Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 746–757
Tetrahedron

A short approach to chaetomellic anhydride A from 2,2-dichloropalmitic acid: elucidation of the mechanism governing the functional rearrangement of the chlorinated pyrrolidin-2-one intermediate

Franco Bellesia,[a] Chiara Danieli,[a] Laurent De Buyck,[b] Roberta Galeazzi,[c] Franco Ghelfi,[a,*] Adele Mucci,[a] Mario Orena,[c] Ugo M. Pagnoni,[a] Andrew F. Parsons[d] and Fabrizio Roncaglia[a]

[a]*Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, I-41100 Modena, Italy*
[b]*Department of Organic Chemistry, Faculty of Biosciences Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*
[c]*Dipartimento di Scienze dei Materiali e della Terra, Università Politecnica delle Marche, Via Brecce Bianche, I-60131 Ancona, Italy*
[d]*Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK*

Received 20 June 2005; revised 26 September 2005; accepted 29 September 2005

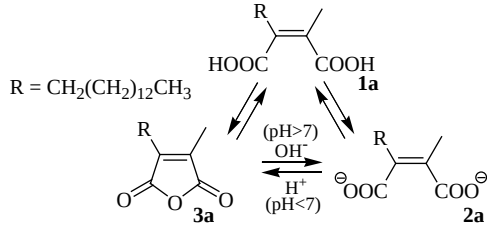
Available online 7 November 2005

Abstract—Chaetomellic anhydride A was efficiently attained in three steps, starting from 2,2-dichloropalmitic acid and 2-(3-chloro-2-propenylamino)pyridine. Atom transfer radical cyclisation selectively formed the cis-stereoisomer of the trichloropyrrolidin-2-one, which underwent a stereospecific functional rearrangement to form a substituted maleimide. The choice of 2-pyridyl, as 'cyclisation auxiliary' in the atom transfer radical cyclisation step, proved beneficial for hydrolysis of the maleimide to form the desired anhydride.

1. Introduction

The screening of natural products to find new anticancer agents for use in the chemotherapeutic intervention of human tumors having mutated ras genes, has led to the evaluation of various microbial fermentation extracts.[1] From this intense screening work, carried out by a research group at Merck, chaetomellic dicarboxylic acids, isolated from the coelomycete *Chaetomella Acutiseta*, have been shown to have promising activities. Of these compounds, chaetomellic acid A (**1a**) (Scheme 1) proved to be the most active substance, inhibiting recombinant human FPTase with a IC_{50} value of 55 nM (Scheme 1).[1,2]

Chaetomellic dicarboxylic acids have a high propensity to cyclize and **1a** was, in fact, isolated as chaetomellic anhydride A (**3a**). The cyclic form, however, is unstable under mild basic conditions (pH=7.5) and is readily hydrolysed to the dicarboxylate anion **2a**, which, apparently, is the biologically active component (Scheme 1).[1] FPTase activity of the diacid anion of **1** is noncompetitive



Scheme 1.

towards the acceptor peptide Ras but is highly competitive with respect to farnesyl pyrophosphate (FPP). This may be explained by the structural similarity between dicarboxylate anion **2a** and FPP, since both possess a hydrophilic head group bound to a hydrophobic tail (Fig. 1). The maleate unit aligns well with the corresponding diphosphate moiety, since the negatively charged oxygen atoms can achieve a spacing within 0.1 Å,[3] while the flexible nature of the aliphatic chain permits it to fill the same space as the hydrophobic end of FPP upon binding to the enzyme.[1] Recently, in an effort to characterize the FPP binding site of rubber transferase, and to identify if species-specific differences exist for this enzyme, Vederas showed that **1** is able to inhibit, in vitro, rubber biosynthesis promoted by rubber transferase from *Hevea Brasiliensis*.[4] More recently

Keywords: Halocompound; Pyrrolidinone; Radical reaction; Rearrangement.
* Corresponding author. Fax: +39 059 373543;
e-mail: ghelfi.franco@unimore.it

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.140

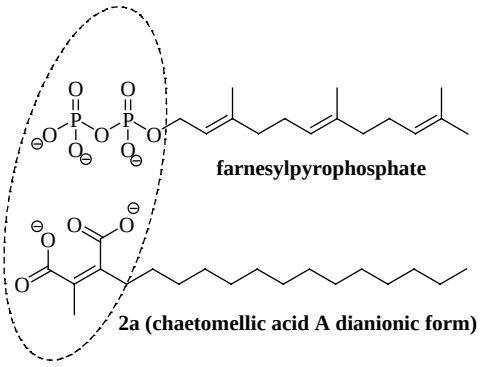


Figure 1. Structural similarity between the dianionic form of chaetomellic acid A (**2a**) and farnesyl pyrophosphate.

the same author found that **1** was also able to reduce the activity of the penicillin-binding protein **1b** (PBP1b), albeit with modest potency.[5]

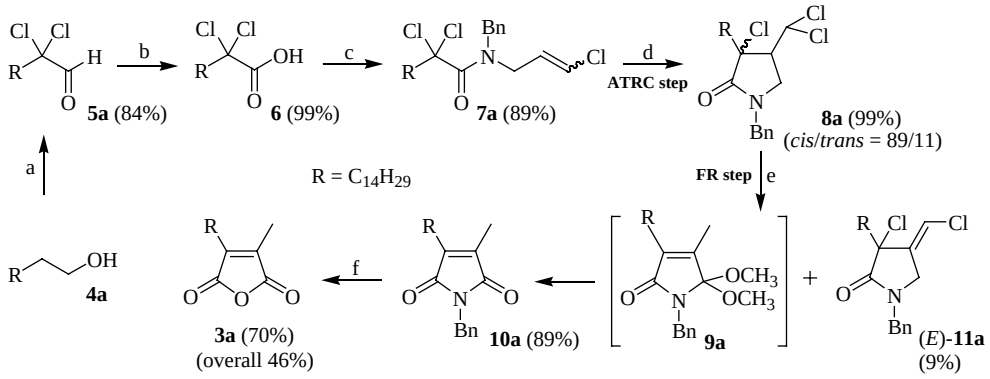
Because of its potent inhibitory activity, chaetomellic acid A has been the subject of considerable synthetic efforts. So far, nine different routes have been devised for the preparation of this interesting product.[2,6–15] In general, the synthesis of anhydride **3a** has been targeted since this compound is more easy to manipulate/isolate than diacid **1a**. The synthetic strategies investigated can be grouped into two general categories: (i) alkylation of maleic precursors[6–11,15,16] and (ii) assembly of the pivotal 1,4-dicarbonyl group.[2,12–14] In spite of the variety of employed methods, 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, (v) or 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. 18,000 €/g.

Recently, our group has disclosed an original and robust route to chaetomellic anhydride A (**3a**) (Scheme 2).[17] Attractive features of the new strategy are: (i) an inexpensive starting material, 2,2-dichloropalmitic (**6**) acid, is easily prepared in two steps from the parent aliphatic alcohol (**4a**), (ii) inexpensive reagents are used, (iii) a halogen atom transfer radical cyclisation (ATRC) is used to efficiently construct the trichlorinated 2-pyrrolidinone **8a**,[18] (iv) an elegant functional rearrangement (FR) of **8a** to a maleimide (**9a**) is employed,[19] (v) the target molecule is prepared in only four steps, (vi) the approach is efficient (an overall yield of 55% from **6**, and 46% from **4a**) and (vii) the synthesis involves simple experimental procedures. Furthermore this route is versatile, as illustrated by the preparation of structural analogues of **3a** such as the chaetomellic anhydride **C** and roccellic acid (a lichens metabolite).[20]

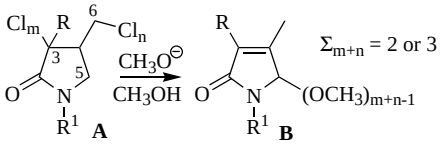
Notwithstanding the long list of advantages of this approach, there still remain a couple of aspects that need to be improved and/or explained, if we want to increase the appeal of the strategy for large scale production of **3a**.

The first aspect that needs improvement concerns the synthetic approach to **3a**. In our previous work, the conversion of the intermediate acetal **9a** to chaetomellic anhydride A (**3a**) is achieved by acid hydrolysis to **10a**, followed, according to Argade's protocol,[9] by a basic hydrolysis, and finally, reaction under acid conditions gives anhydride **3a**. These series of operations are time-consuming and the conditions for the basic hydrolysis (KOH/**10a**, 21 mol/mol, and solvent/**10a**, 28 L/mol) are not compatible with large-scale preparations.

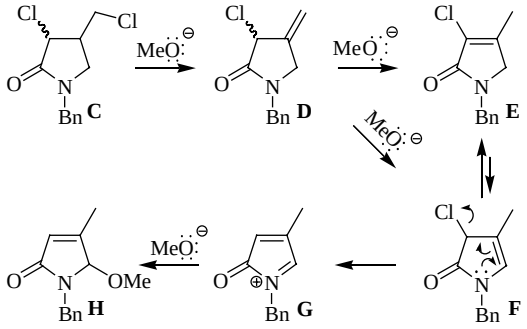
The second aspect concerns the reaction mechanism for the FR of **8a**. The isolation of a moderate amount of (*E*)-**11a**, the *exo*-dehydrohalogenated pyrrolidin-2-one by-produced during the FR reaction of **8a** to **9a**/**10a** (Scheme 2), and the evidence that this compound cannot be regarded as an intermediate in the formation of **9a**/**10a** cast some doubts on the reaction mechanism we formerly proposed to rationalise the FR.[19] The FR of 4-methyl-pyrrolidin-2-ones **A** chlorinated at the C(3) and C(6) positions (these are easily prepared by ATRC of the parent *N*-(3-chloro-2-propenyl)-α-perchloroamides) is a quite general reaction and takes place when **A** is treated with a solution of alkaline methoxide in methanol under mild conditions. In practice two or three of the C–Cl groups at the C(3) and C(6) positions of **A** are replaced by a double bond between carbons C(3) and C(4), and one or two methoxy groups at C(5) (Scheme 3). All transformations from **A** to **B** start with a concerted hydro-halo-elimination (E2) and loss of C(4)–H by either an *endo*- or an *exo*-path is possible. The preferred pathway proceeds by the more stable *anti*-periplanar



Scheme 2. (a) Cl_2, DMF–HCl, $CHCl_3$, 70 °C, 3 h; (b) Br_2, NaOH, CH_2Cl_2/H_2O, 1.5 h; (c) (1) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h, (2) *N*-benzyl-3-Cl-2-propenylamine, Py, 23 °C, 1 h; (d) CuCl–TMEDA, CH_3CN/CH_2Cl_2, argon, 60 °C, 20 h; (e) (1) Na^0, CH_3OH/ether, 25 °C, 20 h, (2) H^+/H_2O; (f) (1) KOH, CH_3OH/THF, reflux, 2 h, (2) H^+/H_2O.



