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Approaches to the γ-lactone unit of CP-225,917 and CP-263,114

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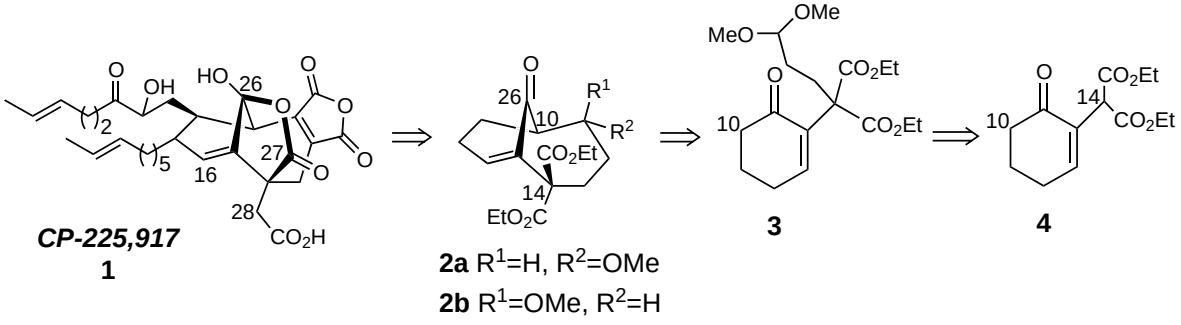
Abstract—Synthesis of the γ-lactone unit of CP-225,917 and CP-263,114 is reported by differentiation of a diester at C14 using either selective monohydrolysis or lactonisation of a C26-alcohol.

CP-225,917 **1**[1] and the closely related natural product CP-263,114[1] have stimulated intense interest amongst synthetic chemists[2–4] due largely to their unique and complex structure, as well as their inhibitory properties on the enzymes *ras*-farnesyl protein transferase and squalene synthase. We have previously reported[5] a concise synthesis (six steps from cyclohexanone) of a model bicyclo[4.3.1]octenone core **2** by intramolecular Mukaiyama aldol reaction of **3**, which in turn was prepared by alkylation of malonate **4** (Scheme 1). A key feature of our proposed strategy was the use of a diester unit at C14[†] initially as an anion stabilising group, but ultimately as a precursor to the C14 quaternary stereocentre. Thus, we envisaged differentiation of these two diastereotopic ester groups, possibly utilising the likely cyclisation of the acid derived from one of them onto the C26 ketone, as in the natural product, forming a pseudoacid derivative. One-carbon homologation of the non-cyclising, C28-ester would then be required to reach the natural product target. In this communication, we report manipulations of the diester in **2** resulting in successful differentiation and homologation, installing the C14 quaternary stereocentre.

We first investigated hydrolysis of the diester unit in the bicyclic model compounds **2** with the aim of effecting selective monohydrolysis or conversion to the diacid and subsequent selective functionalisation. Use of standard basic conditions (aqueous or ethanolic NaOH or KOH) led to formation of unstable products that we were not able to characterise. However, far better results were obtained using the recently developed system of aqueous NaOH containing a small amount of THF.[6] Under these conditions, the diester **2a** was



Scheme 1.

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† Natural product numbering as depicted in the Schemes is used throughout this paper.

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cleanly converted to the monoacid **5a**; isomeric diester **2b** similarly afforded monoacid **5b** (Scheme 2). The structures of both **5a** and **5b** were established by X-ray crystallography;[7] the structure of **5a** is shown in Fig. 1. Interestingly, the crystal structures showed that while the carboxylic acid attached to C14 was *cis*- to the C26-bridgehead carbonyl in both cases, it had not undergone cyclisation to the pseudoacid tautomer. Evidence that this was also the case in solution came from the ^{13}C NMR spectra, where the ketone carbon appeared at 208 ppm (cf. 105.4 ppm[1b] for the C26 lactol carbon in **1**). This behaviour is therefore in contrast to the natural product and—to the best of our knowledge—all related synthetic intermediates that have been reported to date. Attempts to induce cyclisation by heating **5a** in $CDCl_3$ resulted in decomposition.

