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Reinvestigation of the Sulfuric Acid-Catalysed Cyclisation of Brominated 2-Alkyllevulinic Acids to 3-Alkyl-5-methylene-2(5*H*)-furanones

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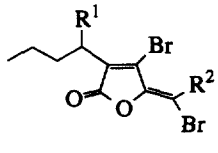
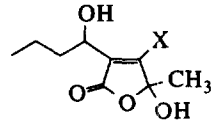
Abstract. A synthesis of ethyl-, butyl-, hexyl- and dodecyl-substituted fimbrolides from alkyl-substituted levulinic acid derivatives through bromination and acid promoted lactonisation is described. The underlying reactions have been investigated using levulinic acid as a model, and the effects of varying the bromination conditions and changing acid concentration on product distribution are discussed. Dibromination proceeds best in $CHCl_3$ and proceeds in EtOH-free $CHCl_3$ without the complication of ester formation. Cyclisation occurs with concomitant oxidation in 98-100% H_2SO_4 but gives highest yields of fimbrolides in 100% H_2SO_4. The formation of related beckerelide substances is also described. © 1997 Elsevier Science Ltd.

Fimbrolides **1-4** are representative of an important class of halogenated lactone natural products isolated from *Delisea* red marine algae.[1-4] They share a common 4-halo-3-butyl-5-halomethylene-2(5*H*)-furanone skeleton but differ in the number and nature of the halogen substituents and the presence or absence of oxygen functionality in the butyl sidechain. Beckerelides **5**, a small, structurally related class of compounds isolated from *Beckerella subcostatum*,[5] possess an OH group in the sidechain, lack the exocyclic double bond of fimbrolides and have fewer halogens. Both classes of lactones show interesting antifungal and antimicrobial properties,[1,2,5] and fimbrolides have been shown to interfere in the function of bacterial autoinduction.[6,7]



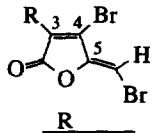
	R^1	R^2
1	H	H
2	OAc	H
3	OH	H
4	H	Br



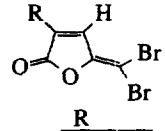
5 X= Br, Cl

There are very few successful syntheses of these novel molecules reported in the literature.[8-13] The majority of recent synthetic attempts focus on the preparation of the oxygenated analogues, but only three reports[8,9,13] describe the synthesis of the parent fimbrolide **1**. One of the latter involves the H_2SO_4-promoted cyclisation of a bromo-substituted levulinic acid[8] and proceeds with concomitant oxidation, however no experimental details concerning the preparation were published. This reaction is remarkable because of its success under seemingly harsh conditions. We report herein a reinvestigation of this synthetic route and a full description of the steps leading to fimbrolide **1**, its 3-ethyl, -hexyl and -dodecyl substituted analogues **6-8**, and

their isomers, **9-12**. In addition, we report the isolation and characterisation of fimbrolide **4** and beckerelide-like derivatives.



	R
6	C_2H_5
7	C_6H_{13}
8	$C_{12}H_{25}$



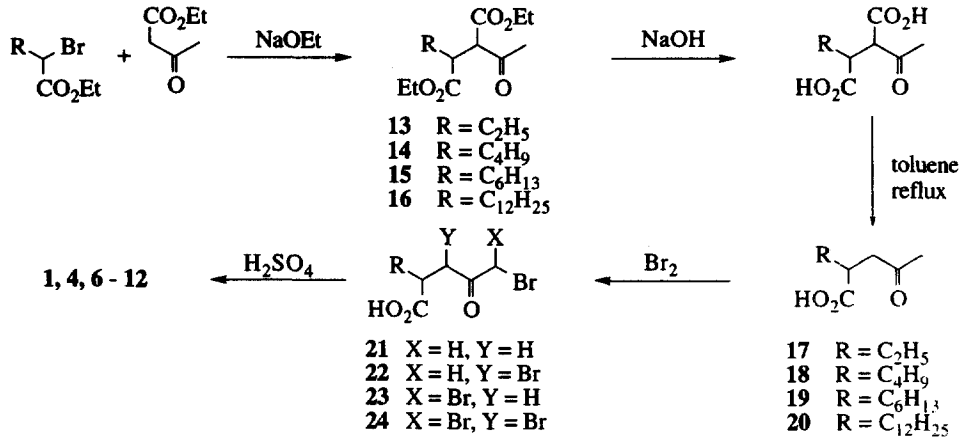
	R
9	C_2H_5
10	C_4H_9
11	C_6H_{13}
12	$C_{12}H_{25}$

RESULTS AND DISCUSSION

Following the method in Scheme 1,[8] ethyl 2-bromoalkanoates were condensed with ethyl acetoacetate by reflux with NaOEt in absolute EtOH until the reaction mixtures were neutral.[14] This process took 6-8 h except in the case of ethyl 2-bromotetradecanoate, which required 24 h at reflux. Reduced pressure distillation and column chromatography afforded the more volatile ester **13**, and diesters **14-16**, respectively, as *ca.* 1.6 : 1 mixtures of diastereoisomers that could not be completely separated upon further treatment by either technique. Typically, the ^{1}H NMR signals for the terminal alkyl methyl groups were observed as overlapping triplets at δ 0.87, while the ester methyl and methylene groups resonated as multiplets at δ 1.25 and 4.15, respectively, and the acetyl proton signals appeared as separate singlets at δ 2.24 and 2.28 whose integration gave a measure of isomer ratios. The proton adjacent to the isolated ester group in each compound appeared as a multiplet at δ 3.13-3.18, and the proton adjacent to the β-keto ester group resonated as two doublets, δ 3.85 and 3.90, each with coupling constants of *ca* 10 Hz, indicative of isomeric compounds.

Hydrolysis[15] of diesters **13-15** was accomplished within 8 h by stirring the esters at room temperature with 1.25M aqueous NaOH, and the diacid products were isolated after acidification of the reaction mixtures with 2M H_2SO_4. No hydrolysis was observed for ester **16** under these conditions, an observation attributed to the insolubility of **16** due to its hydrophobicity. Hydrolysis was eventually achieved by refluxing diester **16** in a 1 : 1 mixture of EtOH and 2M NaOH. The diacids were in all cases quite unstable and underwent partial decarboxylation during isolation. Diester **13** underwent complete decarboxylation under these conditions and in one preparation also gave a product of deacetylation rather than decarboxylation. The crude diacids were therefore briefly heated to reflux in toluene where they underwent rapid, controlled decarboxylation to give the keto-acids **17-20** in good overall yields.

The reported[8] dibromination of keto-acid **18** using Br_2 and a catalytic amount of hydrobromic acid[16] was investigated in $CHCl_3$, petroleum and glacial AcOH solvents. Mass spectrometric examination revealed that bromination under all these conditions gave mixtures of mono-, di-, and tri-bromo keto acids, **21-24** (R = C_4H_9). High field NMR spectroscopy showed the presence of regioisomers, e.g. **22** and **23**, and diastereoisomers, possible in the cases of **22-24**. The products were extremely difficult to separate on preparative scale by chromatography; even GC-MS analysis of the mixture gave inconsistent results. A detailed study of bromination of unsubstituted 4-oxopentanoic acid (levulinic acid) **25** was therefore undertaken.[16-19] Bromination using various solvents and reaction conditions again gave mixtures (Table 1) but, in the absence of diastereomeric possibilities, the brominated products were for the first time fully amenable to analysis using proton, carbon and two dimensional (HSQC and HMBC) NMR techniques.



