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Exploitation of chemical predisposition in synthesis: an approach to the manzamenones

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Full details of the syntheses of manzamenones A, C and F are reported, using an approach modelled on a plausible biogenetic theory. The key step of the approach is a "one-pot" conversion of the antileukemic cyclopentenone, untenone A, to manzamenone A which occurs in reasonable yield and which proceeds *via* a reaction sequence of dehydration, Diels–Alder dimerisation and *retro*-Dieckmann reaction. The synthetic approach has also been applied to the preparation of a number of shorter alkyl chain analogues of the natural products. Using a combination of NMR and X-ray crystallographic data for the shorter alkyl chain analogues of manzamenone A, it is suggested that the relative stereostructures of the majority of the manzamenones should be revised such that the acyl group at the C2 position lies on the α-face and that at the C5 position resides on the β-face.

Introduction

In 1992, Kobayashi and co-workers reported the isolation and structure elucidation of a series of unusual dimeric fatty acid derivatives, the manzamenones A–F (**1**–**6**), from two *Plakortis* sponges collected in Okinawan waters.[1] Manzamenone A (**1**) was reported to display inhibitory activity against protein kinase C. All six original members of the family of natural products possessed the bicyclo[4.3.0]nonane skeleton which is relatively uncommon in natural product chemistry. On the basis of NMR analyses, five of these compounds (**1**, **3**–**6**) were assigned *cis*-fused bicyclic ring systems in which the acyl groups at C2 and C5 are oriented *trans* to each other (Fig. 1).

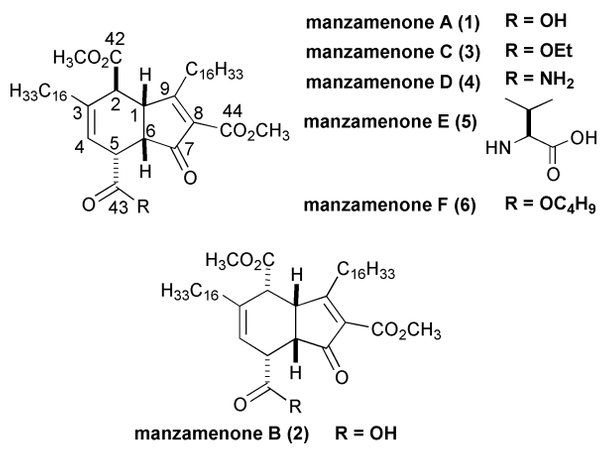


Fig. 1 Originally proposed structures for manzamenones A–F.

More recently, a number of other manzamenones have been isolated which bear some structural similarities to compounds **1**–**6**.[2,3] All of these compounds **7**–**10** are characterised by the fact that they possess two C_{16} chains and at least one methyl ester functionality (Fig. 2).

The original workers proposed that the bicyclo[4.3.0]nonane skeleton common to the majority of the manzamenones was biogenetically derived *via* an *endo*-selective [4 + 2] cyclo-

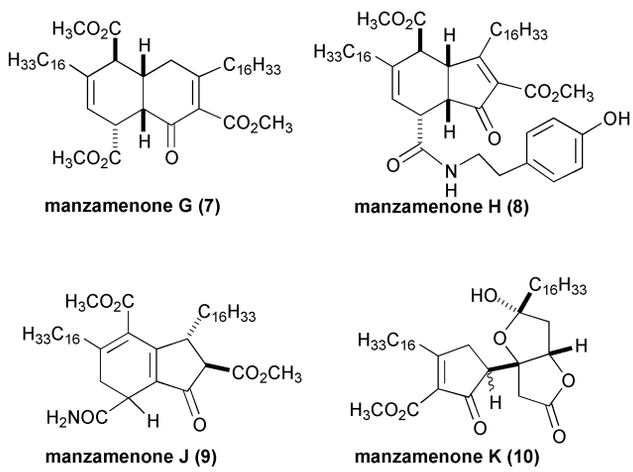
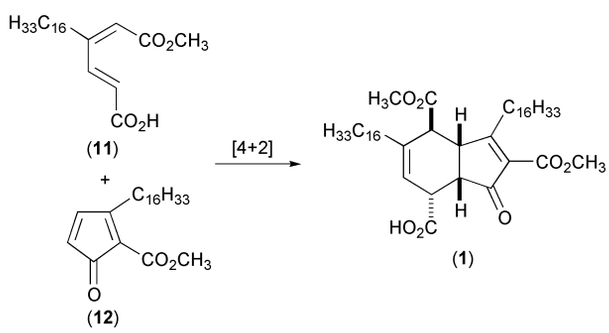


Fig. 2 Originally proposed structures for manzamenones G–K.

addition between an *E,Z*-muconic acid (hexa-2,4-dienedioic acid) derivative **11** and a cyclopentadienone **12** (Scheme 1).[1]



Scheme 1

This hypothesis was supported in 1993 by the isolation of the antileukemic cyclopentenone, untenone A (**16a**) also from a *Plakortis* sponge.[4] This compound, which is a naturally occurring racemate, can be viewed as a "protected form" of the

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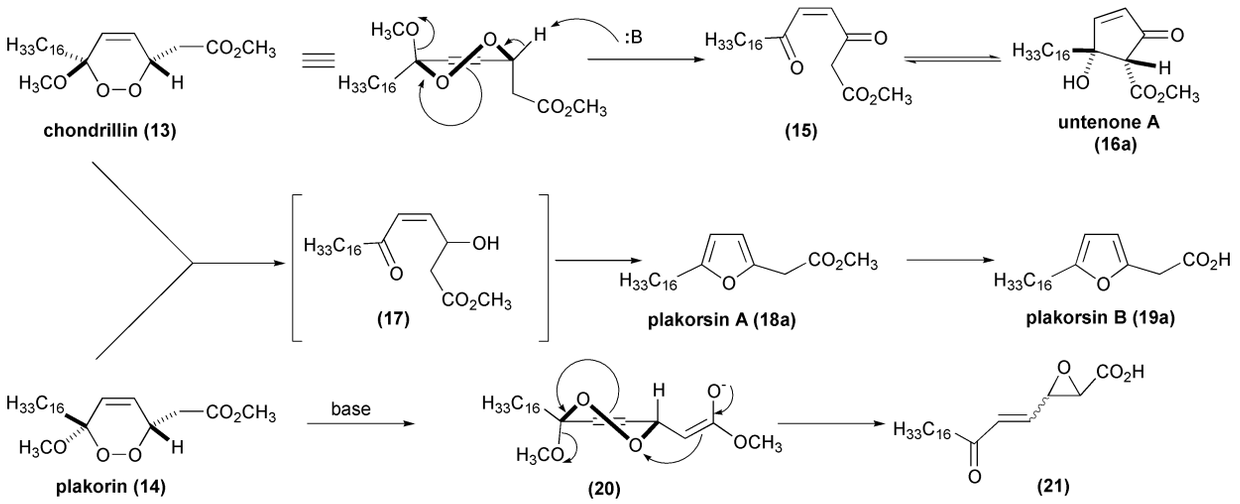
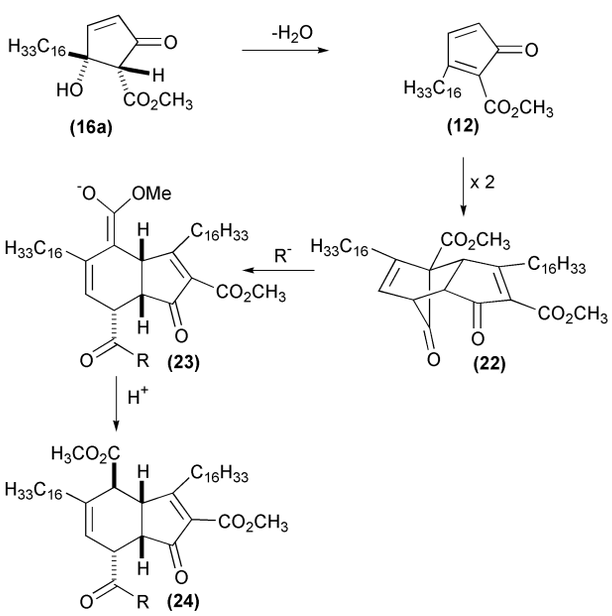


Scheme 2

dienophile required for the biosynthetic Diels–Alder reaction. It seems likely that untenone A is derived biosynthetically by eliminative ring-opening of the cyclic peroxyketal chondrillin (**13**), followed by "aldol-type" ring-closure (Scheme 2).[3,5] This suggestion is supported by the elegant work of Snider and collaborators who demonstrated that an analogue of **13** wherein the C_{16} chain had been replaced by a methyl group, could be transformed into the corresponding analogue of untenone A by treatment with triethylamine.[6]

Recently, Shen and co-workers have reported the isolation of three new fatty acid derivatives, Plakorsin A (**18a**), Plakorsin B (**19a**) and an epoxy-enone (**21**), from a Taiwanese sponge *Plakortis simplex*.[7] The two furan containing compounds may arise from reductive cleavage of the peroxide bond of chondrillin (**13**) or its C6 epimer, plakorin (**14**), followed by dehydrative cyclisation of the intermediate γ-hydroxy-α,β-enone (**17**).[8,9] This is in accord with the observation made by Wells that chemical reduction of **13** with zinc in acetic acid at 50 °C gave the furan **18a** in near quantitative yield.[5] It also seems feasible that the epoxy-enone **21** may arise from an internal S_N2 reaction of the enolate **20** derived from plakorin. A similar transformation was observed by Snider who demonstrated that the methyl analogue of **14** could be transformed into an epoxy-enone related to **21** by treatment with triethylamine.[6]

