions

Chaetomellic acid A (**1a**) is a natural substance which was isolated in 1993 by the Singh's research group, in the form of anhydride **2a**, from the fermentation extracts of the coelomycete *Chaetomella acutiseta* (Scheme 1).[1] The potent and specific inhibition of ras farnesyl-protein transferase (FPTase) by the dianion form **3a** has attracted the attention of laboratories involved in the development of novel anticancer therapeutics.[2]

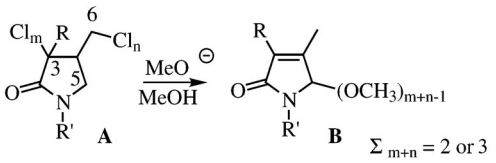


Scheme 1

The oncogene product Ras, which is synthesized in vivo, is a protein that requires post-translational modification in order to become biologically active and capable of transforming mammalian cells. Since farnesylation has appeared to be a critical modification in the Ras activation process, inhibitors of the FPTase enzyme that catalyzes this reaction might thus block *ras*-dependent tumorigenesis.[3]

Studies of structure-activity relationships and pharmacological tests have stimulated the development of chemical syntheses for the production of larger quantities of chaetomellic acid A (**1a**) than that available from natural sources. So far, nine routes have been devised for the preparation of this interesting product.[3] In general, the synthesis of anhydride **2a** has been targeted since this compound is more easy to manipulate/isolate than diacid **1a**. Anhydride **2a** can also be easily hydrolysed to the biologically active dianion **3a** using aqueous base [i.e., pH > 7 (Scheme 1)].[1a] Recently, the dianion of chaetomellic acid A (**3a**) has found application in characterizing the FPP (farnesyl diphosphate) binding site in rubber transferase.[4] The synthetic strategies investigated can be grouped into two general categories: i) alkylation of maleic precursors[5a,5c–g] and ii) assembly of the pivotal 1,4-dicarbonyl group.[5b,h,i] In spite of the variety of methods employed, all of the reported procedures suffer from one or more of the following disadvantages: i) low yields, ii) costly reagents, iii) unstable precursors and/or reactants, iv) harmful solvents, and v) unwieldy protocols. As a result, these procedures are not well-suited for large scale production, as evidenced by the high price of **1a**, which is sold by ICN or Calbio Chem at ca. 18000 /g.

Owing to the appealing properties and uses of **1a**–**3a**, the design of more robust and facile synthetic approaches to these molecules is of current interest. In this paper we report a novel radical route to chaetomellic anhydride A (**2a**). This involves the formation of the carbon-carbon bond between the C(3) and C(4) positions of the furan-2,5-dione ring.[6]



Scheme 2

During our recent studies on the synthesis and reaction of 4-methyl-pyrrolidin-2-ones **A** chlorinated at the C(3) and C(6) positions, we serendipitously discovered that when treated with a solution of alkaline methoxide (in MeOH under mild conditions), these compounds are transformed into the *N*-substituted 5-methoxy or 5,5-dimethoxy-4-methyl-3-pyrrolin-2-ones **B** (Scheme 2).[7]

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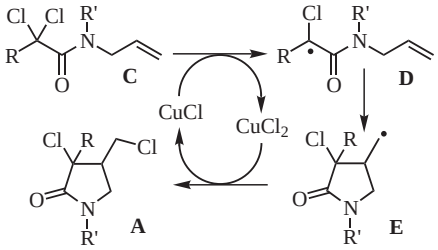
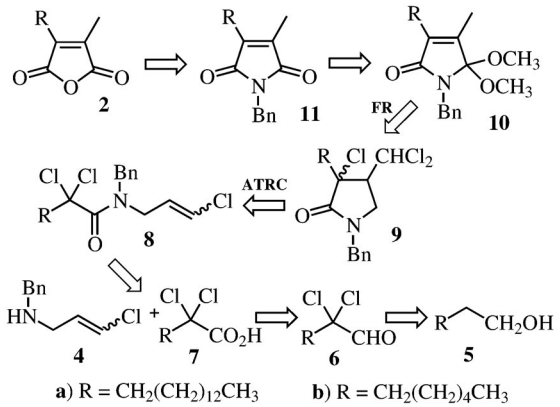
The transformation involves a series of eliminations/substitutions that give rise to a remarkable functional rearrangement (FR), on considering that the starting oxidation state of the molecule is preserved and the functionalities repositioned. In practice two or three of the C–Cl groups at the C(3) and C(6) positions of **A** are replaced by an alkene at C(3)–C(4) and one or two methoxy groups at C(5).

