



Pre-Disposition in Synthesis: An Approach to the Manzamenones

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Abstract: An efficient six step synthesis of the manzamenone analogue **17** from 2-furanacetonitrile is described using an approach modelled on a biogenetic theory. © 1998 Elsevier Science Ltd. All rights reserved.

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 Okinawan sponges of the genus *Plakortis*.¹ All six members of the family of natural products described in the original publication, possessed a bicyclo[4.3.0]nonane skeleton which occurs relatively rarely in natural products (Fig. 1). More recently, several other manzamenones have been isolated which bear close structural similarity to compounds **1-6**.^{2,3}

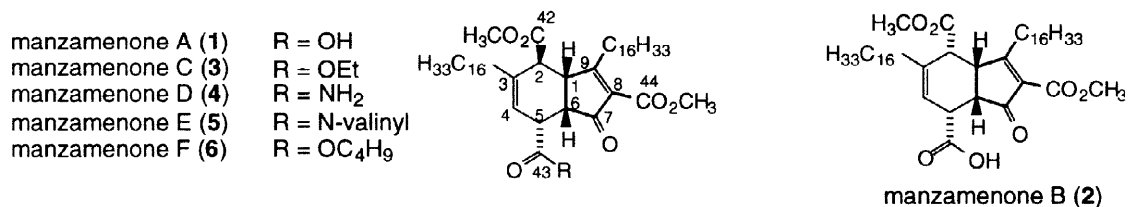
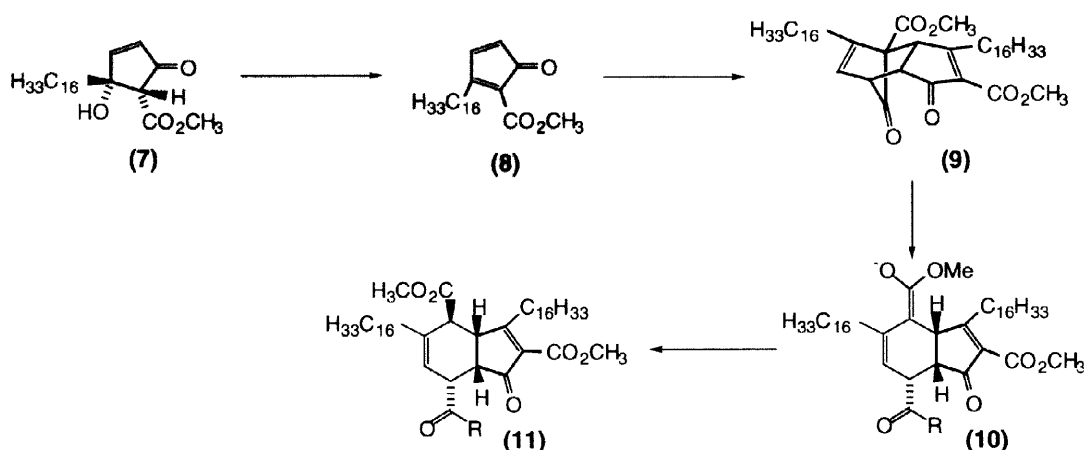


Fig. 1

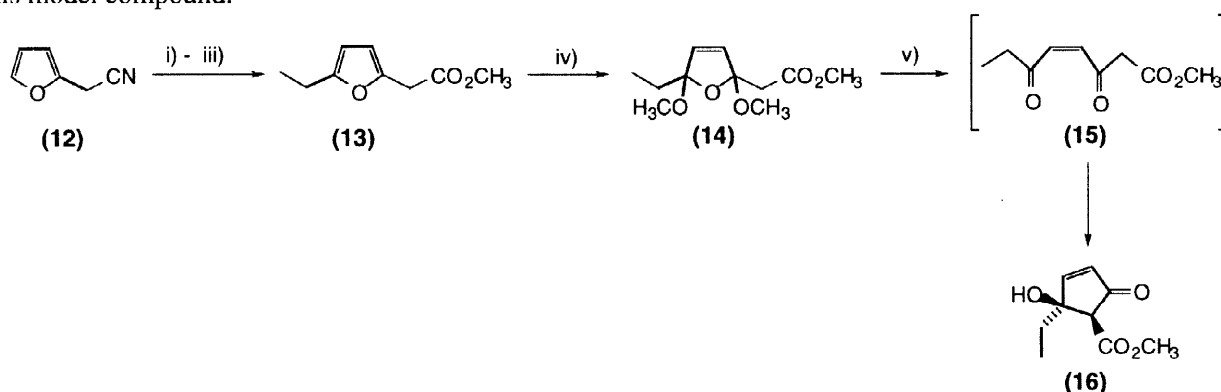
One of the principal goals of our current research is the exploitation of pre-disposed chemical reactions in the total synthesis of natural products and in this regard, we were attracted by the synthetic challenge posed by the manzamenones. It occurred to us that the manzamenones may arise from a biosynthetic pathway whereby a highly reactive cyclopentadienone (**8**) initially dimerises to give a bridged tricyclic adduct. Subsequent nucleophilic attack at the bridging carbonyl of the *exo* cycloadduct (**9**) followed by retro-Dieckmann ring-opening of the strained five-membered ring then leads to the conjugated enolate (**10**). Selective protonation of (**10**) on the α -face provides access to the functionalised bicyclo[4.3.0]nonane skeleton common to the majority of the manzamenones (Scheme 1). Diastereoisomeric compounds such as manzamenone B may arise from protonation of enolate (**10**) on the β -face or may be products of subsequent equilibration. The potent antileukemic cyclopentenone, untenone A (**7**) which is a naturally occurring racemate also isolated from a *Plakortis* sponge⁴ can be viewed as a "protected form" of the cyclopentadienone (**8**).



