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The one-pot, multi-component construction of highly substituted tetrahydropyran-4-ones using the Maitland–Japp reaction†‡

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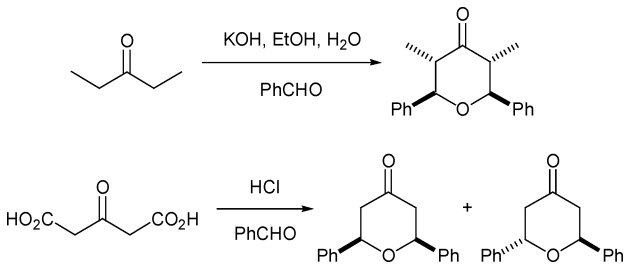
A one-pot, multi-component reaction for the synthesis of highly substituted tetrahydropyran-4-ones, based on the long forgotten Maitland–Japp reaction has been realised. Two different aldehydes and a derivative of a β-ketoester can be condensed regioselectively in the presence of a Lewis acid to form tetrahydropyran-4-ones in excellent yields. The diastereoselectively of the reaction was found to be dependant upon the nature of the Lewis acid and the temperature at which the reaction was carried out. This procedure was also extended to the formation of tetrahydropyran-4-ones in greater than 95% enantiomeric excess.

Introduction

Tetrahydropyran (THP) rings are ubiquitous in the natural product arena, and over the years many methods have been developed for their construction. Some of the most widely used methods are intramolecular epoxide opening, manipulation of carbohydrates,[1] hetero Diels–Alder cyclisations,[2,3] Prins reactions[4,5] and intramolecular Michael reactions.[6] Our interest in the formation of THP rings arose from the reports of Maitland and Japp, who showed that 3-butanone and 2 molecules of benzaldehyde could be condensed in a low yielding process to generate a substituted THP ring.[7] In the 1930s, Cornubert and Robinet investigated the analogous acid mediated condensation of acetonedicarboxylic acid with benzaldehyde. In this case cyclisation proceeded with concomitant decarboxylation to give two stereoisomers of the pyranone product in a 250 : 1 ratio (Scheme 1).[8]

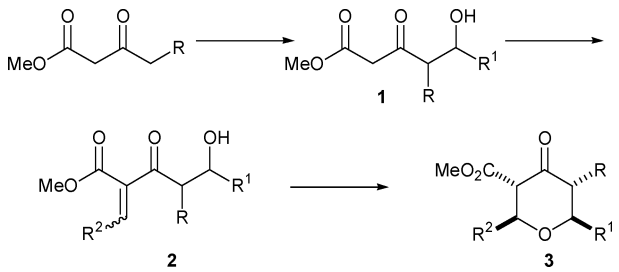


Scheme 1 The Maitland–Japp and Cornubert–Robinet reactions.

It was not until 1968, that the stereochemistry of the pyranone products obtained in the Maitland–Japp and the Cornubert–Robinet reactions were determined. In one of the first uses of high field ^{1}H NMR for stereochemical determination, Whiting and Baxter were able to determine that the major compounds formed in both the Maitland–Japp and the Cornubert–Robinet reactions were the all-equatorial pyranones.[9,10] We were attracted to the multi-component, one-pot nature of the Maitland–Japp reaction and desired to see if, with the application of modern synthetic methods, the Maitland–Japp reaction could be turned into a synthetically useful procedure for the synthesis of highly substituted tetrahydropyran-4-ones.

Results and discussion

We proposed to improve on the Maitland–Japp procedure by developing a reaction utilising a β-ketoester, instead of a ketone, as the building block for the THP ring. Taking advantage of the marked difference in reactivity of the α and γ positions of a β-ketoester would allow for the synthesis of unsymmetrical pyran products. The three reactions that would then constitute the new variant of the Maitland–Japp reaction would be: a regioselective aldol reaction at the γ position of a β-ketoester to give **1**, followed by a Knoevenagel condensation of a second aldehyde at the α position of the β-ketoester to furnish **2**, and then an intramolecular oxy-Michael reaction to give the pyran ring **3**. It was hoped that the new reaction would be under thermodynamic control, and, as in the Maitland–Japp reaction, give the all-equatorial product **3** (Scheme 2).



Scheme 2 Updating the Maitland–Japp reaction.

The two-pot reaction

Studies commenced by the use of Weiler dianion chemistry of methyl acetoacetate,[11] which furnished the δ-hydroxy β-ketoesters **1** in quantitative yields. These aldol products were used in crude form for subsequent reactions, as in most cases purification by column chromatography led to significant degradation of the product to give the enone **4** (Scheme 3).

Attention now turned to developing the Knoevenagel and intramolecular oxy-Michael steps of the reaction pathway. We were hopeful that both steps could be combined in a tandem reaction as literature precedent indicated that both processes could be Lewis acid mediated. Precedent for the Lewis acid catalysis of Knoevenagel reactions was seen in the work of

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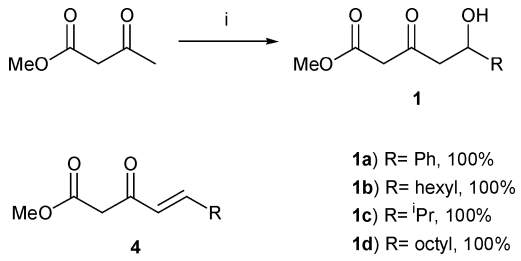


Scheme 3 *Reagents and conditions*: (i) NaH, THF, 0 °C then *n*BuLi, RCHO, −78 °C to RT.

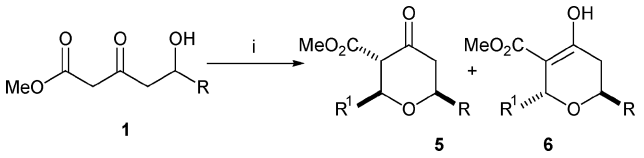
Table 1 The two-pot Maitland–Japp reaction

Compound	R	R^1	Yield (%)[a]	Ratio[b] **5** : **6**
a	Ph	2-Furyl	66	2.6 : 1
b	Ph	Ph	68	6.8 : 1
c	^{i}Pr	^{n}Pr	55	1 : 1
d	^{i}Pr	Hexyl	55	1 : 1.4
e	Heptyl	Ph	80	6.4 : 1
f	Hexyl	^{n}Pr	80	12.3 : 1

[a] Isolated yield after flash column chromatography, calculated over two steps from methyl acetoacetate. [b] Determined from the ^{1}H NMR (400 MHz) of the crude reaction mixture.