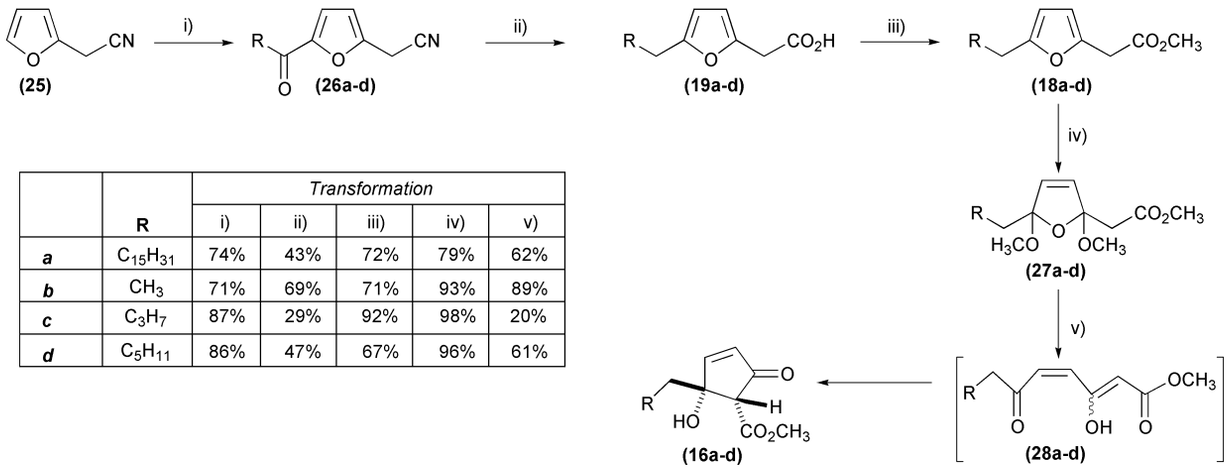
Chemical predisposition refers to the kinetic reaction preferences bestowed upon the functional groups in a molecule by their specific molecular context.[10] We have recently become interested in the exploitation of predisposed chemical reactions in the total synthesis of natural products and we were attracted by the synthetic challenge posed by the manzamenones. Although the Diels–Alder reaction depicted in Scheme 1 may feasibly proceed under the influence of enzyme catalysis, we felt that it did not bear the hallmarks of a predisposed chemical reaction. Not only does it require combination of two "mismatched" electron-deficient partners, but it also invokes the participation of a highly reactive cyclopentadienone as a dienophile. Such species are renowned for their propensity to undergo facile dimerisation reactions and, although they have been trapped as dienes in the Diels–Alder reaction, they react quite poorly as dienophiles with dienes other than themselves.[11,12] Bearing these considerations in mind, it occurred to us that the manzamenones may derive from an alternative biosynthetic pathway (Scheme 3). In our initial proposal which was put forward in 1998, we suggested that untenone A (**16a**) underwent dehydration to give a highly reactive cyclopentadienone **12** which dimerised to give a tricyclic adduct **22**.[13] It was then suggested that nucleophilic attack at the bridging carbonyl of the *exo*-cycloadduct **22** followed by *retro*-Dieckmann ring-opening of the strained five-membered ring would lead to the conjugated enolate **23**. Selective protonation of **23** on the α-face then provided access to the functionalised bicyclo[4.3.0]nonane skeleton common to the majority of the manzamenones. It was recognised that the involvement of enzyme catalysts (controlling the *endo–exo*-selectivity of the cycloaddition and the facial-selectivity of protonation of enolate **23**) could not be ruled out, however, it appeared likely to us, that the core bicyclic structure of the manzamenones was a direct consequence of the inherent reactivity of cyclopentadienone **12** and its dimeric counterpart **22**. We therefore decided to attempt a synthesis of the manzamenones using an approach modelled on the biogenetic theory outlined in Scheme 3.



Scheme 3

Results

In the first instance, a short, high yielding synthesis of (±)-untenone A was required which was suitable for large scale preparation and which could be readily applied to the preparation of analogues of the natural material. This was accomplished in five synthetic operations using readily available furan-2-ylacetonitrile (**25**)[14] as starting material and has allowed the rapid preparation of (±)-untenone A (**16a**) as well as three shorter alkyl chain analogues **16b–d** (Scheme 4).[13,15] Following a slight modification of a literature procedure, Friedel–Crafts acylation of **25** with the relevant acid chloride and $SnCl_4$ gave acylfurans **26a–d**.[16] Ketone reduction using the Huang–Minlon modification of the Wolff–Kishner



	R	Transformation				
		i)	ii)	iii)	iv)	v)
a	$C_{15}H_{31}$	74%	43%	72%	79%	62%
b	CH_3	71%	69%	71%	93%	89%
c	C_3H_7	87%	29%	92%	98%	20%
d	C_5H_{11}	86%	47%	67%	96%	61%

Scheme 4 *Reagents*; i) RCOCl, $SnCl_4$, CH_2Cl_2, −5 °C; ii) H_2NNH_2, NaOH, $HOCH_2CH_2OH$, Δ; iii) CH_2N_2, Et_2O or $TMSCHN_2$, MeOH, RT; iv) Br_2, MeOH, Na_2CO_3, −5 °C to RT; v) dilute H_2SO_4 (aq), dioxane, RT, then 1.0 M $NaHCO_3$.

conditions[17] proved to be a problematic and capricious transformation which was accompanied by concomitant nitrile hydrolysis to give plakorsin B and its shorter chain analogues **19a**–**d** in quite disappointing yields. Esterification using either diazomethane or its "safe" equivalent, $TMSCHN_2$,[18] gave plakorsin A (**18a**)[7] and its analogues **18b**–**d** which were oxidised with one equivalent of bromine in MeOH to give bis-acetals **27a**–**d** as diastereoisomeric mixtures. Finally, exposure of the acetals to mildly acidic conditions followed by brief base treatment furnished untenone A and its analogues **16a**–**d** in reasonable yields and as single diastereoisomers. This final transformation proceeds *via* the intermediate 1,4-dicarbonyl compounds **28a**–**d** and thus bears similarities to the proposed biosynthetic pathway leading to untenone A.[15]

Chronologically, the first untenone A analogue to be prepared in our laboratory was the ethyl compound **16b** which was isolated as a pale yellow oil. A small sample of this material was stored at −5 °C while the synthetic route outlined in Scheme 4 was optimised and more material was prepared. After three months, to our surprise, the pale yellow oil had undergone transformation to a pale orange solid, the ^{1}H NMR spectrum of which showed striking similarities to that of manzamenone A. Indeed, extensive spectroscopic analysis of this material confirmed that it possessed the *cis*-fused bicyclo[4.3.0]nonane skeleton common to the majority of the manzamenones, two methyl esters and a carboxylic acid group. Unambiguous assignment of the relative stereochemistry of **29b** was not feasible despite extensive NMR analysis, however, X-ray crystallographic analysis confirmed our gross structural assignment and indicated the relative stereochemistry of substituents to be as shown in Fig. 3.[13]

It was found subsequently, that simply warming a neat sample of **16b** at 40 °C for 6 days resulted in complete consumption

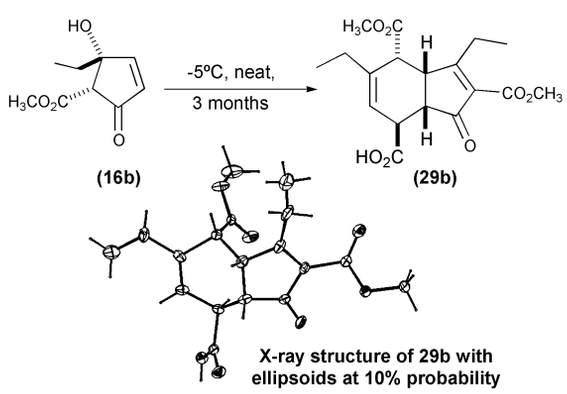


Fig. 3

Table 1

	δ_H-value (ppm)					*J*-value/Hz			
	H-1	H-2	H-4	H-5	H-6	$J_{1,2}$	$J_{4,5}$	$J_{5,6}$	$J_{6,1}$
1	3.2	3.5	6.16	3.62	2.95	6.0	2.1	8.6	7.9
29a	3.2	3.5	6.16	3.63	2.96	6.0	2.1	8.3	7.9
29b	3.24	3.52	6.15	3.62	2.99	5.9	2.2	8.4	7.8
29c	3.21	3.51	6.12	3.63	2.99	6.0	1.6	8.2	8.0
29d	3.2	3.51	6.14	3.64	2.98	5.9	2.2	8.1	7.8

of the cyclopentenone and exclusive formation of **29b**. Similar treatment of the butyl and hexyl compounds **16c** and **16d** led to formation of the corresponding manzamenone analogues **29c** and **29d** which were isolated in 93% and 54% yields respectively (Fig. 4). The relative stereochemistry of substituents in **29d** was

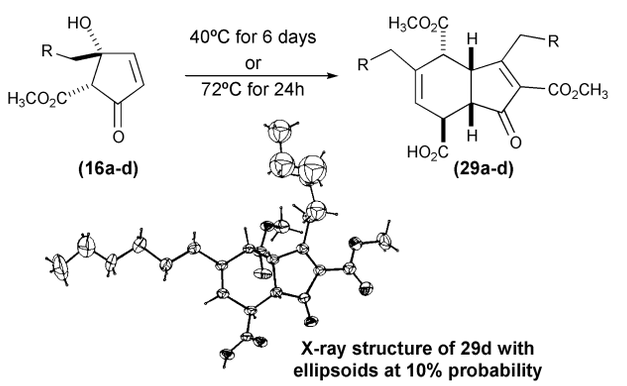


Fig. 4

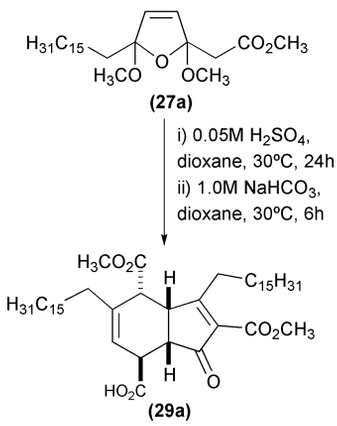
confirmed by X-ray crystallographic analysis to be the same as for the ethyl analogue **29b**.