Scheme 3.



Scheme 4.

conformation.[19] The mechanism, we issued for the illustrative case of the dichloro γ-lactam **C**, is outlined in Scheme 4. After initial formation of the *exo*-methylene intermediate **D**, the double bond was expected to shift inside the ring affording the 4-pyrrolin-2-one **F**, directly or via the formation of Δ^3 intermediate **E**. However, the isomerisation of (*E*)-**11a** was not observed and so the mechanism needs to be further investigated.

Herein, we report that the effectiveness of the FR is linked to the geometry of the starting 4-methyl-pyrrolidin-2-one, since the *exo* C═C bond can only move into conjugation if a hydrogen atom is present at C(3). As a consequence, the higher is the percentage of the cis stereoisomer, which can afford the pivotal 3-pyrrolin-2-one intermediate, the higher the expected yield of the rearranged product. In this work, we describe the use of 2-pyridyl group as a cyclisation auxiliary in the ATRC step, which allowed the final sequence of hydrolyses to be condensed to just a single operation that is linked to the FR in a one-pot reaction. In this way the efficiency of the overall process was substantially improved.

2. Results and discussion

To reduce the number of steps required to convert the intermediate acetal **9a** into the target anhydride **3a**, and develop a method attractive for scale up, we investigated two strategies. In the first instance, we sought to establish acidic conditions that performed the transformation in a straightforward manner, while we also looked at the use of an alternative cyclisation auxiliary that made **9a** and **10a** more susceptible to hydrolysis. Also, since the chlorinated pyrrolidin-2-one **8a** is isolated as a mixture of cis and trans isomers, we sought to elucidate the origin of the side product **11a** and thereby understand the mechanism of the FR. To do this it appeared necessary to isolate the cis and trans isomers for a separate study of their behaviour towards methoxide ion.

Foreseeable problems, including the difficulty in separating *cis*-**8a** and *trans*-**8a**,[17] steered us to use a molecule with a smaller skeleton than **3a**, as a model substrate. For this we choose dimethyl maleic anhydride **3b**, which is a very useful building-block in organic synthesis.[21] This substance, also known as pyrocinchonic anhydride, represents the most simple archetype for chaetomellic anhydride A (**3a**), the long *n*-tetradecylic aliphatic chain on the carbon C(3) in **3a** being here replaced by a methyl group (Fig. 2).

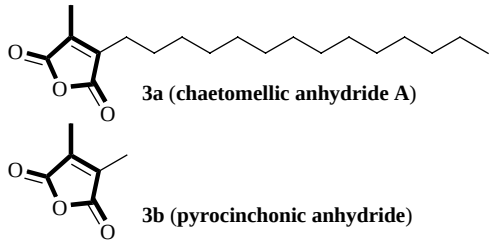
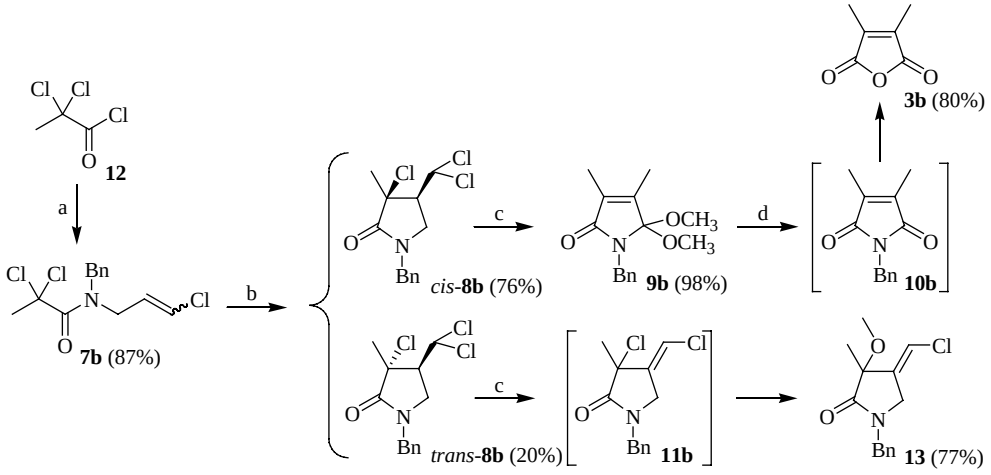


Figure 2. Pyrocinchonic anhydride (**3b**) as a simple archetype for chaetomellic anhydride A (**3a**).

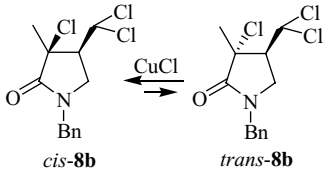
Following the synthetic path developed for the synthesis of **3a** (Scheme 2), 2,2-dichloropropanoyl chloride (**12**) was treated with *N*-benzyl-3-chloro-2-propenylamine to afford amide **7b** in good yield (Scheme 5). Then **7b** was efficiently



Scheme 5. (a) *N*-benzyl-3-Cl-2-propenylamine, Py, rt, 5 h; (b) CuCl–TMEDA, CH_3CN, argon, rt, 20 h; (c) Na^0, CH_3OH, 25 °C, 20 h; (d) CH_3SO_3H/CH_3COOH (1/1), 140 °C, 20 h.

cyclised, using CuCl/*N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) in acetonitrile (AN) at room temperature, to provide the trichlorinated pyrrolidin-2-one **8b** (96%) as a 79:21 mixture of cis-/trans- isomers.

As previously reported,[22–26] the stereogenic centre at C-3 of an 3-alkyl-3-chloro-4-chloroalkyl-γ-lactams is configurationally labile during the ATRC of the parent *N*-allyl α-perchloroamide. This is due to a reversible radical generation at the C(3) centre,[†] promoted by the redox catalyst (Scheme 6).[24,26] Consequently, the stereochemistry of products is directed by thermodynamic factors and the isomer that predominates has the largest appendages at C(3) and C(4) on the opposite sides of the ring, that is, in this example, the *cis*-**8b** isomer predominates (datum also confirmed by computational calculations). Since C(3) epimerization is a gradual process, a higher temperature and a longer reaction time generally improve the selectivity for the cis isomer. In fact when the ATRC of **7b** was carried out at 60 °C, rather than at room temperature, pyrrolidin-2-one **8b** was isolated in the same yield, but with a significantly higher cis-/trans-ratio of 89:11 (compared to 80:20).

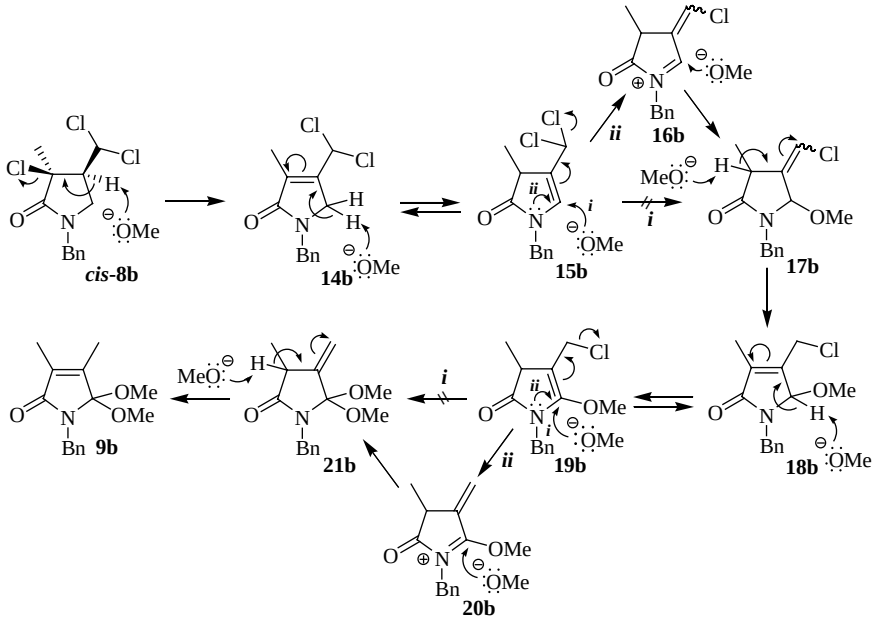


Scheme 6.

In contrast to what was observed for **8a**, we were pleased to see that *cis*-**8b** and *trans*-**8b** were separable by flash chromatography. To get an insight into the FR mechanism, the two compounds were subjected to the FR using methoxide in methanol, following the previously reported protocol (Scheme 5).[19] The major isomer *cis*-**8b** gave almost a quantitative yield (98%) of *N*-benzyl-5, 5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (**9b**).