Lehnert,[12] and an example of using a Lewis acid to promote the intramolecular oxy-Michael reaction was provided by the work of Paterson and Osbourne.[13]

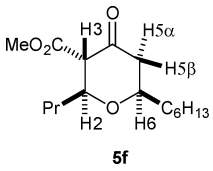
Initial studies focused on using boron trifluoride etherate as the Lewis acid promoter.[14] The δ-hydroxy β-ketoester **1a** was treated with 2-furfural and an equivalent of boron trifluoride etherate in methylene chloride at room temperature. Reaction was found to be rapid (∼1 minute) and, upon ^{1}H NMR analysis of the crude reaction mixture, was found to have given the pyran products **5a** and **6a** in a 2.6 : 1.0 ratio in favour of the 2,6 *cis* isomer **5a** (Scheme 4 and Table 1). The combined Knoevenagel and intramolecular oxy-Michael reaction conditions were applied to a range of δ-hydroxy β-ketoesters and aldehydes, and in all cases the reaction was complete within one hour and gave the pyran products as a mixture of *cis* and *trans* isomers that were separable by column chromatography to give the pyran products **5** and **6** in moderate to good yield (Scheme 4 and Table 1).



Scheme 4 *Reagents and conditions*: (i) R^1CHO, $BF_3{\cdot}OEt_2$, CH_2Cl_2, RT.

Stereochemical assignment of the pyran-4-one products

Evidence to support the stereochemical assignment of the 2,6 *cis* isomer **5** was provided by ^{1}H NMR analysis (Fig. 1). In addition, the X-ray crystal structure was solved for **5b**, which confirmed the stereochemical assignment of the pyran keto-forms (Fig. 2).¶



Coupling constants		nOe correlations	
H2-H3	11.5 Hz	H2-H6	9.9 %
H3-H5β	1.5 Hz	H2-H3	1.4 %
H5β -H6	10.5 Hz	H3-H5β	4.5 %
		H5β -H6	1.0 %
		H5α -H6	5.6 %

Fig. 1 ^{1}H NMR data.

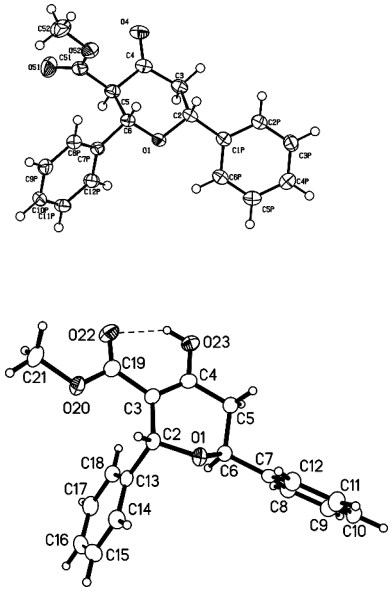
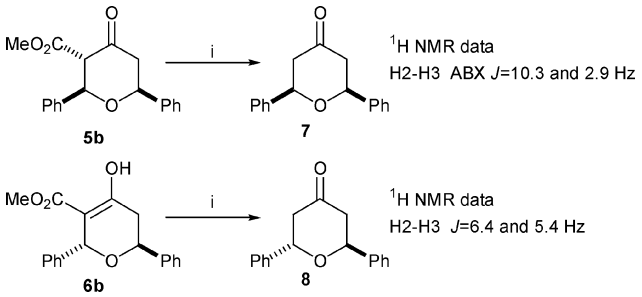


Fig. 2 X-Ray crystal structures for **5b** and **6b**.

The 2,6 *trans* structure **6** was initially incorrectly assigned as the enol form of the 2,6 *cis* isomer.[14] It was not possible to determine the stereochemistry of the 2,6 *trans* isomer **6** by ^{1}H NMR techniques as the two sides of the ring existed in completely separate spin systems and this led to the initial misassignment of the structure of **6**. A gradient NOE experiment indicated that protons *H*6 and *H*2 were not close enough in space to give a positive NOE, eluding to the 2,6 *trans* arrangement of the pyran ring. The first positive evidence that the 2,6 *trans* stereochemical assignment of **6** was correct was seen when a crude mixture of the pyrans **5b** and **6b** was decarboxylated by treatment with hydrogen peroxide and lithium hydroxide to give the two products of the Cornubert–Robinet reaction **7** and **8**, the ^{1}H NMRs of which were readily distinguishable (Scheme 5). The ratio of the *cis* isomer **7** to the *trans* isomer **8** was the same as the ratio of the *cis* isomer **5b** to the *trans* isomer **6b** in the starting material (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) H_2O_2, LiOH, THF–H_2O, 80 °C, 82%.

Unambiguous proof for the 2,6 *trans* structure was provided by the single crystal X-ray structure of **6b** (Fig. 2).¶ Comparison

¶ Diffraction data were acquired on a Bruker SMART1000 (**5b**) or a Bruker SMART APEX (**6b**) CCD area detector diffractometer equipped with an Oxford Cryosystems open-flow cryostat operating at 150 K. The structures were solved by direct methods and refined by full-matrix least-squares on F^2. Crystal data for **5b**. $C_{19}H_{18}O_4$, $M = 310.33$, monoclinic, $a = 13.0132(10)$, $b = 8.6004(7)$, $c = 14.1620(11)$, $\beta = 91.558(2)^\circ$, $V = 1584.4(2)$ Å^3, $T = 150(2)$ K, $Z = 4$, $D_x = 1.301$ g cm^{-3}. Final R_1 [2746 $F > 4\sigma(F)$] = 0.0375, wR_2 [all 3656 F^2] = 0.105. Crystal data for **6b**. $C_{19}H_{18}O_4$, $M = 310.33$, triclinic, $a = 5.5429(5)$, $b = 9.5351(8)$, $c = 15.1955(13)$, $\alpha = 82.937(2)$, $\beta = 85.273(2)$, $\gamma = 77.190(2)^\circ$, $V = 775.9(2)^3$, $T = 150(2)$ K, $Z = 2$, $D_x = 1.328$ g cm^{-3}. Final R_1 [2913 $F > 4\sigma(F)$] = 0.0401, wR_2 [all 3507 F^2] = 0.111. CCDC reference numbers 250776 and 250777. See http://dx.doi.org/10.1039/b508252h for crystallographic data in CIF or other electronic format.

between the crystal structures of **5b** and **6b** also shed light on why the 2,6 *cis* isomer of the pyran rings favoured the keto form, whilst the 2,6 *trans* isomer existed exclusively in the enol form. In the *trans* enol tautomer, a hydrogen bond was seen between the enol proton and the ester carbonyl, as indicated by the ^{1}H NMR of the *trans* compounds in which the enol proton was at 12 ppm. The pyran ring was markedly flattened thus minimising the penalty for having the *C*2 substituent on the ring in a *pseudo* axial position. The 2,6 *cis* isomer was seen to be in a chair conformation with all the substituents equatorial. Furthermore, it was clear to see from the crystal structure that tautomerisation to give the enol form of the 2,6 *cis* isomer would have resulted in a destabilising steric clash between the substituent on *C*2 and the ester group on *C*3.

