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Predisposition in synthesis: efficient routes to (±)-untenone A and (±)-manzamenones A, C and F

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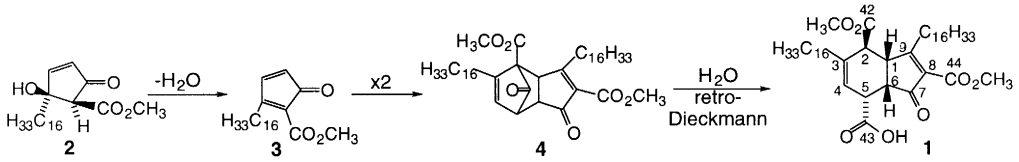
Abstract

Short syntheses of (±)-untenone A, (±)-manzamenones A, C and F from 2-furanacetonitrile are described using an approach modelled on a likely biogenetic pathway. © 2000 Elsevier Science Ltd. All rights reserved.

The isolation of the protein kinase C inhibitor manzamenone A **1** from a *Plakortis* sponge was reported in 1992.[1] This compound is the most abundant member of a growing family of naturally occurring dimeric fatty acid derivatives isolated from this source, all of which have the common structural feature of two fully saturated 16-carbon alkyl chains.[2,3] Recently we proposed a plausible biogenetic pathway for the formation of **1** which commences with the β-hydroxycyclopentenone, untenone A **2**(Scheme 1).[4,5]



Scheme 1.

According to our proposal, dehydration of untenone A gives the reactive cyclopentadienone **3** which dimerises to give cyclo-adduct **4**. Subsequent nucleophilic attack by water at the bridging carbonyl followed by retro-Dieckmann ring-opening of the strained five-membered ring generates the bicyclo[4.3.0] ring system present in manzamenone A and which is common to the majority of the manzamenones.

In our original publication,[5] we described the preparation of the ethyl analogue of untenone A **5** and its conversion into manzamenone analogue **6**, the structure of which was confirmed by X-ray crystallographic analysis (Scheme 2). In this communication, we report the successful preparations of (±)-untenone A, and (±)-manzamenones A, C and F from 2-furanacetonitrile **7** using an approach modelled on what we believe to be a 'predisposed' biosynthetic pathway.

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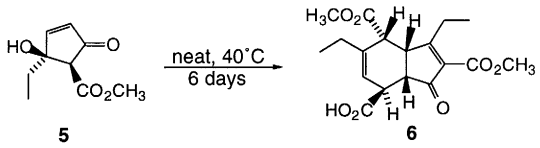
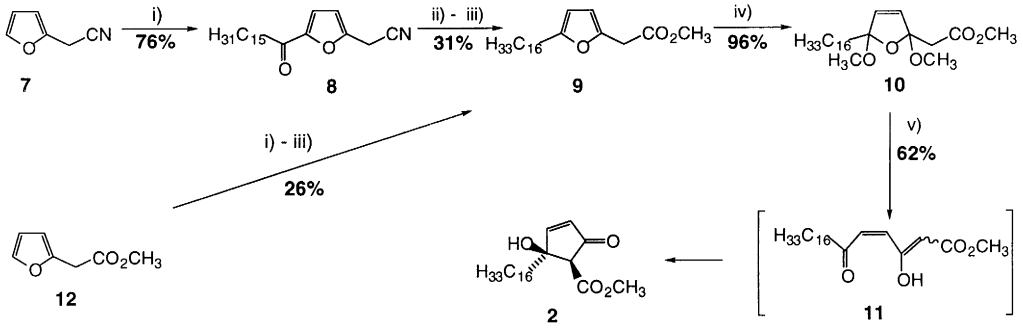


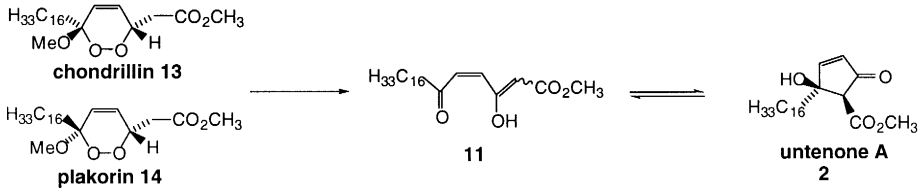
Scheme 2.

(±)-Untenone A **2** was prepared using a similar procedure to that developed for the synthesis of the ethyl analogue **5** (Scheme 3).



Scheme 3. Reagents: (i) $C_{15}H_{31}COCl$, $SnCl_4$, CH_2Cl_2, −5°C, 1 h (ii) H_2NNH_2, NaOH, $HOCH_2CH_2OH$, Δ, 4 h (iii) $TMSCHN_2$, MeOH, rt, 30 min (iv) Br_2, MeOH, rt, 2 h (v) 0.05M H_2SO_4, dioxan, rt, 1 h then 1.0 M $NaHCO_3$, rt, 0.5 h

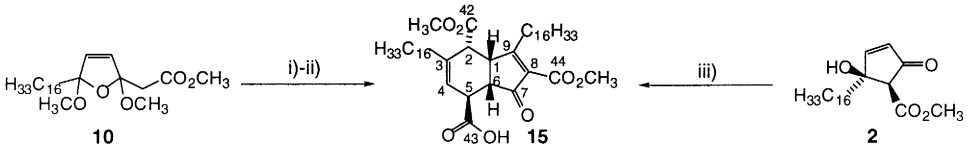
Methyl ester **9** was prepared from 2-furanacetonitrile **7** in 24% overall yield. A problematic transformation in the three step sequence was the Wolff–Kishner reduction of ketone **8** which was accomplished in quite variable yields. An analogous three step transformation of methyl 2-furylacetate **12** provided ester **9** in a slightly improved yield of 26%. Oxidation of the furan ring of **9** with bromine in methanol gave bis-acetal **10** as a 1:1 mixture of diastereoisomers. Careful acidic hydrolysis of **10** in aqueous dioxan followed by base treatment at rt for 0.5h resulted in 'aldol-type' cyclisation to give a single diastereoisomer, the spectroscopic data for which were identical to the literature data for naturally occurring (±)-untenone A **2**.[4] Analysis by ^1H NMR ($CDCl_3$) of the crude product arising from acid hydrolysis of bis acetal **10** indicated the presence of the enol tautomer **11**. This compound is of interest as a likely biosynthetic intermediate linking untenone A **2** and the cyclic peroxy ketals chondrillin **13**[6] and plakorin **14**[7] which have previously been isolated from *Plakortis* sponges (Scheme 4).