On the contrary, when *trans*-**8b** was reacted with the methoxide ion in methanol, the main product (77%) isolated was (*E*)-*N*-benzyl-4-chloromethylen-3-methoxy-3-methyl-2-pyrrolidinone (**13**), a compound with a similar structure to (*E*)-**11a**, which was obtained as a byproduct from the FR of **8a**. Evidently, due to the relatively low steric crowding around the C(3)–Cl group, the conceivable intermediate (*E*)-**11b** underwent facile methoxy-de-halogenation. This behaviour was confirmed by quenching the reaction of *trans*-**8b** after 1 h; this gave (*E*)-**11b**, as the second main product in the reaction mixture, after **13**. A small amount of **9b** was also observed in the attempted FR of *trans*-**8b**, but it was consistent with the small quantity of the *cis*-**8b** contaminating the starting material. These results definitely prove that the efficiency of the FR depends on the diastereoisomeric ratio of the chlorinated pyrrolidin-2-ones, and is consistent with the results obtained for the FR of **8a**[17] (Scheme 2) or equivalent adducts.[20]

In a previous work, we established that the FR starts with a bimolecular hydro-halo-elimination.[19] Hence, the more easily the required *anti*-periplanar conformation is achieved the more favourably the resulting E2 elimination will be. Accordingly, *cis*-**8b** follows the *endo*-dehydrochlorination



Scheme 7.

path to give the 3-pyrrolin-2-one **14b** (Scheme 7), whereas *trans*-**8b** is forced to dehydrohalogenate in the alternative *exo*-direction to afford the 4-alkyliden-pyrrolidin-2-one (*E*)-**11b** (Scheme 5).

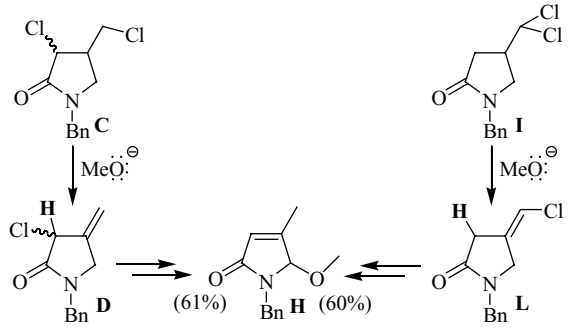
[†] The configurational change through a nucleophilic attack was firmly ruled out by the quantitative recovery of *cis*-**8b** after treatment with LiCl/TMEDA or $CuCl_2$/TMEDA under the same conditions of the ATRC of **7b**.

For compounds **14b** and (*E*)-**11b** the C=C bond lies in a different position. When the C=C bond is in conjugation with the C=O bond, the electron-withdrawing effect of the carbonyl group increases the acidity of vinylogous C(5)–H hydrogen atom.[27,28] This helps migration of the C=C bond from the α,β-position (Scheme 7, adduct **14b**) to the β,γ-position (Scheme 7, adduct **15b**), a clear example of tautomeric equilibrium where the conjugated form is thermodynamically favoured.[28,29] This property is well known and has been extensively used to prepare silyloxypyrroles from α,β-unsaturated γ-lactams,[27,30,31] and also in the manipulation of the (CO)–C=C–CH moiety in open chain compounds.[32–37]

The shift in the position of the C=C bond in **17b** triggers the subsequent substitution of one of the two *exo* chlorines by a C=C *exo*/Δ^3 base catalyzed transposition leading to compound **18b** (Scheme 7). Related reactions involving consecutive prototropic and anionotropic changes have been reported,[38,39] including the transformation of a trialkyl-γ-chloroallylammonium salt into the corresponding trialkyl-α-ethoxyallylammonium salt by reaction with sodium ethoxide, described by Ingold and Rothstein back in 1928.[39] The conversion of **15b** to **17b** is likely to occur by a stepwise mechanism involving the N-1 lone pair and the participation of the acylimmonium cation intermediate **16b** (Scheme 7, path ii).[37] Analogous steps are reasonably implicated along the way from **18b** to acetal **9b**. The alternative direct transformation by a S_N2' substitution (Scheme 7, path i)[40,41] appears doubtful since the nucleophilic substitution of allylic intermediate (*E*)-**11b** proceeded without rearrangement (Scheme 5).

Good evidence for the stepwise mechanism was obtained by analysing the reaction mixture after a short reaction time (2 min). This allowed the detection and separation of the proposed intermediate **18b**. The isolation of **18b** suggests that the Δ^3/Δ^4 transposition of **18b** to **19b** is the slowest step in the rearrangement.

The proposed shift of the *exo* C=C bond (to move inside the ring) was erroneously formulated following experimental evidence which showed that *N*-benzyl-3-chloro-4-chloromethyl-2-pyrrolidinone (**C**) and *N*-benzyl-4-dichloromethyl-2-pyrrolidinone (**I**), two substrates that react by an initial *exo*-elimination, both rearrange in high yield to give *N*-benzyl-4-methyl-3-pyrrolin-2-one (**H**) (Scheme 8).[19] In the light of our current observations, these two examples appear to be exceptional, presumably because both have an acidic α hydrogen at C(3), which allows the *exo* C=C bond to move in to conjugation for the early intermediates **D** and **L** (Scheme 8). In contrast, for adducts analogous to **11b**, the lack of C(3)–H bonds and the insufficient acidity of the C(5)–H proton precludes the transposition.



Scheme 8.

In summary, the configuration of the starting α,γ-halogenated 2-pyrrolidinones influences the FR. For an effective FR the configuration of the precursor should permit an *endo*-elimination. If, however, the reaction is forced to proceed by *exo*-elimination then (for a successful FR) the precursor must have a hydrogen atom at C(3).

Following our studies on the mechanism of the FR, we tackled the problem of the one-pot hydrolysis of **9b** to form anhydride **3b**. The process requires two sequential hydrolyses: the first hydrolysis forms maleimide **10b** from acetal **9b** and the second forms anhydride **3b** from **10b** (Scheme 5). To arrive at a one-pot process we needed a suitable acid that promoted both hydrolyses and initial results using methanesulfonic acid (MSA) are collected in Table 1.

Hydrolysis of **10b** to form **3b** is possible using MSA in acetic acid (Table 1, entries 4–9) but not in aqueous media,

Table 1. Solvolysis of the *N*-benzyl-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one **9b**[a]

Item	Promoter (mL)	Solvent (mL)	*T* (°C)	*t* (h)	Conversion (%)[b]	**10b** (%)[b]	**3b** (%)[b]
1	MSA (0.08)[c]	H_2O (1.2)	100	4	100	100	0
2	MSA (0. 45)	H_2O (1.7)	100	4	100	100	0
3	MSA (0. 45)	H_2O (1.7)	140	4	100	100	0
4	MSA (0.26)	AcOH (1)	100	4	100	95	4
5	MSA (0.26)	AcOH (1)	120	20	100	86	14
6	MSA (0.5)	AcOH (0.5)	100	40	100	53	47
7	MSA (0.5)	AcOH (0.5)	120	20	100	35	65
8	MSA (0.5)	AcOH (0.5)	140	20	100	0	100 (79)[d]
9[e]	MSA (0.65)	AcOH (0.65)	140	20	100	5	95
10	MSA (1.0)	—	25	100	100	100	0
11	H_2SO_4 (0.5)	AcOH (0.5)	120	20	100	0[f]	Traces[f]
12	NaOH (2.5)[c]	H_2O (0.5)	120	3	0	0	0

[a] Substrate 1 mmol.
[b] GC values.
[c] Values in mmol.
[d] Determined on isolated material.
[e] Solvolysis performed directly on the crude product from the FR of *cis*-**8b** after solvent evaporation.
[f] Extensive formation of black resinous material.

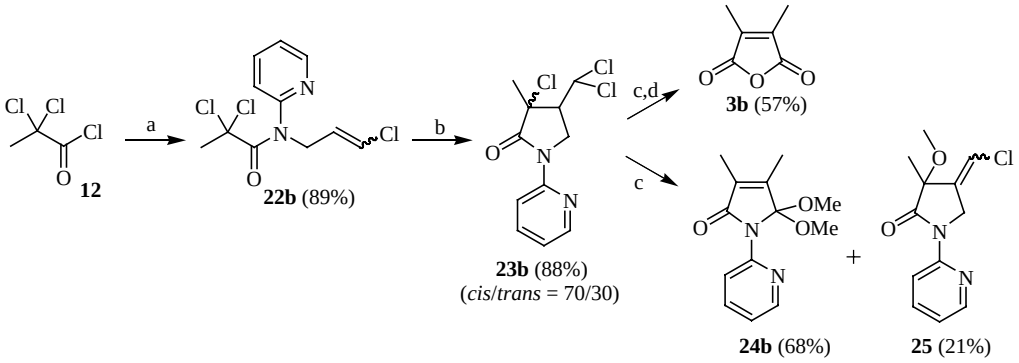
presumably because **10b** is more soluble in acetic acid than in water (Table 1, entries 1–3). The complete conversion of **10b** in to **3b** required 0.5 mL of MSA per mmol of **10b**, together with heating at 140 °C for 20 h (Table 1, entry 8). Unfortunately, when the crude FR product (obtained after reaction solvent evaporation) from *cis*-**8b** was reacted under these conditions, some maleimide **10b** remained (Table 1, entry 9). Also, reaction of **10b** with MSA at room temperature, or the use of H_2SO_4 in place of MSA, or the use of basic conditions were ineffective (Table 1, entries 10–12).