This approach is particularly attractive because the starting polyhalogenated 2-pyrrolidinones **A** can be efficiently prepared from *N*-allyl α-perchloro amides **C** by an atom transfer radical cyclization (ATRC) (Scheme 3). The transformation can be accomplished using redox catalysts[8] such as the complex formed on reaction of CuCl and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA).[9]



Scheme 3

The ring closure is initiated by abstraction of an α-halogen atom from **C** by CuCl/TMEDA and this is followed by a 5-*exo*-*trig* cyclization of the resulting electrophilic α-*N*-allyl-carbamoyl radical **D**. This forms nucleophilic radical **E**, which reacts to afford **A** on abstraction of a chlorine atom from $CuCl_2$/TMEDA. This last step results in the regeneration of the copper(I) catalyst, which can initiate a new reaction cycle (Scheme 3). There are a number of advantages of this type of radical cyclization: i) low cost of the catalyst, ii) ease of work-up and iii) preservation of all of the carbon-halogen groups in the cyclic product.

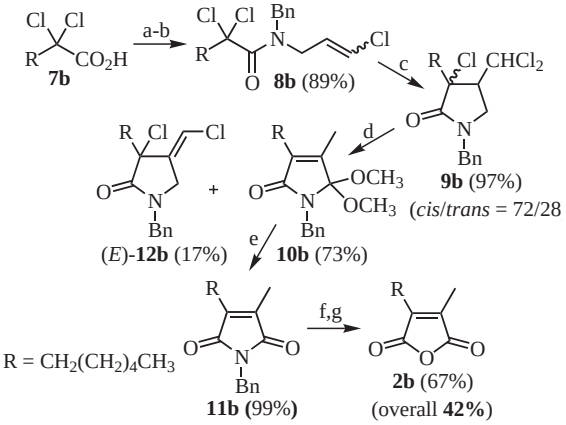


Scheme 4

A retrosynthetic analysis of the anhydride of chaetomellic acid **2a**, which incorporates the FR and ATRC reactions, is shown in Scheme 4. This involves the disconnection of **2a** to give 2,2-dichloro-palmitic acid (**7a**) and *N*-benzyl-3-chloro-2-propenylamine (**4**) as starting materials in a highly convergent approach.

Attractive features of this strategy are the use of a radical cyclization to efficiently construct the substituted 5-membered ring, the elegant functional rearrangement of the resulting pyrrolidinone and the handling of all of the functionalities in line with the 'rule of maximum simplicity'.[10] Furthermore, the starting material **7a** can be secured by a straightforward transformation of the corresponding and inexpensive fatty alcohol 1-hexadecanol.[11]

Having in stock a large amount of 2,2-dichlorooctanoic acid (**7b**),[11] we chose to experiment the viability of the retrosynthetic plan by preparing the more simple target molecule, 3-hexyl-4-methylmaleic anhydride (**2b**). This natural product is a component of essential oils from *Agropyrum repens*,[12a] almond hulls and raisins.[12b] Owing to the reduced size of **2b**, the aliphatic side-chain at C(3) is roughly half the size of that of **2a**, it was believed that the feasibility of the approach would be easier to monitor analytically. In addition, the alkyl chain was believed to be long enough to establish any problems associated with the synthetic route to **2a**.



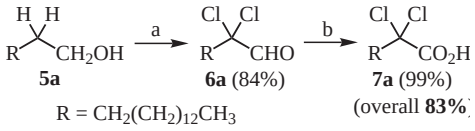
Scheme 5 (a) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h; (b) **4**, pyridine, 23 °C, 1 h; (c) CuCl/TMEDA, MeCN, 25 °C, 20 h; (d) Na, MeOH, 25 °C, 20 h; (e) H^+/H_2O; (f) KOH, MeOH–THF, reflux, 2 h; (g) H^+/H_2O.

The synthetic path from dichloride **7b** to anhydride **2b** is outlined in Scheme 5. At first, 2,2-dichlorooctanoic acid (**7b**) was activated with oxalyl chloride and the resulting acyl chloride treated with *N*-benzyl-3-chloro-2-propenylamine (**4**) to afford amide **8b** in good yield (89%).[9e] Then **8b** was smoothly cyclized using CuCl/TMEDA in MeCN to provide the trihalogenated pyrrolidin-2-one **9b** (97%). This was isolated as an inseparable mixture of *cis*-/*trans*-isomers, in a ratio of 72:28 as indicated by the ^{1}H NMR spectrum.