In cases where the substituent on *C*2 was aromatic, some of the *cis* enol form was seen in the ^{1}H NMR of the crude reaction mixture. This was most marked for 2,6 diphenyl pyran (Table 1, entry b) where the *cis* enol form **9b** constituted 25% of the product in the crude ^{1}H NMR, but upon standing in chloroform, tautomerisation to give entirely the *cis* keto form **5b** was observed. Interestingly, the *cis* enol tautomer **9b** showed a long-range coupling between *H*2 and *H*5*α* and *H*5*β* of 2.0 Hz and a ^{1}H–^{1}H NMR correlation experiment confirmed that a 5-bond coupling was present. The enol form of **9b** was never isolated but a gradient NOE experiment performed on a mixture of the *cis* enol and *cis* keto forms showed a positive NOE of 6% between *H*2 and *H*6, proving the 2,6 *cis* relationship between these two protons (Fig. 3). In Table 1, entry a, the *cis* enol tautomer constituted 7.5% of the total product and for entry e, the amount of *cis* enol compound observed was 15% of the product. In both these cases rapid tautomerisation to give the *cis* keto form was observed upon exposure to chloroform.

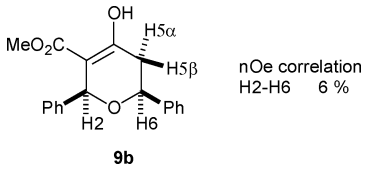
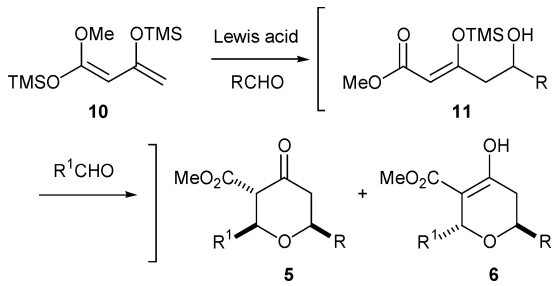


Fig. 3 NOE data.

The one-pot reaction

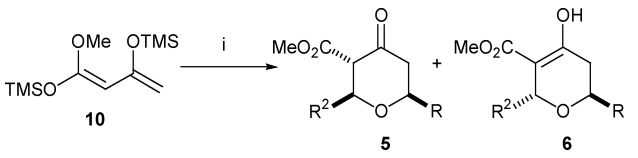
Although many of the problems inherent in the original Maitland–Japp reaction had been surmounted, one of the major advantages had been lost as two separate reactions were now required to generate the pyranone product. It was decided to investigate developing a Lewis acid mediated aldol reaction using Chan's diene[15] **10** as the nucleophile which could be incorporated into the tandem Lewis acid mediated Knoevenagel condensation with a second aldehyde and intramolecular oxy-Michael ring closure (Scheme 6).



Scheme 6 The revised one-pot Maitland–Japp reaction.

Titanium tetrachloride has been reported to catalyse both the Mukiayama aldol reaction[16] and also the Knoevenagel condensation,[12] so it was decided to investigate its use in developing the one-pot reaction. Mukaiyama aldol reaction of **10** with iso-butyraldehyde proceeded smoothly at −78 °C but the Knoevenagel reaction with butanal proved problematic. No reaction occurred at −78 °C and it was only as the reaction approached room temperature that consumption of the aldol product was observed. Analysis of the ^{1}H NMR of the crude reaction mixture showed that small amounts of the pyran product **5c** had been formed but that dehydration products **4** constituted the majority of the product mixture. It was found, however, that no additional Lewis acid was required to promote the Knoevenagel/oxy-Michael steps and when only one equivalent of titanium tetrachloride was used in the reaction, cleaner formation of the pyran products **5c**–**6c** as a 1 : 1 mixture of isomers was observed. However, the desired pyran products were still heavily contaminated with enone products **4**. Indeed, when the Mukaiyama aldol reaction was conducted and then allowed to warm to room temperature, without addition of the second aldehyde, a complex, non separable, mixture of compounds was observed by ^{1}H NMR. In contrast, the δ-hydroxy β-ketoester **1c** derived from Chan's diene **10** and iso-butyraldehyde was stable to a variety of Lewis acidic conditions at room temperature, which we reasoned was due to the elimination of silanol being a more facile process than the elimination of water.

Evidently in order to develop a viable one-pot pyran forming reaction the aldol product would need to be in the non-silylated form before addition of the second aldehyde. Indication as to how this might be achieved came from the work of Soriente *et al.*,[17] therefore, trifluoroacetic acid in THF was added to the aldol product **11a** and this gave the δ-hydroxy β-ketoester **1a** in quantitative yield. This enabled the subsequent Knoevenagel/oxy-Michael reactions to proceed without problem. Using this approach, a viable protocol for the one-pot pyran forming reaction was quickly developed (Scheme 7 and Table 2).



Scheme 7 *Reagents and conditions*: (i) $TiCl_4$ or $Yb(OTf)_3$, RCHO, −78 °C then TFA, R^2CHO, −78 °C–RT.

The reaction proved general to a range of aldehydes and, in all cases, gave completely chemoselective addition of the coupling partners (Scheme 7, Table 2). It was decided to investigate the effect that using a different Lewis acid would have on the reaction so ytterbium triflate was used in place of titanium tetrachloride. The pyran forming reaction was performed in exactly the same way as in the titanium tetrachloride case and gave comparable yields of the pyran products. The distribution of products varied markedly from the titanium tetrachloride case, however, favouring the 2,6 *cis* isomer **5** (Scheme 7, Table 3). The reasons for this remarkable change in selectivity will be discussed later.

Table 2 The $TiCl_4$ promoted one-pot Maitland–Japp reaction

Compound	R	R^1	Yield (%)[a]	Ratio[b] **5** : **6**
b	Ph	Ph	98	1 : 3
c	^{i}Pr	^{n}Pr	98	1 : 1
g	^{i}Pr	Ph	82	1 : 3
h	^{i}Pr	$(CH_2)_2C{=}CH_2$	88	1 : 4
i	^{n}Pr	CH_2OBn	88	1 : 1
j	Cyhex	Ph	74	1 : 2
k	Pr	*p*-$MeOC_6H_4$	93	1 : 3
l	Ph	^{i}Pr	80	1 : 0

[a] Isolated yield after flash column chromatography. [b] Determined from the ^{1}H NMR (400 MHz) of the crude reaction mixture.