As our studies on the solvolysis of *N*-benzylmaleimide **10b** were not completely satisfactory, we searched for an auxiliary more suited to removal by hydrolysis. In this respect, we were helped by the work of Baumann[42] who discovered an elegant way to prepare dimethylmaleic anhydride by dimerization of maleic anhydride using 2-aminopyridine. Interestingly, the last step in the synthesis involved acid hydrolysis of *N*-(2-pyridyl)-3,4-dimethyl-maleimide.[42] This strategy was used by Argade for the preparation of chaetomellic anhydride A from 2-bromo-palmitoyl chloride—the final step in the synthesis involved hydrolysis of a *N*-(2-pyridyl)maleimide derivative.[13,14]

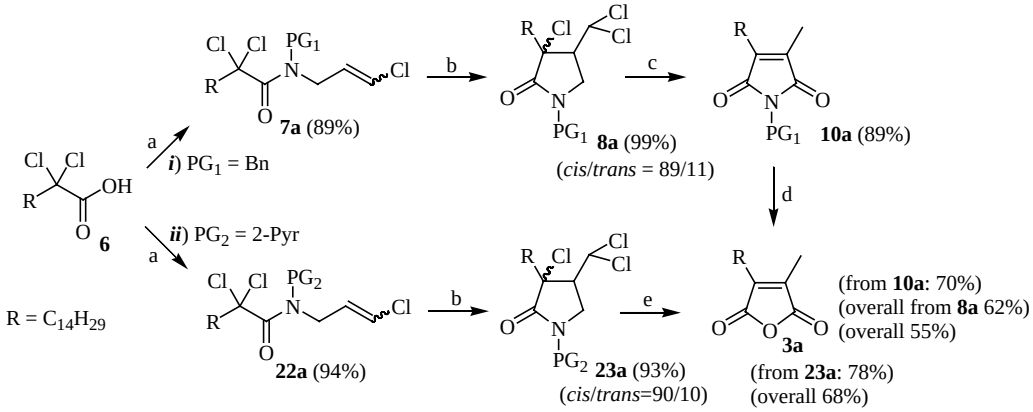
The apparent vulnerability of *N*-(2-pyridyl)maleimides to acid conditions spurred us to investigate the ATRC and FR reactions of a precursor with a 2-pyridyl auxiliary (Scheme 9). *N*-(3-Chloro-2-propenyl)-*N*-(2-pyridyl)-2, 2-dichloropropanamide (**22b**) was easily prepared, in excellent yield (89%), by a metathesis reaction between **12** and 2-(3-chloro-2-propenylamino)pyridine. An ATRC reaction of **22b** (under similar conditions to amide **7b**) afforded the halogenated pyrrolidin-2-one (**23b**) as a mixture of cis-/trans- isomers (70:30) in an excellent yield (88%). The FR of *cis*-**23b**/*trans*-**23b** was accomplished using the same conditions as for **8b**. As expected, along with the desired acetal **24b**, isolated in a respectable yield of 68%, we also recovered a moderate amount (21%) of the *exo*-dehydrohalogenated pyrrolidin-2-one (*E*)-**25**.

In order to develop a one-pot hydrolysis reaction, we investigated the reaction of crude product **24b** (isolated by solvent evaporation of the FR reaction mixture) with the acid conditions reported by Baumann (H_2SO_4 4 N 1 mL/mmol of substrate, heating at 110 °C) (Scheme 9). The reaction was completed in just one hour and pyrocinchonic anhydride was recovered in a satisfactory yield of 57%. If one takes into account that only the *cis*-**23b** component can rearrange, the yield of pyrocinchonic anhydride increases to 81%.

When compared with the one-pot transformation of *N*-benzyl lactam *cis*-**8b** to **3b** (Scheme 5), the parallel



Scheme 9. (a) 2-(3-chloro-2-propenylamino)pyridine, Py, argon, 35 °C, 20 h; (b) CuCl–TMEDA, CH_3CN, Argon, rt, 20 h; (c) Na^0, CH_3OH, 25 °C, 20 h; (d) H_2SO_4 4 N, 110 °C, 1 h.



Scheme 10. (a) (1) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h, (2) *N*-benzyl-3-Cl-2-propenylamine (path ***i***) or 2-(3-chloro-2-propenylamino)pyridine (path ***ii***), Py, 23 °C, 1 h; (b) CuCl–TMEDA, CH_3CN, argon, 60 °C, 20 h; (c) (1) Na^0, CH_3OH/ether, 25 °C, 20 h, (2) H^+/H_2O; (d) (1) KOH, CH_3OH/THF, reflux, 2 h, (2) H^+/H_2O; (e) (1) Na^0, CH_3OH/ether, 25 °C, 20 h, (2) H_2SO_4 4 N, 110 °C, 2 h.

one-pot conversion of the *N*-(2-pyridyl) lactam **23b** to the same anhydride (Scheme 9) has some advantages including: (i) a lower reaction temperature, (ii) total conversion of precursor and (iii) a simplified purification procedure because byproduct **25** remains in the acidic aqueous phase.

The good result using the new one-pot hydrolysis method spurred us to apply this method to the synthesis of chaetomellic anhydride A. Thus, the *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichlorohexadecanamide **22a** was prepared and cyclised to give to **23a** (as an inseparable pair of cis-/trans- isomers in a ratio of 90:10) adhering to standard protocols (Scheme 10, path ***ii***). Both products were delivered in high yields. It is noted that, owing to the polar nature of the 2-pyridyl substituent, **22a** was completely soluble in acetonitrile, so the ATRC step did not require dilution with a less polar cosolvent (e.g., CH_2Cl_2) as was required for the *N*-benzyl amide **7a** (Scheme 2).[17] The ensuing FR of **23a** was accomplished using sodium in methanol (at 25 °C), after which the solvent was removed under vacuum and the residue dissolved in 4 N H_2SO_4. The solution was then heated to 110 °C to give, after 2 h, the target anhydride **3a** in a respectable 78% yield. No effort was spent to recover the side product derived from *exo*-elimination. The overall yield of chaetomellic anhydride A (**3a**) using this three step approach was 68% (Scheme 10, path ***ii***), which is significantly higher than the 55% yield observed with the previously reported four step process (Scheme 10, path ***i***). The increased efficiency is due to the increased effectiveness of the one-pot conversion of **23a** to **3a** (78%) compared to the stepwise conversion of **8a** to **3a** (overall 62% yield).

3. Computational investigation

In order to investigate the major thermodynamic stability of *cis*-**8b** with respect to *trans*-**8b**, a complete, extensive unconstrained conformational analysis of both isomers was performed by using AMBER* force field[43] and the Monte Carlo[44] conformational search (MC/EM) varying all the degrees of freedom including H_2O as implicit solvent that was chosen in order to simulate the polarity of the solution media (methanol). All the conformers within the energy gap of 6.0 kcal/mol were kept and subsequently only those which lie below 3.6 kcal/mol were fully analysed. Within this energy gap, 11 conformers were observed for compound *cis*-**8b**, and 12 conformers for *trans*-**8b**. Then the lowest energy conformation for both diastereomers was optimized at ab initio level by using the density functional method B3LYP/6-31G* and it resulted that *cis*-**8b** is 4.5 kcal/mol more stable than *trans*-**8b**. Thus, the reaction path leading to the chaetomellic anhydride (Scheme 5) is the most relevant one, the preferential formation of the major isomer *cis*-**8b** being explained by its thermodynamic stability.

It is worth mentioning that a similar trend was observed when the conformational analysis was carried out with the corresponding cis- and trans-compounds having at C-3 a C12 chain in place of the methyl, since the cis-isomer resulted again more stable than the trans-one. However, in this case a large number of low energy conformations were found for both diastereomers, and the energy difference among the two lowest ones resulted to be only 0.2 kcal/mol.

4. Conclusion

Chaetomellic anhydride A has been efficiently obtained in just three steps, starting from 2,2-dichloropalmitic acid and 2-(3-chloro-2-propenylamino)pyridine. The choice of 2-pyridyl, as 'cyclisation auxiliary'[45] in the ATRC step, allowed the FR to be combined with the final hydrolysis step in a straightforward one-pot reaction. We have also succeeded in unravelling the FR mechanism. The FR, which is promoted by bases in protic solvents, is observed for a variety of polyhalogenated pyrrolidin-2-ones issued by ATRC of *N*-allyl-α-perchloroamides.[17,19,20] We have discovered that for an effective FR the configuration of the starting α,γ-halogenated 2-pyrrolidinones is critical and should be arranged in such a way that initial *endo*-elimination is possible. However, even for those substrates forced to undergo *exo*-eliminations, provided that at least one hydrogen atom is present at C(3), the FR can proceed.

The procedure, here reported, can also be fruitfully used for a short laboratory scale preparation of the versatile building-block pyrocinchonic anhydride. Computational investigations to confirm the proposed pathway and studies of the exact role of the 2-pyridyl substituent on the hydrolysis reaction are in progress and will be reported in due course.

5. Experimental

5.1. General

Reagents and solvents were standard grade commercial products, purchased from Aldrich, Acros, Fluka or RdH, and used without further purification, except acetonitrile and CH_2Cl_2 that were dried over three batches of 3 Å sieves (5% w/v, 12 h). The silica gel used for flash chromatography was Silica Gel 60 Merck (0.040–0.063 mm). *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.[46] 2,2-Dichloropalmitic (**6**)[17] acid and 2,2-dichloropropanoyl chloride (**11**)[25] were prepared according given procedures. ^{1}H NMR, IR and MS spectra were recorded on Bruker DPX 200 and Bruker Avance400, Perkin Elmer 1600 Series FTIR, and HP 5890 GC-HP 5989A MS instruments, respectively. The structural assignment of compounds **8b**, **13**, **18b**, **23a**, **23b** and **25** 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 **13**, **18b** and **25** allowed us to unambiguously establish their regiochemistry, whereas NOESY experiments enabled the configuration of the double bond in **13** and **25**, and the relative stereochemistry at the C(3) and C(4) carbons in **8b**, **23a** and **23b**, to be determined.

5.2. Computational details

Molecular mechanics calculations were performed on SGI IRIX 6.5 Octane2 workstations using the implementation of

Amber all-atom force field (AMBER*) within the framework of Macromodel version 5.5.[47] The solvent effect was included by the implicit water GB/SA solvation model of Still et al.[48] The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search of Chang-Guida-Still. For each search, at least 1000 starting structures for each variable torsion angle was generated and minimized until the gradient was less than 0.05 kJ/(Å mol). The cyclic moieties containing the amide bonds were also included into the search. Duplicate conformations and those with an energy in excess of 6 kcal/mol above the global minimum were discarded.

All DFT calculations were carried out using the standard tools available in the Gaussian 98 package,[49] with the DFT/B3LYP functional (i.e., Becke's three parameter hybrid functional with the Lee-Yang-Parr correlation functional)[50] and the 6-31G(d) basis set.