The ensuing functional rearrangement of **9b** was accomplished using Na in MeOH (at 25 °C) following the literature procedure.[7] However, along with the desired acetal **10b**, isolated in a respectable yield of 73%, we also recovered a moderate amount (17%) of the *exo*-dehydrohalogenated pyrrolidin-2-one (*E*)-**12b**. This product was believed to be an intermediate in the transformation of **9b**

to **10b** and so we subjected **12b** to the FR reaction conditions but, surprisingly, only unreacted **12b** was isolated. Even at 80 °C no rearrangement was observed, however, at this higher temperature some degradation of (*E*)-**12b** occurred. Evidently this compound cannot be regarded as an intermediate in the FR reaction of **9b** to **10b**. Acetal **10b** was then quantitatively converted into *N*-benzyl-3-hexyl-4-methyl-maleimide (**11b**) by reaction with CH_3SO_3H/H_2O at 100 °C. Finally, on hydrolysis of **11b**, using the procedure devised by Argade,[5e] we isolated the desired anhydride **2b**. Overall, a good yield of 42% was achieved over the 5 steps from **7b**.

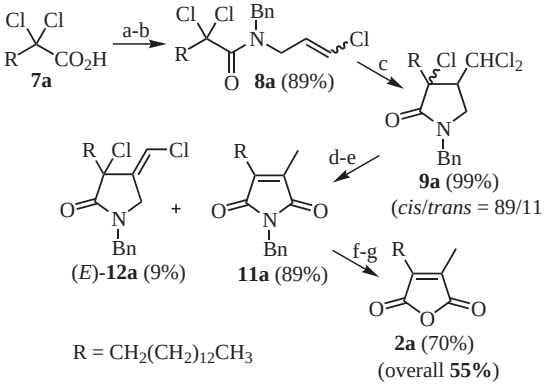
Encouraged by the success of the strategy to prepare 3-hexyl-4-methylmaleic anhydride **2b**, we concentrated our efforts on preparing chaetomellic anhydride A (**2a**). The required starting material, 2,2-dichloropalmitic acid (**7a**), was easily prepared on a large scale from 1-hexadecanol (**5a**), following a two-step protocol.[11a] While the initial oxidation-chlorination of alcohol **5a** to give 2,2-dichlorohexadecanal (**6a**) was efficiently achieved using the classical system of Cl_2/DMF·HCl (84%),[11a] for the ensuing oxidation of the intermediate aldehyde **6a** we devised a novel and more practical method: this involved treatment of **6a** with Br_2/NaOH to give 2,2-dichloropalmitic acid (**7a**) in quantitative yield (Scheme 6).[13]



Scheme 6 (a) Cl_2, DMF·HCl, $CHCl_3$, 70 °C, 3 h; (b) Br_2, NaOH, CH_2Cl_2–H_2O, 1.5 h.

The acid **7a** was then converted into the corresponding acyl chloride using oxalyl chloride and then immediately treated with allyl amine **4** to furnish the amide **8a** in high yield (84%). For the subsequent cyclization, since **8a** is insoluble in MeCN (because of its lipophilicity), some CH_2Cl_2 was added to MeCN to increase the solubility of the substrate. In spite of the adjustment, the ATRC (mediated by CuCl/TMEDA) worked well and afforded the expected γ-lactam **9a** in 99% yield as an inseparable pair of *cis*/*trans* isomers in a ratio of 89:11. It should be noted that the selectivity for the *cis*-isomer of **9a** was much higher than that observed in the cyclization of **8b** to give **9b** (72:28). This is due to the different reaction temperatures (namely 60 °C and 25 °C) under which the ring closure of **8a** and **8b** were accomplished. Since the C(3) stereocenter of lactams of type **A** is configurationally unstable under the reaction conditions, the higher the reaction temperature the greater the equilibration between the *cis*- (more stable) and *trans*-isomers (less stable).[9d,e]

Substrate solubility was also a problem when **9a** was treated with CH_3ONa/MeOH in the following FR step. As before, the problem was circumvented by the addition of a less polar co-solvent, in this case Et_2O, to the reaction mixture. An acidic work-up was also adopted following the functional rearrangement so as to shorten the synthetic path and directly form the maleimide intermediate **11a**: this was recovered in excellent yield (89%). As observed for the reaction of **9b**, a small amount (9%) of (*E*)-**12a** was isolated, which arose from a parasitic *exo*-dehydro-halogenation. The synthesis of chaetomellic anhydride A (**2a**) was completed by hydrolysis of **11a**, using conditions reported in the literature, which gave **2a** in a respectable yield of 70%.[5e] The overall yield of chaetomellic anhydride A (**2a**) using this 4-step approach was 55% (Scheme 7). Similar results were also obtained when the *N*-benzyl group of allyl amine **4** was changed to the smaller-sized *N*-propyl group.



Scheme 7 (a) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h; (b) **4**, pyridine, 23 °C, 1 h; (c) CuCl/TMEDA, MeCN–CH_2Cl_2, 60 °C, 20 h; (d) Na, MeOH–Et_2O, 25 °C, 20 h; (e) H^+/H_2O; (f) KOH, MeOH–THF, reflux, 2 h; (g) H^+/H_2O.