Table 3 The $Yb(OTf)_3$ promoted one-pot Maitland–Japp reaction

Compound	R	R^1	Yield (%)[a]	Ratio[b] **5** : **6**
b	Ph	Ph	98	2.5 : 1
c	^{i}Pr	^{n}Pr	91	10 : 1
g	^{i}Pr	Ph	80	2.5 : 1
h	^{i}Pr	$(CH_2)_2C{=}CH_2$	93	2 : 1
i	^{n}Pr	CH_2OBn	81	6 : 1
j	Cyhex	Ph	86	11 : 1
k	Pr	*p*-$MeOC_6H_4$	91	2 : 1
l	Ph	^{i}Pr	75	1 : 0

[a] Isolated yield after flash column chromatography. [b] Determined from the ^{1}H NMR (400 MHz) of the crude reaction mixture.

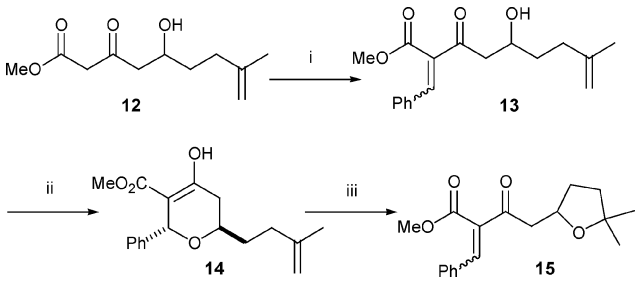
Investigation of the reaction mechanism

One of the major benefits of the original Maitland–Japp reaction was that it delivered single isomers of the tetrahydropyran product. However, our updated version of the Maitland–Japp reaction furnished mixtures of diastereomers. In order to understand the diastereoselectivity of the reaction, we needed to establish whether the pyran forming step was reversible and under thermodynamic control. To this end, the 2,6 *cis* **5b** and the 2,6 *trans* **6b** isomers were separated and resubmitted to the pyran forming reaction conditions for 18 hours. For each Lewis acid the same isomeric distribution of products was established, irrespective of the starting isomer, proving that the reaction was under thermodynamic control (Table 4).

As can be seen for entries 1 and 2 in Table 4, the equilibrium for the reaction mediated by titanium tetrachloride was found to be markedly temperature dependent, favouring the 2,6 *cis* isomer **5b** at −78 °C and the 2,6 *trans* isomer **6b** at 0 °C. However, this temperature dependence was not found to be general for all the reactions studied. In the case of the formation of the pyrans **5g** and **6g** the equilibrium was found to be 1.3 : 1.0 in favour of the 2,6 *trans* isomer **6g** at room temperature, but, contrary to the previous example, when the product was stirred at −84 °C for 24 hours under the reaction conditions the equilibrium was found to have moved even further in favour of the 2,6 *trans* isomer **6g**.

From the evidence above we concluded that the reaction was under thermodynamic control. It must, therefore, hold that the two Lewis acids, titanium tetrachloride and ytterbium triflate, interact with the two diastereomers of the product differently. It had already been established that the 2,6 *trans* isomer **6** favours the enol tautomer whilst the 2,6 *cis* isomer **5** exists predominantly in the keto form. It can therefore be postulated that the diastereoselectivity of the pyran forming reaction is dependent on how well a particular Lewis acid can coordinate to the enol framework, thereby stabilising the 2,6 *trans* isomer **6**. We propose that titanium tetrachloride could form a chelate with the 2,6 *trans* isomer **6** that would stabilise it with respect to the 2,6 *cis* isomer **5**. It can be hypothesised that the energy penalty for having a *pseudo* axial substituent in the 2,6 *trans* isomer **6** is not particularly large as it can be seen in the crystal structure (Fig. 2) that the pyran ring is markedly flattened, reducing any 1,3 diaxial interactions. The 2,6 *cis* isomer **5** has all its substituents in equatorial positions and tautomerisation to the enol form is disfavoured, as a steric clash would arise between the *C*2 and *C*3 substituents. We suggest that in the absence of Lewis acid that the 2,6 *cis* isomer **5** would be favoured over the 2,6 *trans* isomer **6**, and that it is due to the low solubility of ytterbium triflate in methylene chloride, precluding complexation to all the pyran molecules in solution, that led to the increased amount of the 2,6 *cis* isomer **5** seen with ytterbium triflate.

Further evidence that the Lewis acid mediated cyclisation reaction was reversible was seen when enone **13**, obtained by Knoevenagel condensation of benzaldehyde with the δ-hydroxy β-ketoester **12**,[14,18] was exposed to the pyran forming conditions, and gave the furan **15** as a 1 : 1 mixture of geometrical isomers (Scheme 8). Quenching of the reaction after 30 seconds resulted in the exclusive formation of the pyran **14**, which, when resubmitted to the reaction conditions, gave the furan **15**. The conclusion drawn was that the pyran forming reaction was reversible, and with time the thermodynamically more stable furan product was formed by 5-*exo*-*trig* cyclisation of the alcohol onto the pendant double bond.



Scheme 8 *Reagents and conditions*: (i) PhCHO, CH_2Cl_2, EDDA, 56%; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, <1 min, 0 °C, 92%; (iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 20 min, 0 °C, 80%.

Reaction kinetics

Having established that the reaction was under thermodynamic control, experiments were performed in order to determine how fast the equilibrium distribution of *cis* and *trans* isomers was arrived at. This was achieved by conducting the addition of the second aldehyde at a number of different temperatures and monitoring the reaction at set intervals. The first system studied was the formation of the bisphenyl pyrans **5b** and **6b**. Although the Knoevenagel reaction did not take place at −78 °C, it did occur slowly at −65 °C, with only a 38% conversion after 5 hours reaction time. However, the only product observed in the ^{1}H NMR was the 2,6 *cis* isomer **5b**, indicating that the 2,6 *cis* isomer **5b** is the kinetic product at −65 °C. The reaction was much more rapid at −40 °C giving appreciable amounts of the pyran product (13%) after 1 hour. The only product formed at this time was the 2,6 *cis* isomer **5b**, indicating that at −40 °C this was the kinetic product. However, after 5 hours some of the 2,6 *trans* isomer **6b** was observed.

When the study was carried out at room temperature a further complication arose as a new compound was seen in the ^{1}H NMR of the aliquot removed after 1 minute. This new compound was not seen in the ^{1}H NMR of the aliquot removed after 48 hours, suggesting that its formation was reversible.