Scheme 1

It was immediately apparent that mono- and dibrominations using laboratory grade $CHCl_3$ (stabilised with 1-2% EtOH) yielded significant amounts of bromo ethyl esters in addition to the corresponding acids. Fortunately this did not interfere with the analysis of the position of bromination by NMR spectroscopy. In this solvent, treatment with one mole equivalent of Br_2 gave unreacted acid **25** (16%), 3-bromo- **26** (21%), 5-bromo- **27** (41%), and 3,5-dibromo- **28** (22%) levulinic acids and their esters, consistent with the preference for monobromination at position 5 in MeOH.[18,19] Alternatively, treatment with two mole equivalents of Br_2 led to acid/ester mixtures of 3,5-dibromo- **28** (72%), along with isomeric 5,5-dibromolevulinic acid **29** (9%), and 3,5,5-tribromolevulinic acid **31** (19%). Treatment of **25** with two equivalents of Br_2 in MeOH afforded the same dibromo keto acids **28**, **29** and **31**, as their methyl esters, in a ratio of 63 : 20 : 8 together with a little of the 5-bromo ester **27** (Table 1). Ester formation was avoided by use of fresh water-washed and distilled $CHCl_3$. The bromination was slower in EtOH-free $CHCl_3$ and there was a decrease in the proportion of 3,5-dibromolevulinic acid **28** with a concomitant increase in the yield of 3-bromo- and 3,3-dibromolevulinic acids. **26** and **30**, and a decrease in the amount of 3,5,5-tribromolevulinic acid **31**. A similar decrease in rate was observed in CH_2Cl_2 and there was an even more pronounced decrease in **28** and increase in **26** with no change in the amount of 3,3-dibromolevulinic acid **30**. The structure of the unexpected compound **30** was confirmed through an HMBC experiment in which the three proton signal at δ 2.70 (assigned to H5) correlated with quaternary carbon signals at δ 195.1 (C4) and 58.1 (C3). Similarly the methylene proton signal at δ 3.8 (H2) correlated with quaternary carbon signals at δ 195.1 (C4), 173.4 (C1) and 58.1 (C3). When three equivalents of Br_2 were used the amount of tribromo acid **31** increased more rapidly than its isomer **30** but at the expense of both **26** and **28**. After prolonged reflux a third tribromo acid, **32**, emerged as a significant product. These variations in product ratio became relevant when considering mechanism (see later).

With this information in hand, the bromination of 2-ethyllevulinic acid **17** was studied in EtOH-free $CHCl_3$ with two mol equivalents of Br_2. Analysis of the complex mixture after reaction at reflux for one hour revealed the presence of diastereomeric 3,5-dibromo and 3,5,5-tribromo keto acids, **33** and **34** along with a mixture of lactones, e.g. **35** and **36**, corresponding to cyclic forms of the dibromo and tribromo acids. The proportion of these lactones increased as the period of reflux was increased (Scheme 2). Protons from the CH_2Br group of the major isomer of representative lactone **35** appeared in the ^1H NMR spectrum as a pair of mutually coupled doublets at δ 3.65 and 3.77. Both signals showed long-range heteronuclear coupling to C5

(δ 100.3) and C4 (δ 49.4). Meanwhile, the proton signal for the $CHBr_2$ group of the corresponding lactone **36** resonanted at δ 5.86 and correlated with the carbon-13 signal at δ 45.2.

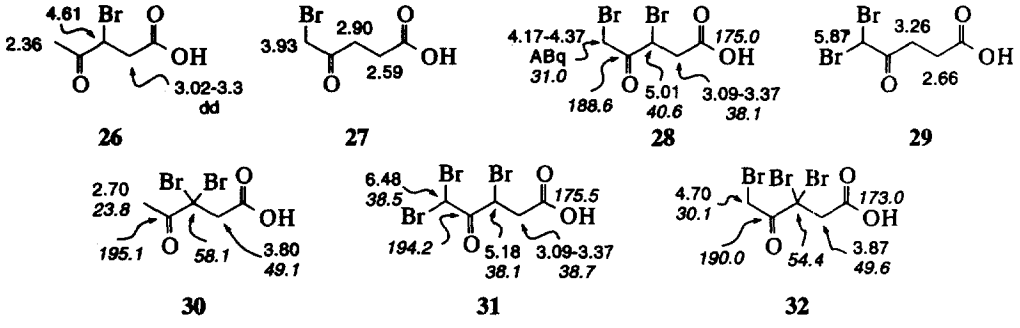


Figure 1. Selected proton and carbon-13 chemical shift data for keto acids **26-32**

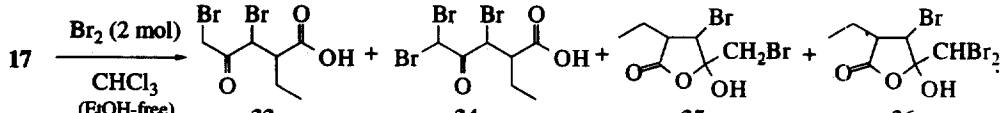
Table 1. Product distribution from bromination of levulinic acid **25**

Solvent[a]	Br_2 (mol equiv)	Percent ratio of bromo acids/esters						
		26	**27**	**28**	**29**	**30**	**31**	**32**
MeOH[b]	1	28	61	3	–	–	–	–
$CHCl_3$[c]	1	21	41	22	–	–	–	–
MeOH	2	trace	9	63	20	–	8	–
$CHCl_3$	2	trace	–	72	9	–	19	–
$CHCl_3$ (EtOH-free)	2	10	–	64	trace	24	2	trace
CH_2Cl_2	2	19	–	49	2	22	7	trace
Petroleum (60-80°C)	2	22	–	70	1	6	1	–
AcOH	2	4	–	66	5	7	19	–
CH_2Cl_2	3	18	–	43	4	28	6	trace
$CHCl_3$ (EtOH-free)	3	4	–	34	1	38	21	3
$CHCl_3$[d] (EtOH-free)	3	trace	–	35	1	28	23	12

[a] Reaction performed for 1 h at 50°C. [b] Reaction in Mg-dried MeOH at reflux for 1 h with 8% recovery of methyl levulinate (ref 18). [c] Recovery of levulinic acid/ethyl levulinate 16%. [d]Reaction for 7 h at reflux.

Lactone formation from dibromoketo acid **22** (R = C_4H_9) is reported[8] to proceed best in 100% H_2SO_4,[20] and is accompanied by oxidation to yield fimbrolide **1**. Repetition of this treatment on several 2-alkyl dibromoketo acids **22** (R = alkyl) led in our hands to mixtures of variously halogenated fimbrolides (5-alkylidene-2(5*H*)-furanones) and beckerelides (5-halomethyl-2(5*H*)-furanones). In order to understand this reaction fully, attention was again turned to a simpler system and the cyclisation of (i) pure 3,5-dibromolevulinic acid **28** and (ii) the mixture of dibromo and tribromo levulinic acids (Table 1) prepared by

bromination of acid **25** with 2 mol equivalents of bromine. The latter study was of practical importance because as mentioned earlier similarly brominated alkyl-substituted levulinic acids could not be purified.

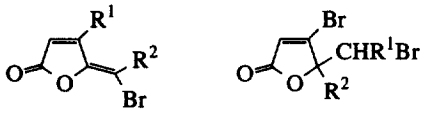


reflux, 1 h	38	:	22	:	30	:	10
reflux, 5 h	27	:	18	:	39	:	16

Scheme 2

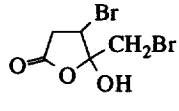
It has been reported[21] that conc. H_2SO_4 (98%, d 1.84) promotes conversion of 3,5-dibromolevulinic acid **28** into 4-bromo-5-(bromomethylene)-2(5*H*)-furanone **37** along with minor products (10-15%), while similar treatment using 20% oleum gives the isomeric 5-(dibromomethylene)-2(5*H*)-furanone **38** as the major product. Spectroscopic data and chemical structures were not provided for the minor substances, but the mechanism of formation of the major product was postulated to involve an enol-lactonisation process followed by oxidation. This mechanism easily explains the formation of furanone **37** from the 3,5-dibromo acid **28** but requires 5,5-dibromolevulinic acid **29** as precursor of the isomeric furanone **38**.

In our hands, treatment of pure 3,5-dibromolevulinic acid **28** with conc. H_2SO_4 (98%) gave 4-bromo-5-(bromomethylene)-2(5*H*)-furanone **37** (54%), 5-(dibromomethylene)-2(5*H*)-furanone **38** (8%) and 5-(bromomethylene)-2(5*H*)-furanone **39** (2%), along with small amounts of beckerelide derivatives **40-42** (so called because of their similarity to natural beckerelides). The major furanones **37** and **38** were identified by comparison of their spectroscopic data with those reported in the literature.[21] In the proton NMR spectrum of furanone **39** the 5-CHBr signal appeared as a singlet at δ 6.12 while the same signal for the 4-bromo analogue **37** resonated at δ 6.42 and those for H3 and H4 appeared as mutually coupled doublets at δ 6.32 and 7.40, respectively. The beckerelide derivatives **40** and **42** were evident through the appearance in their NMR spectra of the 5-CH_2Br protons as sets of mutually coupled methylene signals at δ 3.64, 3.82 (*J* 11.3 Hz) and 4.04, 4.23 (*J* 12.3 Hz), respectively. Beckerelide **41** gave characteristic NMR signals at δ 5.86 and 43.4, for the 5-$CHBr_2$ group, and a quaternary carbon signal at δ 104.3 for C5.



