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A Synthetic Approach to the Plakortones

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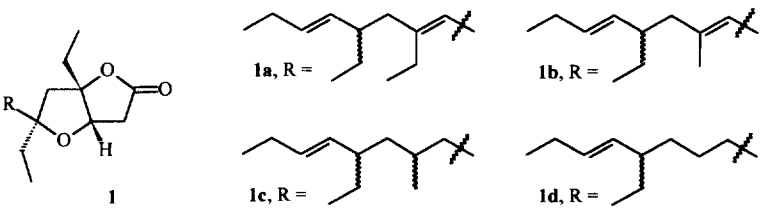
Abstract: The reaction of Grignard reagents with α-hydroxy-γ-ketocarboxylic acids leads to the formation of tetrasubstituted γ-butyrolactones, one of which was converted into a bicyclic lactone **10** *via* consecutive bromoacetylation, Wittig cyclisation and hydrogenation. This represents an efficient methodology for the synthesis of the plakortones, **1-4**.

Keywords: Natural products, furans, lactones, Wittig reaction.

In 1996 Patil *et al.* reported the isolation of four novel metabolites, the plakortones A-D **1a-d**, from the sponge *Plakortis halichondrioides*.[1] These were identified as a novel class of activators of cardiac sarcoplasmic reticulum (SR) Ca^{2+} pumping ATPase, a property which may be of value in correcting relaxation abnormalities observed in some forms of human heart failure.[1]



These metabolites were characterised by the presence of a 2,6-dioxabicyclo[3.3.0]octan-3-one subunit and we envisaged the synthesis of this portion of the molecule using the intramolecular Wittig cyclisation of a stabilised phosphorane and a lactone, followed by hydrogenation of the bicyclic tetronate thus formed (Scheme 1).[2]

Scheme 1

The preparation of the lactone required for this sequence was visualised as occurring *via* the addition of Grignard reagents to an α-hydroxy-γ-ketocarboxylic acid, these being prepared by the base catalysed condensation of methyl ketones with 2-oxobutyric acid **2** using a modification of a related literature procedure.[3] Thus reaction of acetophenone with **2** under basic conditions gave the required substrate **3** in 57% yield, which on treatment with an excess of ethyl magnesium bromide, followed by acid catalysed lactonisation gave a 95:5 mixture of **4** and **5** in 65% yield. The major lactone **4** was isolated by crystallisation (petroleum ether (40/60)/diethyl ether) and the relative stereochemistry determined by X-ray crystallography (Fig 1). As can be seen this lactone possesses the opposite relative stereochemistry to that found in the tetrahydrofuran ring of the plakortones. In order to obtain the correct lactone stereochemistry we reversed the order of introduction of the two γ-substituents and prepared substrate **6** from butanone and 2-oxobutyric acid **2** in 83% yield. Treatment of **6**

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with an excess of phenyl magnesium bromide followed by acidic work up, gave an 85:15 ratio of the required lactone **5** and the previously isolated **4** in 48% combined yield (Scheme 2).

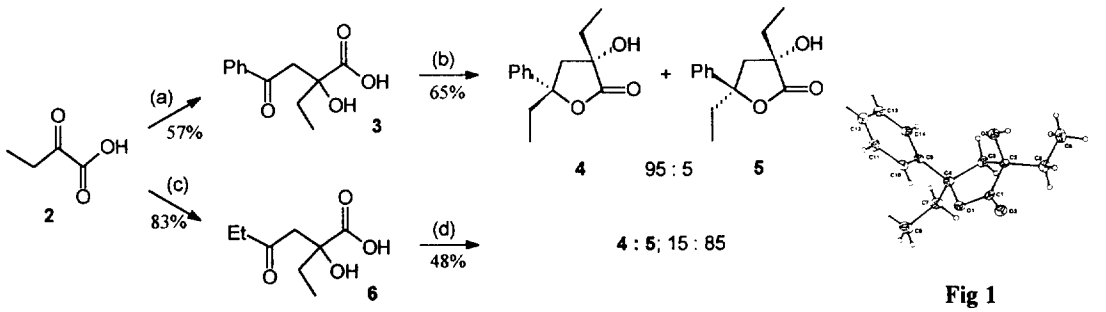
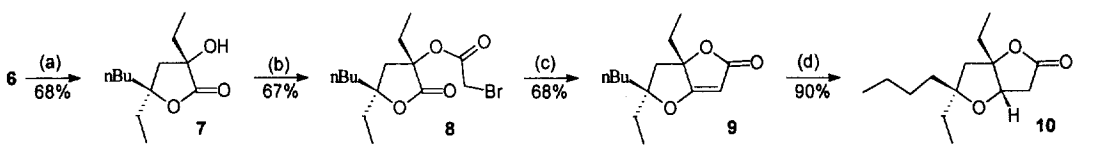


Fig 1

Scheme 2: (a) PhCOMe/KOH/MeOH/H_2O. (b) i) EtMgBr/THF/Et_2O; ii) tartaric acid (aq). (c) EtCOMe/NaOH/MeOH/H_2O. (d) i) PhMgBr/THF/Et_2O; ii) tartaric acid (aq).

Confident that we could prepare the required lactone with the correct relative stereochemistry we embarked upon the synthesis of the ring system found in the plakortones. Thus treatment of **6** with an excess of butyl magnesium bromide led to the formation of the lactone **7** in 68% yield, as essentially a single isomer (>95:5). Reaction of this with bromoacetyl bromide gave **8** in 67% yield, which on treatment with triphenylphosphine in acetonitrile, followed by the addition of DBU and reflux, gave the bicyclic tetronate **9** in 68% yield. Finally, reduction of **9** with hydrogen and Pd/C furnished **10** in 90% yield (Scheme 3). Comparison of the ^1H and ^{13}C nmr of **10** with the data reported for the structurally similar plakortone D **1d**, gave an excellent correlation.[4]



Scheme 3: (a) i) *n*-BuMgBr/THF//0°C-rt/ 48hrs, ii) tartaric acid (aq). (b) $BrCOCH_2Br$/Py/DMAP/DCM//0°C-rt/16hrs. (c) PPh_3/MeCN/40°C/90 min, then DBU/MeCN/0°C to reflux 90 min. (d) H_2/Pd/C/EtOAc/10min.

We have thus shown that by a combination of the stereoselective addition of Grignard reagents to α-hydroxy-γ-ketocarboxylic acids, intramolecular Wittig cyclisation and hydrogenation, we can rapidly access synthetic analogues of the naturally occurring plakortones. We are currently developing this methodology with our aim being the total synthesis of the plakortone metabolites.

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4. Selected data for **10**, **^{1}H nmr** (250 MHz): δ = 0.82 (t, J = 7.5 Hz, CH_3), 0.88 (t, J = 7.5 Hz, CH_3), 0.99 (t, J = 7.4Hz, CH_3), 1.1-1.75 (m, 10H), 1.87 (d, J = 14.4 Hz, CH), 2.24 (d, J = 14.4 Hz, CH), 2.60 (dd, J = 0.7, 18.3 Hz, CH), 2.70 (dd, J = 4.3, 18.3 Hz, CH), 4.33 (dd, J = 0.7, 4.3 Hz, CH).
   ^{13}C nmr (62.9 MHz): δ = 8.4, 8.5, 14.0 (3 x CH_3), 23.1, 26.0, 30.3, 31.3, 37.4, 38.1, 45.0, (7 x CH_2), 80.5 (CH), 87.3 (C), 97.7 (C), 175.5 (C=O).