Table 4 Equilibration studies on **5b** and **6b**

Entry	Equilibration conditions	Temp	**5b** : **6b** ratio when **5b** was resubmitted[a]	**5b** : **6b** ratio when **6b** was resubmitted[a]
1	$TiCl_4$–TFA	0 °C	29 : 71	29 : 71
2	$TiCl_4$–TFA	−78 °C	75 : 25	75 : 25
3	$BF_3{\cdot}OEt_2$	RT	44 : 56	44 : 56
4	$Yb(OTf)_3$–TFA	RT	71 : 29	71 : 29

[a] Determined from the ^{1}H NMR (400 MHz) of the crude reaction mixture.

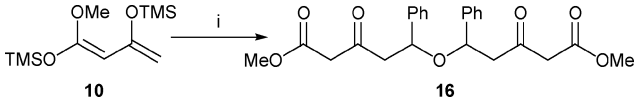
Table 5 Time dependence of the pyran ratio (**5b** : **6b**) in the $TiCl_4$ promoted Maitland–Japp reaction at 20 °C

Entry	Time/min	Dimer (%)[a]	Conversion (%)[b]	Ratio **5b** : **6b**
1	0.5	0	0	—
2	1	50	26	85 : 15
3	10	41	59	41 : 59
4	60	41	50	36 : 64
5	2880	0	100	25 : 75

[a] % of starting material present as dimer. [b] % of starting material converted to pyran.

It is suggested that this compound is the dimer **16** resulting from Lewis acid mediated formation of a benzylic carbocation followed by formation of an ether linkage (Scheme 9, Table 5). Indeed, when the aldol reaction was run as normal and quenched with TFA and then heated at 30 °C, without addition of a second equivalent of benzaldehyde, clean conversion to this new compound was observed. If the formation of the dimer **16** is discounted it can be seen that at room temperature the 2,6 *cis* isomer **5b** is still the kinetic product, with the 2,6 *trans* isomer **6b** predominating after 10 min.

The study was repeated for the reaction catalysed by ytterbium triflate, and at room temperature it was found that the 2,6 *cis* isomer **5b** was the kinetic product with none of the 2,6 *trans* **6b** isomer seen until 5 minutes had elapsed. None of the dimer **16** was observed at any point in the reaction.



Scheme 9 *Reagents and conditions*: (i) PhCHO, $TiCl_4$, CH_2Cl_2, −78 °C then TFA 30 °C, 2 hr, 73%.

In order to establish whether the formation of the 2,6 *cis* isomer **5** as the kinetic product was a general feature of the pyran forming reaction it was decided to expand the study to include different substrates. The one-pot titanium tetrachloride and ytterbium triflate mediated formation of the pyrans **5g** and **6g** was studied at room temperature. In both cases the first product formed (1 min) was the 2,6 *cis* isomer **5g** and with time (60 min for $TiCl_4$ and 20 min for $Yb(OTf)_3$) the equilibrium distribution was established. In the case of the $TiCl_4$ reaction, complete consumption of starting material took 20 min although in the case of the $Yb(OTf)_3$ mediated reaction complete consumption of starting material took only 5 min. It was important to note, however, that the rate of the reaction was much slower than that observed for the formation of the bisphenyl pyran, with amounts of the 2,6 *trans* isomer **6g** being formed before the reaction had gone to completion.

There are 4 possible modes of cyclisation available once the Knoevenagel condensation has occurred (Fig. 4). In the transition state depicted as **A**, the oxygen attacks the bottom face of the (*Z*)-enone to give the 2,6 *cis* pyran and both the R substituents are in favourable *pseudo* equatorial positions. If the alcohol attacks the top face of the (*Z*)-enone **C** to give the 2,6 *trans* isomer then R^1 is in an unfavourable *pseudo* axial position. Addition to the bottom face of the (*E*)-enone **B** gives the 2,6 *cis* product but in this case both R substituents are in unfavourable *pseudo* axial positions. Finally, addition of the oxygen nucleophile to the bottom face of the (*E*)-enone to give the 2,6 *trans* isomer leads to the transition state **D** where R^2 is in a *pseudo* axial position. Using this analysis it can be hypothesised that the mode of cyclisation depicted as **A** will have the lowest energy barrier of the four modes to achieve the correct confirmation for cyclisation and will therefore lead to the kinetic product **5**.

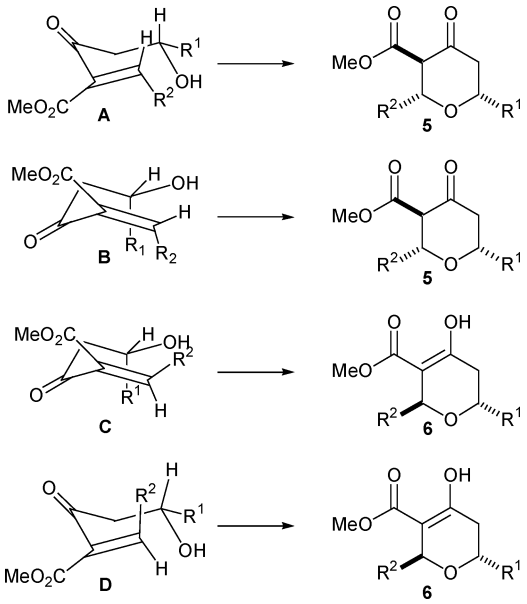
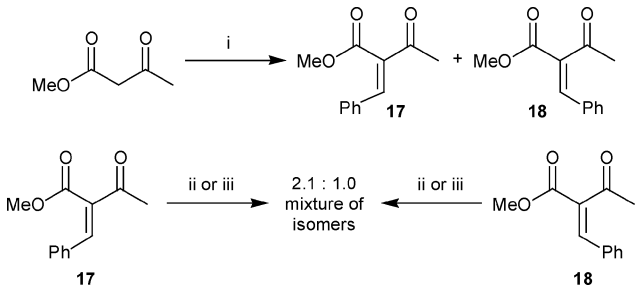


Fig. 4 Modes of cyclisation.

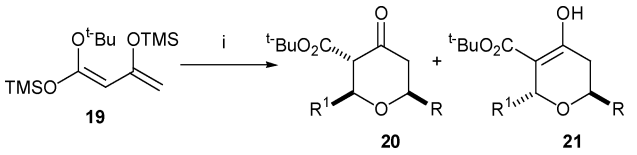
In order to establish whether all four modes of cyclisation were accessible it was necessary to investigate whether scrambling of the enone double bond geometry was possible under the reaction conditions. The (*Z*)-**17** and (*E*)-**18** isomers of the Knoevenagel product of methyl acetoacetate and benzaldehyde were separated by column chromatography and were then submitted to the Lewis acid reaction conditions (Scheme 10). Rapid double bond scrambling was observed by analysis with TLC and after 12 hours ^{1}H NMR analysis showed that the same ratio of *E* and *Z* isomers was present in each reaction. It had therefore been shown that all **4** modes of cyclisation in Fig. 4 were valid.