	R^1	R^2
37	Br	H
38	H	Br
39	H	H
46	Br	Br

	R^1	R^2
40	H	OH
41	Br	OH
42	H	Br
43	Br	Br



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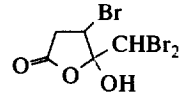

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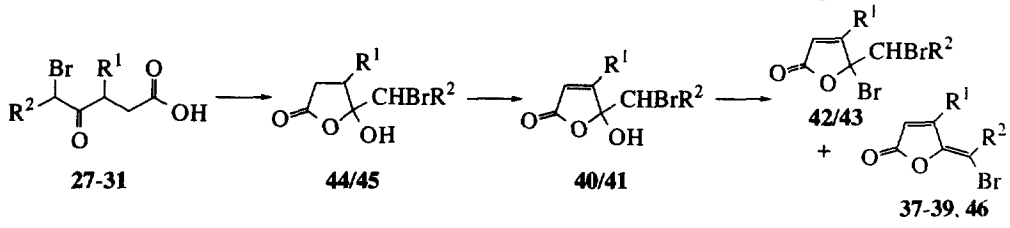
It is clear from these results that 3,5-dibromolevulinic acid **28** is not just undergoing simple lactonisation and oxidation. A more likely postulate (Scheme 3) is that a degree of bromine exchange takes place, possibly by disproportionation, prior to cyclisation. For example, a new mixture of bromo acids, **27-31**, might be established. Subsequent acid-promoted cyclisation, probably by closure of the carboxylic acid group on to the

γ-keto group, and oxidation would then afford various beckerelide structures, including **40** and **41**. Evolution of HBr during the bromine exchange process could then explain formation of bromobeckerelides, *eg* **42** and as yet unseen **43**. Alternatively, loss of water under the strongly dehydrating conditions provides a pathway to the major products, the natural and unnatural fimbrolide skeletons of **37** and **38**, from intermediates **44** and **45**, respectively, through prior or subsequent oxidation.

Concentrated H_2SO_4 (d 1.84) treatment of the crude dibromination mixture (containing 3,5-dibromo-, 5,5-dibromo- and 3,5,5-tribromo-levulinic acids, **28**, **29** and **31**, respectively, and their ethyl esters. (ratio 72:9:19)) obtained by bromination of levulinic acid **25** in laboratory grade $CHCl_3$ (stabilised with EtOH) gave a mixture of furanoids from which 4-bromo-5-(bromomethylene)-2(5*H*)-furanone **37** (21%), 5-(dibromomethylene)furanone **38** (5%) and 5-(bromomethylene)-2(5*H*)-furanone **39** (4%) were again isolated. Similar treatment of the purely ester fraction (after separation of the acids) led to a significant increase in the yield of furanone **39** (17%) indicating that dehydrobromination was more facile in the case of ester cyclisation. Importantly for later discussion, formation of 4-bromo-5-(dibromomethylene)-2(5*H*)-furanone **46** was not observed in these reactions. In conclusion, the overall distribution of products (except for the higher yield of furanone **39**) appeared insensitive to the use of pure or crude dibromo levulinic acid samples.



Scheme 3

With this improved knowledge of the reactions, lactonisation of the crude bromo compounds derived from treatment of keto acids **17-20** with two mole equivalents of bromine in $CHCl_3$ was investigated.

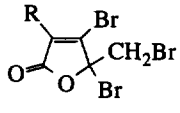
Treatment with conc. H_2SO_4 of the mixed dibromo keto acid **22** (R = C_4H_9) derived from bromination of **17** in petroleum or $CHCl_3$ afforded fimbrolide **1** together with a significant amount of lactone **47** (analogous to **42**) (Table 2). This new product was evident through the appearance in the ^1H NMR spectrum of a pair of mutually coupled doublets at δ 4.06 and 4.22 (*J* 11.8 Hz) in place of the alkenyl signal of **1** (δ 6.25) (see later). Also, the alkenyl ^{13}C NMR signals for C5 and 5-CHBr in compound **1** had been replaced by quaternary and methylene carbon signals at δ 89.7 and 34.3, respectively. The proton signals were readily assigned to those of a CH_2Br group, and the position of the quaternary carbon signal was in agreement with that of a bromoether carbon at C5.[2] The presence of a Br substituent at C5 was supported by a high resolution mass fragment at *m/z* 310.9081 in the electron impact mass spectrum that confirmed the molecular formula. An obviously similar but much more polar compound, **48** (R_f 0.25 in CH_2Cl_2), was also detected in trace amounts from the cyclisation reaction. The ^1H NMR spectrum of **48** showed the presence of a single isolated proton resonance at δ 5.87, assigned to the $CHBr_2$ proton, and an exchangeable signal at δ 4.40, due to the OH group. In support of the structure, there was in the ^{13}C NMR spectrum a distinctive resonance at δ 102.4, for the quaternary C5 carbon, at higher chemical shift than the same carbon signal from **47** (Table 3), and a methine carbon signal at δ 44.8 for the $CHBr_2$ carbon attached to C5. The ^1H and ^{13}C NMR chemical shift data conformed closely with corresponding values for the natural substance **49**.[4]

Table 2. Product distribution from bromination and acid promoted cyclisation of keto acid **18**

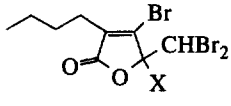
Bromination solvent	Cyclisation acid	Products (% ratios)					
	H_2SO_4 (%)	**1**	**10**	**4**	**47**	**48**	**51**
petroleum	98	65	15	–	20	trace	–
petroleum	100	23	33	33	–	–	11[a]
$CHCl_3$	98	46	28	–	26	–	–
$CHCl_3$	100	76	16	8	trace	–	–
AcOH	100	9	21	70	trace	–	–

[a] Product tentatively assigned as structure **51** (^{1}H NMR δ 5.95; ^{13}C NMR δ 92.6, 144.2)

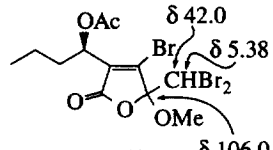
Use of this bromination/cyclisation combination with keto acid **20** afforded the corresponding fimbrolide **8** and beckerelide **50**.



47 R = C_4H_9
50 R = $C_{12}H_{25}$



48 X = OH
51 X = Br



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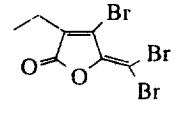

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The literature preparation of fimbrolide **1**[18] gave highest yields from lactonisation using a large excess of 100% H_2SO_4.[20] Repetition of the above experiment using $CHCl_3$ as solvent for bromination and 100% H_2SO_4 for cyclisation gave markedly more fimbrolide **1** than observed with conc. H_2SO_4, less of the isomer **10** and only traces of beckerelide **47**. In contrast, the reaction using bromo keto acid **22** (R = C_4H_9) prepared in petroleum gave a decrease in the amount of fimbrolide **1**, an increase in the amount of isomer **10**, but a similar absence of beckerelide **47**. In the latter sequence, significant amounts of tribrominated products, **4** and **51**, were evident, and the yield of tribromo fimbrolide **4** was very high when AcOH was used as the bromination solvent. The reaction outcome is therefore sensitive to the type of solvent used in the bromination step as well as acid concentration. It is noteworthy that the highest yield of fimbrolide **1** was observed using the $CHCl_3$/100% H_2SO_4 combination.

Similar treatment of the crude dibromo keto acids derived in $CHCl_3$ from **17**, **19** and **20** with 100% H_2SO_4 also afforded fimbrolides **6-8**, respectively, as the major products, along with minor amounts of the isomeric fimbrolides **9**, **11** and **12**, and varying amounts of their tribromo analogues. Tribromo fimbrolide **52**, analogous to **4**, was isolated as a crystalline substance and was identified by comparison of carbon-13 chemical shift values with those of **4** (Table 3).