In summary, a short, simple, convergent and efficient synthesis of chaetomellic anhydride A (**2a**) has been developed from inexpensive precursors. This represents the first application of the FR reaction (using CH_3ONa/MeOH) of polychlorinated γ-lactams [generated by the ATRC of *N*-(3-chloro-2-propenyl)-α-perchloroamides] to a furan-2,5-dione target molecule. This novel synthetic approach is well suited to the preparation of structural analogues of **2a** with various alkyl side-chains at the C(3) position. Moreover, this methodology could be applied to the synthesis of related natural products, with interesting biological properties, including tyromicine A[14] and roccellic acid.[15] Our studies on the synthesis of these and similar molecules are well underway and will be reported in due course.

Reagents and solvents were standard grade commercial products, purchased from Aldrich, Acros, Fluka or RdH, and used without further purification, except for MeCN and CH_2Cl_2 that were dried over three batches of 3 Å sieves (5% w/v, 12 h). Chlorine (99.8%) was supplied by Praxair. *N*-Benzyl-3-chloro-2-propenylamine (as a 58:42 mixture of *E*/*Z* isomers) was prepared by *N*-alkylation of benzylamine with 1,3-dichloro-2-propene, following the procedure of Shipman.[16] 2,2-Dichlorooctanoic acid was prepared according to a literature procedure.[11a] ^{1}H NMR, IR and MS spectra were recorded on Bruker DPX 200 and Bruker AMX 400 (both used for NMR), Perkin Elmer 1600 Series FTIR, and HP 5890 GC–HP 5989A MS instruments, respectively. The structural assignment of compounds

9a, **9b**, **12a** and **12b** was determined by homonuclear Nuclear Overhauser Enhancement and heteronuclear H,C inverse-detection NMR correlation techniques. The direct and long-range H,C correlations on **12a** and **12b** allowed us to unambiguously establish their regiochemistry, whereas NOESY experiments enabled the configuration of the double bond in **12a** and **12b**, and the relative stereochemistry at the C(3) and C(4) carbons in **9a** and **9b** to be determined.

Preparation of *N*-Benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichlorooctanamide (8b); Typical Procedure

2,2-Dichlorooctanoic acid (**7b**, 6.42 g, 30.1 mmol) was weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a $CaCl_2$ tube on the side arm. Next, anhyd CH_2Cl_2 (16.5 mL) was added under Ar. The solution was thermostated at 23 °C, and under stirring, DMF (50 μL) and $(COCl)_2$ (5.23 mL, 60 mmol) were injected using a syringe. The side arm stopcock was opened to vent out any gases (CO, CO_2 and HCl) produced during the reaction. After 2 h, solvent and excess oxalyl chloride were removed under reduced pressure. The crude acyl chloride was diluted with anhyd CH_2Cl_2 (40 mL), then the solution, thermostated at 23 °C, was treated with a solution of pyridine (3.64 mL, 45 mmol) and amine **4** (8.08 g, 45 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 h and then washed with HCl (2.5% w/v, 2 × 45 mL). Flash chromatography of the crude product on silica gel, using petroleum ether (bp 40–60 °C)–Et_2O (9.8:0.2) as eluant, gave amide **8b** (10.07 g, 89%) as a mixture of *E*/*Z* stereoisomers.

***N*-Benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichlorooctanamide (8b)**

Colourless oil.

IR (film): 1660 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.93 (m, 3 H), 1.38 (m, 6 H), 1.76 (m, 2 H), 2.53 (m, 2 H), 3.7–5.2 (m br s, 4 H), 5.7–6.3 (br s, 2 H), 7.33 (m, 5 H).

MS (EI): *m*/*z* = 375 (1) [M^+], 340 (29), 300 (32), 180 (23), 132 (13), 91 (100).

Anal. Calcd for $C_{18}H_{24}Cl_3NO$: C, 57.38; H, 6.42; N, 3.72. Found: C, 57.26; H, 6.51; N, 3.67.

Cyclization of *N*-Benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichlorooctanamide (8b); Typical Procedure

CuCl (0.99 g, 1.0 mmol) and dichloride **8b** (3.77 g, 10 mmol) were weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap). Anhydrous MeCN (15 mL) and TMEDA (302 μL, 2 mmol) were then added under Ar. The mixture was stirred at 25 °C and after 20 h diluted with HCl (5% w/v, 20 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were concentrated and the crude product was purified using flash chromatography on silica gel, eluting with petroleum ether (bp 40–60 °C)–Et_2O (8.5:1.5). This gave 2-pyrrolidinone **9b** (3.67 g, 97%) as a 72:28 mixture of inseparable *cis*- and *trans*-diastereoisomers as indicated by the ^1H NMR spectrum.