This selective monohydrolysis had cleanly differentiated the two diastereotopic esters, but progression of the total synthesis would require the C28-ester to be hydrolysed to the acid to allow homologation by e.g. Arndt–Eistert reaction. In an attempt to protect acid **5a** as its *tert*-butyl ester prior to selective hydrolysis of the C28-ethyl ester, we discovered that treatment with DCC/DMAP/^{t}BuOH led to decarboxylation, affording **6a**. It was subsequently established that this transformation could be effected with DMAP alone in THF. Ester **6a** was obtained as predominantly a single diastereomer, the relative configuration of which was determined by X-ray crystallography.[7] This unplanned but not entirely surprising result led to a new synthetic opportunity: the installation of the C14-stereocentre via alkylation at C14 with an α-bromoacetate. Treatment of **6a** with LiHMDS followed by methyl bromoacetate afforded a single diastereomer of the product **7** with the desired spectroscopic characteristics. However, spectroscopic data did not allow us to assign the C14-stereochemistry. This was achieved by reduction of the C26-ketone with $NaBH_4/CeCl_3$, whereupon cyclisation of the resulting C26-alcohol occurred onto the methyl ester rather than the ethyl ester, leading to **8** and establishing that the alkylation had taken place on the undesired face, *syn*- to the bridgehead carbonyl. In the C11-epimeric series, monoacid **5b** also underwent decarboxylation to **6b** as essentially a single diastereomer. However, attempts to alkylate **6b** have not been successful to date. Nevertheless, this selective hydrolysis–decarboxylation–alkylation sequence provides a highly concise method for introducing the C14-stereocentre, albeit with C14 stereochemistry epimeric to the natural product.

In view of the failure of the C14-acid in **5** to undergo the expected cyclisation onto the C26 ketone, we investigated reduction at C26 and lactonisation of the resulting hydroxyl group as an alternative method for differentiation of the C14-diester unit. Reaction of **2b** with $NaBH_4/CeCl_3$ pleasingly provided the lactol **9** in good yield, resulting from C26-reduction, lactonisation and subsequent lactone reduction (Scheme 3).[8] Protection afforded methyl acetal **10**, paving the way for reduction of the remaining ethyl ester to the aldehyde **11**. One-carbon homologation to **12** was then accom-