The spectroscopic data for fimbrolides **1** and **4** were in agreement with those reported for the natural products.[1] Compounds **1**, **6-8** all showed sharp ^{1}H NMR singlet resonances at δ 6.25, which were characteristic of the protons on the exocyclic double bond in the configuration shown. Meanwhile, the only low field ^{1}H NMR signal in the spectra of isomeric fimbrolides **9-12** was a narrow triplet signal at δ 7.26 (J < 1 Hz) that was assigned to H4 of the furanone ring. In the ^{13}C NMR spectra, the signals for C5 resonated at almost identical positions, δ 149.9 and 149.7, respectively, in the two isomeric series, those for the C5-substituent carbon, 5-CXBr, occurred at higher chemical shift in the spectra of compounds **1**, **6-8**, (δ 90.9)

than in the spectra of compounds **9-12** (δ 78.8), and only minor chemical shift differences were observed for C3 and C4 between the two series (Table 3). The ^{1}H and ^{13}C NMR spectroscopic assignments for compounds **9-12** were made unambiguous by an HMBC experiment on compound **12**. In particular, the proton signal at δ 7.26 showed two three-bond couplings, one to C2 (δ 168.3) and the other to the bromomethylene carbon (δ 78.7), and two two-bond couplings to C3 (δ 138.0) and C5 (δ 149.7). It is noteworthy that these compounds were not mentioned in the earlier literature and might have been overlooked because of the near coincidence of the H4 signal with that of the residual $CHCl_3$ solvent signal.

Table 3. Selected carbon-13 chemical shift data for compounds **1**, **4**, **6-12**, **47**, **48**, **50**, **52**

Position	**3-Br,5-CHBr**				**3-H,5-CBr_2**				**3-Br,5-CBr_2**		**Beckerelides**		
Ring	**6**	**1**	**7[a]**	**8**	**9**	**10**	**11**	**12[a]**	**52**	**4**	**47[a]**	**50**	**48**
C2	165.8	166.1	166.0	166.0	168.5	166.7	168.7	166.6	164.7	164.8	166.4	166.4	167.7
C3	133.7	133.8	133.9	133.9	139.4	138.0	138.1	138.0	138.9	138.0	135.6	135.6	[b]138.9
C4	129.6	130.1	130.0	130.1	133.5	134.0	134.0	133.9	128.1	128.4	144.3	144.3	[b]137.6
C5	149.9	149.9	149.9	149.9	149.7	149.7	149.7	149.7	144.7	144.7	89.7	89.7	102.4
5-CXBr	90.9	90.9	90.8	90.8	78.8	78.8	78.7	78.7	81.6	81.5	34.4	34.4	44.8
Other													
C1'	18.8	25.1	25.2	25.3	19.2	25.4	25.7	25.7	19.6	25.8	25.1	25.3	24.9
C2'	11.3	29.3	26.8	26.9	11.5	29.3	27.3	27.2	11.1	28.8	28.7	26.6	28.7
C3'		22.4	28.8	25.8		22.2	28.8	[b]29.6		22.3	22.2	[b]29.6	22.4
C4'		13.6	31.3	29.6		13.7	31.4	[b]29.6		13.7	13.6	[b]29.6	13.7
C5'			22.4	29.6			22.4	[b]29.6				[b]29.5	
C6'			13.9	29.4			14.0	[b]29.4				[b]29.4	
C7'				29.3				[b]29.3				[b]29.3	
C8'				29.2				[b]29.2				[b]29.2	
C9'				29.15				29.1				29.0	
C10'				31.9				31.9				31.9	
C11'				22.6				22.6				22.7	
C12'				14.1				14.0				14.1	

[a]Assignments confirmed by HSQC and/or HMBC NMR experiments. [b]Values within the same column may be interchanged.

Isolation of compounds **47**, **48**, **50**, and **51** indicates that oxidation to the butenolide structure occurs in sulfuric acid with relative ease, along with lactone formation, but that elaboration of the exocyclic halomethylene group at position 5 is sensitive to the quality of the acid catalyst. It is not certain whether formation of the halomethylene double bond occurs before, after or in competition with formation of these secondary products.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. Microanalyses were performed by Dr H.P. Pham of The University of New South Wales Microanalytical Laboratory. ^{1}H NMR spectra were obtained in $CDCl_3$ on a Bruker AC300F (300 MHz) or a Bruker DMX500 (500 MHz) spectrometer. ^{13}C NMR were obtained in the same solvent on a Bruker AC300F (75.5 MHz) or a Bruker DMX500 (125.8 MHz) spectrometer. Chemical shifts were measured on the δ scale internally referenced to the solvent peaks: $CDCl_3$ (δ 7.26, δ 77.04). Ultraviolet spectra were measured on an Hitachi U-3200 spectrophotometer and refer to solutions in absolute MeOH.

Infrared spectra were recorded on a Perkin-Elmer 298 or a Perkin-Elmer 580B spectrophotometer and refer to paraffin mulls. The electron impact mass spectra were recorded on an VG Quattro mass spectrometer at 70eV ionisation voltage and 200°C ion source temperature. FAB spectra were recorded on an AutoSpecQ mass spectrometer. Column chromatography was carried out using Merck silica gel 60H (Art. 7736), whilst preparative thin layer chromatography was performed on 2 mm plates using Merck silica gel $60GF_{254}$ (Art. 7730).

Preparation of Diesters 13-16

Diethyl 2-acetyl-3-ethylbutanedioate 13 Ethyl 2-bromobutyrate (11.0 g, 0.056 mol) was added over 2 h to a stirred solution of ethyl acetoacetate (7.33 g, 0.056 mol) and NaOEt (4.03 g, 0.059 mol) in absolute EtOH (15 mL) at reflux. Heating was continued for 8 h until the solution became neutral to moist litmus. The mixture was cooled to r.t., the precipitate of NaBr was filtered off, and the solution was evaporated to yield a pale yellow oil. Distillation gave *diester 13* as a colourless oil (8.40 g, 61%) b.p. 150°C/20 mmHg. ν_{max} 2960, 2925, 1800, 1730, 1520, 1450, 1360, 1260, 1205, 1150, 1085, 950, 840 cm^{-1}. ^1H NMR δ: 0.88, t, *J* 8.2 Hz, CH_3; 1.25, m, $CO_2CH_2C\underline{H}_3$; 1.55, 2H, CH_2; 2.42 and 2.27, 2 x s, 3H, $COCH_3$; 3.13, m, CH; 3.85 and 3.90, 2 x d, *J* 11.3 Hz, CH; 4.15, m, $CO_2C\underline{H}_2CH_3$. ^{13}C NMR Isomer A (57%) δ: 10.6, CH_3; 14.0 and 14.1, $CO_2CH_2\underline{C}H_3$; 23.1, CH_2; 29.5, $CO\underline{C}H_3$; 45.1, CH; 60.6 and 60.7, $CO_2\underline{C}H_2CH_3$; 60.8, CH; 167.8, $\underline{C}O_2CH_2CH_3$; 173.8, $\underline{C}O_2CH_2CH_3$; 201.4, CO. ^{13}C NMR Isomer B (43%) δ: 11.0, CH_3; 13.9 and 14.1, $CO_2CH_2\underline{C}H_3$; 23.1, CH_2; 30.2, $CO\underline{C}H_3$; 45.3, CH; 60.6, CH; 61.6 and 61.7, $CO_2\underline{C}H_2CH_3$; 168.2, $\underline{C}O_2CH_2CH_3$; 173.6, $\underline{C}O_2CH_2CH_3$; 201.7, CO. Mass spectrum: *m/z* 245 (M+1, 23%); 199 (37); 171 (22).