***N*-Benzyl-3-chloro-4-dichloromethyl-3-hexyl-2-pyrrolidinone (9b)**

Yellow-orange oil.

IR (film): 1708 (C=O) cm^{-1}.

^1H NMR [400 MHz, $CDCl_3$, *cis*-diastereoisomer (72%)]: δ = 0.90 (m, 3 H), 1.33 (br m, 8 H), 2.37 (m, 2 H), 3.0–3.4 (m, 3 H), 4.42 (d, *J* = 14.7 Hz, 1 H), 4.61 (d, *J* = 14.7 Hz, 1 H), 5.99 (m, 1 H), 7.33 (m, 5 H)

^1H NMR [400 MHz, $CDCl_3$, *trans*-diastereoisomer (28%)]: δ = 0.90 (m, 3 H), 1.33 (br m, 8 H), 2.37 (m, 2 H), 3.0–3.4 (m, 2 H), 3.61 (dd, *J* = 6.9, 10.6 Hz, 1 H), 4.35 (d, *J* = 14.7 Hz, 1 H), 4.69 (d, *J* = 14.7 Hz, 1 H), 5.90 (d, *J* = 4.2 Hz, 1 H), 7.33 (m, 5 H).

^{13}C NMR [100 MHz, $CDCl_3$, *cis*-diastereoisomer (72%)]: δ = 14.00, 22.52, 25.02, 29.05, 31.40, 37.17, 47.05, 47.15, 49.40, 71.75, 71.91, 128.08, 128.11, 128.97, 135.21, 169.97.

^{13}C NMR [100 MHz, $CDCl_3$, *trans*-diastereoisomer (28%)]: δ = 14.03, 22.52, 24.63, 29.07, 31.42, 33.14, 45.39, 47.13, 54.56, 70.59, 71.33, 128.06, 128.39, 128.85, 135.18, 169.99.

MS (EI) *m*/*z* = 340 (29) [$M^+ - 35$], 293 (20), 291 (21), 256 (12), 208 (83), 91 (100).

Anal. Calcd for $C_{18}H_{24}Cl_3NO$: C, 57.38; H, 6.42; N, 3.72. Found: C, 57.44; H, 6.53; N, 3.59.

Rearrangement of 2-Pyrrolidinone 9b; Typical Procedure

In a Schlenk tube fitted with a perforable septum (blocked by a screw cap), MeOH (30 mL) and Na (1.84 g, 80 mmol) were added. When the effervescence ceased, the solution was thermostated at 25 °C and **9b** (7.54 g, 20 mmol) in MeOH (30 mL) was added by syringe. The reaction mixture was stirred for 20 h, then diluted with water (10 mL), extracted with CH_2Cl_2 (2 × 80 mL) and the combined organic layers concentrated. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)–Et_2O gradient (from 10:0–8.5:1.5), gave acetal **10b** (4.84 g, 73%) and the dehydrohalogenated γ-lactam **12b** (1.16 g, 17%).

***N*-Benzyl-3-hexyl-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (10b)**

Orange oil.

IR (film): 1711 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.85 (m, 3 H), 1.28 (br m, 6 H), 1.49 (m, 2 H), 1.74 (s, 3 H), 2.30 (t, *J* = 6.1 Hz, 2 H), 2.75 (s, 6 H), 4.33 (s, 2 H), 7.22 (m, 3 H), 5.45 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.02, 13.82, 22.38, 23.22, 28.35, 29.01, 31.34, 41.37, 50.42, 112.60, 127.10, 128.06, 129.40, 137.19, 137.54, 143.75, 169.71.

MS (EI): *m*/*z* = 331 (33) [M^+], 316 (4), 300 (41), 284 (16), 272 (15), 261 (14), 226 (8), 211 (24), 91 (100).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.37; H, 8.80; N, 4.37.

***(E)*-*N*-Benzyl-3-chloro-4-chloromethylen-3-hexyl-2-pyrrolidinone (12b)**

Colourless liquid.

IR (film): 1713 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.6 Hz, 3 H), 1.24 (br m, 8 H), 2.09 (ddd, *J* = 5.5, 10.9, 13.6 Hz, 1 H), 2.33 (ddd, *J* = 4.8, 11.3, 13.6 Hz, 1 H), 3.83 (dd, *J* = 2.2, 15.5 Hz, 1 H), 3.96 (dd, *J* = 2.5, 15.5 Hz, 1 H), 4.52 (d, *J* = 14.4 Hz, 1 H), 4.60 (d, *J* = 14.4 Hz, 1 H), 6.46 (t, *J* = 2.4 Hz, 1 H), 7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.98, 22.42, 24.96, 28.97, 31.41, 39.86, 46.95, 47.62, 67.40, 119.31, 128.08, 128.21, 128.94, 135.05, 136.78, 170.03.