Scheme 10 *Reagents and conditions*: (i) PhCHO, PhH, AcOH, piperidine, reflux, 64%; (ii) $TiCl_4$, TFA, CH_2Cl_2, 36 h; (iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 36 h.

Use of *tert*-butyl esters

Now that we understood that the reaction was under thermodynamic control and that the 2,6 *cis* and 2,6 *trans* isomers were rapidly interconverting under the reaction conditions, we initiated attempts to develop a reaction that would give us only one diastereomer of the pyran product. Given that the 2,6 *cis* isomer **5** favoured the keto form whilst the 2,6 *trans* isomer **6** existed exclusively as the enol tautomer, this led us to consider using decarboxylation as a way in which to favour the formation of the 2,6 *cis* isomer. It was postulated, that if conditions could be found to effect an *in situ* decarboxylation of the pyranone product, that the 2,6 *cis* isomer **5** might be decarboxylated faster than the 2,6 *trans* isomer **6**, thereby funnelling the reaction towards the 2,6 *cis* isomer. To enable an *in situ* decarboxylation to be developed it was decided to investigate the use of the diene **19** (Scheme 11) as it was envisaged that the *tert*-butyl ester would be removed upon prolonged exposure to trifluoroacetic



Scheme 11 *Reagents and conditions*: (i) $TiCl_4$, RCHO, −78 °C then TFA, py, R^1CHO, −78 °C–RT.

Table 6 The Maitland–Japp reaction of diene **19**

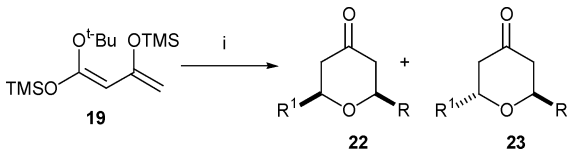
Compound	R	R^1	Yield (%)[a]	Ratio[b] **20** : **21**
a	^{i}Pr	^{n}Pr	92	14 : 1
b	Ph	Ph	98	4 : 1
c	Ph	Cyhex	91	2 : 1
d	Ph	^{i}Pr	44	10 : 1

[a] Isolated yield after flash column chromatography. [b] Determined from the ^{1}H NMR (400 MHz) of the crude reaction mixture.

acid. The diene **19** was synthesised in the same way as Chan's diene,[19] in an 80% yield from *tert*-butyl acetoacetate.

The conditions developed for the pyran forming reaction based on Chan's diene were applied to the diene **19**, however, to avoid decomposition of the initial aldol product during the reaction, pyridine was added to the reaction after the initial aldol reaction had gone to completion and prior to addition of the second aldehyde. Using these new conditions the pyran products **20** and **21** were formed in good yield, although no *in situ* decarboxylation was observed (Scheme 11, Table 6). It was a surprise, however, to discover that in all cases the 2,6 diastereoselectivity was completely reversed, with respect to the titanium tetrachloride promoted pyran forming reaction using Chan's diene, giving predominantly the 2,6 *cis* isomer **20**.

With the use of forcing conditions it did prove possible to effect an *in situ* decarboxylation of the pyran products. After the pyran reaction was complete, trifluoroacetic acid was added to the reaction mixture. Stirring of the reaction for 12 hours at room temperature gave a more polar compound, although subsequent heating gave the pyran-4-one products **22** and **23** in moderate yield (Scheme 12, Table 7). It was interesting to note that in the reaction to give the bisphenyl product, entry 1 Table 10, the ratio of the 2,6 *cis* to the 2,6 *trans* isomer was exactly the same as that seen when the reaction was stopped to give the ester compound. This suggests that the conditions employed for the decarboxylation did not alter the equilibrium between the 2,6 *cis* and the 2,6 *trans* compounds and implies that the *trans* isomer undergoes decarboxylation by tautomerising to the keto form of the 2,6 *trans* isomer.



Scheme 12 *Reagents and conditions*: (i) $TiCl_4$, RCHO, −78 °C then TFA, py, R^1CHO, −78 °C to RT, then TFA, 12 h then py, 80 °C, 6 h.

Table 7 The decarboxylative Maitland–Japp reaction

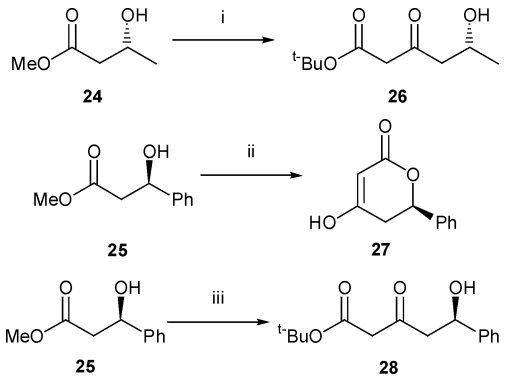
Compound	R	R^1	Yield (%)[a]	Ratio[b] **22** : **23**
b	Ph	Ph	92	4 : 1
d	Ph	^{i}Pr	64	10 : 1
e	C_8H_{17}	Ph	33	5 : 1

[a] Isolated yield after flash column chromatography. [b] Determined from the ^{1}H NMR (400 MHz) of the crude reaction mixture.

Asymmetric synthesis of tetrahydropyran-4-ones

The development of the Maitland–Japp reaction had furnished a one-pot, chemo- and diastereoselective process that was applicable to a wide range of aldehydes to give the tetrahydropyran-4-one products in good yields. To be a truly useful process to the synthetic chemist it was deemed necessary to develop an asymmetric version of the reaction. We rationalised that if the sense of chirality of the initially formed hydroxyl stereocentre could be controlled, then it may prove possible to use this stereocentre to control the sense of the other stereocentres formed in the cyclisation reaction. However, under the reaction conditions there is the clear potential for the hydroxyl stereocentre to racemise either *via* a retro-aldol reaction or *via* formation of a stabilised cation. This would obviously thwart any attempt to develop an asymmetric version of the Maitland–Japp reaction.