5.3. Preparation of 2-(3-chloro-2-propenylamino) pyridine

2-Aminopyridine (11.29 g, 120 mmol) was weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a stirring bar. Next, toluene (30 mL) and 1,3-dichloropropene (mixture of *E*/*Z* isomers, 5.55 mL, 60 mmol) were added under argon. The solution, under vigorous stirring, was heated at 100 °C. After 20 h, the reaction mixture was diluted with H_2O (30 mL) and petroleum ether (bp 40–60 °C; 30 mL). The organic layer was separated, whereas the aqueous phase was extracted with a 1/1 solution of toluene/petroleum ether (20 mL). The organic extracts were collected and concentrated under vacuum. The crude product was recovered (6.59 g, 65%) as a pale yellow liquid, which did not require further purification; bp 119–121 °C (0.6 mmHg). [Found: C, 57.0; H, 5.4; N, 16.7. $C_8H_9ClN_2$ requires C, 56.98; H, 5.38; N, 16.61]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ trans isomer 3.96 (2H, dt, J=1.2, 5.9 Hz, NHCH_2), 4.7 (1H, br s, N*H*); 6.05 (1H, dt, J=13.8, 5.8 Hz, NHCH$_2$C*H*), 6.22 (1H, dt, J=13.8, 1.3 Hz, C*H*Cl), 6.38 (1H, dt, J=8.4, 0.9 Hz, C(3)*H*), 6.60 (1H, ddd, J=7.3, 5.0, 0.9 Hz, C(5)*H*), 7.42 (1H, ddd, J=8.4, 7.3, 2.0 Hz, C(4)*H*), 8.09 (1H, ddd, J=5.0, 2.0, 0.9 Hz, C(6)*H*); cis isomer 4.13 (2H, dt, J=1.7, 6.1 Hz, NHCH_2), 4.8 (1H, br s, N*H*); 5.94 (1H, dt, J=7.5, 6.1 Hz, NHCH$_2$C*H*), 6.17 (1H, dt, J=7.5, 1.7 Hz, C*H*Cl), 6.40 (1H, dt, J=8.4, 0.9 Hz, C(3)*H*), 6.60 (1H, ddd, J=7.3, 5.0, 0.9 Hz, C(5) *H*), 7.43 (1H, ddd, J=8.4, 7.3, 2.0 Hz, C(4)*H*), 8.09 (1H, ddd, J=5.0, 2.0, 0.9 Hz, C(6)*H*); *m*/*z* (EI): 168 (28%, M^+), 133 (100), 119 (40), 116 (10), 107 (12), 79 (22), 78 (30).

5.4. Preparation of *N*-benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichloropropanamide (7b)

In a double-necked rounded bottom flask (100 mL), fitted with a dropping funnel and a reflux condenser, closed on the top with a $CaCl_2$ tube, CH_2Cl_2 (15.0 mL), *N*-benzyl-3-chloro-2-propenylamine (mixture of *E*/*Z* stereoisomers, 1.82 g, 10 mmol) and pyridine (1.0 mL, 12 mmol) were introduced. A CH_2Cl_2 (5 mL) solution of 2,2-dichloropropanoyl chloride (**12**) (1.61 g, 10 mmol) was then carefully added to the stirred solution cooled in a ice-bath (15 min). Next, the bath was removed and the reaction mixture left at room temperature, while stirring. After 20 h, the mixture was washed in sequence with HCl 2.5% w/v (2×15 mL) and NaOH 2.5% w/v (20 mL). The organic phase was then separated and concentrated. Flash-chromatography of the crude product on silica gel, using petroleum ether (bp 40–60 °C)–diethyl ether (9.5/0.5) as eluent, afforded 2.67 g of **7b** (87%), as a mixture of *E*/*Z* stereoisomers; pale yellow oil. [Found: C, 50.9; H, 4.6; N, 4.6. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.40 (3H, s, Cl_2CCH_3), 3.7–5.1 (4H, br m, CH_2NCH_2), 5.7–6.3 (2H, br m, C*H*=C*H*), 7.2–7.4 (5H, br s, Ar(H)); IR (film): 1660 (C=O) cm^{-1}; *m*/*z* (EI): 305 (3%, M^+), 270 (17), 230 (22), 91 (100).

5.5. Cyclisation of *N*-benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichloropropanamide (7b)

CuCl (40 mg, 0.4 mmol) and the 2,2-dichloro-amide **7b** (1.23 g, 4 mmol) were weighted in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a magnetic stirrer bar. Dry acetonitrile (4 mL) and TMEDA (121 μL, 0.8 mmol) were then added under argon. The mixture was stirred at room temperature and after 20 h diluted with HCl_{aq} 5% w/v (5 mL) and extracted with CH_2Cl_2 (3×6 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with a petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 5/5). This gave the pyrrolidinones *cis*-**8b** (0.94 g, 76%), as a white crystalline solid, and *trans*-**8b** (0.24 g, 20%), as a yellow oil. The isomers could also be separated by crystallization from diethyl ether.

5.5.1. cis-N-Benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*cis*-8b). Mp 103–104 °C. [Found: C, 50.8; H, 4.6; N, 4.5. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.97 (3H, s, C(3)CH_3), 2.90 (1H, dt, J=7.3, 9.3 Hz, C(4)*H*), 3.08 (1H, dd, J=10.2, 9.2 Hz, C(5)*H*), 3.38 (1H, dd, J=10.2, 7.2 Hz, C(5)*H*), 4.38 (1H, d, J=14.7 Hz, N(1)C*H*Ar), 4.66 (1H, d, J=14.7 Hz, N(1)C*H*Ar), 5.98 (1H, d, J=9.4 Hz, C(4)C*H*), 7.20–7.40 (5H, m, C*H*Ar); ^{1}H NMR (CD_3OD, 400 MHz): δ 1.92 (3H, s, C(3)CH_3), 3.15 (2H, m, C(4)*H*, C(5)*H*), 3.49 (1H, m, C(5)*H*), 4.34 (1H, d, J=14.8 Hz, N(1)C*H*Ar), 4.71 (1H, d, J=14.8 Hz, N(1)C*H*Ar), 6.20 (1H, m, C(4)C*H*), 7.24–7.40 (5H, m, C*H*Ar); ^{13}C NMR (CD_3OD, 400 MHz): δ 26.30 (*C*H$_3$), 47.80 (N*C*H$_2$), 48.65 (N*C*H$_2$), 55.47 (*C*(4)), 69.94 (*C*(3)), 73.06 (C(4)*C*H), 129.05 (*Ar*), 129.11 (*Ar*), 129.95 (*Ar*), 136.61 (*Ar*), 172.63 (*C*=O); IR (KBr): 1707 (C=O) cm^{-1}; *m*/*z* (EI): 305 (3%, M^+), 270 (100), 187 (17), 186 (33), 91 (100).

5.5.2. trans-N-Benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*trans*-8b). [Found: C, 50.8; H, 4.6; N, 4.5. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.82 (3H, s, C(3)CH_3), 3.30 (2H, m, C(4)*H*, C(5)*H*), 3.62 (1H, m, C(5)*H*), 4.38 (1H, d, J=14.7 Hz, N(1)C*H*Ar), 4.68 (1H, d, J=14.7 Hz, N(1)C*H*Ar), 5.89 (1H, d, J=4.6 Hz, C(4)C*H*), 7.24–7.40 (5H, m, C*H*Ar); ^{1}H NMR (CD_3OD, 400 MHz): δ 1.77 (3H, s, CH_3C(3)), 3.37 (2H, m, *H*C(4), *H*C(5)), 3.65

(1H, m, *H*C(5)), 4.47 (1H, d, $J=14.6$ Hz, N(1)C*H*Ar), 4.57 (1H, d, $J=14.6$ Hz, N(1)C*H*Ar), 6.33 (1H, d, $J=5.3$ Hz, C(4)C*H*), 7.27–7.40 (5H, m, C*H*Ar); ^{13}C NMR (CD_3OD, 400 MHz): δ 21.34 (*C*H_3), 46.98 (N*C*H_2), 48.02 (N*C*H_2), 56.34 (*C*(4)), 69.16 (*C*(3)), 72.60 (C(4)*C*H), 129.10 (*Ar*), 129.41 (*Ar*), 129.90 (*Ar*), 136.52 (*Ar*), 172.90 (*C*=O); IR (film): 1709 (C=O) cm^{-1}; *m*/*z* (EI): 305 (3%, M^+), 270 (100), 187 (17), 186 (33), 91 (100).

5.6. Rearrangement of *cis*-*N*-benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*cis*-8b)

In a Schlenk tube, fitted with a perforable septum blocked by a screw cap, ethyl ether/CH_3OH 2:1 (3 mL) and *cis*-**8b** (0.61 g, 2 mmol) were added. The solution was thermostated at 25 °C. Apart, in a second Schlenk tube, Na^0 (0.184 g, 8 mmol) was carefully dissolved in CH_3OH (3 mL), and when the effervescence ceased, the alkaline solution was thermostated at 25 °C, after which it was poured into the first Schlenk tube. The reaction mixture was stirred for 20 h. Then it was diluted with water (2 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were collected and concentrated. Flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 10/0 to 5/5) as eluent, afforded *N*-benzyl-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (**9b**) (0.514 g, 98%), as a pale yellow microcrystalline solid. Mp 63–64 °C. [Found: C, 68.7; H, 7.3; N, 5.4. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.77 (3H, q, $J=1.2$ Hz, C(4)C*H*$_3$), 1.90 (3H, q, $J=1.3$ Hz, C(3)C*H*$_3$), 2.78 (6H, s, OC*H*$_3$), 4.37 (2H, s, NC*H*$_2$Ar), 7.27–7.40 (5H, m, C*H*Ar), ^{13}C NMR ($CDCl_3$, 400 MHz): δ 8.02 (C(3)*C*H$_3$), 9.07 (C(4)*C*H$_3$), 41.40 (*C*H$_2$), 50.51 (O*C*H$_3$), 112.73 (*C*(5)), 127.17 (*C*(4′)Ar), 128.09 (*C*(3′)Ar, *C*(5′)Ar), 129.34 (*C*(2′)Ar, *C*(6′)Ar), 132.70 (*C*(3)), 137.39 (*C*(1′)Ar), 144.06 (*C*(4)), 170.13 (*C*=O); IR (KBr): 1712 (C=O) cm^{-1}; *m*/*z* (EI): 262 (8%, $M^+ + 1$), 261 (43), 231 (12), 230 (45), 214 (24), 202 (15), 156 (13), 141 (38), 91 (100).

