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A synthetic approach to the plakoridines modeled on a biogenetic theory

Laura L. Etchells, Ali Sardarian† and Roger C. Whitehead*

The School of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK

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Abstract—An expedient synthetic route to the fully substituted pyrrolidine ring system of the plakoridines is described using an approach modeled on a plausible biosynthetic pathway.

1. Introduction

Plakoridines A and B (**1** and **2**) are two unusual, heterocyclic natural products which were isolated during the last decade from Okinawan marine sponges of the genus *Plakortis*.[1,2] These novel compounds have unprecedented structures which contain a tyramine unit and a fully substituted pyrrolidine ring system (Fig. 1). An elegant, 14-step asymmetric synthesis of (−)-plakoridine A has been reported by Ma and Sun[3] and this indicated that the natural products are essentially racemic (natural **1**: $[\alpha]_D^{20}$ −0.4 (*c* 0.5, $CHCl_3$); (−)-**1**: $[\alpha]_D^{22}$ −43.0 (*c* 0.5, $CHCl_3$)). Initial studies have shown that plakoridine A (**1**) is cytotoxic towards murine lymphoma L1210 cells.

Compounds **1** and **2** are members of a biogenetically related group of natural products comprising the manzamenones (e.g., **3** and **4**),[2,4,5] untenone A (**5**),[6] the plakorsins (e.g., **6**)[7] and the cyclic peroxyketals, chondrillin (**7**)[8] and plakorin (**8**) (Fig. 2).[9]

A possible biosynthetic link between untenone A (**5**) and manzamenone A (**3**) was put forward by ourselves a few years ago and proceeds via dehydrative dimerisation of **5** to give a bridged tricyclic intermediate **10** which undergoes retro-Dieckmann ring opening, mediated by a molecule of water, to give **3** (Scheme 1).[10] Untenone A (**5**) can be envisaged as the product of aldol-cyclisation of (*Z*)-methyl-3,6-dioxo-4-docosenoate (**9**). A synthesis of **3** using an approach modeled on this theory provides support for the plausibility of the proposal.[10c,d]

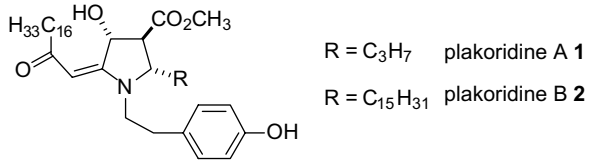

Figure 1.

Kobayashi and co-workers noted a structural motif present in the plakoridines which could be derived from **9** and we now propose a plausible biosynthetic pathway which may link the tri-carbonyl compound **9**, or its diastereoisomer **11** to **1** and **2** (Scheme 2). Thus, for plakoridine A (**1**), Mannich reaction between **9**/**11** and the imine **12**, derived formally from condensation of tyramine with butyraldehyde, gives β-amino ester **13**. Subsequent intramolecular conjugate addition results in 5-*exo*-trig ring closure to give the heterocycle **14**. Finally, internal redox, via a series of prototropic shifts somewhat akin to those which occur during the Amadori rearrangement, results in generation of the thermodynamically stable vinylogous amide moiety present in **1**.

The challenging multi-component nature of the cascade sequence of reactions leading to the plakoridines prompted us to investigate the synthesis of these compounds, as well as unnatural analogues, using an approach modeled on the biogenetic theory. We report herein the results of our initial studies in this area.

Keywords: Biomimetic; Cascade; Natural product; Fatty acid.
* Corresponding author. Tel.: +44 161 275 7856; fax: +44 161 275 4939; e-mail: roger.whitehead@man.ac.uk
† Present address: The Department of Chemistry, The College of Sciences, The University of Shiraz, Shiraz 71454, Iran.