Diethyl 2-acetyl-3-butylbutanedioate 14 Ethyl 2-bromohexanoate (10.0 g, 0.045 mol) and ethyl acetoacetate (5.83 g, 0.045 mol) were condensed together as described for **13**. The crude product was chromatographed on silica gel using EtOAc/petroleum (1 : 4) as the eluent to yield *diester 14* (R_f 0.75) as an oil (7.81 g, 64%). ν_{max} 2950, 2850, 1740, 1710, 1450, 1360, 1280, 1240, 1180, 1150, 1085, 1020, 950, 845 cm^{-1}. ^1H NMR δ: 0.89, t, *J* 8.2 Hz, CH_3; 1.24, m, CH_2 and $CO_2CH_2C\underline{H}_3$; 2.25 and 2.28, 2 x s, $COCH_3$; 3.17, m, CH; 3.86 and 3.90, 2 x d, *J* 10.3 Hz, CH; 4.14, m, $CO_2C\underline{H}_2CH_3$. ^{13}C NMR Isomer A (61%) δ: 13.7, CH_3; 14.0 and 14.1, $CO_2CH_2\underline{C}H_3$; 22.4, 28.3, CH_2; 29.4, $COCH_3$; 29.6, CH_2; 43.8, CH; 60.5 and 60.6, $CO_2\underline{C}H_2CH_3$; 61.3, CH; 167.7, $\underline{C}O_2CH_2CH_3$; 174.0, $\underline{C}O_2CH_2CH_3$; 201.3, CO. ^{13}C NMR Isomer B (39%) δ: 13.7, CH_3; 13.9 and 14.1, $CO_2CH_2\underline{C}H_3$; 22.4, 28.7 and 29.7, CH_2; 30.2, $COCH_3$; 43.9, CH; 60.9, CH; 61.5 and 61.6, $CO_2\underline{C}H_2CH_3$; 168.1, $\underline{C}O_2CH_2CH_3$; 173.7, $\underline{C}O_2CH_2CH_3$; 201.6, CO. Mass spectrum: *m/z* 273 (M+1, 62%); 227 (54); 199 (24).

Diethyl 2-acetyl-3-hexylbutanedioate 15 This diester was prepared from ethyl 2-bromooctanoate (5.0 g, 0.02 mol) and ethyl acetoacetate (2.60 g, 0.02 mol) as described for **13**. The crude product was chromatographed on silica gel using EtOAc/petroleum (1 : 4) as the eluent to yield *diester 15* as an oil (3.71 g, 62%). ^1H NMR δ: 0.86, t, *J* 7.2 Hz, CH_3; 1.26, m, CH_2 and $CO_2CH_2C\underline{H}_3$; 1.50, m, CH_2; 2.24 and 2.27, 2 x s, $COCH_3$; 3.18, m, CH; 3.84 and 3.89, 2 x d, *J* 10.7 Hz, CH; 4.14, m, $CO_2C\underline{H}_2CH_3$. ^{13}C NMR Isomer A (64%) δ: 14.0, CH_3; 14.0 and 14.1, $CO_2CH_2\underline{C}H_3$; 22.5, 26.2 and 29.0, CH_2; 29.5, $COCH_3$; 30.0 and 31.5, CH_2; 43.8, CH; 60.4 and 60.6, $CO_2\underline{C}H_2CH_3$; 61.4, CH; 167.8, $\underline{C}O_2CH_2CH_3$; 174.1, $\underline{C}O_2CH_2CH_3$; 201.4, CO. ^{13}C NMR Isomer B (36%) δ: 14.0, CH_3; 14.0 and 14.1, $CO_2CH_2\underline{C}H_3$; 22.5, 26.2, 28.9 and 30.1, CH_2; 30.3, $COCH_3$; 31.6, CH_2; 44.0, CH; 61.0, CH; 61.7 and 61.8, $CO_2\underline{C}H_2CH_3$; 168.1, $\underline{C}O_2CH_2CH_3$; 173.9, $\underline{C}O_2CH_2CH_3$; 201.7, CO. Mass spectrum: *m/z* 301 (M+1, 100%); 255 (29); 227 (6); 213 (10).

Diethyl 2-acetyl-3-dodecylbutanedioate 16 Ethyl 2-bromomyristate (5.0 g, 0.015 mol), ethyl acetoacetate (1.94 g, 0.015 mol) and NaOEt (1.02 g, 0.015 mol) were reacted together as described for **13** except that the mixture was heated under reflux for 24 h. The crude product was chromatographed on silica gel using EtOAc/petroleum (1 : 4) as the eluent to yield *diester **16*** as an oil (2.86 g, 50%). ^{1}H NMR δ: 0.86, t, *J* 6.9 Hz, CH_3; 1.24, m, CH_2 and $CO_2CH_2C\underline{H}_3$; 1.48, m, CH_2; 2.25 and 2.28, 2 x s, $COCH_3$; 3.18, m, CH; 3.85 and 3.90, 2 x d, *J* 10.7 Hz, CH; 4.14, m, $CO_2C\underline{H}_2CH_3$. ^{13}C NMR Isomer A (60%) δ: 14.0, CH_3; 14.0 and 14.1, $CO_2CH_2\underline{C}H_3$; 22.7, 26.5 and 29.2, CH_2; 29.4, $COCH_3$; 29.5, 29.9 and 31.8, CH_2; 43.9, CH; 60.6, 2x, $CO_2\underline{C}H_2CH_3$; 61.3, CH; 167.8, $\underline{C}O_2CH_2CH_3$; 174.1, $\underline{C}O_2CH_2CH_3$; 201.4, CO. ^{13}C NMR Isomer B (40%) δ: 14.0, CH_3; 14.0 and 14.1, $CO_2CH_2\underline{C}H_3$; 22.7, 26.5, 29.1, 29.5 and 30.0, CH_2; 30.2, $COCH_3$; 31.8, CH_2; 44.1, CH; 60.9, CH; 61.5 and 61.6, $CO_2\underline{C}H_2CH_3$; 168.2, $\underline{C}O_2CH_2CH_3$; 173.9, $\underline{C}O_2CH_2CH_3$; 201.7, CO. Mass spectrum: *m/z* 385 (M+1, 100%); 339 (64); 311 (12); 297 (10).

Preparation of Keto Acids 17-20

2-Ethyl-4-oxopentanoic acid 17 Diester **13** (3.90 g) was stirred with aq. NaOH (5%, 70 mL) overnight and the mixture extracted with Et_2O (50 mL). The aqueous solution was cooled in ice, acidified with 2M aq. H_2SO_4 and the product isolated with the aid of Et_2O to yield *keto acid **17*** as a colourless oil (1.84 g, 80%). ν_{max} 3400, 3150, 2950, 2920, 1700, 1450, 1400, 1350, 1280, 1225, 1160, 1080, 1000, 915 cm^{-1}. ^{1}H NMR δ: 0.86, t, *J* 7.6 Hz, $(H2')_3$; 1.52, m, $(H1')_2$; 2.08, s, $(H5)_3$; 2.43, m, H2; 2.75, m, $(H3)_2$; 10.34, br s, COOH. ^{13}C NMR δ: 11.2, CH_3; 24.5, CH_2; 29.7, CH; 41.1, CH_3; 44.0, CH_2; 180.8, CO_2H; 207.2, CO. Mass spectrum: *m/z* 145 (M+1, 30%); 127 (100).

2-(2-Oxopropyl)hexanoic acid 18 Diester **14** (3.75 g) was hydrolysed with aq. NaOH (5%, 70 mL) overnight at r.t. The solution was acidified, extracted with Et_2O (3 x 40 mL), and the extracts washed with H_2O (50 mL), dried and evaporated. The residual oil was dissolved in toluene (30 mL) and the solution refluxed for 1 h. Evaporation of the solvent gave *keto acid **18*** as a pale yellow oil (1.92 g, 81%). ν_{max} 3410, 3150, 2940, 2850, 1705, 1460, 1410, 1360, 1280, 1240, 1160, 920 cm^{-1}. ^{1}H NMR δ: 0.87, t, *J* 7.6 Hz, $(H6)_3$; 1.27, m, $(H4)_2$-$(H5)_2$; 1.48-1.55, m, $(H3)_2$; 2.13, s, $(H3')_3$; 2.48, m, H2; 2.83, m, $(H1')_2$; 8.84, br s, CO_2H. ^{13}C NMR δ: 13.7, CH_3; 22.4, CH_2; 28.9, CH_2; 29.8, CH; 31.2, CH_2; 39.8, CH_3; 44.6, CH_2; 181.0, CO_2H; 207.8, CO. Mass spectrum: *m/z* 173 (M+1, 38%); 155 (100).