Following the previous procedure but carrying out the work up after 2 min at 25 °C we succeeded in isolating the *N*-benzyl-4-chloromethyl-3-methyl-5-methoxy-3-pyrrolin-2-one (**18b**) (as the main product in the reaction mixture), as a colourless oil. [Found: C, 63.1; H, 6.1; N, 5.3. $C_{14}H_{16}ClNO_2$ requires C, 63.28; H, 6.07; N, 5.27]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.01 (3H, t, $J=1.1$ Hz, C(3)C*H*$_3$), 3.02 (3H, s, OC*H*$_3$), 4.18 (1H, d, $J=14.8$ Hz, NC*H*Ar), 4.19 (1H, dq, $J=12.0$, 1.1 Hz, C*H*Cl), 4.33 (1H, d, $J=12.0$ Hz, C*H*Cl), 4.98 (1H, d, $J=14.8$ Hz, NC*H*Ar), 5.31 (1H, q, $J=1.1$ Hz, *H*C(5)), 7.20–7.40 (5H, m, C*H*Ar); ^{13}C NMR (400 MHz, $CDCl_3$): 8.92 (*C*H$_3$), 35.18 (*C*H$_2$Cl), 43.62 (N*C*H$_2$), 50.48 (O*C*H$_3$), 86.0 (*C*(5)), 127.62 (*Ar*), 128.44 (*Ar*), 128.70 (*Ar*), 136.16 (*C*(3)), 136.81 (*Ar*), 143.55 (*C*(4)) 169.58 (*C*=O); IR (film) 1695 (C=O) cm^{-1}; *m*/*z* (EI): 265 (31%, M^+), 250 (3), 235 (14), 234 (18), 233 (22), 230 (44), 200 (10), 170 (12), 91 (100).

5.7. Rearrangement of *trans*-*N*-benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*trans*-8b)

Following the procedure for the rearrangement of *cis*-**8b**, *trans*-**8b** (0.61 g, 2 mmol) gave (*E*)-*N*-benzyl-4-chloromethylen-3-methoxy-3-methyl-2-pyrrolidinone (**13**) (0.41 g, 77%), as a colourless oil. [Found: C, 63.1; H, 6.1; N, 5.3. $C_{14}H_{16}ClNO_2$ requires C, 63.28; H, 6.07; N, 5.27]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (3H, s, C(3)C*H*$_3$), 3.17 (3H, s, OC*H*$_3$), 3.82 (1H, dd, $J=15.3$, 2.7 Hz, C(5)*H*$_2$), 3.92 (1H, dd, $J=15.3$, 2.7 Hz, C(5)*H*$_2$), 4.53 (1H, d, $J=14.6$ Hz, NC*H*$_2$Ar), 4.61 (1H, d, $J=14.6$ Hz, NC*H*$_2$Ar), 6.30 (1H, t, $J=2.7$ Hz, C=C*H*Cl), 7.20–7.40 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 24.80 (C(3)*C*H$_3$), 46.51 (*C*H$_2$Ar), 46.98 (*C*(5)), 52.38 (O*C*H$_3$), 80.14 (*C*(3)), 116.48 (C=*C*HCl), 127.78 (*C*Ar), 127.96 (*C*Ar), 128.70 (*C*Ar), 135.08 (*C*Ar), 136.26 (*C*(4)), 171.95 (*C*=O); IR (film): 1707 (C=O) cm^{-1}; *m*/*z* (EI): 265 (1%, M^+), 235 (24), 230 (96), 229 (38), 214 (6), 174 (7), 132 (38), 97 (100), 91 (63).

Following the previous procedure but carrying out the work up after 1 h at 25 °C we succeeded in isolating a small amount of (*E*)-*N*-benzyl-4-chloromethyl-3-methoxy-3-methyl-2-pyrrolidinone (**11b**) (as the second main product in the reaction mixture after **13**), as a colourless oil. [Found: C, 58.0; H, 4.9; N, 5.2. $C_{13}H_{13}Cl_2NO$ requires C, 57.80; H, 4.85; N, 5.18]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.89 (3H, s, C(3)C*H*$_3$), 3.90 (1H, dd, $J=14.9$, 2.5 Hz, C(5)*H*$_2$), 4.00 (1H, dd, $J=14.9$, 2.5 Hz, C(5)*H*$_2$), 4.48 (1H, d, $J=14.7$ Hz, NC*H*$_2$Ar), 4.69 (1H, d, $J=14.7$ Hz, NC*H*$_2$Ar), 6.54 (1H, t, $J=2.5$ Hz, C=C*H*Cl), 7.23–7.42 (5H, m, Ar*H*); IR (film) 1715 (C=O) cm^{-1}; *m*/*z* (EI): 269 (10%, M^+), 234 (100), 125 (17), 91 (83), 65 (23).

5.8. Hydrolysis of *N*-benzyl-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (9b)

In a Schlenk tube, were added acetal **9b** (0.52 g, 1 mmol), acetic acid (0.5 mL) and methanesulfonic acid (0.5 mL). The mixture, under vigorous stirring, was heated to 140 °C for 20 h, after which time it was diluted with H_2O (4 mL) and then extracted with CH_2Cl_2 (3×4 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)–ethyl acetate gradient (from 10/0 to 8.5/1.5) as eluent, gave 3,4-dimethylmaleic anhydride (**3b**) (0.10 g, 79%), as a pale brown microcristalline solid. Mp 92–94 °C. The MS spectrum is consistent with that of an authentical sample purchased from Aldrich.

5.9. Preparation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichloropropanamide (22b)

In a double-necked round bottom flask (100 mL), fitted with a dropping funnel and a reflux condenser, closed on the top with a $CaCl_2$ tube, CH_2Cl_2 (20 mL), 2-(3-chloro-2-propenylamino)pyridine (mixture of *E*/*Z* stereoisomers, 4.22 g, 25 mmol) and pyridine (2.43 mL, 30 mmol) were introduced. A CH_2Cl_2 (5 mL) solution of 2,2-dichloropropanoyl chloride (**12**) (4.84 g, 30 mmol) was then carefully added to the stirred solution cooled in a ice-bath (15 min). Next, the bath was removed and the reaction mixture left at room temperature, under stirring. After 20 h, the mixture was diluted with brine–H_2O (10 mL/20 mL) and basified with NaOH (pellets). Then diethyl ether (40 mL) was added. The organic phase was separated while the aqueous layer was further washed with diethyl ether–CH_2Cl_2 (1/1, 3× 20 mL). The combined organic extracts were finally

concentrated under reduced pressure. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 7/3) as eluent, gave amide **22b** (6.53 g, 89%, mixture of two *E*/*Z* stereoisomers) as a pale yellow oil. [Found: C, 45.1; H, 3.7; N, 9.4. $C_{11}H_{11}Cl_3N_2O$ requires C, 45.00; H, 3.78; N, 9.54]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.35 (3H, s, *trans* CCl_2CH_3), 4.78 (2H, d, J=5.8 Hz, *trans* C=CCH_2N), 4.94 (2H, dd, J=6.1, 1.5 Hz, *cis* C=CCH_2N), 5.91–6.14 (2H, m, *cis*+*trans* HC=C*H*), 7.26 (1H, ddd, J=7.3, 4.9, 1.1 Hz, C(5′)Ar*H*), 7.41 (1H, dt, J=8.4, 1.1 Hz, C(3′)Ar*H*), 7.76 (1H, ddd, J=8.4, 7.3, 2.0 Hz, C(4′)Ar*H*), 8.54 (1H, ddd, J=4.9, 2.0, 1.1 Hz, C(6′)Ar*H*); IR (film): 1670 (C=O) cm^{-1}; *m*/*z* (EI): 292 (13%, M^+), 257 (68), 167 (42), 131 (100), 78 (30), 75 (33).

5.10. Cyclisation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichloropropanamide (22b)

CuCl (99 mg, 1 mmol) and the 2,2-dichloroamide **22b** (2.94 g, 10 mmol) were weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a magnetic stirrer bar. Dry acetonitrile (10 mL) and TMEDA (302 μL, 2 mmol) were then added under argon. The mixture was stirred at room temperature and after 20 h diluted with $NaOH_{aq}$ (0.3% w/v, 20 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 8/2). This gave the pyrrolidinones *cis*-**23b** (1.82 g, 62%), as a pale orange crystalline solid, and *trans*-**23b** (0.76 g, 26%), as an orange solid.

5.10.1. cis-N-(2-Pyridyl)-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*cis*-23b). Mp 112–114 °C. [Found: C, 45.1; H, 3.8; N, 9.5. $C_{11}H_{11}Cl_3N_2O$ requires C, 45.00; H, 3.78; N, 9.54]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (3H, s. C(3)CH_3), 3.02 (1H, dt, J=9.8, 7.4 Hz, C(4)*H*), 3.73 (1H, dd, J=12.0, 9.9 Hz, C(5)*H*), 4.54 (1H, dd, J=12.0, 7.4 Hz, C(5)*H*), 6.11 (1H, d, J=9.7 Hz, C(4)C*H*Cl_2), 7.12 (1H, ddd, J=7.3, 5.0, 1.2 Hz, C(5′)Ar*H*), 7.74 (1H, ddd, J=8.5, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.37 (1H, dt, J=8.5, 1.0 Hz, C(3′)Ar*H*), 8.39 (1H, ddd, J=5.0, 2.1, 0.9 Hz, C(6′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 25.87 (C(3)*C*H$_3$), 47.33 (*C*(5)), 53.93 (*C*(4)), 69.66 (*C*(3)), 71.36 (C(4)*C*HCl_2), 115.09 (*C*(3′)Ar), 120.65 (*C*(5′)Ar), 138.05 (*C*(4′)Ar), 147.77 (*C*(6′)Ar), 150.70 (*C*(2′)Ar), 169.66 (*C*=O); IR (KBr): 1706 (C=O) cm^{-1}; *m*/*z* (EI): 292 (8%, M^+), 257 (5), 209 (23), 173 (100), 145 (23).