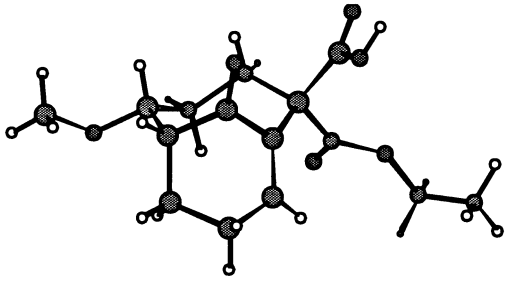
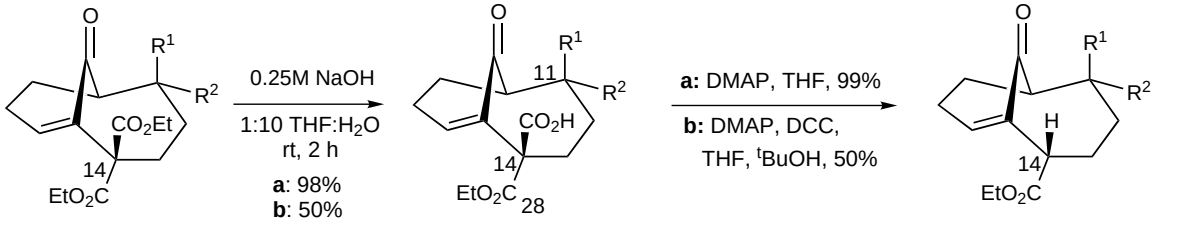
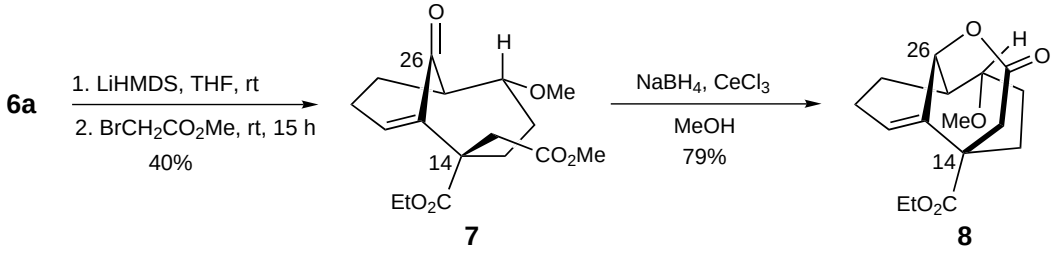
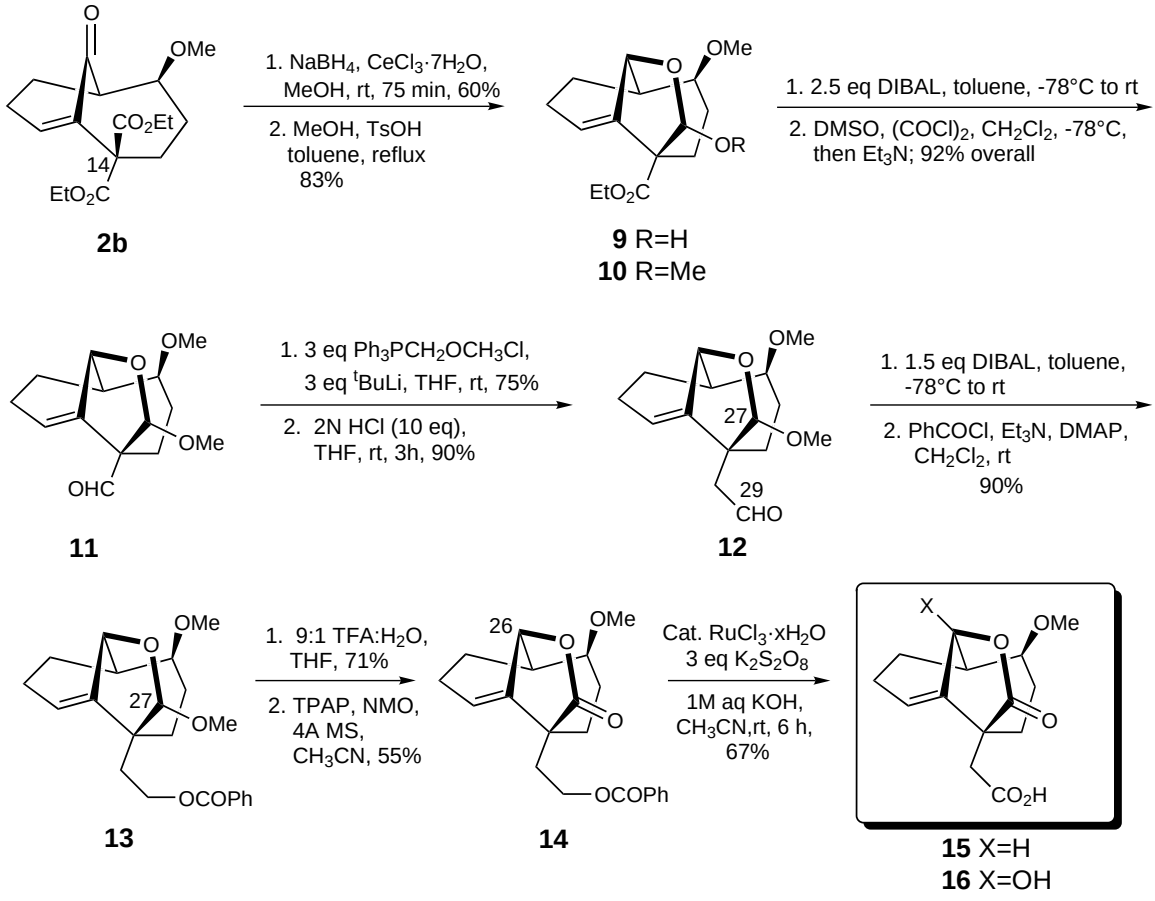


Figure 1. Chem3D representation of the X-ray crystal structure of **5a**.





Scheme 2.