2-(2-Oxopropyl)-octanoic acid 19 Diester **15** (3.60 g) was hydrolysed and decarboxylated as described for keto acid **18** to give *keto acid **19*** as a pale yellow oil (1.83 g, 76%). ν_{max} 3250, 2930, 2850, 1730, 1710, 1460, 1410, 1370, 1250, 1160, 1020, 930 cm^{-1}. ^{1}H NMR δ: 0.86, t, *J* 7.6 Hz, $(H8)_3$; 1.25, m, $(H4)_2$-$(H7)_2$; 1.45-1.63, m, $(H3)_2$; 2.14, s, $(H3')_3$; 2.50, m, H2; 2.85, m, $(H1')_2$; 9.46, br s, CO_2H. ^{13}C NMR δ: 14.0, CH_3; 22.5, CH_2; 26.9, CH_2; 29.0, CH_2; 29.9, CH; 31.5, CH_2; 31.6, CH_2; 39.9, CH_3; 44.6, CH_2; 181.3, CO_2H; 207.1, CO. Mass spectrum: *m/z* 201 (M+1, 31%); 183 (100).

2-(2-Oxopropyl)-tetradecanoic acid 20 Aq. NaOH (2M, 14 mL) was added to a solution of diester **16** (4.20 g) in EtOH (15 mL). The mixture was refluxed for 2 h and then concentrated under reduced pressure. The residual aqueous solution was washed with Et_2O (50 mL) and then acidified with 2M aq. H_2SO_4. The sticky white precipitate was isolated with the aid of Et_2O to yield *keto acid **20*** as a white crystalline solid (2.62 g, 84%) m.p. 48-49°C. ν_{max} 3500, 3450, 2950, 2910, 2850, 1695, 1460, 1395, 1362, 1250, 1230, 1190, 1160, 930 cm^{-1}. ^{1}H NMR δ: 0.88, t, *J* 6.6 Hz, $(H14)_3$; 1.25, m, $(H4)_2$-$(H13)_2$; 1.48-1.64, m, $(H3)_2$; 2.17, s, $(H3')_3$; 2.53, m, H2; 2.88, m, $(H1')_2$; 10.34, br s, CO_2H. ^{13}C NMR δ: 14.1, CH_3; 22.7, CH_2; 27.0, CH_2; 29.4, CH_2; 29.4, CH_2; 29.7, CH_2; 29.8, CH; 31.6, CH_2; 31.9, CH_2; 40.0, CH_3; 44.6, CH_2; 181.5, CO_2H; 207.0, CO. Mass spectrum: *m/z* 285 (M+1, 88%); 267 (100).

Synthesis of 3-alkyl-4-bromo-5-(bromomethylene)- and 3-alkyl-5-(dibromomethylene)-2(5*H*)-furanones

Bromination of keto acids

(i) *In $CHCl_3$.* A solution of Br_2 (5 g, 0.031 mol) in $CHCl_3$ (8 mL) was added dropwise over a period of 0.5 h to a solution of keto acid (0.014 mol) in $CHCl_3$ (15 mL) containing 30% HBr in AcOH (6 drops). The mixture was warmed at 50°C for 0.5 h, then at reflux for 1 h, and cooled to r.t. The resulting solution was washed successively with H_2O (20 ml), aq. $Na_2S_2O_3$ (0.5M, 20 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness to yield the crude bromo acid (76-84%), which was used without further purification.

(ii) *In petroleum.* Method (i) was followed with the exception that $CHCl_3$ was replaced by an equal volume of petroleum (b.p. 60-80°C).

(iii) *In glacial AcOH.* A solution of Br_2 (5 g, 0.031 mol) in glacial AcOH (8 mL) was added dropwise to a warm (35-40°C) solution of the keto acid (0.014 mol) in glacial AcOH (10 mL). The mixture was stirred for 1 h, cooled to r.t. and diluted with H_2O (100 mL). The residue was extracted with Et_2O (3 x 50 mL), washed with sat. aq. $NaHCO_3$ (2 x 60 mL), aq. $Na_2S_2O_3$ (0.5M, 30 mL) and H_2O (50 mL). The organic layer afforded the crude bromo keto acid (82-86%) yield.

Preparation of 3,5-dibromolevulinic acid.[22] Levulinic acid **25** (2.32 g, 0.020 mol) and Br_2 (7.0 g, 0.044 mol) were reacted together in EtOH-free $CHCl_3$ according to method (i). The resulting oil, which solidified upon standing, was recrystallized from $CHCl_3$ to give *3,5-dibromolevulinic acid **28*** as colourless prisms (1.90 g, 40%) m.p. 112-114°C (lit.[22] m.p. 113°C). ν_{max} 2920, 2850, 1720, 1700, 1435, 1410, 1380, 1320, 1245, 1210, 1150, 1100, 1020, 980, 910 cm^{-1}. ^1H NMR δ: 3.04, dd, *J* 17.4, 6.2 Hz, H_a2; 3.36, dd, *J* 17.4, 8.2 Hz, H_b2; 4.17, d, *J* 13.3 Hz, H_a5; 4.37, d, *J* 13.3 Hz, H_b5; 5.01, dd, *J* 8.2, 6.2 Hz, H3. ^{13}C NMR δ: 30.9, C5; 38.1, C2; 40.5, C3; 175.6, C1; 194.2, C4. Mass spectrum: *m/z* 276 (M($^{81}Br_2$), <1%), 274 (M(^{81}Br, ^{79}Br), <1), 272 (M($^{79}Br_2$), < 1), 259 (2), 257 (4), 255 (2), 231 (2), 229 (4), 227 (2), 195 (14), 191 (14), 181 (21), 179 (22), 167 (30), 165 (30), 123 (50), 121 (50), 108 (40), 106 (42), 95 (44), 93 (54).

Acid-promoted lactone formation

Concentrated (98%, d 1.84) or 100% H_2SO_4 (15 mL) was added to crude dibromo keto acid (2.0 g) at ambient temperature and the mixture was heated in an oil-bath at 110-120°C for 20 min. The mixture was cooled to r.t. then slowly poured on to crushed ice and the resulting dark solution was extracted with CH_2Cl_2 (3 x 50 mL). The extracts were washed with H_2O, dried and evaporated, the resulting oil was column chromatographed on silica using (1 : 1) CH_2Cl_2/petroleum (60-80°) and the non-polar fraction was further purified by high performance liquid chromatography using EtOAc/hexane (0.7 : 99.3).

*Reaction of 3,5-dibromolevulinic acid **28** with conc. H_2SO_4.* Conc. H_2SO_4 (5 mL of 98%, d 1.84) was added to 3,5-dibromolevulinic acid **28** (0.5 g, 1.8 mmol) at ambient temperature and the mixture was heated in an oil-bath at 110-120°C for 20 min. The mixture was cooled to r.t., slowly poured on to crushed ice, and the resulting emulsion extracted with CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 layer was washed with brine (2 x 20 mL), dried over Na_2SO_4 and evaporated. The crude product was shown by ^1H and ^{13}C NMR spectroscopy to contain:

4-Bromo-5-(bromomethylene)-2(5H)-furanone[21] ***37*** (54%). ^1H NMR δ: 6.42, s, 5-CHBr; 6.50, s, H3. ^{13}C NMR δ: 93.8, 5-CHBr; 121.0, C3; 135.3, C4; 151.1, C5; 165.5, C2.

5-(Dibromomethylene)-2(5H)-furanone[21] ***38*** (8%). ^1H NMR δ: 6.40, d, *J* 5.1 Hz, H3; 7.67, d, *J* 5.1 Hz, H4. ^{13}C NMR δ: 81.2, 5-CBr_2; 122.4, C3; 140.7, C4; 150.7, C5; 167.7, C2.

5-(Bromomethylene)-2(5H)-furanone ***39*** (2%), isolated by chromatography from the CH_2Cl_2/petroleum fraction as prisms m.p. 80-82°C (CH_2Cl_2/petroleum). ν_{max} 2905, 2840, 1770, 1740, 1630, 1540. 1450, 1370, 1290, 1160, 1100, 1070, 915, 880, 815, 770, 720 cm^{-1}. λ_{max} 284 (ε_{max} 13535). ^1H NMR δ: 6.12, s, 5-CHBr; 6.32, d, *J* 5.1 Hz, H3; 7.40, d, *J* 5.1 Hz, H4. ^{13}C NMR δ: 92.5, 5-CHBr; 120.7, C3; 141.8, C4; 152.4, C5; 168.3, C2. Mass spectrum: *m/z* 176 (M(^{81}Br), 100%), 174 (M(^{79}Br), 100), 148 (44), 142 (40), 122 (26), 120 (24), 95 (30).