(±)-Untenone A (**16a**) is a solid at 40 °C and it was necessary, therefore, to heat this material at its melting point (~72 °C) for 24 hours, after which time **29a** was isolated in 48% yield after purification by chromatography. Interestingly, on one occasion it was found that **29a** could be obtained directly from bis-acetal **27a** without isolation of untenone A. Thus, acidic hydrolysis of **27a** at slightly elevated temperature (30 °C) followed by treatment of the crude product with $NaHCO_3$ in aqueous dioxane for an extended reaction time (6 h) furnished **29a** in 26% yield after chromatography (Scheme 5).[15]

There is a very clear correlation between the ^{1}H NMR data for compounds **29a**–**d** which indicates that they all possess the same relative stereostructures (*i.e.* H1, H2 and H6 all *cis*; H5 and H6 *trans*) (Table 1). Consequently, the relative

Table 2

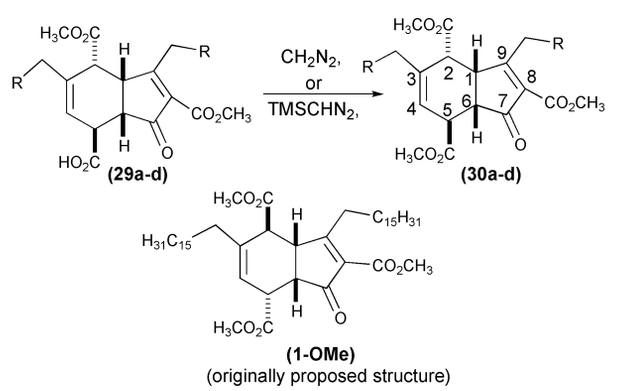
	δ_H-value (ppm)					*J*-value/Hz			
	H-1	H-2	H-4	H-5	H-6	$J_{1,2}$	$J_{4,5}$	$J_{5,6}$	$J_{6,1}$
1-OMe	3.17	3.43	5.76	3.67	3.31	6.0	2.1	6.4	7.9
30a	3.17	3.44	5.77	3.68	3.32	6.0	2.1	6.1	7.9
30b	3.22	3.46	5.77	3.68	3.33	6.2	2.2	6.2	7.9
30c	3.21	3.48	5.80	3.69	3.35	6.1	2.1	6.0	7.9
30d	3.18	3.44	5.77	3.68	3.32	6.0	2.0	6.1	7.9



Scheme 5

stereochemistry at C2 and C5 of these compounds is inverted when compared with the structure originally proposed for manzamenone A (**1**). A structural dilemma becomes apparent when the data for authentic manzamenone A (**1**)[1] and synthetic **29a** are compared as the two sets of data are identical.

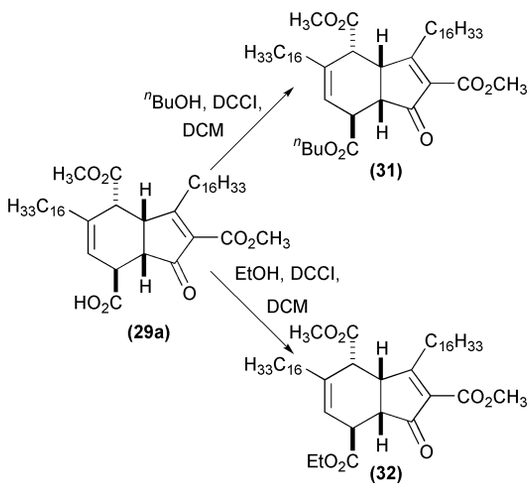
The four synthetic compounds **29a**–**d** were derivatised as their methyl esters **30a**–**d** (Scheme 6). Comparison of the ^{1}H



Scheme 6

NMR data for these compounds again indicated a strong correlation which is consistent with all of the analogues possessing the same relative stereostructures. Furthermore, the literature data for the methyl ester of naturally occurring manzamenone A (**1-OMe**) are identical to those for synthetic **30a** and visual comparison of the ^{1}H NMR spectra of authentic (**1-OMe**) and synthetic **30a** confirms the identity of the two samples (Table 2).

Given the X-ray crystallographic data for **29b** and **29d**, and given the NMR data presented here, it is our conclusion that the stereostructure for manzamenone A should be revised to that depicted for **29a**. A further relevant observation in this regard is that treatment of **29a** with ^{n}BuOH or EtOH and dicyclohexylcarbodiimide (DCCI) in dichloromethane gave butyl ester **31** and ethyl ester **32** in 57% and 41% yields respectively (Scheme 7). The spectroscopic data for **31** and **32** were identical to the literature data for naturally occurring manzamenones F and C respectively and we believe therefore, that the relative



Scheme 7

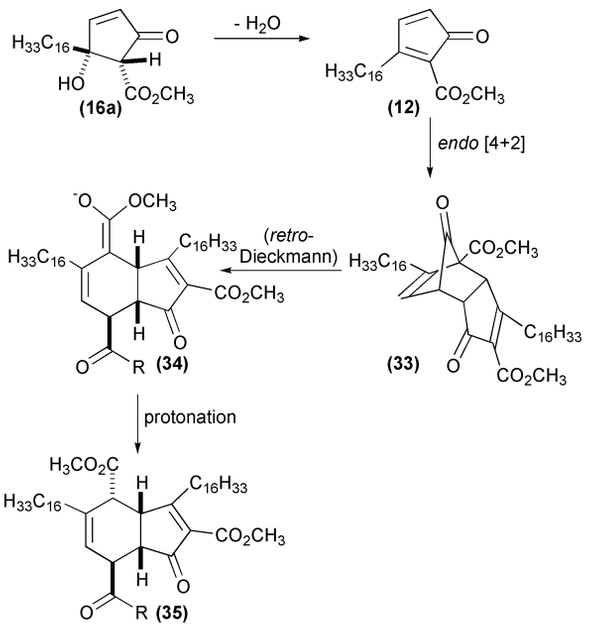
stereostructures of these natural products should also be reassigned in accord with the revised structure for manzamenone A (*i.e.* manzamenone F = **31**, manzamenone C = **32**).

Mechanistic considerations

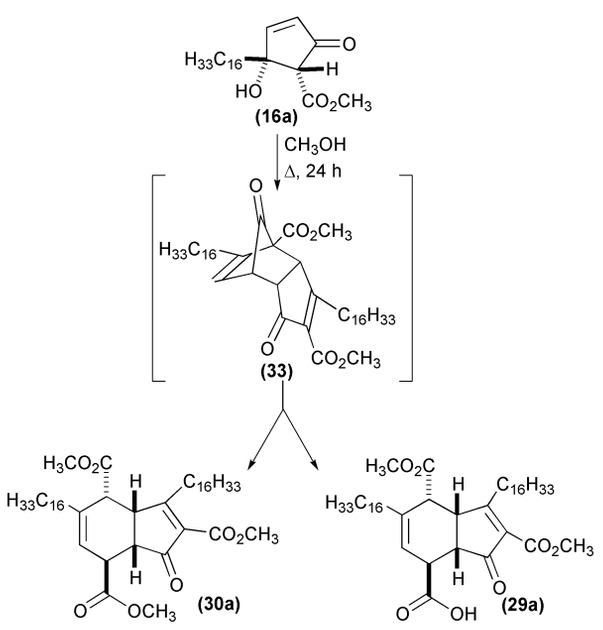
Given the findings reported above, it has been necessary to modify our original biosynthetic proposal which was outlined in Scheme 3.[13] The revised structures of the majority of the manzamenones, in which the C2 substituent lies on the α-face and the C5 substituent resides on the β-face, is completely in accord with predictions founded on the *inherent* reactivity of cyclopentadienone **12**. Thus, preferential *endo*-dimerisation of the reactive cyclopentadienone **12**, leads to tricyclic adduct **33**. Subsequent nucleophilic attack at the bridging carbonyl of **33** followed by *retro*-Dieckmann ring-opening leads to the conjugated enolate **34**. Selective protonation of **34** on the convex, and more accessible β-face, then provides access to the bicyclic skeleton common to the majority of the manzamenones (Scheme 8).

At the present time, it has not proved possible to isolate the dimer **33** reflecting the high reactivity of this proposed intermediate towards nucleophilic attack at the bridging carbonyl. However, it has been possible to gain indirect evidence for the intermediacy of such a species: thus, warming a sample of (±)-untenone A with nineteen equivalents of methanol at 40 °C for twenty four hours furnished manzamenone A (**29a**) and its methyl ester (**30a**) in a ratio of 2 : 9 together with a small amount of another, unidentified, diastereoisomer. Since simply heating **29a** in methanol at 40 °C resulted in only very slow conversion to **30a**, it seems most likely that the two products arise from a competition between water and methanol for the reactive bridging carbonyl of the cycloadduct **33** (Scheme 9).

When the above reaction was carried out in methanol-d_4 the tetradeuterated compound **36a** was the major compound to be isolated (Fig. 5). Selective incorporation of deuterium at C2 and not at C5 is in accord with our mechanistic proposal and, importantly, implies that the products from our reactions do not arise from thermodynamic equilibration of the epimerisable centre at C5.