5.10.2. trans-N-(2-Pyridyl)-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*trans*-23b). Mp 104–105 °C. [Found: C, 45.1; H, 3.8; N, 9.5. $C_{11}H_{11}Cl_3N_2O$ requires C, 45.00; H, 3.78; N, 9.54]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89 (3H, s. C(3)CH_3), 3.41 (1H, dt, J=7.4, 4.3 Hz, C(4)*H*), 4.32 (1H, dd, J=12.3, 4.1 Hz, C(5)*H*), 4.43 (1H, dd, J=12.3, 7.4 Hz, C(5)*H*), 5.99 (1H, d, J=4.4 Hz, C(4)C*H*Cl_2), 7.12 (1H, ddd, J=7.3, 4.8, 1.2 Hz, C(5′)Ar*H*), 7.74 (1H, ddd, J=8.5, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.39 (1H, dt, J=8.5, 1.0 Hz, C(3′)Ar*H*), 8.41 (1H, ddd, J=4.8, 2.1, 0.9 Hz, C(6′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 21.19 (C(3)*C*H$_3$), 45.51 (*C*(5)), 54.00 (*C*(4)), 68.45 (*C*(3)), 70.82 (C(4)*C*HCl_2), 114.97 (*C*(3′)Ar), 120.51 (*C*(5′)Ar), 137.98 (*C*(4′)Ar), 147.77 (*C*(6′)Ar), 150.83 (*C*(2′)Ar), 169.72 (*C*=O); IR (KBr): 1717 (C=O) cm^{-1}; *m*/*z* (EI): 292 (8%, M^+), 257 (5), 209 (23), 173 (100), 145 (23).

5.11. Rearrangement of *N*-(2-pyridyl)-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (23b)

Following the procedure for the rearrangement of *cis*-**8b**, **23b** (mixture 71/29 of cis/trans stereoisomers, 0.59 g, 2 mmol) gave the 3-pyrrolin-2-one **24b** (0.34 g, 68%), as a pale brown solid, and the lactam **25** (0.11 g, 21%), as a yellow oil.

5.11.1. N-(2-Pyridyl)-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (24b). Mp 70-72 °C. [Found: C, 63.1; H, 6.5; N, 11.2. $C_{13}H_{16}N_2O_3$ requires C, 62.89; H, 6.50; N, 11.28]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.87 (3H, q, J=1.2 Hz, C(4)CH_3), 1.96 (3H, q, J=1.2 Hz, C(3)CH_3), 3.14 (6H, s, C(5)OCH_3), 7.11 (1H, ddd, J=7.3, 5.0, 1.2 Hz, C(5′)Ar*H*), 7.64 (1H, dt, J=8.5, 1.0 Hz, C(3′)Ar*H*), 7.71 (1H, ddd, J=8.5, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.54 (1H, ddd, J=5.0, 2.1, 1.2 Hz, C(6′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 8.19 (C(3)*C*H$_3$), 9.25 (C(4)*C*H$_3$), 51.09 (O*C*H$_3$), 113.93 (*C*(5)), 117.05 (*C*(3′)Ar), 120.57 (*C*(5′)Ar), 132.37 (*C*(3)), 137.69 (*C*(4′)Ar), 145.46 (*C*(4)), 148.90 (*C*(6′)Ar), 149.57 (*C*(2′)Ar), 169.16 (*C*=O); IR (KBr): 1713 (C=O) cm^{-1}; *m*/*z* (EI): 248 (1%, M^+), 233 (5), 217 (39), 203 (100), 135(12), 78 (23).

5.11.2. (E)-N-(2-Pyridyl)-4-chloromethylen-3-methoxy-3-methyl-2-pyrrolidinone (25). [Found: C, 57.1; H, 5.2; N, 11.0. $C_{12}H_{13}ClN_2O_2$ requires C, 57.04; H, 5.19; N, 11.09]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.56 (3H, s, C(3)CH_3), 3.26 (3H, s, C(3)OCH_3), 4.63 (1H, dd, J=17.0, 2.8 Hz, C(5)*H*), 4.81 (1H, dd, J=17.0, 2.6 Hz, C(5)*H*), 6.39 (1H, t, J=2.7 Hz, C=C*H*Cl), 7.12 (1H, ddd, J=7.3, 5.0, 0.9 Hz, C(5′)Ar*H*), 7.75 (1H, ddd, J=8.5, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.42 (1H, ddd, J=5.0, 2.1, 0.9 Hz, C(6′)Ar*H*), 8.53 (1H, dt, J=8.5, 1.0 Hz, C(3′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 25.37 (C(3)*C*H$_3$), 47.72 (*C*(5)), 52.83 (O*C*H$_3$), 81.71 (*C*(3)), 115.16 (*C*(3′)Ar), 116.83 (C=*C*HCl), 120.45 (*C*(5′)Ar), 135.53 (*C*(4)=CHCl), 137.96 (*C*(4′)Ar), 147.73 (*C*(6′)Ar), 150.75 (*C*(2′)Ar), 172.35 (*C*=O); IR (film): 1723 (C=O) cm^{-1}; *m*/*z* (EI): 252 (19%, M^+), 222 (19), 217 (43), 216 (32), 189 (9), 185 (10), 173 (18), 157 (15), 132 (32), 97 (100), 78 (31).

5.12. One-pot preparation of 3,4-dimethylmaleic anhydride (3b)

Pyrrolidin-2-one **24b** (a 71/29 mixture of cis/trans stereoisomers, 1.18 g, 4 mmol) was first rearranged following the procedure described for the rearrangement of *cis*-**8b**. After the 20 h period at 25 °C, the solvent was removed under vacuum and the residue treated with H_2SO_4 4 N (4 mL). The resulting mixture was then heated at 110 °C for 1 h, after which time it was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were concentrated under vacuum, giving anhydride **3b** (0.29 g, 57%).

5.13. Preparation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichlorohexadecanamide (22a)

2,2-Dichlorohexadecanoic acid (**6**) (6.51 g, 20 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, dry CH_2Cl_2 (10.5 mL) was added under argon. The solution was thermostated at 23 °C, and while stirring, DMF (33 μL) and $(COCl)_2$ (2.64 mL, 40 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 dry CH_2Cl_2 (10 mL), then the solution, thermostated at 23 °C, was treated with a solution of pyridine (3.49 mL, 40 mmol) and 2-(3-chloro-2-propenylamino)pyridine (mixture of *E*/*Z* stereoisomers, 7.60 g, 45 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h and then washed with NaOH 1 M (2× 20 mL). Next, the organic phase was recovered and concentrated. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 9/1) as eluent, gave amide **22a** (8.95 g, 94%, mixture of two *E*/*Z* stereoisomers), as a yellow oil. [Found: C, 60.7; H, 7.7; N, 5.9. $C_{24}H_{37}Cl_3N_2O$ requires C, 60.57; H, 7.84; N, 5.89]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (3H, t, J=6.5 Hz, $CH_2CH_2CH_3$), 1.27 (22H, br s, $(CH_2)_n$), 1.62 (2H, qn, J=7.1 Hz, $CCl_2CH_2CH_2$), 2.49 (2H, m, CCl_2CH_2) 4.70 (1H, d, J=5.8 Hz, *trans* C=CCH_2N), 4.87 (1H, dd, J=6.2, 1.4 Hz, *cis* C=CCH_2N), 5.93–6.16 (2H, m, *cis*+*trans* HC=CH), 7.25 (1H, ddd, J=7.3, 4.9, 1.1 Hz, C(5′)ArH), 7.41 (1H, dt, J=8.4, 1.1 Hz, C(3′)ArH), 7.76 (1H, ddd, J=8.4, 7.3, 2.0 Hz, C(4′)ArH), 8.54 (1H, ddd, J=4.9, 2.0, 1.1 Hz, C(6′)ArH); IR (film): 1669 (C=O) cm^{-1}; *m*/*z* (EI): 475 (11%, M^++1), 439 (100), 403 (25), 257 (38), 195 (47), 167 (72), 131 (94), 75 (43).

5.14. Cyclisation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichlorohexadecanamide (22a)

CuCl (99 mg, 1 mmol) and **22a** (4.76 g, 10 mmol) were weighed into a Schlenk tube fitted with a perforable septum (blocked by a screw cap). Dry acetonitrile (10 mL) and TMEDA (302 μL, 2 mmol) were then added, under argon. The mixture was stirred at 60 °C and after 20 h the mixture was diluted with $NaOH_{aq}$ 0.3% w/v (20 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether (bp 40–60 °C)–ethyl acetate gradient (from 10/0 to 9.4/0.6). This gave the pyrrolidinone **23a** (4.43 g, 93%), as an 90/10 (^{1}H NMR spectrum) mixture of inseparable *cis*-/*trans*-diastereoisomers; pale yellow oil. [Found: C, 60.7; H, 7.9; N, 5.9. $C_{24}H_{37}Cl_3N_2O$ requires C, 60.57; H, 7.84; N, 5.89]; ^{1}H NMR ($CDCl_3$, 400 MHz): *cis* diastereoisomer (90%) δ 0.89 (3H, t, J=6.5 Hz, $CH_2CH_2CH_3$), 1.10–1.60 (24H, br m, $C(3)CH_2(CH_2)_{12}CH_3$), 2.40 (2H, m, $C(3)CH_2$), 3.23 (1H, dt, J=7.5, 9.3 Hz, C(4)H), 3.73 (1H, dd, J=9.4, 11.6 Hz, C(5)H), 4.50 (1H, dd, J=7.5, 11.6 Hz, C(5)H), 6.10 (1H, d, J=9.3 Hz, $CHCl_2$), 7.09 (1H, ddd, J=7.4, 4.9, 1.0 Hz, C(5′)ArH), 7.70 (1H, ddd, J=8.4, 7.4, 1.9 Hz, C(4′)ArH), 8.37 (2H, m, C(3′)ArH, C(6′)ArH), ^{13}C NMR ($CDCl_3$, 400 MHz): δ 14.07 (CH_3), 22.63 (CH_3CH_2), 25.52 ($C(3)CH_2CH_2$), 29.17, 29.30, 29.40, 29.44, 29.52, 29.59 ($(CH_2)_9$), 31.86 ($CH_3CH_2CH_2$), 37.14 ($C(3)CH_2$), 47.00 (C(5)), 48.37 (C(4)), 71.60 ($CHCl_2$), 73.26 (C(3)), 114.99 (C(3′)Ar), 120.48 (C(5′)Ar), 137.87 (C(4′)Ar), 147.64 (C(6′)Ar), 150.68 (C(2′)Ar), 168.95 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz): *trans* diastereoisomer (10%) δ 0.89 (3H, t, J=6.5 Hz, $CH_2CH_2CH_3$), 1.10–1.60 (24H, br m, $C(3)CH_2(CH_2)_{12}CH_3$), 2.40 (2H, m, $C(3)CH_2$), 3.34 (1H, dt, J=4.2, 5.5 Hz, C(4)H), 4.37 (2H, d, J=5.5 Hz, C(5)H_2), 5.98 (1H, J=4.2 Hz, $CHCl_2$), 7.09 (1H, ddd, J=7.4, 4.9, 1.0 Hz, C(5′)ArH), 7.70 (1H, ddd, J=8.4, 7.4, 1.9 Hz, C(4′)ArH), 8.37 (2H, m, C(3′)ArH, C(6′)ArH), ^{13}C NMR ($CDCl_3$, 400 MHz): δ 14.07 (CH_3), 22.63 (CH_3CH_2), 24.42 ($C(3)CH_2CH_2CH_2$), 29.17, 29.30, 29.40, 29.44, 29.52, 29.59 ($(CH_2)_9$), 31.66 ($CH_3CH_2CH_2$), 32.95 ($C(3)CH_2$), 45.37 (C(5)), 53.34 (C(4)), 70.51 ($CHCl_2$), 72.66 (C(3)), 114.81 (C(3′)Ar), 120.26 (C(5′)Ar), 137.87 (C(4′)Ar), 147.64 (C(6′)Ar), 150.68 (C(2′)Ar), 169.04 (C=O); IR (film) 1726 (C=O) cm^{-1}; *m*/*z* (EI): 475 (2%, $M+H^+$), 439 (39), 369 (18), 355 (53), 280 (25), 278 (26), 195 (100).