MS (EI): *m*/*z* = 340 (1) [$M^+ + 1$], 304 (40), 268 (9), 255 (57), 91 (100).

Anal. Calcd for $C_{18}H_{23}Cl_2NO$: C, 63.53; H, 6.81; N, 4.12. Found: C, 63.39; H, 6.93; N, 4.22.

Hydrolysis of Acetal 10b; Typical Procedure

In a Schlenk tube, were added acetal **10b** (0.33 g, 1 mmol), H_2O (1 mL) and two drops of methanesulfonic acid. The mixture, under vigorous stirring, was heated to 100 °C for 6 h, after which time it was neutralized with $NaHCO_3$ (5% w/v) and then extracted with

CH_2Cl_2 (2 × 3 mL). The organic phases were collected and concentrated. Following flash chromatography of the crude product on silica gel, using petroleum ether (bp 40–60 °C)–Et_2O (9.5:0.5) as eluent, the desired maleimide **11b** (0.28 g, 98%) was recovered.

_N_-Benzyl-3-hexyl-4-methylmaleimide (11b)
Colourless oil.

IR (film): 1693 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.2 Hz, 3 H), 1.32 (br m, 6 H), 1.52 (m, 2 H), 1.95 (s, 3 H), 2.36 (t, *J* = 7.3 Hz, 2 H), 4.63 (s, 2 H), 7.24 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.48, 13.85, 22.36, 23.59, 27.96, 29.05, 31.31, 41.34, 127.46, 128.22, 128.43, 136.67, 136.89, 141.16, 171.48, 171.73.

MS (EI): *m*/*z* = 285 (66) [M^+], 97 (83), 137 (100), 91 (89).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.62; H, 8.02; N, 4.85.

Hydrolysis of _N_-Benzylmaleimide 11b
According to Argade's protocol,[5e] maleimide **11b** (0.57 g, 2 mmol) was hydrolysed to anhydride **2b** (0.26 g, 67%).

3-Hexyl-4-methylmaleic Anhydride (2b)[12a]
Colourless liquid.

IR (film): 1706 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.2 Hz, 3 H), 1.30 (br m, 6 H), 1.58 (m, 2 H), 2.08 (s, 3 H), 2.46 (t, *J* = 7.1 Hz 2 H).

MS (EI): *m*/*z* = 196 (3) [M^+], 168 (6), 140 (13), 139 (9), 127 (9), 126 (100), 43 (50).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.44; H, 8.08.

Preparation of 2,2-Dichlorohexadecanal (6a); Typical Procedure
1-Hexadecanol (**5a**) (290.4 g, 1198 mmol) was dissolved in DMF (386 g), $CHCl_3$ (420 mL) and CH_2Cl_2 (120 mL), and the mixture was kept at 30–35 °C to prevent crystallization. In a three-necked flask (2 L), protected against light and equipped with an internal electronic thermometer, reflux condenser and chlorine inlet, was added a magnetic stirring bar followed by DMF·HCl (60 g), DMF (20 g) and $CHCl_3$ (80 mL). The mixture was preheated to 50–60 °C, then the flow of Cl_2 was started. After 1 min, the solution containing 1-hexadecanol (**5a**) was added through a dropping funnel, whereby the temperature increased to an optimum value of 67–69 °C. The addition of 1-hexadecanol (**5a**) was carried out over 100–150 min and a slight excess of chlorine was maintained over this period. The stream of Cl_2 was stopped 2–10 min after adding the alcohol (and also rinsing the dropping funnel with 25 mL of CH_2Cl_2) and 30–50 min later, evacuation of Cl_2–CH_2Cl_2–$CHCl_3$ was started by means of a membrane pump. When three quarters of the volume of the solvent (CH_2Cl_2–$CHCl_3$) was collected, the residue (Important: No chlorine must remain in solution) was extracted with petroleum ether (bp 45–50 °C, 500 mL) and the bottom layer (containing DMF·HCl) was washed again with petroleum ether (250 mL). DMF·HCl can subsequently be recovered by distillation (bp 60 °C/12 mmHg). The petroleum ether layers were then combined, washed with HCl (5 N, 2 × 100 mL) and dried over $MgSO_4$. The crude product was distilled to give dichloride **6a** (311.3 g, 84%) as a colourless liquid (bp 131–135 °C/0.05 mmHg).[11a]