In order to assess the feasibility of an asymmetric Maitland–Japp reaction it was decided to study the cyclisation of δ-hydroxy β-ketoesters synthesised from starting materials available from the chiral pool. The compounds **24** and **25** were commercially available in enantiomerically pure form, and the Claisen condensation of **24** with the anion of *tert*-butyl acetate proceeded smoothly to give the δ-hydroxy β-ketoester **26** in respectable yield.[20] However, when these conditions were applied to **25** the δ-hydroxy β-ketoester **28** was formed in only 50% conversion, by analysis of the ^{1}H NMR of the crude reaction mixture, and was found to be inseparable from the starting material. In an attempt to drive the reaction to completion the temperature of the reaction was raised but this resulted in the formation of the lactone **27**. It eventually proved possible to deliver the desired product **28** in 82% yield by extending the reaction time at −20 °C to 12 hours (Scheme 13).

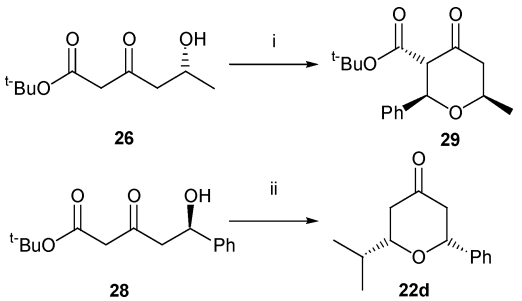


Scheme 13 *Reagents and conditions*: (i) $CH_3CO_2{}^tBu$, LDA, −78 °C, 72%; (ii) $CH_3CO_2{}^tBu$, LDA, −78 °C–RT, 55%; (iii) $CH_3CO_2{}^tBu$, LDA, −20 °C, 82%.

With the enantiomerically pure precursors to cyclisation in hand, the previously developed cyclisation conditions were employed. Treatment of **26** with benzaldehyde and titanium tetrachloride/pyridine gave the pyran product **29** in a 10.0 : 1.0 ratio in favour of the 2,6 *cis* isomer with no erosion of enantiomeric excess by chiral shift ^{1}H NMR spectroscopy. In the case of **28** the decarboxylative variant of the reaction was used to give the 2,6 *cis* substituted pyranone **22d**, in a 10 : 1.0 ratio to the 2,6 *trans* isomer, again with no loss of enantiomeric excess by chiral shift ^{1}H NMR spectroscopy (Scheme 14). For details of chiral shift NMR experiments see supporting information.‡

Conclusions

A number of cyclisation strategies inspired by the Maitland–Japp reaction have been developed. The two-pot approach utilised an anionic aldol reaction followed by a Lewis acid mediated Knoevenagel condensation and concomitant oxy-Michael ring closure to give the pyran products in reasonable yield. By using a Lewis acid mediated aldol reaction it was possible to



Scheme 14 *Reagents and conditions*: (i) $TiCl_4$, py, PhCHO, 55%; (ii) $TiCl_4$, $(CH_3)_2CHCHO$, TFA, py, reflux, 70%.

develop a one-pot reaction that gave the pyran products in excellent yield. The reaction mechanism was elucidated and it proved possible to alter the diastereoselectivity of the reaction by changing the Lewis acid and the nature of the diene used in the reaction. The transfer of chiral information in the pyran forming reaction has been demonstrated and this led to the formation of enantiomerically pure pyran products in good yield. Work is ongoing to develop an asymmetric aldol reaction which can be combined with the Knoevenagel/oxy-Michael reactions and thus develop a one-pot procedure for the asymmetric synthesis of highly functionalised tetrahydropyran-4-ones.

Experimental

General

All NMR spectra were recorded as chloroform solutions. Thin layer chromatography (TLC) was performed on pre-coated plates (0.25 mm) silica UV254. The plates were developed using ultraviolet light, basic potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluka. Dichloromethane was distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenoneketyl. Benzene, DMSO and MeCN were all distilled from calcium hydride prior to use. Hexane was distilled prior to use. All other solvents and reagents were used as received from commercial suppliers.

General method for synthesis of aldol products

To a slurry of sodium hydride (414 mg, 10.34 mmol) in THF (20 mL) at 0 °C was added methyl acetoacetate (100 mg, 8.62 mmol) slowly over 5 min during which time gas evolution was observed. The colourless solution was stirred for 10 min at 0 °C and then *n*-butyllithium (3.79 mL, 9.48 mmol, 2.5 M in hexanes) was added. The light yellow solution was stirred at room temperature for 20 min and was then cooled in an acetone–dry ice bath. Once the internal temperature had reached −78 °C the aldehyde (9.48 mmol) was added over a 5 min period. The solution was kept at −78 °C for 5 min and was then warmed to room temperature over 30 min. The light yellow solution was stirred for 30 min and then H_2O (10 ml) was added. The mixture was extracted with EtOAc (50 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the aldol products **1** which were used without further purification.

5-Hydroxy-3-oxo-5-phenyl-pentanoic acid methyl ester 1a[21]. Colourless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.27 (5H, m, Ph), 5.20 (1H, dd, J = 9.3, 3.4 Hz, H-5), 3.74 (3H, s, OMe), 3.51 (2H, s, H-2), 3.02 (1H, dd, J = 17.2, 9.3 Hz, H-4), 2.91 (1H, dd, J = 17.2, 3.4 Hz, H-4) ppm.

5-Hydroxy-6-methyl-3-oxo-heptanoic acid methyl ester 1b. Colourless oil. ν_{max} (film) 3424 (OH), 2961, 2876, 1743 (C=O), 1713 (C=O), 1439, 1327, 1272, 1042 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.84 (1H, ddd, J = 9.1, 5.8, 2.9 Hz, H-5), 3.74 (3H, s, OMe), 3.51 (2H, s, H-2), 2.71 (1H, dd, J = 17.3, 2.9 Hz, H-4), 2.61 (1H, dd, J = 17.3, 9.1 Hz, H-4), 1.70 (dseptets, J = 6.7, 5.8 Hz, H-6), 0.93 (3H, d, J = 6.7 Hz, H-7 or 8), 0.91 (3H, d, J = 6.7 Hz, H-7 or 8) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.9, 167.5, 72.2, 52.4, 49.8, 46.8, 33.1, 18.5, 17.6 ppm; m/z (ES+) 252 (20%, M^+ + Na + CH_3CN), 211 (100%, M^+ + Na), 171 (40%, M^+ − OH); HRMS: found (M^+ + Na), 211.0962. $C_9H_{16}O_4$ requires (M^+ + Na), 211.0946.