Scheme 8



Scheme 9

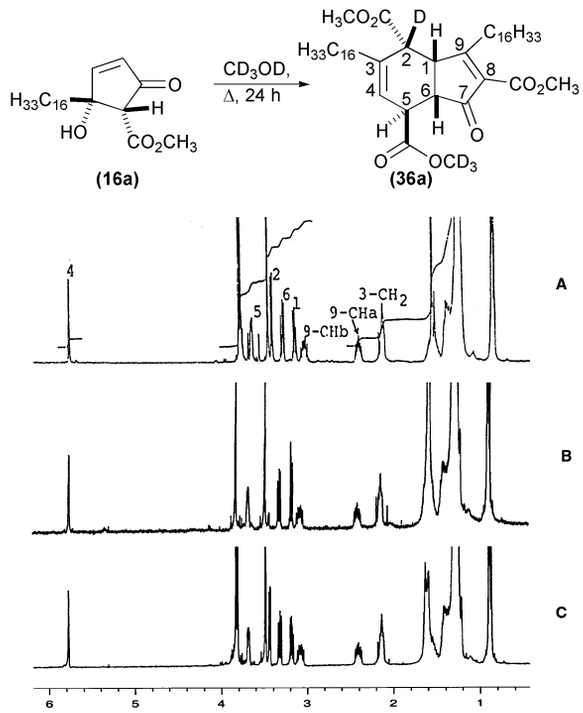


Fig. 5 **A**: ^{1}H NMR (400 MHz) of **1-OMe** in $CDCl_3$ reprinted with permission from *J. Org. Chem.*, 1992, **57**, 5255. Copyright 1992 American Chemical Society. **B**: ^{1}H NMR (400 MHz) of **36a** in $CDCl_3$. **C**: ^{1}H NMR (400 MHz) of **30a** in $CDCl_3$.

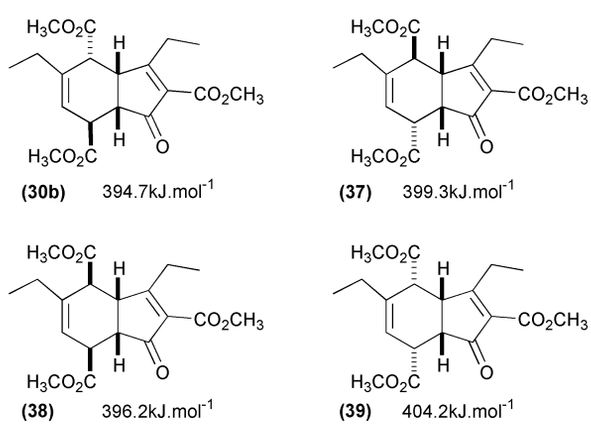


Fig. 6

Molecular modelling studies have also been carried out on the four possible diastereoisomers **30b** and **37** to **39**, arising from dimerisation of the ethyl analogue of untenone A (Fig. 6). Conformational searching was carried out on each of the four isomers, using the Monte Carlo submode of the program MacroModel[19] and the MM2* parameter set for energy minimisation, to obtain the global minimum energy structure in each case. Interestingly, the diastereoisomer of lowest energy (**30b**) was the same as that arising from our synthetic investigations. In that isomer, the ester group at C2 adopts a *pseudo*-axial position, with the *pseudo*-equatorial position being strongly disfavoured by interactions with the two ethyl groups. On the basis of this information, it seems that the relative stereostructure that we now propose for the majority of the manzamenones is one which would be predicted on both kinetic and thermodynamic grounds.

Conclusion

In conclusion, we have described efficient synthetic routes to the fatty acid derived natural products, untenone A, manzamenones A, C and F and Plakorsins A and B, using an approach modelled on a plausible biogenetic theory. Our approach has also been applied to the synthesis of a number of shorter alkyl chain analogues of the natural products. On the basis of X-ray crystallographic data for the ethyl and hexyl analogues of manzamenone A, we believe that the relative stereostructures of the majority of the manzamenones should be revised such that the acyl group at the C2 position lies on the α-face and that at the C5 position resides on the β-face. The key transformation in our approach is the "one-pot" conversion of untenone A to manzamenone A which occurs in reasonable yield and which proceeds *via* a reaction sequence of dehydration, Diels–Alder dimerisation and *retro*-Dieckmann reaction. Manzamenones G and K are the two members of this family of natural products which are not immediately amenable to our synthetic approach and research in our laboratories is continuing with the aim of preparing these two unusual compounds.

Experimental

Solvents were dried and distilled before use. Chromatography was performed over Merck silica gel 60 (40–63 μm). IR spectra

were recorded on a Perkin–Elmer 881 spectrometer or an AT1-Mattson Genesis Series FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX400 FT-NMR, a Varian Inova 400 MHz spectrometer, a Varian Inova 300 MHz spectrometer or a Bruker DMX250 pulse FT-NMR spectrometer. Chemical shifts are referenced to the residual solvent peak. Mass spectra were recorded on Fisons VG Autospec (EI/CI, low and high resolution), Fisons VG Trio 2000 quadrupole (EI/CI, low resolution), Kratos Concept 1S (EI/CI, high resolution) and Micromass Platform (electrospray) spectrometers.

(5-Palmitoylfuran-2-yl)acetonitrile (26a)

Palmitoyl chloride (5.14 g, 18.7 mmol) was dissolved in dry dichloromethane (14 mL) under an atmosphere of nitrogen and a 1.0 M solution of tin(IV) chloride in dichloromethane (28.1 mL, 28.1 mmol) was added dropwise at −5 °C. The reaction mixture was stirred for 45 minutes when a solution of furan-2-ylacetonitrile (2.0 g, 18.7 mmol) in dichloromethane (14 mL) was added dropwise over 30 minutes. The reaction mixture was stirred for a further 45 minutes when it was poured carefully onto ice. The organic layer was separated, washed sequentially with water and saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to dryness. Purification by crystallisation from petroleum ether (bp 40–60) afforded (5-palmitoylfuran-2-yl)acetonitrile as a colourless solid (4.62 g, 74%). Mp 68.6–68.9 °C; ν_{max} (film)/cm^{-1} 2260 (w, CN), 1667 (s, C=O); δ_H(300 MHz; $CDCl_3$) 0.87 (3H, t, *J* 6.7, C*H*$_3$), 1.14–1.38 (24H, m, 12 × C*H*$_2$), 1.64–1.74 (2H, m, C*H*$_2$), 2.77 (2H, t, *J* 7.5, C*H*$_2$C=O), 3.86 (2H, s, C*H*$_2$CN), 6.53 (1H, d, *J* 3.5, furan C(3)*H*), 7.13 (1H, d, *J* 3.5, furan C(4)*H*); δ_C (75.4 MHz; $CDCl_3$) 14.00 (*C*H$_3$), 17.87, 22.58, 24.16, 29.18, 29.25, 29.29, 29.36, 29.50, 29.55, 29.57, 31.82 and 38.33 (15 × *C*H$_2$, some overlapping), 110.80 (furan *C*(3)H or furan *C*(4)H), 114.37 (*C*N), 117.68 (furan *C*(3)H or furan *C*(4)H), 147.33 and 152.99 (furan *C*(2) and *C*(5)), 189.14 (*C*=O); *m*/*z* (CI/NH_3) 363 (MNH_4^+, 100%), 346 (MH^+, 10), 166 (15), 149 (33) (Found (EI): 345.2669, $C_{22}H_{35}NO_2$ requires 345.2668).

(5-Hexadecylfuran-2-yl)acetic acid (19a)

A mixture of (5-palmitoylfuran-2-yl)acetonitrile (0.57 g, 1.65 mmol) and hydrazine monohydrate (0.7 g, 13.98 mmol) in ethylene glycol (9 mL) was heated under reflux until it became homogeneous. Sodium hydroxide (1.22 g, 31 mmol) was added. The mixture was heated under reflux for 1 hour when an additional portion of hydrazine monohydrate (0.7 g, 13.98 mmol) was added and the mixture was heated under reflux for a further 3 hours. Ethylene glycol was removed by vacuum distillation to give a black residue which was redissolved in water. The pH of the solution was adjusted to ~4 using 2 M HCl and the organic material was extracted with diethyl ether. The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product which was purified by crystallisation from methanol to give (5-hexadecylfuran-2-yl)acetic acid as a pale-yellow solid (0.25 g, 43%). Mp 63.1–63.3 °C (Found: C, 75.2; H, 11.2. $C_{22}H_{38}O_3$ requires C, 75.4; H, 10.9%); ν_{max} (film)/cm^{-1} 1705 (s, C=O); δ_H(300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 6.6, C*H*$_3$), 1.22–1.42 (26H, m, 13 × C*H*$_2$), 1.58–1.65 (2H, m, C*H*$_2$), 2.59 (2H, t, *J* 7.6, CH_2CH_2-furan), 3.69 (2H, s, C*H*$_2$CO$_2$H), 5.93 (1H, d, *J* 2.9, furan C(3)*H* or furan C(4)*H*), 6.13 (1H, d, *J* 2.9, furan C(3)*H* or furan C(4)*H*), 10.7–11.1 (1H, br, CO_2H); δ_C(75.4 MHz; $CDCl_3$) 14.03 (*C*H$_3$), 22.62, 27.90, 27.95, 29.13, 29.29, 29.49, 29.60, 29.63, 31.86 and 33.86 (16 × *C*H$_2$, some overlapping), 105.41 and 108.80 (furan *C*(3)H and *C*(4)H), 144.66 and 156.44 (furan *C*(2) and *C*(5)), 176.07 (*C*OOH); *m*/*z* (EI) 350 (M^+, 30%), 139 (30), 49 (100) (Found 350.2828. $C_{22}H_{38}O_3$ requires 350.2821).