Oxidation of 2,2-Dichlorohexadecanal (6a); Typical Procedure
2,2-Dichlorohexadecanal (**6a**) (108.3 g, 350 mmol) was stirred with CH_2Cl_2 (250 mL) and H_2O (250 mL) on a water bath at around 13–15 °C. Then Br_2 (21 mL, 410 mmol) was added in one portion followed by the dropwise addition of a solution of NaOH (42.0 g, 1050 mmol) in H_2O (300 mL), over a period of 40–80 min. The mixture soon became difficult to stir magnetically and homogenization was then effected by manual shaking. Towards the end of the dropwise addition, the inner temperature of the reaction mixture reached 32–33 °C. About 30 min after the addition of the aqueous hydroxide some $NaHSO_3$ was added (to remove any unreacted bromine) followed by an excess of concd HCl (37.5%, 200–250 mL). The dried ($MgSO_4$) organic layer was distilled to recover most of the CH_2Cl_2 and this was followed by evaporation under reduced pressure (at 60–65 °C). The residue was then recrystallised from petroleum ether (bp 40–60 °C, 120–140 mL) by leaving overnight at near 4 °C. The first crop of crystals was isolated on vacuum filtration and subsequent concentration and cooling of the mother liquor gave further acid **7a** (112.7 g, 99%) as a white solid; mp 33–35 °C (petroleum ether).[11a]

Preparation of _N_-Benzyl-_N_-(3-chloro-2-propenyl)-2,2-dichlorohexadecanamide (8a)
Following the procedure for the preparation of **8b**, 2,2-dichlorohexadecanoic acid (**7a**, 9.76 g, 30 mmol) gave amide **8a** (13.06 g, 89%) as a mixture of two diastereoisomers.

***N*-Benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichlorohexadecanamide (8a)**
Colourless oil.

IR (film): 1660 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.2 Hz, 3 H), 1.29 (m, 22 H), 1.75 (m, 2 H), 2.51 (m, 2 H), 3.7–5.2 (m, br s, 4 H), 5.7–6.3 (br s, 2 H), 7.31 (m, 5 H).

MS (EI): *m*/*z* = 487 (2) [M^+], 452 (32), 412 (52), 180 (33), 91 (100).

Anal. Calcd for $C_{26}H_{40}Cl_3NO$: C, 63.87; H, 8.25; N, 2.86. Found: C, 64.03; H, 8.08; N, 2.94.

Cyclization of _N_-Benzyl-_N_-(3-chloro-2-propenyl)-2,2-dichlorohexadecanamide (8a); Typical Procedure
CuCl (0.99 g, 1.0 mmol) and **8a** (4.89 g, 10 mmol) were weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap). Anhydrous MeCN (8 mL), anhyd CH_2Cl_2 (5 mL) and TMEDA (302 μL, 2 mmol) were then added under Ar. The mixture was stirred at 60 °C and after 20 h the mixture was diluted with HCl (5% w/v, 20 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were concentrated and purification by flash chromatography on silica gel, eluting with petroleum ether (bp 40–60 °C)–Et_2O (8.5:1.5), gave the 2-pyrrolidinone **9a** (4.84 g, 99%), as an 89:11 mixture of inseparable *cis*- and *trans*-diastereoisomers.

***N*-Benzyl-3-chloro-4-dichloromethyl-3-tetradecyl-2-pyrrolidinone (9a)**
White powder.

IR (KBr): 1701 (C=O) cm^{-1}.

^1H NMR [400 MHz, $CDCl_3$, *cis*-diastereoisomer (89%)]: δ = 0.89 (t, *J* = 6.1 Hz, 3 H), 1.27 (br m, 24 H), 2.39 (m, 2 H), 3.0–3.5 (m, 3 H), 4.41 (d, *J* = 14.7 Hz, 1 H), 4.62 (d, *J* = 14.7 Hz, 1 H), 6.00 (m, 1 H), 7.30 (m, 5 H).

^1H NMR [400 MHz, $CDCl_3$, *trans*-diastereoisomer (11%)]: δ = 0.89 (t, *J* = 6.1 Hz, 3 H), 1.27 (br m, 24 H), 2.39 (m, 2 H), 3.0–3.5 (m, 2 H), 3.61 (dd, *J* = 6.9, 10.6 Hz, 1 H), 4.32 (d, *J* = 14.7 Hz, 1 H), 4.71 (d, *J* = 14.7 Hz, 1 H), 5.89 (d, *J* = 4.2 Hz, 1 H), 7.30 (m, 5 H).

^{13}C NMR [100 MHz, $CDCl_3$, *cis*-diastereoisomer (89%)]: δ = 14.14, 22.72, 25.62, 29.29, 29.38, 29.50, 29.62, 29.69, 31.95, 37.18, 47.08, 47.13, 49.42, 71.70, 71.94, 128.08, 128.98, 135.20, 169.99.