5.15. One-pot preparation of 3-tetradecyl-4-methylmaleic anhydride (chaetomellic anhydride A) (3a)

In a Schlenk tube, fitted with a perforable septum blocked by a screw cap, ethyl ether/CH_3OH 1:1 (1.6 mL) and **23a** (0.48 g, 1 mmol) were added. The solution was thermostated at 25 °C. In a second Schlenk tube, Na^0 (92 mg, 4 mmol) was carefully dissolved in CH_3OH (1.5 mL), and when the effervescence ceased, the alkaline solution was thermostated at 25 °C, after which it was poured into the first Schlenk tube. The reaction mixture was stirred for 20 h. Next, in the same Schlenk tube, was added H_2SO_4 (4 N, 0.25 mL), the solvent removed under vacuum and the residue treated with H_2SO_4 (4 N, 0.75 mL) and water (0.25 mL). The mixture was then heated at 110 °C for 2 h (under a current of argon to remove CH_3OH released from hydrolysis of **23a**), after which time it was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (3×3 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)–ethyl acetate gradient (from 10/0 to 9/1), gave **3a** (0.24 g, 78%),[1] as a pale yellow oil. [Found: 73.86; H, 10.52. $C_{19}H_{32}O_3$ requires C, 73.98; H, 10.46]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (3H, t, J=6.7 Hz, $CH_2CH_2CH_2CH_3$), 1.25 (22H, br s, $CH_2(CH_2)_9CH_2$), 1.57 (2H, m, $C(3)CH_2CH_2$), 2.07 (3H, s, $C(4)CH_3$), 2.45 (2H, t, J=7.6 Hz, $C(3)CH_2$); IR (film): 1766 (C=O) cm^{-1}; *m*/*z* (EI): 308 (5, M^+), 290 (15), 280 (4), 263 (7), 235 (8), 150 (33), 126 (100), 43 (45).

Acknowledgements

We thank the Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST) for financial assistance, and the Fondazione Cassa di Risparmio di Modena for the financial support given for the acquisition of the Bruker Avance400 Spectrometer.

References and notes

1. Singh, S. B.; Zink, D. L.; Liesch, J. M.; Goetz, M. A.; Jenkins, R. G.; Nallin-Omstead, M.; Silverman, K. C.; Bills, G. F.; Mosley, R. T.; Gibbs, J. B.; Albers-Schonberg, G.; Lingham, R. B. *Tetrahedron* **1993**, *49*, 5917–5926.
2. Singh, S. B.; Jayasuriya, H.; Silverman, K. C.; Bonfiglio, C. A.; Williamson, J. M.; Lingham, R. B. *Bioorg. Med. Chem.* **2000**, *8*, 571–580.
3. Scholte, A. A.; Eubanks, L. M.; Poulter, C. D.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 763–770.
4. Mau, C. J. D.; Garneau, S.; Scholte, A. A.; Van Fleet, J. E.; Vederas, J. C.; Cornish, K. *Eur. J. Biochem.* **2003**, *270*, 3939–3945.
5. Garneau, S.; Qiao, L.; Chen, L.; Walker, S.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 6473–6494.
6. Kar, A.; Argade, N. P. *J. Org. Chem.* **2002**, *67*, 7131–7134.
7. Deshpande, A. M.; Natu, A. A.; Argade, N. P. *J. Org. Chem.* **1998**, *63*, 9557–9558.
8. Slade, R. M.; Branchaud, B. P. *J. Org. Chem.* **1998**, *63*, 3544–3549.
9. Desai, S. B.; Argade, N. P. *J. Org. Chem.* **1997**, *62*, 4862–4863.
10. Poigny, S.; Guyot, M.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2175–2177.
11. Ratemi, E. S.; Dolence, J. M.; Poulter, C. D.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 6296–6301.
12. Kates, M. J.; Schauble, J. H. *J. Org. Chem.* **1996**, *61*, 4164–4167.
13. Argade, N. P.; Naik, R. H. *Bioorg. Med. Chem.* **1996**, *4*, 881–883.
14. Argade, N. P.; Naik, R. H. Indian Patent IN 184694; *Chem. Abstr*. **2004**, *141*, 260541.
15. Slade, R. M.; Branchaud, B. P. *Tetrahedron Lett.* **1994**, *35*, 4071–4072.
16. Singh, S. B. *Tetrahedron Lett.* **1993**, *34*, 6521–6524.
17. De Buyck, L.; Cagnoli, R.; Ghelfi, F.; Merighi, G.; Mucci, A.; Pagnoni, U. M.; Parsons, A. F. *Synthesis* **2004**, 1680–1686.
18. Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11.
19. Ghelfi, F.; Stevens, C.; Laureyn, I.; Van Meenen, E.; Rogge, T. M.; De Buyck, L.; Nikitin, K. V.; Grandi, R.; Libertini, M. C.; Pagnoni, U. M.; Schenetti, L. *Tetrahedron* **2003**, *59*, 1147–1157.
20. De Buyck, L.; Danieli, C.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F. *Tetrahedron* **2005**, *60*, 2871–2877.
21. Mangaleswaran, S.; Argade, N. P. *Synthesis* **2002**, 865–868.
22. Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *53*, 14031–14042.
23. Bellesia, F.; Forti, L.; Ghelfi, F.; Ghirardini, G.; Libertini, E.; Pagnoni, U. M.; Pinetti, A.; Prochilo, N. *Synth. Commun.* **1999**, *29*, 3739–3748.
24. Iwamatsu, S.; Kondo, H.; Matsubara, K.; Nagashima, H. *Tetrahedron* **1999**, *55*, 1687–1706.
25. Ghelfi, F.; Bellesia, F.; Forti, L.; Ghirardini, G.; Grandi, R.; Libertini, E.; Montemaggi, M. C.; Pagnoni, U. M.; Pinetti, A.; De Buyck, L.; Parsons, A. F. *Tetrahedron* **1999**, *55*, 5839–5852.
26. Slough, G. A. *Tetrahedron Lett.* **1993**, *34*, 6825–6828.
27. Planas, L.; Viret, J. P.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087–3092.
28. Baker, J. T.; Sifniades, S. *J. Org. Chem.* **1979**, *44*, 2798–2800.
29. Schmidlin, T.; Tamm, C. *Helv. Chim. Acta* **1980**, *63*, 121–131.
30. Dudot, B.; Micouin, L.; Baussanne, I.; Royer, J. *Synthesis* **1999**, 688–694.
31. Ciavatta, M. L.; Villani, G.; Trivellone, E.; Cimino, G. *Tetrahedron Lett.* **1995**, *36*, 8673–8676.
32. Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2005**, *15*, 593–601.
33. Kim, S.; Lim, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5378–5380.
34. Domingo, L. R.; Gil, S.; Parra, M.; Sáez, J. A.; Torres, M. *Tetrahedron* **2003**, *59*, 6233–6239.
35. Nesmeyanov, A. N.; Freidlina, R. K.; Zarharkin, L. I. *Quart. Rev.* **1956**, *10*, 330–370.
36. Cason, J.; Allinger, N. L.; Sumrell, G. *J. Org. Chem.* **1953**, *18*, 850–856.
37. Owen, L. N.; Sultanbawa, M. U. S. *J. Chem. Soc.* **1949**, 3105–3109.
38. Owen, L. N.; Sultanbawa, M. U. S. *J. Chem. Soc.* **1949**, 3089–3098.
39. Ingold, K. J.; Rothstein, E. *J. Chem. Soc.* **1929**, 8–14.
40. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley: New York, 2001; pp 421–423.
41. Kormos, B. L.; Cramer, C. J. *J. Org. Chem.* **2003**, *68*, 6375–6386.
42. Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1984**, *67*, 1897–1905.
43. Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *4*, 230–252.
44. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
45. Cagnoli, R.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Schenetti, L. *Tetrahedron* **2003**, *59*, 9951–9960.
46. Ince, J.; Ross, T. M.; Shipman, M.; Slawin, A. M. Z. *Tetrahedron* **1996**, *52*, 7037–7044.
47. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.
48. Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *12*, 6127–6129.
49. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Patersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malik, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzales, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. *Gaussian 98*, Revision A.9; Gaussian Inc.: Pittsburgh, PA, 1998.
50. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.