(5-Hexadecylfuran-2-yl)acetic acid methyl ester (18a)

5-Hexadecylfuran-2-ylacetic acid (0.11 g, 0.3 mmol) was dissolved in a mixture of methanol (0.6 mL) and toluene (2.1 mL). A 2 M solution of trimethylsilyldiazomethane in hexane (173 μl, 0.35 mmol) was added and the reaction mixture was then stirred at room temperature for 1 hour after which time, residual solvents were removed directly *in vacuo*. Purification of the residue by flash column chromatography (SiO_2; petrol ether (bp 40–60 °C)–ethyl acetate, 9 : 1) furnished (5-hexadecylfuran-2-yl)acetic acid methyl ester as a colourless solid (79 mg, 72%). Mp 38.5–39.0 °C (Found: C, 75.5; H, 11.4. $C_{22}H_{40}O_3$ requires C, 75.8; H, 11.1%); ν_{max} (film)/cm^{-1} 1744 (C=O); δ_H(300 MHz; $CDCl_3$) 0.89 (3H, t, *J* 6.7, C*H*$_3$), 1.21–1.34 (26H, m, 13 × C*H*$_2$), 1.58–1.64 (2H, m, C*H*$_2$), 2.58 (2H, t, *J* 7.6, CH_2CH_2-furan), 3.64 (2H, s, C*H*$_2$CO$_2$CH$_3$), 3.71 (CO$_2$C*H*$_3$), 5.90 (1H, d, *J* 3.0, furan C(3)*H* or furan C(4)*H*), 6.09 (1H, d, *J* 3.0, furan C(3)*H* or furan C(4)*H*); δ_C(75.4 MHz; $CDCl_3$) 14.00 (*C*H$_3$), 22.61, 27.93, 29.11, 29.31, 29.50, 29.61, 29.64, 31.87 and 33.86 (16 × *C*H$_2$, many overlapping), 51.95 (CO$_2$*C*H$_3$), 105.35 and 108.33 (furan *C*(3)H and *C*(4)H), 145.39 and 156.09 (furan *C*(2) and *C*(5)), 169.92 (*C*O$_2$CH$_3$); *m*/*z* (EI) 364 (M^+, 100%), 305 (30), 153 (95) (Found 364.2973. $C_{23}H_{40}O_3$ requires 364.2977).

Mixture of bis-acetals (27a)

(5-Hexadecylfuran-2-yl)acetic acid methyl ester (0.15 g, 0.41 mmol) was dissolved in a mixture of methanol (1.5 mL) and ether (0.3 mL) and solid sodium carbonate (0.18 g, 1.72 mmol) was added. A solution of bromine (75 mg, 0.47 mmol) in methanol (0.9 mL) was added dropwise and after stirring at room temperature for one hour, the reaction mixture was poured into brine solution (6 mL). The organic material was extracted into Et_2O (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the bis-acetal as a 1 : 1 mixture of diastereoisomers (0.138 g, 79%). Mp 33.7–34.5 °C; ν_{max} (film)/cm^{-1} 1745 (C=O); δ_H(300 MHz; $CDCl_3$) 0.88 (6H, t, *J* 6.7, C*H*$_3$ for both diastereoisomers), 1.17–1.95 (60H, m, 30 × C*H*$_2$), 2.60–3.11 (2H, ABq, J_{AB} 14.4, C*H*$_2$CO$_2$CH$_3$ for one diastereoisomer), 2.65–3.11 (2H, ABq, J_{AB} 14.4, C*H*$_2$CO$_2$CH$_3$ for one diastereoisomer), 3.20, 3.25, 3.28 and 3.33 (4 × 3H, s, 4 × acetal OC*H*$_3$), 3.69 and 3.70 (2 × 3H, s, CO$_2$C*H*$_3$ for both diastereoisomers), 5.98 (1H, d, *J* 5.9, alkene C*H* for one diastereoisomer), 6.01 (1H, d, *J* 5.9, alkene C*H* for one diastereoisomer), 6.25 (1H, d, *J* 5.9, alkene C*H* for one diastereoisomer), 6.30 (1H, d, *J* 5.9, alkene C*H* for one diastereoisomer); *m*/*z* (EI) 395 ($(M - OCH_3)^+$, 54%), 363 (55), 321 (30), 201 (56), 169 (58), 48 (100) (Found 395.3164. $C_{24}H_{43}O_4$ requires 395.3161).

General procedure for the preparation of untenone A and its analogues

(±)-Untenone A (16a). A mixture of diastereoisomeric bis-acetals (0.77 g, 1.8 mmol) was dissolved in dioxane (10 mL) and a 0.3 M solution of sulfuric acid (2 mL) was added. The reaction mixture was stirred at room temperature for 1 hour when a 1 M solution of sodium bicarbonate (2 mL) was carefully added and the mixture was stirred at room temperature for a further 30 minutes. Et_2O (10 mL) was added, the organic phase was collected and the aqueous phase was extracted with EtOAc (10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2; hexane–ethyl acetate; 3 : 2) furnished (±)-untenone A as a colourless solid (0.43 g, 62%). Mp 69.6–70.4 °C (Lit.,[20] mp 74–75 °C) (Found: C, 72.5; H, 10.5. $C_{23}H_{40}O_4$ requires C, 72.6; H, 10.6%); ν_{max} (film)/cm^{-1} 3482 (OH), 1740 (s, C=O, ester), 1700 (s, C=O, enone); δ_H(300 MHz; $CDCl_3$) 0.87 (3H, t, *J* 6.25, C*H*$_3$), 1.17–1.38 (28H, m, 14 × C*H*$_2$), 1.62–1.83 (2H, m, C(6)*H*$_2$), 3.45 (1H, s, C(5)*H*), 3.64 (1H, s, O*H*), 3.78 (3H, s, CO$_2$C*H*$_3$), 6.17 (1H, d, *J* 5.6, C(2)*H*), 7.50 (1H, d, *J* 5.6, C(3)*H*); δ_C(75.4 MHz; $CDCl_3$) 14.00 (*C*H$_3$), 22.58, 23.75, 29.25, 29.33, 29.42, 29.49, 29.58, 29.66, 31.82 and 40.30

(15 × CH_2, some overlapping), 52.76 (*C*(5)H), 60.78 (CO_2CH_3), 79.80 (C(4)), 132.26 (*C*(2)H), 166.88 (*C*(3)H), 168.92 (CO_2CH_3), 199.88 (enone *C*=O); *m*/*z* (CI/NH_3) 398 (MNH_4^+, 12%), 365 (6), 278 (18), 234 (90), 84 (100) (Found 398.3273. $C_{23}H_{44}NO_4$ requires 398.3270).

Ethyl analogue of (±)-untenone A (16b). Pale yellow oil. ν_{max} (film)/cm^{-1} 3473 (br, OH), 1739 (s, C=O, ester), 1708 (s, C=O, enone); δ_H(400 MHz; $CDCl_3$) 0.99 (3H, t, *J* 7.7, C(7)H_3), 1.75–1.95 (2H, m, C(6)H_2), 3.45 (1H, s, C(5)*H*), 3.66 (1H, s, O*H*), 3.78 (3H, s, CO_2CH_3), 6.20 (1H, d, *J* 6, C(2)*H*), 7.51 (1H, d, *J* 6, C(3)*H*); δ_C(100.4 MHz; $CDCl_3$) 8.07 (*C*(7)H_3), 33.07 (*C*(6)H_2), 52.88 (CO_2CH_3), 60.34 (*C*(5)H), 80.16 (*C*(4)), 132.52 (*C*(2)H), 166.79 (*C*(3)H), 169.03 (CO_2CH_3), 199.95 (*C*(1)); *m*/*z* (CI) 185 (MH^+, 14%), 167 ($(M - OH)^+$, 55), 135 (26), 123 (100), 95 (14) (Found 185.0808. $C_9H_{12}O_4$ requires 185.0814).

Butyl analogue of (±)-untenone A (16c). Pale yellow oil. ν_{max} (film)/cm^{-1} 3485 (br, OH), 1737 (s, C=O, ester), 1705 (s, C=O, enone); δ_H(300 MHz; $CDCl_3$) 0.92 (3H, t, *J* 6.7, C(9)H_3), 1.25–1.5 (4H, m, C(7)H_2 and C(8)H_2), 1.66–1.92 (2H, m, C(6)H_2), 3.47 (1H, s, C(5)*H*), 3.71 (1H, s, O*H*), 3.79 (3H, s, CO_2CH_3), 6.19 (1H, d, *J* 5.7, C(2)*H*), 7.53 (1H, d, *J* 5.7, C(3)*H*); δ_C(75.4 MHz; $CDCl_3$) 13.80 (*C*(9)H_3), 22.76, 25.87 (*C*(7)H_2 and *C*(8)H_2), 40.00 (*C*(6)H_2), 52.81 (CO_2CH_3), 60.77 (*C*(5)H), 79.78 (*C*(4)), 132.26 (*C*(2)H), 166.92 (*C*(3)H), 168.96 (CO_2CH_3), 199.81 (*C*(1)); *m*/*z* (CI) 230 (MNH_4^+, 100%), 197 (52) (Found 212.1047. $C_{11}H_{16}O_4$ requires 212.1049).

Hexyl analogue of (±)-untenone A (16d). Colourless oil. ν_{max} (film)/cm^{-1} 3464 (br, OH), 1743 (s, C=O, ester), 1711 (s, C=O, enone); δ_H(250 MHz; $CDCl_3$) 0.88 (3H, t, *J* 6.8, C(11)H_3), 1.23–1.41 (8H, m, C(7)H_2 to C(10)H_2), 1.70–1.80 (2H, m, C(6)H_2), 3.46 (1H, s, C(5)*H*), 3.66 (1H, s, O*H*), 3.79 (3H, s, OCH_3), 6.19 (1H, d, *J* 6, C(2)*H*), 7.50 (1H, d, *J* 6, C(3)*H*); δ_C(62.8 MHz; $CDCl_3$) 14.04 (*C*(11)H_3), 22.53, 23.8, 29.4, 31.62, 40.37 (*C*(6)H_2 to *C*(10)H_2), 52.94 (CO_2CH_3), 60.86 (*C*(5)H), 79.90 (*C*(4)), 132.38 (*C*(2)H), 167.10 (*C*(3)H), 169.06 (CO_2CH_3), 200.06 (*C*(1)); *m*/*z* (CI) 241 (MH^+, 20%), 223 ($(M - OH)^+$, 100), 165 (50), 123 (45), 94 (15) (Found 241.1447. $C_{13}H_{21}O_4$ requires 241.1441).