^{13}C NMR [100 MHz, $CDCl_3$, *trans*-diastereoisomer (11%)]: δ = 14.14, 22.72, 24.66, 29.29, 29.38, 29.50, 29.62, 29.69, 31.95, 33.16,

45.37, 47.12, 54.58, 70.55, 71.35, 128.08, 128.34, 128.87, 135.20, 170.02.

MS (EI): *m*/*z* = 488 (11) [M^+ + 1], 452 (32), 382 (7), 368 (14), 293 (36), 291 (48), 208 (66), 91 (100).

Anal. Calcd for $C_{26}H_{40}Cl_3NO$: C, 63.87; H, 8.25; N, 2.86. Found: C, 63.92; H, 8.16; N, 2.94.

Rearrangement of *N*-Benzyl-3-chloro-4-dichloro-methyl-3-tetradecyl-2-pyrrolidinone (9a); Typical Procedure

In a Schlenk tube fitted with a perforable septum (blocked by a screw cap) were added MeOH (30 mL) and Na (1.84 g, 80 mmol). When the effervescence ceased, the solution was thermostated at 25 °C and a solution of **9a** (9.78 g, 20 mmol) in Et_2O (30 mL) was added by syringe. The reaction mixture was then stirred for 20 h, after which time it was acidified with HCl (5% w/v) and left stirring at 25 °C for a further 20 h. Subsequently, the mixture was extracted with CH_2Cl_2 (2 × 80 mL) and the combined organic layers concentrated under reduced pressure. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)– Et_2O gradient (from 10:0–8.5:1.5), gave maleimide **11a** (7.07 g, 89%) and the dehydrohalogenated γ-lactam **12a** (0.80 g, 9%).

***N*-Benzyl-4-methyl-3-tetradecylmaleimide (11a).**

Colourless oil.

IR (film): 1710 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.3 Hz, 3 H), 1.27 (br m, 22 H), 1.53 (m, 2 H), 1.97 (s, 3 H), 2.38 (t, *J* = 7.3 Hz, 2 H), 4.64 (s, 2 H), 7.30 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.67, 14.09, 22.66, 23.70, 28.15, 29.25, 29.33, 29.46, 29.53, 29.57, 29.60, 29.66, 31.89, 41.42, 127.59, 128.20, 128.36, 128.55, 136.70, 136.99, 171.64, 171.93.

MS (EI): *m*/*z* = 397 (63) [M^+], 215 (100), 204 (28), 137 (61), 91 (53).

Anal. Calcd for $C_{26}H_{39}NO_2$: C, 78.54; H, 9.89; N, 3.52. Found: C, 78.63; H, 9.91; N, 3.64.

(*E*)-*N*-Benzyl-3-chloro-4-chloromethylen-3-tetradecy-l-2-pyrrolidinone (12a)

Brownish oil.

IR (film): 1720 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3 H), 1.26 (br m, 24 H), 2.07 (ddd, *J* = 5.5, 11.0, 13.5 Hz, 1 H), 2.33 (ddd, *J* = 5.1, 11.2, 13.5 Hz, 1 H), 3.83 (dd, *J* = 2.5, 15.1 Hz, 1 H), 3.98 (dd, *J* = 2.5, 15.1, 1 H), 4.55 (d, *J* = 14.7 Hz, 1 H), 4.62 (d, *J* = 14.7 Hz, 1 H), 6.46 (t, *J* = 2.5 Hz, 1 H), 7.32 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.09, 22.67, 25.02, 29.26, 29.34, 29.42, 29.56, 20.61, 29.64, 29.67, 31.91, 39.86, 46.96, 47.61, 67.36, 119.28, 128.07, 128.20, 128.94, 135.03, 136.79, 170.04.

MS (EI): *m*/*z* = 451 (11) [M^+], 416 (65), 380 (12), 368 (8), 255 (78), 234 (16), 91 (100).

Anal. Calcd for $C_{26}H_{39}Cl_2NO$: C, 69.01; H, 8.69; N, 3.10. Found: C, 69.14; H, 8.65; N, 3.23.

Hydrolysis of *N*-Benzyl-3-tetradecyl-4-methylmaleimide (11a)

According to Argade's protocol,[5e] maleimide **11a** (0.795 g, 2 mmol) was hydrolysed to anhydride **2a** (0.432 g, 70%).

3-Tetradecyl-4-methylmaleic Anhydride (Chaetomellic Anhydride A) (2a)[1a]

Pale yellow oil.

IR (film): 1766 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.25 (br s, 22 H), 1.57 (m, 2 H), 2.07 (s, 3 H), 2.45 (t, *J* = 7.6 Hz, 2 H).

MS (EI): *m*/*z* = 308 (5) [M^+], 290 (15), 280 (4), 263 (7), 235 (8), 150 (33), 126 (100), 43 (45).

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.86; H, 10.52.

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