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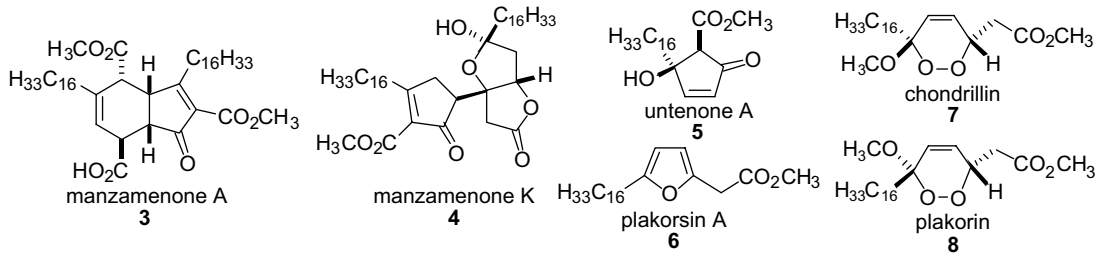
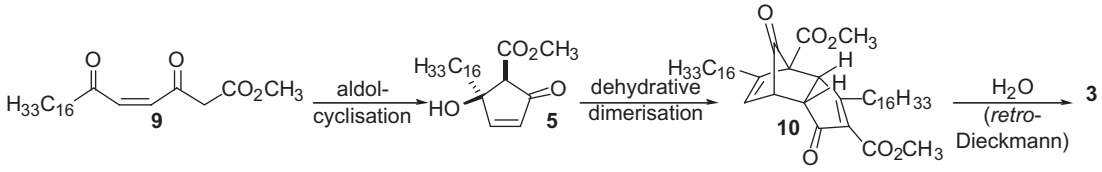
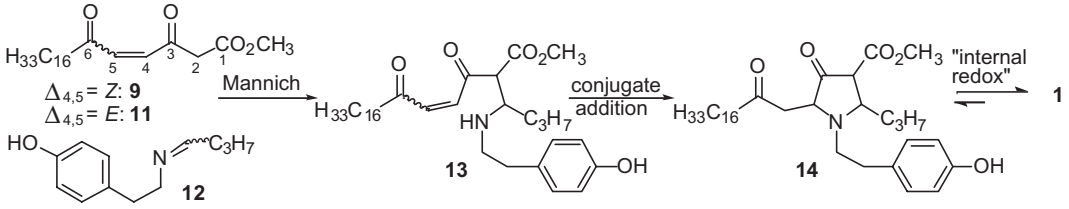


Figure 2.



Scheme 1.



Scheme 2.

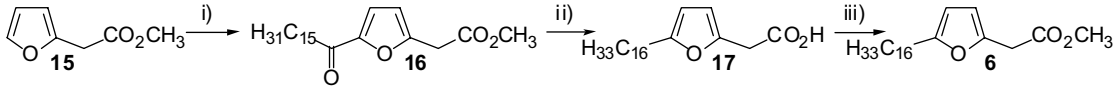
2. Results and discussion

The furan fatty acid derivative plakorsin A (**6**) was envisaged to be a key intermediate in the synthetic approach to the plakoridines. As described previously, this compound can be prepared in three synthetic operations from the methyl ester of 2-furan acetic acid (**15**) (Scheme 3).[10b] Thus, Friedel–Crafts acylation of **15** gave ketone **16** and subsequent reduction of the ketone carbonyl, using the Huang–Minlon modification of the Wolff–Kishner conditions,[11] gave 5-hexadecyl-furan-2-yl-acetic acid (plakorsin B, **17**) in moderate yield. Esterification of the free carboxyl group of **17**, which is liberated under the basic reduction conditions, was then accomplished using either trimethylsilyldiazomethane, or methanol in the presence of an acid catalyst, to give **6**.

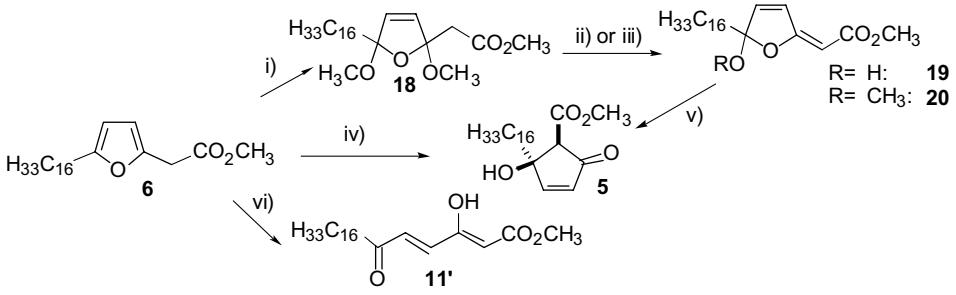
We considered that the putative biosynthetic precursors to the plakoridines, (*Z*)- and (*E*)-enediones **9** and **11**, might be synthesised by oxidative cleavage of the furan ring of **6** and we therefore carried out an extensive investigation into the outcome of the exposure of **6** to a variety of oxidation conditions (Scheme 4).