General procedure for the preparation of manzamenone A and its analogues

(±)-Manzamenone A (29a). A neat sample of (±)-untenone A (0.169 g, 0.44 mmol) was heated at ~72 °C for 24 h. The resulting solid was purified by flash column chromatography (SiO_2; hexane–ethyl acetate; 3 : 2 then ethyl acetate–acetic acid; 100 : 0.1) to provide manzamenone A as a colourless solid (0.079 g, 48%). Mp 60–65 °C; ν_{max} (KBr)/cm^{-1} 3448 (OH), 1740 (C=O), 1711 (C=O); δ_H(250 MHz; $CDCl_3$) 0.88 (6H, t, *J* 6.6, C(25)H_3 and C(41)H_3), 1.26–1.58 (56H, m, 28 × CH_2), 2.15–2.25 (2H, m, C(10)H_2), 2.40–2.52 (1H, m, one of C(26)H_2), 2.96 (1H, dd, *J* 8.3, 7.9, C(6)*H*), 3.10–3.19 (1H, m, one of C(26)H_2), 3.20 (1H, dd, *J* 7.9, 6.0, C(1)*H*), 3.50 (1H, d, *J* 6.0, C(2)*H*), 3.55 (3H, s, C(42)O_2CH_3), 3.63 (1H, dd, *J* 8.3, 2.1, C(5)*H*), 3.87 (3H, s, C(44)O_2CH_3), 6.16 (1H, d, *J* 2.1, C(4)*H*); δ_C(100.4 MHz; $CDCl_3$) 14.1 (*C*(25)H_3 and *C*(41)H_3, overlapping), 22.7, 27.1, 27.9, 29.3, 29.4, 29.5, 29.6, 29.7, 29.9 and 31.9 (28 × CH_2, many overlapping), 30.7 (*C*(26)H_2), 36.8 (*C*(10)H_2), 41.2 (*C*(5)H), 44.5 (*C*(1)H), 45.8 (*C*(2)H), 46.7 (*C*(6)H), 52.2 (2 × CO_2CH_3, overlapping), 123.2 (*C*(4)H), 132.4 (*C*(8)), 137.2 (*C*(3)), 162.7 (*C*(44)O_2CH_3), 170.2 (*C*(42)O_2CH_3), 172.9 (*C*(43)O_2H), 188.4 (*C*(9)), 207.6 (*C*(7)=O); *m*/*z* (−ve ion electrospray) 742 ($(M - H)^-$, 100%), 669 (28), 113 (32).

Ethyl analogue of (±)-manzamenone A (29b). Colourless solid. Mp 70 °C; ν_{max} (film)/cm^{-1} 3760–2675 (br, OH), 1733 (s, C=O), 1695 (s, C=O); δ_H(400 MHz; $CDCl_3$) 1.11 (3H, t, *J* 7.3, C(11)H_3), 1.23 (3H, t, *J* 7.7, C(13)H_3), 2.22–2.30 (2H, m, C(10)H_2), 2.51–2.57 (1H, m, one of C(12)H_2), 2.99 (1H, dd, *J* 8.4, 7.8, C(6)*H*), 3.10–3.15 (1H, m, one of C(12)H_2), 3.24 (1H, dd, *J* 7.8, 5.9, C(1)*H*), 3.52 (1H, d, *J* 5.9, C(2)*H*), 3.55 (3H, s, C(14)O_2CH_3), 3.62 (1H, dtd, *J* 8.4, 2.6, 2.2, C(5)*H*), 3.88 (3H, s, C(16)O_2CH_3), 6.15 (1H, ~dt, *J* 2.2, 1.7, C(4)*H*); δ_C(100.6 MHz; $CDCl_3$) 11.63 and 12.05 (*C*(11)H_3 and *C*(13)H_3), 24.03 and 29.63 (*C*(10)H_2 and *C*(12)H_2), 41.15 (*C*(5)H), 44.11 (*C*(1)H), 45.76 (*C*(2)H), 46.74 (*C*(6)H), 52.19 (2 × CO_2CH_3, overlapping), 122.22 (*C*(4)H), 132.13 and 138.59 (*C*(3) and *C*(8)), 162.65 and 170.17 (2 × CO_2CH_3), 172.93 (*C*(15)O_2H), 188.97 (C(9)), 207.51 (*C*(7)=O); *m*/*z* (CI) 351 (MH^+), 305 (90), 273 (70), 247 (100), 217 (29), 187 (22), 128 (21) (Found 351.1438. $C_{18}H_{23}O_7$ requires 351.1444).

Butyl analogue of (±)-manzamenone A (29c). Pale yellow oil. ν_{max} (film)/cm^{-1} 3700–2750 (br, OH), 1740–1680 (br s, C=O); δ_H(400 MHz; $CDCl_3$) 0.92 and 0.96 (2 × 3H, t, *J* 7.2, C(13)H_3 and C(17)H_3), 1.24–1.65 (8H, m, C(11)H_2, C(12)H_2, C(15)H_2 and C(16)H_2), 2.14–2.28 (2H, m, C(10)H_2), 2.42–2.49 (1H, m, one of C(14)H_2), 2.99 (1H, dd, *J* 8.2, 8.0, C(6)*H*), 3.09–3.17 (1H, m, one of C(14)H_2), 3.21 (1H, dd, *J* 8.0, 6.0, C(1)*H*), 3.51 (1H, d, *J* 6.0, C(2)*H*), 3.54 (3H, s, C(18)O_2CH_3), 3.63 (1H, dtd, *J* 8.2, 2.2, 1.6, C(5)*H*), 3.90 (3H, s, C(20)O_2CH_3), 6.12 (1H, ~d, *J* 1.6, C(4)*H*); δ_C(100.6 MHz; $CDCl_3$) 13.69 and 13.87 (*C*(13)H_3 and *C*(17)H_3), 22.26, 22.95, 29.14 and 29.94 (*C*(11)H_2, *C*(12)H_2, *C*(15)H_2 and *C*(16)H_2), 30.34 (*C*(14)H_2), 36.41 (*C*(10)H_2), 41.16 (*C*(5)H), 44.27 (*C*(1)H), 45.84 (*C*(2)H), 46.50 (*C*(6)H), 52.13 and 52.15 (2 × CO_2CH_3), 123.06 (*C*(4)H), 132.34 and 137.15 (*C*(3) and *C*(8)), 162.71 and 170.24 (2 × CO_2CH_3), 173.44 (*C*(19)O_2H), 187.85 (C(9)), 207.11 (*C*(7)=O); *m*/*z* (CI) 424 (MNH_4^+, 5%), 407 (MH^+, 10), 110 (60), 98 (65), 83 (63), 58 (100) (Found 407.2069. $C_{22}H_{31}O_7$ requires 407.2070).

Hexyl analogue of (±)-manzamenone A (29d). Colourless solid. Mp 95 °C; ν_{max} (film)/cm^{-1} 3600–2400 (br, OH), 1735 (s, C=O), 1680 (s, C=O); δ_H(250 MHz; $CDCl_3$) 0.89 (6H, t, *J* 6.6, C(15)H_3 and C(21)H_3), 1.23–1.58 (16H, m, C(11)H_2–C(14)H_2 and C(17)H_2–C(20)H_2), 2.11 (2H, br, C(10)H_2), 2.18–2.23 (1H, m, one of C(16)H_2), 2.98 (1H, dd, *J* 8.1, 7.8, C(6)*H*), 3.10–3.15 (1H, m, one of C(16)H_2), 3.20 (1H, dd, *J* 7.8, 5.9, C(1)*H*), 3.51 (1H, d, *J* 5.9, C(2)*H*), 3.54 (3H, s, C(22)O_2CH_3), 3.64 (1H, dd, *J* 8.1, 2.2, C(5)*H*), 3.87 (3H, s, C(24)O_2CH_3), 6.14 (1H, d, *J* 2.2, C(4)*H*); δ_C(62.8 MHz; $CDCl_3$) 14.1 (*C*(15)H_3 and *C*(21)H_3), 22.5, 22.6, 27.0, 27.9, 28.9, 29.5, 31.4, 31.7 (*C*(11)H_2–*C*(14)H_2 and *C*(17)H_2–*C*(20)H_2), 30.6 (*C*(16)H_2), 36.7 (*C*(10)H_2), 41.2 (*C*(5)H), 44.3 (*C*(1)H), 45.8 (*C*(2)H), 46.5 (*C*(6)H), 52.2 (2 × CO_2CH_3, overlapping), 123.1 (*C*(4)H), 132.3 and 137.2 (*C*(3) and *C*(8)), 162.7 and 170.2 (2 × CO_2CH_3), 173.4 (*C*(23)O_2H), 188.0 (*C*(9)), 207.2 (*C*(7)=O); *m*/*z* (CI) 463 (MH^+, 65%), 385 (30), 359 (100), 274 (20) (Found 463.2677. $C_{26}H_{39}O_7$ requires 463.2696).