4-Bromo-5-bromomethyl-5-hydroxy-2(5H)-furanone ***40*** (3%). ^1H NMR δ: 3.64, d, *J* 11.3 Hz, 5-CH_aH_bBr; 3.82, d, *J* 11.3 Hz, 5-CH_aH_bBr; 6.44, s, H3.

4-Bromo-5-dibromomethyl-5-hydroxy-2(5H)-furanone ***41*** (trace). ^1H NMR δ: 5.86, s, $CHBr_2$; 6.52, s, H3. ^{13}C NMR δ: 43.4, 5-$CHBr_2$; 104.3, C5; 125.3, C3; 146.2, C4; 166.7, C2.

5-Bromomethyl-4,5-dibromo-2(5H)-furanone ***42*** (2%). ^1H NMR δ: 4.04, d, *J* 12.3 Hz, 5-CH_aH_bBr: 4.23, d, *J* 12.3 Hz, 5-CH_aH_bBr; 6.51, s, H3.

Reaction of crude dibromo 2-ethyl-3-oxopentanoic acid with H_2SO_4. Treatment of crude dibromo 2-ethyl-3-oxopentanoic acid (4.2 g, 0.014 mol) [from bromination of **17** by method (i)] with 100% H_2SO_4 (10 mL) gave, after chromatography, three products:

(E)-4-Bromo-5-(bromomethylene)-3-ethyl-2(5H)-furanone ***6:*** a white solid (1.64 g, 42%) m.p. 26-27°C (Found: *m/z* 279.8731. $C_7H_6Br_2O_2$ ($^{79}Br_2$) requires *m/z* 279.8734). ν_{max} 3070, 2920, 2850, 1780, 1635, 1600, 1450, 1370, 1320, 1290, 1230, 1180, 1080, 1035, 980, 930, 870, 780, 750 cm^{-1}. λ_{max} 285 nm (ε 20060). ^1H NMR δ: 1.15, t, *J* 7.7 Hz, $(H2')_3$; 2.40, q, *J* 7.7 Hz, $(H1')_2$; 6.24, s, 5-CHBr. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 284 (M ($^{81}Br_2$), 40%); 282 (M (^{81}Br, ^{79}Br), 20); 280 (M ($^{79}Br_2$), 42); 203 (60); 201 (62); 175 (60); 173 (62); 159 (32); 149 (38); 145 (24); 122 (48); 120 (36).

5-(Dibromomethylene)-3-ethyl-2(5H)-furanone ***9:*** a white solid (0.67 g, 17%) m.p. 69-70°C (Found: *m/z* 279.8731. $C_7H_6Br_2O_2$ ($^{79}Br_2$) requires *m/z* 279.8734). ν_{max} 3090, 2930, 2850, 1780, 1600, 1460, 1380, 1260, 1170, 1070, 1030, 960, 840, 720 cm^{-1}. λ_{max} 302 nm (ε 32522). ^1H NMR δ: 1.20, t, *J* 7.3Hz, $(H2')_3$; 2.37, q, *J* 7.3 Hz, $(H1')_2$; 7.27, bs, 5-CHBr. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 284 (M ($^{81}Br_2$), 50%); 282 (M (^{81}Br, ^{79}Br), 100); 280 (M ($^{79}Br_2$), 52); 243 (22); 241 (44); 239 (24); 200 (18); 133 (22); 131 (20).

4-Bromo-5-(dibromomethylene)-3-ethyl-2(5H)-furanone ***52:*** a colourless oil (0.23 g, 5%) (Found: *m/z* 357.7835. $C_7H_5Br_3O_2$ ($^{79}Br_3$) requires *m/z* 357.7840). ν_{max} 2940, 2900, 2830, 1770, 1750, 1580, 1440, 1370, 1320, 1290, 1220, 1080, 1035, 1000, 935, 840, 715 cm^{-1}. λ_{max} 305 nm (ε 9919). ^1H NMR δ: 1.15, t, *J* 7.6Hz, $(H2')_3$; 2.42, t, *J* 7.6 Hz, $(H1')_2$. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 364 (M ($^{81}Br_3$), 36%); 362 (M ($^{81}Br_2$, ^{79}Br), 100); 360 (M ($^{81}Br\,^{79}Br_2$), 100); 358 (M ($^{79}Br_3$), 38); 283 (28); 281 (52); 279 (28); 255 (22); 223 (22); 202 (30); 200 (52); 198 (26); 174 (24); 172 (48); 170 (20); 149 (50); 143 (38); 131 (34); 117 (32).

Reaction of crude dibromo 2-(2-oxopropyl)hexanoic acid with H_2SO_4. Cyclisation of crude dibromo 2-(2-oxopropyl)hexanoic acid (4.95 g, 0.015 mol) [from bromination of **18** by method (i)] with 100% H_2SO_4 (10 mL) gave, after chromatography, five products:

(E)-4-Bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone[3] ***1:*** a pale yellow oil (0.98 g, 21%). ν_{max} 2960, 1792, 1615, 1261, 1100, 1020 cm^{-1}. ^1H NMR δ: 0.93, t, *J* 7.2 Hz, $(H4')_3$; 1.35, m, $(H3')_2$; 1.56, $(H2')_2$; 2.40, t, *J* 7.2 Hz, $(H1')_2$; 6.25, s, 5-CHBr. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 313, (M+1 ($^{81}Br_2$), 10%); 311 (M+1 (^{81}Br, ^{79}Br), 20); 309, (M+1 ($^{79}Br_2$), 18).

*3-Butyl-5-(dibromomethylene)-2(5H)-furanone **10**:* a white solid (0.79 g, 17%) m.p. 48-49°C (Found: *m/z* 309.9066. $C_9H_{10}Br_2O_2$ (^{81}Br, ^{79}Br) requires *m/z* 309.9027). ν_{max} 3080, 2900, 2840, 1740, 1590, 1445, 1330, 1255, 1040, 960, 890, 840, 820, 705 cm^{-1}. λ_{max} 303 nm (ε 19682). ^1H NMR δ: 0.92, t, *J* 7.2Hz, $(H4')_3$; 1.32, m, $(H3')_2$; 1.56, m, $(H2')_2$; 2.32, t, *J* 7.3 Hz, $(H1')_2$; 7.27, br s, H4. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 312 (M ($^{81}Br_2$), 7%); 310 (M (^{81}Br, ^{79}Br), 14); 308 (M , 7); 283 (6); 281 (12); 279 (7); 270 (19); 268 (35); 266 (20); 231 (72); 229 (72); 202 (16); 200 (32); 198 (16); 189 (30); 187 (30); 172 (16); 161 (14); 159 (14); 149 (28).

*4-Bromo-3-butyl-5-(dibromomethylene)-2(5H)-furanone[3] **4**:* a pale yellow oil (0.82 g, 14%). ^1H NMR δ: 0.94, t, *J* 7.4Hz, $(H4')_3$; 1.38, m, $(H3')_2$; 1.58, m, $(H2')_2$; 2.41, t, *J* 7.3 Hz, $(H1')_2$. ^{13}C NMR see Table 1.

*4-Bromo-5-bromo-5-bromomethyl-3-butyl-2(5H)-furanone **47**:* a colourless oil (0.35 g, 6%) (Found: *m/z* 388.8013 (M+1). $C_9H_{11}Br_3O_2$ ($^{79}Br_3$) requires *m/z* 387.8324). ν_{max} 2960, 2925, 2860, 1790, 1640, 1460, 1415, 1380, 1270, 1230, 1190, 1110, 1080, 1020, 935, 890, 840, 805, 760, 730 cm^{-1}. λ_{max} 287 nm (ε 17009). ^1H NMR δ: 0.92, t, *J* 7.2Hz, $(H4')_3$; 1.36, m, $(H3')_2$; 1.56, m, $(H2')_2$; 2.42, t, *J* 7.3 Hz, $(H1')_2$; 4.06, d, *J* 11.8 Hz, 5-CH_aH_bBr; 4.22, d, *J* 11.8 Hz, 5-CH_aH_bBr. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 394 (M ($^{81}Br_3$), <1%); 392 (M ($^{81}Br_2$, ^{79}Br), <1); 390 (M ($^{81}Br\,^{79}Br_2$), 1); 388 (M ($^{79}Br_3$), 1); 350 (1); 348 (2); 346 (2); 344 (1); 313 (18); 311 (38); 309 (26); 269 (7); 267 (12); 265 (6); 201 (12); 190 (20); 188 (20); 177 (16); 175 (16); 167 (16); 149 (100).