Scheme 3.

plished via reaction with methoxymethylphosphonium ylide. Acidic hydrolysis of the desired intermediate enol ethers required careful optimisation since longer reaction times resulted in a mixture of products due to hydrolysis of the methyl acetal and cyclisation of the resulting lactol hydroxyl onto the C29-aldehyde. Provided short reaction times were used, **12** could be obtained in excellent yields. This process therefore offers a simple alternative to other homologation methods reported in this natural product series.[3a,c,d] Oxidation of the aldehyde **12** to the corresponding acid could be accomplished with sodium chlorite, but exposure to acidic conditions led to cyclisation of the C29-acid onto C27 to give a lactone that was expected not to be amenable to re-oxidation at C27. In order to avoid this complication, the aldehyde **12** was reduced to the corresponding alcohol which was then protected as the benzoate **13**, allowing manipulation of the lactol ether at C27 to be investigated. Acidic hydrolysis (TFA/H_2O) of **13** led to a mixture of lactol epimers which was oxidised (TPAP/NMO) to lactone **14**. For attempted re-oxidation at the C26 bridgehead position, we expected that basic conditions would be required to allow lactone opening and oxidation of the open chain hydroxy acid. In the event, oxidation with a catalytic amount of $RuCl_3{\cdot}xH_2O$ and 3 equiv. $K_2S_2O_8$ did not oxidise the C26 position, but it did result in cleavage of the benzoate ester and installation of the C29 carboxylic acid, leading to **15**.[9] When this experiment was repeated using 6 equiv. $K_2S_2O_8$, **15** was still the major product along with a small amount of a compound tentatively assigned as **16**, but this could not be produced in significant quantities. This reluctance of the C26-position to undergo oxidation in lactone derivatives has precedent in the studies of Nicolaou,[3a,10] but it is interesting to note that Clive and co-workers were recently able to effect this transformation using $RuO_2/NaOH$[4e] in a model compound possessing the anhydride unit of the natural product.

In conclusion, these studies have revealed several interesting aspects of the chemistry of C14 acid/ester derivatives related to the CP-compounds. The observation that the acid **5** exists as the acyclic form rather than the pseudoacid tautomer appears to be unprecedented in this natural product series. Decarboxylation and alkylation of this compound provides a highly concise route to C14-*epi*-derivatives of the natural product. In an alternative approach, we have demonstrated that reduction of the C26-ketone may be used as an effective method for differentiation of the C14-diester, as well as a new way of homologating at C28. Compound **15** contains the lactone unit of the natural product, with only the C26 carbon at the incorrect oxidation level. Application of the strategies outlined herein to more complex substrates is currently underway.

Acknowledgements

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7. We thank Dr. A. J. P. White, Department of Chemistry, Imperial College, for these structure determinations; details will be reported in a full account of this work. Crystallographic data for **5a** (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 187181.
8. A similar synthetic sequence was carried out starting from **2a**, as far as the C11 epimer of compound **14**.
9. Data for **15**: Amorphous colourless solid, ν_{max} (KBr disk) 3500–2500, 1776, 1725, 1215, 1072, 1038 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.49 (1H, ddd, $J=7.1$, 2.6, 2.6, H16), 4.66 (1H, br s, H26), 3.26 (3H, s, OCH_3), 3.08 (1H, d AB, $J=17.6$ Hz, CH_2CO_2H), 2.88 (1H, ddd, $J=11.0$, 5.8, 2.2 Hz, H11), 2.81 (1H, d AB, $J=17.6$ Hz, CH_2CO_2H), 2.39–2.33 (2H, m), 2.20 (1H, m), 1.98 (1H, m), 1.90–1.81 (2H, m), 1.78–1.68 (3H, m), 1.47 (1H, ddd, $J=12.6$, 12.6, 3.6 Hz); δ_C (125 MHz, $CDCl_3$) 179.4 (s, C=O lactone), 173.7 (s, CO_2H), 140.6 (s), 116.4 (d, C16), 85.7 (d, C11), 81.7 (d, C26), 56.9 (q, OCH_3), 49.02 (s, C14), 41.7 (d), 41.0 (t), 36.5 (t, C28), 26.8 (t), 24.8 (t), 20.8 (t); m/z (CI (+)) 267 (2%, M+H). Found for $M+H^+$ 267.1234, Calcd for $C_{14}H_{19}O_5$ 267.1232.
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