General procedure for the esterification of manzamenone A and its analogues

(±)-43-*O*-Methylmanzamenone A (30a). A freshly distilled solution of diazomethane[21] in Et_2O was added to a solution of (±)-manzamenone A (50.0 mg, 0.067 mmol) in Et_2O (2 mL) until effervescence had ceased. Excess diazomethane was destroyed by the addition of AcOH and residual solvents were then removed directly *in vacuo*. Purification by flash column chromatography (SiO_2; petrol ether (bp 40–60 °C)–ethyl acetate, 15 : 1) gave 43-*O*-methylmanzamenone A contaminated with a very small quantity of an unknown by-product as a cream solid (30 mg, 59%). Clean material was obtained by further purification using reversed phase HPLC [Rainin Dynamax C18 (21.4 × 250 mm); eluent: MeOH; detection: UV at 254 nm]. Mp 69–70 °C (Lit.,[1] mp 63–64 °C); ν_{max} (film)/cm^{-1} 1738 (br s, C=O); δ_H(400

MHz; $CDCl_3$) 0.88 (6H, t, *J* 6.6, C(25)H_3 and C(41)H_3), 1.26–1.72 (56H, m, 28 × CH_2), 2.10–2.16 (2H, m, C(10)H_2), 2.36–2.45 (1H, m, one of C(26)H_2), 3.04–3.11 (1H, m, one of C(26)H_2), 3.17 (1H, dd, *J* 7.9, 6.0, C(1)*H*), 3.32 (1H, dd, *J* 7.9, 6.1, C(6)*H*), 3.44 (1H, d, *J* 6.0, C(2)*H*), 3.48 (3H, s, C(42)O_2CH_3), 3.66–3.70 (1H, m, C(5)*H*), 3.80 and 3.82 (2 × 3H, s, C(43)O_2CH_3 and C(44)O_2CH_3), 5.77 (1H, d, *J* 2.1, C(4)*H*); δ_C(75.4 MHz; $CDCl_3$) 14.04 (*C*(25)H_3 and *C*(41)H_3, overlapping), 22.61, 27.13, 27.64, 29.11, 29.28, 29.40, 29.58, 29.62, 30.08, 31.85 and 36.83 (30 × *C*H_2, many overlapping), 41.57 (*C*(5)H), 42.80 (*C*(1)H), 45.82 (*C*(6)H), 46.65 (*C*(2)H), 51.77, 51.82 and 52.55 (C(42)$O_2C$$H_3$, C(43)$O_2C$$H_3$ and C(44)$O_2C$$H_3$), 122.95 (*C*(4)H), 132.71 and 136.72 (*C*(3) and *C*(8)), 163.51, 170.61 and 174.20 (*C*(42)$O_2$$CH_3$, *C*(43)$O_2$$CH_3$ and *C*(44)$O_2$$CH_3$), 182.87 (*C*(9)), 202.10 (*C*(7)=O); *m*/*z* (CI) 758 (MH^+, 4%), 700 (4), 306 (45), 160 (45) (Found 756.5914. $C_{47}H_{80}O_7$ requires 756.5904).

Ethyl analogue of (±)-43-*O*-methylmanzamenone A (30b). Colourless oil. ν_{max} (film)/cm^{-1} 1734 (br s, C=O); δ_H(400 MHz; $CDCl_3$) 1.06 (3H, t, *J* 7.4, C(11)H_3), 1.22 (3H, t, *J* 7.6, C(13)H_3), 2.11–2.25 (2H, m, C(10)H_2), 2.43–2.52 (1H, m, one of C(12)H_2), 3.04–3.14 (1H, m, one of C(12)H_2), 3.22 (1H, dd, *J* 7.9, 6.2, C(1)*H*), 3.33 (1H, dd, *J* 7.9, 6.2, C(6)*H*), 3.46 (1H, d, *J* 6.2, C(2)*H*), 3.50 (3H, s, C(14)O_2CH_3), 3.68 (1H, dtd, *J* 6.2, 2.7, 2.2, C(5)*H*), 3.81 and 3.83 (2 × 3H, s, C(15)O_2CH_3 and C(16)O_2CH_3), 5.77 (1H, ~d, *J* 2.2, C(4)*H*); δ_C(100.4 MHz; $CDCl_3$) 11.77 (*C*(11)H_3), 11.94 (*C*(13)H_3), 23.57 (*C*(12)H_2), 29.72 (*C*(10)H_2), 41.64 (*C*(5)H), 42.52 (*C*(1)H), 46.03 (*C*(6)H), 46.69 (*C*(2)H), 51.9 and 52.65 (C(14)$O_2C$$H_3$, C(15)$O_2C$$H_3$ and C(16)$O_2C$$H_3$, two overlapping), 122.11 (*C*(4)H), 132.51 and 138.18 (C(3) and C(8)), 163.62, 170.66 and 174.32 (*C*(14)-$O_2$$CH_3$, *C*(15)$O_2$$CH_3$ and *C*(16)$O_2$$CH_3$), 183.79 (C(9)), 202.19 (*C*(7)=O); *m*/*z* (CI) 365 (MH^+, 100%), 333 (45), 273 (55) (Found 365.1603. $C_{19}H_{25}O_7$ requires 365.1600).

Butyl analogue of (±)-43-*O*-methylmanzamenone A (30c). Pale yellow oil. ν_{max} (film)/cm^{-1} 1730 (br s, C=O); δ_H(300 MHz; $CDCl_3$) 0.94 and 0.98 (2 × 3H, t, *J* 7.2, C(13)H_3 and C(17)H_3), 1.24–1.71 (8H, m, C(11)H_2, C(12)H_2, C(15)H_2 and C(16)H_2), 2.13–2.23 (2H, m, C(10)H_2), 2.38–2.51 (1H, m, one of C(14)H_2), 3.06–3.18 (1H, m, one of C(14)H_2), 3.21 (1H, dd, *J* 7.9, 6.1, C(1)*H*), 3.35 (1H, dd, *J* 7.9, 6.0, C(6)*H*), 3.48 (1H, d, *J* 6.1, C(2)*H*), 3.52 (3H, s, C(18)O_2CH_3), 3.66–3.72 (1H, m, C(5)*H*), 3.83 and 3.85 (2 × 3H, s, C(19)O_2CH_3 and C(20)O_2CH_3), 5.80 (1H, d, *J* 2.1, C(4)*H*); δ_C(75.4 MHz; $CDCl_3$) 13.68 and 13.80 (*C*(13)H_3 and *C*(17)H_3), 22.18, 22.82, 29.23, 29.70, 29.82 and 36.51 (*C*(10)H_2 to *C*(12)H_2 and *C*(14)H_2 to *C*(16)H_2), 41.56, 42.80, 45.81 and 46.67 (*C*(1)H, *C*(2)H, *C*(4)H and *C*(5)H), 51.78, 51.82 and 52.55 (C(18)$O_2C$$H_3$, C(19)$O_2C$$H_3$ and C(20)$O_2C$$H_3$), 122.96 (*C*(4)H), 132.76 and 136.65 (*C*(3) and *C*(8)), 163.52, 170.62 and 174.19 (*C*(18)$O_2$$CH_3$, *C*(19)$O_2$$CH_3$ and *C*(20)$O_2$$CH_3$), 182.78 (*C*(9)), 202.04 (*C*(7)=O); *m*/*z* (CI) 438 (MNH_4^+, 30%), 421 (MH^+, 100), 244 (18), 214 (20), 197 (20) (Found 421.2224. $C_{23}H_{33}O_7$ requires 421.2226).

Hexyl analogue of (±)-43-*O*-methylmanzamenone A (30d). Colourless oil. ν_{max} (film)/cm^{-1} 1735 (br s, C=O); δ_H(250 MHz; $CDCl_3$) 0.89 (6H, t, *J* 6.4, C(15)H_3 and C(21)H_3), 1.19–1.41 (16H, m, C(11)H_2 to C(14)H_2 and C(17)H_2 to C(20)H_2), 2.13 (2H, m, C(10)H_2), 2.40 (1H, m, one of C(16)H_2), 3.06 (1H, m, one of C(16)H_2), 3.18 (1H, dd, *J* 7.9, 6.0, C(1)*H*), 3.32 (1H, dd, *J* 7.9, 6.1, C(6)*H*), 3.44 (1H, d, *J* 6.0, C(2)*H*), 3.48 (3H, s, C(22)O_2CH_3), 3.68 (1H, dd, *J* 6.1, 2.0, C(5)*H*), 3.80 and 3.82 (2 × 3H, s, C(23)O_2CH_3 and C(24)O_2CH_3), 5.77 (1H, ~d, *J* 2.0, C(4)*H*); δ_C(62.8 MHz; $CDCl_3$) 14.4 (*C*(15)H_3 and *C*(21)H_3 overlapping), 22.89, 22.95, 27.53, 28.07, 29.21, 29.83, 30.55, 31.84, 32.02, 37.29 (*C*(10)H_2 to *C*(14)H_2 and *C*(16)H_2 to *C*(20)H_2), 42.03 (*C*(5)H), 43.26 (*C*(1)H), 46.27 (*C*(6)H), 47.1 (*C*(2)H), 52.3 and 53.0 (C(22)$O_2C$$H_3$, C(23)$O_2C$$H_3$ and C(24)$O_2C$$H_3$, two overlapping), 123.4 (*C*(4)H), 132.8 and 137.2 (*C*(3) and *C*(8)), 163.6, 171.1 and 174.7 (*C*(22)$O_2$$CH_3$, *C*(23)$O_2$$CH_3$ and *C*(24)$O_2$$CH_3$), 183.3 (*C*(9)), 202.6 (*C*(7)=O); *m*/*z* (CI) 477 (MH^+, 100%), 445 (30), 385 (50) (Found 477.2834. $C_{27}H_{41}O_7$ requires 477.2852).