Treatment of **6** with bromine in methanol gave the bis-acetal **18** in excellent yield and as a mixture of diastereoisomers.[12] This compound, a protected form of (*Z*)-methyl-3,6-dioxo-4-docosenoate (**9**), was then hydrolysed under mildly acidic conditions to give **19**,[13] a cyclic hemi-ketal tautomer of **9**. Confirmation of the structural identity of **19** was possible by comparison of its spectroscopic data with those of ketal **20** which was prepared in unambiguous fashion by base-mediated elimination of methanol from **18**. Oxidation of **6** using *m*CPBA[14] at low temperature followed by a mildly basic aqueous work-up furnished untenone A (**5**) as the major product. This transformation presumably proceeds via the intermediate formation of (*Z*)-enedione **9**, or a tautomer thereof, and accordingly, exposure of hemi-ketal **19** to mildly basic conditions also led to the formation of untenone A (**5**) in good yield.

The propensity with which the tautomer **19** of (*Z*)-enedione **9** underwent conversion to untenone A prompted us to conclude that the diastereoisomeric enedione **11** would be a more appropriate substrate in our synthetic approach to the plakoridines. The commonly used



Scheme 3. Reagents and conditions: (i) $C_{15}H_{31}COCl$, $SnCl_4$, CH_2Cl_2, −5 °C, 1 h, 98%; (ii) H_2NNH_2, NaOH, $HOCH_2CH_2OH$, Δ, 72 h, 60%; (iii) $TMSCHN_2$, CH_3OH, toluene, rt, 1 h, 72% or CH_3OH, Amberlite® IR 120 (H), Δ, 72 h, 69%.



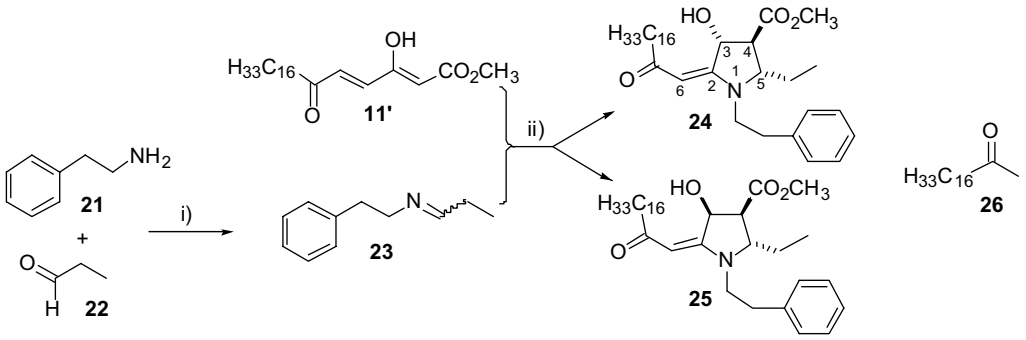
Scheme 4. Reagents and conditions: (i) Br_2, CH_3OH, Na_2CO_3, rt, 2 h, 84%; (ii) 0.005 M H_2SO_4, H_2O, dioxane, rt, 1.5 h; (iii) KHMDS, THF, −78 °C to rt, 79%; (iv) *m*CPBA, CH_2Cl_2, −10 °C to rt, 2 h then work-up with $NaHCO_{3(aq)}$, 56%; (v) $NaHCO_3$, H_2O, dioxane, rt, 74% from **18**; (vi) Br_2, acetone, H_2O, −20 °C to 10 °C, 6 h, 56% (75% based on recovered **6**).

procedure for the conversion of furan derivatives to the corresponding (*E*)-enediones is that developed by Piancatelli and co-workers which employs PCC as the oxidant.[15] Exposure of **6** to this reagent gave the enol tautomer **11′** of (*E*)-enedione **11**, in variable and often disappointing yields. After much experimentation however, a satisfactory procedure for the preparation of **11′** was developed based on the work of Jurczak and Pikul.[16] Thus, under carefully controlled conditions, a solution of **6** in a mixture of acetone and water (5:1) was treated with 1 equiv of bromine at −20 °C. After stirring for 3 h, the temperature was allowed to rise to −10 °C and after a further 3 h, the reaction was quenched before purification by flash chromatography furnished **11′** in 56% isolated yield (or 75% yield based on recovered **6**). If the reaction mixture was allowed to warm to room temperature or excess bromine was added, competitive bromination of the product resulted in an erosion of the isolated yield of **11′**.

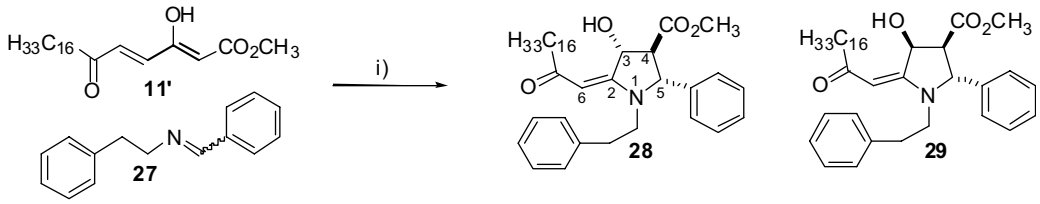
With enol **11′** in hand, we were in a position to investigate the cascade reaction sequence leading to the plakoridines. The ultimate aim of our investigations was to develop a procedure suitable for the preparation of a range of unnatural analogues of **1/2** and, in the first instance therefore, we elected to prepare an imine which differed slightly from the one implicated in the biosynthesis of the natural products.