Scheme 1

While the involvement of enzyme catalysts, favouring *exo*-cycloaddition and/or controlling protonation of the intermediate enolate, cannot be ruled out, it nevertheless appeared plausible to us that the core bicyclic structure of the manzamenones is a direct consequence of the inherent reactivity of cyclopentadienone (**8**) and, subsequently, of its dimeric counterpart (**9**). It was therefore our intention to attempt the synthesis of the manzamenones using an approach modelled on our biogenetic theory, hopefully deriving significant benefits by designing and executing a total synthesis using the principles of pre-disposed chemistry.

In the first instance, a short, high yielding synthesis of β -hydroxy- β -alkyl cyclopent-2-enones was required suitable for large scale work and which could be readily applied to the preparation of analogues of untenone A. We wish to report here the development and partial optimisation of a synthesis of the ethyl analogue of untenone A (**16**) and furthermore, the outcome of initial investigations into the chemical reactivity of this model compound.



Reagents; i) CH_3COCl , SnCl_4 , CH_2Cl_2 , -5°C , 1h, 71% ii) H_2NNH_2 , NaOH , $\text{HOCH}_2\text{CH}_2\text{OH}$, Δ , 4h, 69% iii) TMSCHN_2 , MeOH , RT, 30min, 71% iv) Br_2 , MeOH , -5°C to RT, 2h, 93% v) 0.005M H_2SO_4 , RT, 30min then 1.0M NaHCO_3 , 89%

Scheme 2

2-Furanacetonitrile (**12**) was prepared according to the procedure of Plucker and Amstutz⁵ which employs 2-furaldehyde as starting material and is ideally suited to large scale work. Following a slight modification of a procedure reported by Finch and co-workers,⁶ Friedel-Crafts acylation of (**12**) with acetyl chloride and SnCl_4 followed by ketone reduction using the Huang-Minlon modification of the Wolff-Kishner conditions (and concomitant hydrolysis of the nitrile) gave 5-ethyl-2-furanacetic acid. Esterification using the "safe" diazomethane equivalent, $\text{Me}_3\text{SiCHN}_2$ ⁷ gave ester (**13**) which was oxidised with one equivalent of bromine in

MeOH to give bis-acetal (**14**) as a mixture of diastereoisomers. Finally, exposure of (**14**) to mildly acidic conditions followed by brief base treatment furnished the untenone A analogue (**16**) in excellent yield and almost exclusively as a single diastereoisomer (Scheme 2). This final transformation presumably proceeds *via* the intermediate 1,4-dicarbonyl compound (**15**) and thus bears clear similarities to the proposed biosynthetic pathway leading to untenone A.

Findings from our initial experiments into the reactivity of (**16**), were extremely encouraging. Heating a neat liquid sample of the cyclopentenone at 40°C for 6 days resulted in complete conversion of (**16**) to a single new product (**17**), which was a solid at room temperature. 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.⁸ Unfortunately, unambiguous assignment of the relative stereochemistry of (**17**) was not feasible by NMR analysis, including extensive nOe measurements. However, X-ray crystallographic analysis confirmed our structural assignment with the relative stereochemistry of substituents as shown below (Fig. 2);⁹ i.e. identical to the relative stereochemistry of substituents proposed for 5-*epi*-43-*O*-methylmanzamenone B (**18**).³