Scheme 4.

During a repeat of the synthetic sequence to prepare greater quantities of **2**, we were disappointed to find that hydrolysis of bis-acetal **10** at slightly elevated temperature (30°C) followed by treatment of the crude product with $NaHCO_3$ in aqueous dioxan at 30°C for an extended reaction time (6 h) furnished only trace amounts of untenone A. Purification by flash chromatography however, allowed isolation of a principal product **15** in 26% yield**.** This compound could also be prepared in 48% yield by simply heating a neat sample of (±)-untenone A **2** to just above its melting point (~70°C) for 24 h. Extensive NOE measurements on the synthetic material **15** were inconclusive and all attempts to obtain crystals

suitable for X-ray crystallographic analysis were unsuccessful. The near identity of the ^{1}H NMR data for compound **15** and the ethyl analogue **6**, however, represents very clear evidence for the stereochemical assignment of **15** as depicted in Fig. 1 (i.e. H1, H2 and H6 all *cis*; H5 and H6 *trans*). Thus, compound **15** apparently possesses inverted stereochemistry at both C2 and C5 when compared to the proposed structure for manzamenone A **1**.[1]

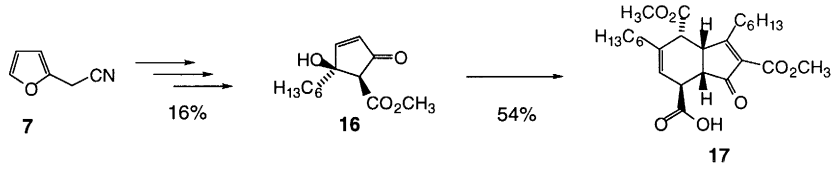


Reagents; i) 0.05M H_2SO_4, dioxan, 30°C, 24h ii) 1.0M $NaHCO_3$, dioxan, 30°C, 6h iii) Δ, 24h

	δ_H-value (ppm)					*J*-value (Hz)			
	H-1	**H-2**	**H-4**	**H-5**	**H-6**	$J_{1,2}$	$J_{4,5}$	$J_{5,6}$	$J_{6,1}$
(**15**)	3.2	3.5	6.16	3.63	2.96	6.0	2.1	8.3	7.9
(**6**)	3.24	3.52	6.15	3.62	2.99	5.9	2.2	8.4	7.8
(**1**)	3.2	3.5	6.16	3.62	2.95	6.0	2.1	8.6	7.9
(**17**)	3.2	3.51	6.14	3.64	2.98	5.9	2.2	8.1	7.8

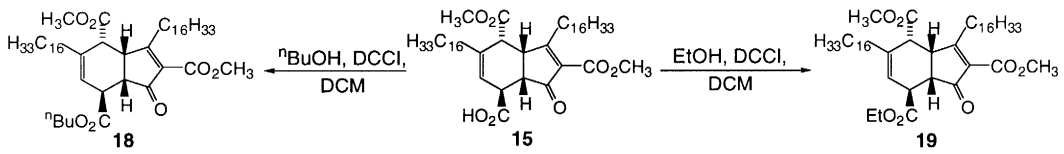
Fig. 1.

Examination of the information presented in Fig. 1 reveals that the ^{1}H NMR data for synthetic **15** is identical to that reported for naturally occurring manzamenone A.[1] Given the X-ray crystallographic data for **6** and given the available NMR evidence, it is our conclusion that the product of our synthetic sequence is manzamenone A and that the stereostructure **1** previously proposed for the natural product should therefore be revised to that depicted for **15**. This conclusion is further supported by the finding that the hexyl analogue **17** prepared using a similar reaction sequence, possesses the same relative stereostructure as the ethyl analogue **6** as confirmed by X-ray crystallographic analysis (Scheme 5). The ^{1}H NMR data for **17** is also almost identical to the corresponding data for manzamenone A (Fig. 1).



Scheme 5.

The reasonable yield of the transformation of **2** to **15** has allowed the preparation of sufficient quantities of **15** to permit further synthetic transformations to be carried out. Thus, treatment of **15** with ^{n}BuOH and DCCI in dichloromethane gave butyl ester **18** in 56% yield and, in a similar fashion, ethyl ester **19** was prepared in 41% yield from **15** (Scheme 6). The spectroscopic data for the synthetic samples of **18** and **19** were identical to the literature data for naturally occurring manzamenones F and C respectively which is in accord with a reassignment of the stereostructures of these natural products consistent with the revised structure of manzamenone A (i.e. manzamenone F=**18**, manzamenone C=**19**).



Scheme 6.

In summary, we have successfully synthesised (±)-untenone A **2** and (±)-manzamenones A, F and C from 2-furanacetonitrile **7**. Of particular interest is the 'two-pot' transformation of bis acetal **10** to **15** which involves a 5-step sequence of reactions (acetal hydrolysis, aldol cyclisation, dehydration, dimerisation and retro-Dieckmann reaction) and which took place with an overall yield of 26%.

Acknowledgements

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