Imine **23**, contaminated with ~15% of phenethylamine (**21**), was prepared in straightforward fashion according to the procedure of Tashiro and co-workers (Scheme 5).[17] Pleasingly, prolonged storage at rt of a solution of **23** and enol **11′** in $CDCl_3$ resulted in substantial conversion to two plakoridine-type structures. Purification by chromatography allowed isolation of clean samples of both compounds.[18,19] The structural assignment of the major isomer **24** was supported by the near identity of its ^1H NMR spectrum with that of **1** and, in particular, by the similar magnitude of the vicinal coupling constants between the ring hydrogens of the respective pyrrolidine cores ($J_{3,4} = J_{4,5} = 6.0$ Hz for **24**; $J_{3,4} = J_{4,5} = 5.5$ Hz for **1**).[3] A significant NOE observed from C(3)*H* to C(5)*H* was also consistent with a *syn* relative stereochemistry at these two centres in **24**. The structure of the minor isomer **25** was tentatively assigned by virtue of two pieces of evidence: an increased vicinal coupling constant between C(3)*H* and C(4)*H* ($J_{3,4} = 8.5$ Hz) and the absence of an observable NOE from C(3)*H* to C(5)*H*. Interestingly, extended storage at rt of a sample of **25** in $CDCl_3$ resulted in gradual isomerisation to give **24** (ratio of **25**:**24**;1:1.5 after 55 d) which indicates that the relative stereochemistry of the natural plakoridines may be under thermodynamic control. A third non-polar product was also isolated from this reaction, hexadecyl methyl ketone (**26**). Although a definitive mechanistic rationale for the origin of this compound is not apparent, it is plausible that **26** may derive from a retro-Mannich reaction of an initial cyclised intermediate of type **14** (Scheme 2).

In order to probe the scope of the biomimetic cascade sequence, we have also investigated the reaction of enol **11′** with an imine derived from an aromatic aldehyde.



Scheme 5. Reagents and conditions: (i) H_2O, rt, 3 h, 97%; (ii) $CDCl_3$, rt, 12 d, 38% for **24**, 4% for **25**, 15% for **26**.



Scheme 6. Reagents and conditions: (i) $CDCl_3$, rt, 10 d, 39%.

Thus imine **27**, contaminated with <5% phenethylamine (**21**), was exposed at rt to **11′** in $CDCl_3$ (Scheme 6). After 10 d, analysis by ^{1}H NMR indicated substantial formation of plakoridine analogue **28** and a small quantity of diastereoisomer **29**. Purification by flash chromatography did not allow separation of the isomers and provided **28** contaminated with <5% of **29**. The relative stereochemistry of **28** was assigned by analogy with that of **24** and by the similar magnitude of the vicinal coupling constant between C(3)*H* and C(4)*H* ($J_{3,4}$ = 6.4 Hz). The observation of a strong NOE between C(4)*H* and the *ortho* hydrogens of the aromatic substituent at C5 and a weak NOE between C(3)*H* and C(5)*H* are also in accord with the proposed structure.

In summary, we have prepared two unnatural analogues of the plakoridines in five linear steps from the methyl ester of 2-furan acetic acid (**15**), using an approach modeled on a plausible and apparently unprecedented biosynthetic pathway. Preliminary studies indicate that the relative stereochemistry of the natural products is under thermodynamic control. We consider that the yield of the key biomimetic transformation (~40%) is reasonable given the complexity of the cascade sequence. Investigations are now underway to further delineate the scope of the synthetic route and to investigate the factors controlling the efficiency of the final transformation.