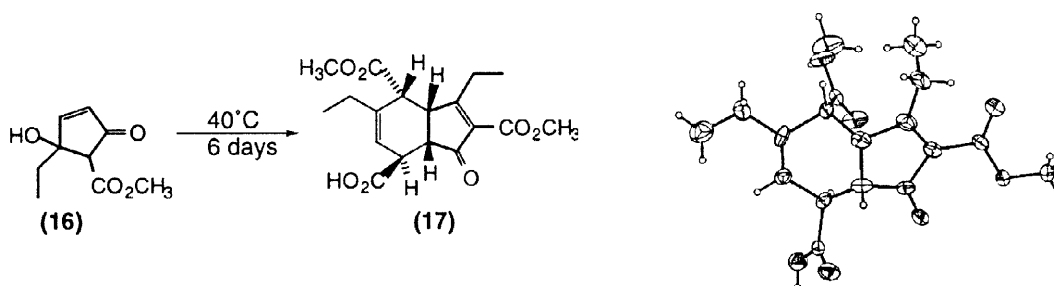
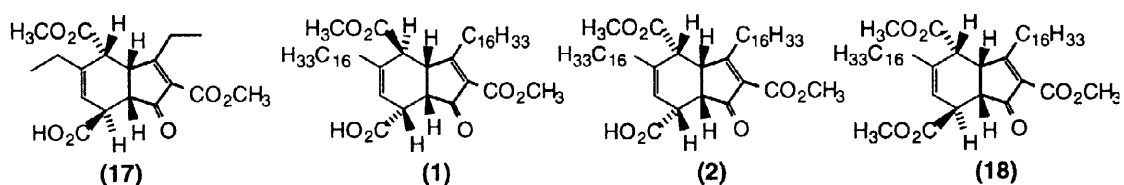


Fig. 2

Although the stereochemical assignment of (**17**) was initially disappointing, it is interesting to compare the ¹H NMR data for compound (**17**) with the corresponding data for the diastereoisomers, manzamenones A (**1**), B (**2**) and 5-*epi*-43-*O*-methylmanzamenone B (**18**). Such a comparison indicates a clear correlation between our data and those for manzamenone A (**1**).



Compound	δ-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}
(17)	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
(2)	3.88	3.24	6.11	3.41	3.46	0.5	2.1	5.0	7.1
(18)	4.00	3.16	5.71	3.76	3.25	0	8.1	1.3	7.5

Fig. 3

Further work is currently underway to investigate this latter point in more detail, to identify intermediates in the dimerisation reaction and to apply the knowledge gained from this short model synthesis to the preparation of the manzamenones themselves.

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8. Selected spectroscopic data for compound (**17**); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1733, 1695, 1661, 1623; δ_{H} (400MHz; CDCl_3) 1.11 (3H, t, J 7.3Hz, C(11)H₃), 1.23 (3H, t, J 7Hz, C(13)H₃), 2.22-2.30 (2H, m, C(10)H₂), 2.51-2.57 (1H, m, one of C(12)H₂), 2.99 (1H, dd, J 7.8 and 8.4Hz, C(6)H), 3.10-3.15 (1H, m, one of C(12)H₂), 3.24 (1H, dd, J 7.8 and 5.9Hz, C(1)H), 3.52 (1H, d, J 5.9Hz, C(2)H), 3.55 (3H, s, C(14)O₂CH₃), 3.62 (1H, ddt, J 8.4, 2.2 and 2.6Hz, C(5)H), 3.88 (3H, s, C(16)O₂CH₃), 6.15 (1H, ~dt, J 2.2 and 1.7Hz, C(4)H); δ_{C} (100.6MHz; CDCl_3) 11.63 (C11), 12.05 (C13), 24.03 (C12), 29.63 (C10), 41.15 (C5), 44.11 (C1), 45.76 (C2), 46.74 (C6), 52.19 (overlapping, 2 x OCH₃), 122.22 (C4), 132.13 (C8), 138.59 (C3), 162.65 (C16), 170.17 (C14), 172.93 (C15), 188.97 (C9), 207.51 (C7); m/z (CI) 351.1438 (MH⁺. C₁₈H₂₃O₇ requires 351.1444), 305 (90%), 273 (70), 247 (100), 217 (29), 187 (22), 128 (21).
9. Crystal Data, (**17**), C₁₈H₂₂O₇, M=350.36, monoclinic, spacegroup P2₁/a, a=11.628(13), b=11.417(12), c=14.112(15)Å, β =101.40(1)°, U = 1837Å³, Z=4, dc=1.267Mgm⁻³, F(000)=744. 3401 independent reflections were collected on a MARresearch Image Plate. The structure was determined by direct methods and refined on F² to an R of 0.089. Coordinates have been deposited at the Cambridge Crystallographic Data Centre.