*4-Bromo-3-butyl-5-dibromomethyl-5-hydroxy-2(5H)-furanone **48**:* a pale yellow oil (0.31 g, 5%). ^1H NMR δ: 0.92, t, *J* 7.2 Hz, $(H4')_3$; 1.39, m, $(H3')_2$; 1.57, m, $(H2')_2$; 2.39, t, *J* 7.2 Hz, $(H1')_2$; 4.40, br s, OH; 5.87, s, 5-$CHBr_2$. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 392 (M-18 ($^{81}Br_3$), 6%), 390 (M -18 ($^{81}Br_2$, ^{79}Br), 14), 388 (M-18 (^{81}Br, $^{79}Br_2$), 14), 386 (M-18 ($^{79}Br_3$), 6), 350 (12), 348 (28), 346 (28), 344 (12), 313 (22), 311 (92), 309 (100), 307 (54), 269 (53), 267 (82), 265 (44), 239 (22), 229 (20), 201 (24).

Reaction of crude dibromo 2-(2-oxopropyl)octanoic acid with H_2SO_4. Cyclisation of crude dibromo 2-(2-oxopropyl)octanoic acid (4.6 g, 0.013 mol) [from bromination of **19** by method (i)] with 100% H_2SO_4 (10 mL) gave, after chromatography, two products:

*(E)-4-Bromo-5-(bromomethylene)-3-hexyl-2(5H)-furanone **7**:* a pale yellow oil (2.04 g, 47%) (Found: *m/z* 337.9339. $C_{11}H_{14}Br_2O_2$ (^{81}Br, ^{79}Br) requires *m/z* 337.9340). ν_{max} 3090, 2920, 2850, 1775, 1640, 1610, 1450, 1280, 1240, 1175, 1025, 980,755 cm^{-1}. λ_{max} 286 nm (ε 13003). ^1H NMR δ: 0.86, t, *J* 6.8 Hz, $(H6')_3$; 1.27, m, $(H3')_2$-$(H4')_3$; 1.55, m, $(H2')_2$; 2.36, t, *J* 7.3 Hz, $(H1')_2$; 6.23, s, 5-CHBr. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 341 (M+1 ($^{81}Br_2$), 10%); 339 (M+1 (^{81}Br, ^{79}Br), 20); 337 (M+1 ($^{79}Br_2$), 18); 270 (32); 268 (65); 265 (34); 259 (100); 257 (100).

*5-(Dibromomethylene)-3-hexyl-2(5H)-furanone **11**:* a white solid (0.37 g, 8.5%) m.p. 69-70°C (Found: *m/z* 337.9344. $C_{11}H_{14}Br_2O_2$ (^{81}Br, ^{79}Br) requires *m/z* 337.9340). ν_{max} 3100, 2910, 2860, 1760, 1600, 1450, 1375, 1255, 1060, 1010, 960, 900, 840, 830, 740, 710 cm^{-1}. λ_{max} 304 nm (ε 22753). ^1H NMR δ: 0.88, t, *J* 6.8 Hz, $(H6')_3$; 1.27, m, $(H3')_2$-$(H4')_2$; 1.58, m, $(H2')_2$; 2.33, t, *J* 7.3 Hz, $(H1')_2$; 7.27, br s, H4. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 341 (M+1 ($^{81}Br_2$), 10%); 340 (18); 339 (M+1 (^{81}Br, ^{79}Br), 19); 338 (24); 337 (M+1 ($^{79}Br_2$), 18); 336 (16); 270 (50); 268 (74); 265 (52); 259 (100); 257 (100); 240 (23); 223 (18); 202 (23); 200 (54); 198 (28); 189 (58); 187 (58); 172 (34); 159 (26); 149 (53).

Reaction of crude dibromo 2-(2-oxopropyl)tetradecanoic acid with sulfuric acid. Cyclisation of crude dibromo 2-(2-oxopropyl)tetradecanoic acid (2.2 g, 0.005 mol) [from bromination of **20** by method (i)] with 100% H_2SO_4 (10 mL) gave, after chromatography, three products:

(E)-4-Bromo-5-(bromomethylene)-3-dodecyl-2(5H)-furanone 8: a white solid (0.21 g, 10%) m.p. 55-57°C (Found: *m/z* 421.0350 (M+1). $C_{17}H_{26}Br_2O_2$ ($^{79}Br_2$) requires *m/z* 420.0298). ν_{max} 3120, 2910, 2850, 1770, 1635, 1600, 1455, 1370, 1185, 1105, 1040, 970, 785, 760, 715 cm^{-1}. λ_{max} 286 nm (ε 49088). ^1H NMR δ: 0.87, t, *J* 6.9Hz, $(H12')_3$; 1.24-1.28, m, $(H3')_2$-$(H11')_2$; 1.56, m, $(H2')_2$; 2.39, t, *J* 7.4 Hz, $(H1')_2$; 6.25, s, 5-CHBr. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 424 (M ($^{81}Br_2$), <1%); 422 (M (^{81}Br, ^{79}Br), <1); 420 (M ($^{79}Br_2$), <1); 343 (100); 341 (100); 268 (32); 189 (18).

5-(Dibromomethylene)-3-dodecyl-2(5H)-furanone 12: a white solid (0.97 g, 46%) m.p. 88-89°C (Found: *m/z* 422.0265. $C_{17}H_{26}Br_2O_2$ (^{81}Br, ^{79}Br) requires *m/z* 422.0279). ν_{max} 3080, 2900, 2840, 1750, 1595, 1450, 1340, 1260, 1060, 960, 900, 840, 825, 710 cm^{-1}. λ_{max} 303 nm (ε 15005). ^1H NMR δ: 0.88, t, *J* 7.0Hz, $(H12')_3$; 1.24-1.36, m, $(H3')_2$-$(H11')_2$; 1.58, m, $(H2')_2$; 2.34, t, *J* 7.7 Hz, $(H1')_2$; 7.27, br s, H4. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 424 (M ($^{81}Br_2$), 4%); 422 (M (^{81}Br, ^{79}Br), 8); 420 (M ($^{79}Br_2$), 4); 344 (32); 343 (100); 341 (97); 268 (50); 267 (43); 266 (32); 189 (28), 172 (34).

4-Bromo-5-bromo-5-bromomethyl-3-dodecyl-2(5H)-furanone 50: a white solid (0.15 g, 6%) m.p. 24-25°C (Found: *m/z* 500.9450 (M+1). $C_{17}H_{27}Br_3O_2$ ($^{79}Br_3$) requires *m/z* 499.9561). ν_{max} 3070, 2920, 2815, 1790, 1630, 1450, 1410, 1370, 1290, 1262, 1170, 1110, 1080, 1020, 920, 880, 820, 745, 710 cm^{-1}. λ_{max} 243 nm (ε 86622). ^1H NMR δ: 0.88, t, *J* 7.0Hz, $(H12')_3$; 1.25-1.30, m, $(H3')_2$-$(H11')_2$; 1.59, m, $(H2')_2$; 2.40, t, *J* 7.4 Hz, $(H1')_2$; 4.06, d, *J* 11.4 Hz, 5-CH_aH_bBr; 4.22, d, *J* 11.4 Hz, 5-CH_aH_bBr. ^{13}C NMR see Table 1. Mass spectrum: *m/z* 507 (M+1 ($^{81}Br_3$), <1%); 505 (M+1 ($^{81}Br_2$, ^{79}Br), <1); 503 (M+1 ($^{81}Br\,^{79}Br_2$), <1); 501 (M+1 ($^{79}Br_3$), <1); 425 (8); 423 (14); 421 (8); 343 (12); 341 (13); 263 (16); 231 (14); 229 (16); 217 (14); 215 (15); 203 (22); 201 (22); 190 (78); 188 (78); 177 (22); 175 (24); 160 (22); 145 (22); 143 (20); 123 (30).

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