Acknowledgements

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18. Spectroscopic data for compound **24**: ν_{max} (film)/cm^{-1} 3460w (O–H), 2923s and 2853s (C–H), 1740s (C=O), 1624m (C=O), 1534s; δ_H (500 MHz; $CDCl_3$) 0.81 and 0.82 (2 × 3H, 2 × t, *J* 7.0, C(23)H_3 and C(27)H_3), 1.13–1.28 (26H, m, C(10)H_2–C(22)H_2), 1.48–1.58 (3H, m, C(9)H_2 and one of C(26)H_2), 1.72–1.81 (1H, m, one of C(26)H_2), 2.25–2.35 (2H, m, C(8)H_2), 2.75 (1H, ddd, *J* 15.0, 9.5, 5.5, one of C(29)H_2), 2.84 (1H, ~t, *J* 6.0, C(4)*H*), 2.81–2.88 (1H, m, one of C(29)H_2), 3.25 (1H, ddd, *J* 15.0, 9.5, 6.5, one of C(28)H_2), 3.41 (1H, ddd, *J* 15.0, 9.0, 5.5, one of C(28)H_2), 3.64–3.67 (1H, m, C(5)*H*), 3.68 (3H, s, CO_2CH_3), 5.04 (1H, s, C(6)*H*), 5.14 (1H, d, *J* 5.5, C(3)*H*), 7.12 (2H, d, *J* 7.5, C(31/35)*H*), 7.19 (1H, t, *J* 7.5, C(33)*H*), 7.26 (2H, t, *J* 7.5, C(32/34)*H*); δ_C (100 MHz; $CDCl_3$) 8.33 and 14.10 (*C*(23)H_3 and *C*(27)H_3), 22.67, 25.44, 26.25, 29.34, 29.55, 29.68 and 31.91 (*C*(9)H_2–*C*(22)H_2 and *C*(26)H_2, many coincident), 32.01 (*C*(29)H_2), 43.49 (*C*(8)H_2), 45.84 (*C*(28)H_2), 51.56 (*C*(4)H), 52.50 (CO_2 *C*H_3), 66.04 (*C*(5)H), 75.72 (*C*(3)H), 90.28 (*C*(6)H), 126.91 (*C*(33)H), 128.58 and 128.81 (*C*(31/35)H and *C*(32/34)H), 137.94 (*C*(30)), 165.79 (*C*(2)), 172.73 (*C*O_2CH_3), 199.83 (*C*(7)=O); *m/z* (CI/NH_3) 542 (MH^+, 100%), 526 (15), 274 (40), 162 (32), 104 (40); (Found 542.4201: $C_{34}H_{56}NO_4$ (MH^+) requires 542.4204).

19. Spectroscopic data for compound **25**: ν_{max} (film)/cm^{-1} 3470w (O–H), 2923s and 2852s (C–H), 1742s (C=O), 1620m (C=O), 1531s; δ_H (500 MHz; $CDCl_3$) 0.79 (3H, t, *J* 7.5, C(23)H_3 or C(27)H_3), 0.81 (3H, t, *J* 7.0, C(23)H_3 or C(27)H_3), 1.16–1.24 (26H, m, C(10)H_2–C(22)H_2), 1.36–1.45 (1H, m, one of C(26)H_2), 1.47–1.55 (2H, m, C(9)H_2), 1.67–1.75 (1H, m, one of C(26)H_2), 2.25–2.30 (2H, m, C(8)H_2), 2.81–2.94 (2H, m, C(29)H_2), 3.07 (1H, dd, *J* 8.5, 4.5, C(4)*H*), 3.25 (1H, ddd, *J* 16.0, 9.5, 6.0, one of C(28)H_2), 3.38 (1H, ddd, *J* 16.0, 10.0, 6.0, one of C(28)H_2), 3.70 (3H, s, CO_2 CH_3), 4.06 (1H, ~ dt, *J* 9.0, 4.5, C(5)*H*), 5.03 (1H, s, C(6)*H*), 5.28 (1H, d, *J* 8.5, C(3)*H*), 7.16–7.21 (3H, m, C(31/35)*H* and C(33)*H*), 7.28 (2H, t, *J* 7.5, C(32/34)*H*); δ_C (100 MHz; $CDCl_3$) 8.99 and 14.12 (*C*(23)H_3 and *C*(27)H_3), 22.69, 25.06, 26.28, 29.36, 29.55, 29.69 and 31.92 (*C*(9)H_2–*C*(22)H_2, *C*(26)H_2 and *C*(29)H_2 many coincident), 43.38 (*C*(8)H_2), 46.14 (*C*(28)H_2), 49.26 (*C*(4)H), 52.15 (CO_2CH_3), 66.13 (*C*(5)H), 73.31 (*C*(3)H), 90.24 (*C*(6)H), 126.84 (*C*(33)H), 128.60 and 128.81 (*C*(31/35)H and *C*(32/34)H), 138.16 (*C*(30)), 165.51 (*C*(2)), 171.00 (CO_2CH_3), 199.83 (*C*(7)=O); *m*/*z* (+ve ion electrospray) 542 (MH^+, 100%); (Found 542.4201: $C_{34}H_{56}NO_4$ (MH^+) requires 542.4204).