(±)-Manzamenone C (32)

A mixture of manzamenone A (50 mg, 0.067 mmol), dry ethanol (44 mg, 0.96 mmol), dicyclohexylcarbodiimide (250 mg, 1.2 mmol) and DMAP (82 mg, 0.67 mmol) in DCM (8 mL) was stirred under an atmosphere of nitrogen at 0 °C for four hours. The reaction mixture was then washed sequentially with water (2 × 7 mL) and a 5% aqueous solution of acetic acid (2 × 7 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2; petrol ether (bp 40–60 °C)–ethyl acetate, 5 : 1) gave manzamenone C as a colourless oil (21 mg, 41%). ν_{max} (film)/cm^{-1} 1735 (br s, C=O); δ_H(250 MHz; $CDCl_3$) 0.88 (6H, t, *J* 6.9, C(25)H_3 and C(41)H_3), 1.1–1.6 (56H, m, C(11)H_2 to C(24)H_2 and C(27)H_2 to C(40)H_2), 1.32 (3H, t, *J* 7.1, C$H_3$$CH_2$O), 2.06–2.15 (2H, m, C(10)H_2), 2.34–2.45 (1H, m, one of C(26)H_2), 3.04–3.08 (1H, m, one of C(26)H_2), 3.17 (1H, dd, *J* 7.9, 6.2, C(1)*H*), 3.32 (1H, dd, *J* 7.9, 6.0, C(6)*H*), 3.44 (1H, d, *J* 6.2, C(2)*H*), 3.48 (3H, s, C(42)O_2CH_3), 3.65 (1H, dd, *J* 6.0, 2.2, C(5)*H*), 3.82 (3H, s, C(44)O_2CH_3), 4.25 (2H, m, CH_3CH_2O), 5.76 (1H, ~d, *J* 2.2, C(4)*H*); δ_C(62.8 MHz; $CDCl_3$) 14.1 (*C*(25)H_3, *C*(41)H_3 and *C*$H_3$$CH_2$O, all overlapping), 22.7, 27.2, 27.8, 29.2, 29.3, 29.4, 29.5, 29.7, 29.8, 30.2, 31.9 and 36.9 (*C*(10)H_2 to *C*(24)H_2 and *C*(26)H_2 to *C*(40)H_2 many overlapping), 41.9 (*C*(5)H), 42.9 (*C*(1)H), 45.8 (*C*(6)H), 46.7 (*C*(2)H), 51.9 (C(42)$O_2C$$H_3$ and C(44)$O_2C$$H_3$, overlapping), 61.5 ($CH_3$*C*$H_2$O), 123.3 (*C*(4)H), 132.8 and 136.8 (*C*(3) and *C*(6)), 163.7, 170.7 and 173.8 (*C*(42)$O_2$$CH_3$, *C*(44)$O_2$$CH_3$ and *C*(43)$O_2$$CH_2CH_3$), 183.0 (*C*(9)), 202.2 (*C*(7)=O); *m*/*z* (CI) 772 (MH^+, 100%), 724 (30), 679 (45), 97 (15) (Found 771.6184. $C_{48}H_{83}O_7$ requires 771.6139).

(±)-Manzamenone F (31)

A mixture of manzamenone A (50 mg, 0.067 mmol), *n*-butanol (71 mg, 1.01 mmol), dicyclohexylcarbodiimide (250 mg, 1.2 mmol) and DMAP (82 mg, 0.67 mmol) in DCM (8 mL) was stirred under an atmosphere of nitrogen at 0 °C for four hours. The reaction mixture was then washed sequentially with water (2 × 7 mL) and a 5% aqueous solution of acetic acid (2 × 7 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2; petrol ether (bp 40–60 °C)–ethyl acetate, 5 : 1) gave manzamenone F as a colourless oil (31 mg, 57%). ν_{max} (film)/cm^{-1} 1732 (br s, C=O); δ_H(250 MHz; $CDCl_3$) 0.87 (6H, t, *J* 6.6, C(25)H_3 and C(41)H_3), 0.95 (3H, t, *J* 5.0, C(4′)H_3), 1.25–1.36 (56H, m, C(11)H_2 to C(24)H_2 and C(27)H_2 to C(40)H_2), 1.37–1.46 (2H, m, C(3′)H_2), 1.62–1.7 (2H, m, C(2′)H_2), 2.09–2.17 (2H, m, C(10)H_2), 2.33–2.45 (1H, m, one of C(26)H_2), 3.07–3.12 (1H, m, one of C(26)H_2), 3.17 (1H, dd, *J* 7.9, 6.1, C(1)*H*), 3.32 (1H, dd, *J* 7.9, 6.1, C(6)*H*), 3.44 (1H, d, *J* 6.1, C(2)*H*), 3.47 (3H, s, C(42)O_2CH_3), 3.65 (1H, dd, *J* 6.1, 2.5, C(5)*H*), 3.81 (3H, s, C(44)O_2CH_3), 4.19 (2H, m, C(1′)H_2), 5.75 (1H, ~d, *J* 2.5, C(4)*H*); δ_C(62.8 MHz; $CDCl_3$) 14.1 and 14.5 (*C*(25)H_3, *C*(41)H_3 and *C*(4′)H_3, two overlapping), 19.5, 23.1, 27.6, 28.1, 29.6, 29.8, 29.9, 30.07, 30.1, 30.6, 31.0, 32.3, 37.3 (*C*(2′)H_2, *C*(3′)H_2, *C*(10)H_2 to *C*(24)H_2 and *C*(26)H_2 to *C*(40)H_2 many overlapping), 42.3 (*C*(5)H), 43.3 (*C*(1)H), 46.2 (*C*(6)H), 47.1 (*C*(2)H), 52.3 (C(42)$O_2C$$H_3$ and C(44)$O_2C$$H_3$, overlapping), 65.9 (*C*(1′)H_2), 123.7 (*C*(4)H), 133.2 and 137.1 (*C*(3) and *C*(8)), 164.0, 171.1 and 174.3 (*C*(42)$O_2$$CH_3$, *C*(44)$O_2$$CH_3$ and *C*(43)$O_2$$CH_2CH_3$), 183.3 (*C*(9)), 202.6 (*C*(7)=O); *m*/*z* (CI) 800 (MH^+, 25%), 742 (95), 639 (100), 514 (27), 414 (40) (Found 799.6466. $C_{50}H_{87}O_7$ requires 799.6453).

Tetradeuterated analogue of (±)-43-*O*-methylmanzamenone A (36a)

A mixture of untenone A (50.0 mg, 0.132 mmol) in CD_3OD (0.10 mL) was warmed at 40 °C for 24 h and the residual solvent was then removed *in vacuo*. Purification of the residue by flash column chromatography (SiO_2; petrol ether (bp 40–60 °C)–ethyl acetate, 15 : 1) gave the tetradeuterated compound **36a** as a colourless solid which was contaminated with a very small quantity of an unknown by-product (25.0 mg, 50%). Clean material was obtained by further purification by reversed phase HPLC [Rainin Dynamax C18 (21.4 × 250 mm); eluent: MeOH; detection: UV at 254 nm]. Mp 67–68 °C ν_{max} (film)/cm^{-1} 1737 (br s, C=O); δ_H(400 MHz; $CDCl_3$) 0.88 (6H, t, *J* 6.8, C(25)H_3 and C(41)H_3), 1.16–1.70 (56H, m, C(11)H_2 to C(24)H_2 and C(27)H_2 to C(40)H_2), 2.08–2.18 (2H, m, C(10)H_2), 2.38–2.46 (1H, m, one of C(26)H_2), 3.04–3.12 (1H, m, one of C(26)H_2), 3.17 (1H, d, *J* 8.0, C(1)*H*), 3.32 (1H, dd, *J* 8.0, 6.0, C(6)*H*), 3.49 (3H, s, C(42)O_2CH_3), 3.68 (1H, dd, *J* 6.0, 2.2, C(5)*H*), 3.83 (3H, s, C(44)O_2CH_3), 5.78 (1H, d, *J* 2.2, C(4)*H*); δ_C(75.4 MHz; $CDCl_3$) 14.12 (*C*(25)H_3 and *C*(41)H_3, overlapping), 22.69, 27.21, 27.72, 29.20, 29.31, 29.36, 29.44, 29.49, 29.58, 29.66, 29.70, 29.79, 30.17, 31.93 and 36.85 (30 × *C*H_2, many overlapping), 41.65, 42.80 and 45.87 (*C*(1)H, *C*(5)H and *C*(6)H), 51.83 and 51.89 (C(42)O_2CH$_3$ and C(44)O_2CH$_3$), 123.06 (*C*(4)H), 132.83 and 136.73 (*C*(3) and *C*(8)), 163.60, 170.69 and 174.30 (*C*(42)O_2CH$_3$, *C*(43)O_2CD$_3$ and *C*(44)O_2CH$_3$), 182.87 (*C*(9)), 202.14 (*C*(7)=O); *m*/*z* (EI) 760 (M^+, 3%), 725 (16), 670 (33), 225 (98), 49 (100) (Found 760.6150. $C_{47}H_{76}D_4O_7$ requires 760.6155).

X-Ray crystallographic analysis of 29b and 29d †

Crystal data. 29b, $C_{18}H_{22}O_7$, *M* = 350.36, monoclinic, spacegroup $P2_1/a$, *Z* = 4, *a* = 11.628(13), *b* = 11.418(12), *c* = 14.112(15) Å, *β* = 101.40(1)°, *U* = 1837 Å^3, d_{calc} = 1.267 g cm^{-3}

29d, $C_{26}H_{38}O_7$, *M* = 462.56, monoclinic, spacegroup $P2_1/c$, *Z* = 4, *a* = 12.691(14), *b* = 17.33(2), *c* = 12.358(14) Å, *β* = 93.44(1)°, *U* = 2713 Å^3, d_{calc} = 1.133 g cm^{-3}.

Intensity data were collected with Mo-Kα radiation using the MARresearch Image Plate System. The crystals were positioned at 70 mm from the Image Plate. 100 frames were measured at 2° intervals with a counting time of 2 min to give 7670, 9632 reflections respectively of which 3401, 5307 were independent (*R*int = 0.0848, 0.0664). Data analysis was carried out with the XDS program.[22] The structures were solved using direct methods with the Shelx86 program.[23] In **29d**, one of the alkyl chains is disordered over two positions each refined with 50% occupancy. Apart from these disordered atoms, all non-hydrogen atoms in both structures were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structures were refined on F^2 using Shelxl.[24] The final *R* values were *R*1 0.0897, 0.1132, and *wR*2 0.2198, 0.3133 for 1208, 2079, data with $I > 2\sigma(I)$.

† CCDC reference number(s) 175318 and 158875. See http://www.rsc.org/suppdata/p1/b1/b110829h/ for crystallographic files in .cif or other electronic format.

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