5-Hydroxy-3-oxo-undecanoic acid methyl ester 1c. Colourless oil. ν_{max} (film) 3453 (OH), 2927, 2856, 1747 (C=O), 1714 (C=O), 1437, 1323, 1240 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.08 (1H, dddd, J = 8.8, 7.7, 4.4, 2.9 Hz, H-5), 3.73 (3H, s, OMe), 3.48 (2H, s, H-2), 2.71 (1H, dd, J = 17.2, 2.9 Hz, H-4), 2.63 (1H, dd, J = 17.2, 8.8 Hz, H-4), 1.52–1.22 (11H, m, H-6–10 + OH), 0.86 (3H, t, J = 7.0 Hz, H-11) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.6, 167.3, 67.5, 52.4, 49.6, 36.4, 31.7, 29.6, 29.1, 25.3, 22.5, 14.0 ppm; m/z (EI+) 294 (30%, M^+ + CH_3CN + Na), 253 (100%, M^+ + Na), 213 (40%, M^+ − Me); HRMS: found (M^+ + CH_3CN + Na), 294.1696. $C_{12}H_{22}O_4$ requires (M^+ + CH_3CN + Na), 294.1681; Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found C, 62.80; H 9.83%.

5-Hydroxy-3-oxo-tridecanoic acid methyl ester 1d. Colourless oil. ν_{max} (film) 3418 (OH), 2924, 2855, 1746 (C=O), 1714 (C=O), 1438, 1323, 1260 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.05 (1H, dddd, J = 8.8, 7.7, 4.4, 2.9 Hz, H-5), 3.73 (3H, s, OMe), 3.49 (2H, s, H-2), 2.71 (1H, dd, J = 17.6, 2.9 Hz, H-4), 2.64 (1H, dd, J = 17.6, 8.8 Hz, H-4), 1.52–1.21 (15H, m, H-6–12 + OH), 0.86 (3H, t, J = 7.0 Hz, H-13) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.8, 167.5, 67.6, 52.5, 49.7, 36.5, 33.7, 31.9, 29.6, 29.3, 25.6, 25.5, 22.7, 14.2 ppm; m/z (ES+) 281 (100%, M^+ + Na), 241 (30%, M^+ − Me); HRMS: found (M^+ + Na), 281.1732. $C_{14}H_{26}O_4$ requires (M^+ + Na), 281.1728

General procedure for the pyran forming reaction

To a stirred mixture of the δ-hydroxy β-ketoester (0.25 mmol) in CH_2Cl_2 (2 ml) at room temperature was added the aldehyde (0.30 mmol) followed by boron trifluoride etherate (32 μL, 0.25 mmol). The yellow solution was stirred at room temperature for 3 h and was then taken up in EtOAc (20 ml) and washed with 5% sodium metabisulfite (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 19 EtOAc–petroleum ether) gave the pyran products **5** and **6**.

(2*R, 3*R**, 6*R**)-2-Furyl-6-phenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 5a.** White solid. Mp: 88–90 °C; ν_{max} (film) 2950, 2920, 2845, 1745 (C=O), 1716 (C=O), 1657, 1440, 1345, 1264, 1217 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.44 (1H, dd, J = 1.8, 0.6 Hz, H-16), 7.43–7.30 (5H, m, Ph), 6.44 (1H, d, J = 3.2 Hz, H-14), 6.37 (1H, dd, J = 3.2, 1.8 Hz, H-15), 5.20 (1H, d, J = 11.1 Hz, H-2), 4.89 (1H, dd, J = 10.8, 3.4 Hz, H-6), 4.03 (1H, dd, J = 11.1, 0.9 Hz, H-3), 3.73 (3H, s, OMe), 2.83 (1H, dd, J = 14.6, 3.4 Hz, H-5eq), 2.77 (1H, ddd, J = 14.6, 10.8, 0.9 Hz, H-5ax) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 200.7, 183.2, 150.7, 143.3, 128.7, 128.6, 126.1, 125.9, 110.4, 109.1, 78.6, 73.8, 60.6, 52.4, 48.7 ppm; m/z (CI+) 318 (62%, M^+ + NH_4), 301 (22%, M^+ + H), 283 (28%, M^+ − OH) 222 (58%), 205 (52%, M^+ + H-furfural); HRMS: found (M^+ + NH_4), 318.1342. $C_{17}H_{16}O_5$ requires (M^+ + NH_4), 318.1341.

(2*R, 6*S**)-2-Furyl-4-hydroxy-6-phenyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6a.** White solid. Mp: 81–83 °C; ν_{max} (film) 2958, 2930, 1729 (C=O), 1466, 1275, 1124, 1073 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.16 (1H, s, OH), 7.42 (1H, dd, J = 1.8, 0.9 Hz, H-16), 7.37–7.28 (5H, m, Ph), 6.35 (1H, dd, J = 3.2, 1.8 Hz, H-15), 6.26 (1H, ddd, J = 3.2, 0.9, 0.6 Hz, H-14), 5.77 (1H, brs, H-2), 4.74 (1H, dd, J = 10.8, 4.1 Hz, H-6), 3.71 (3H, s, OMe), 2.69 (1H, ddd, J = 18.1, 10.8,

0.9 Hz, H-5), 2.58 (1H, dd, J = 18.1, 4.1 Hz, H-5) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.0 (s), 170.7 (s), 153.3 (s), 142.8 (d), 140.6 (s), 128.5 (d), 127.9 (d), 125.9 (d), 110.0 (d), 109.8 (d), 97.1 (s), 69.2 (d), 67.0 (d), 51.7 (q), 35.5 (t), ppm; m/z (EI+) 300 (23%, M^+), 268 (100%), 250 (43%); HRMS: found (M^+), 300.0994. $C_{17}H_{16}O_5$ requires (M^+), 300.0998.

(2*R, 3*R**, 6*S**)-2,6-Bisphenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 5b.** White solid. Mp: 133–135 °C; ν_{max} (film) 2953, 2921, 1747 (C=O), 1717, (C=O), 1496, 1455, 1274, 1067, 757, 699 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50–7.30 (10H, m, Ph), 5.13 (1H, d, J = 10.6 Hz, H-2), 4.95 (1H, dd, J = 11.3, 3.0 Hz, H-6), 3.77 (1H, dd, J = 10.6, 0.8 Hz, H-3), 3.70 (3H, s, OMe), 2.86 (1H, dd, J = 14.3, 3.0 Hz, H-5eq), 2.79 (1H, ddd, J = 14.3, 11.2, 0.8 Hz, H-5ax) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 201.1 (s), 167.8 (s), 139.9 (s), 138.6 (s), 128.8 (d), 128.8 (d), 128.6 (d), 128.1 (d), 126.8 (d), 125.6 (d), 81.0 (d), 78.9 (d), 64.6 (d), 52.1 (q), 48.9 (t) ppm; m/z (CI+) 310 (62%, M^+), 293 (100%, $M^+ - OH$); HRMS: found (M^+), 310.1195. $C_{19}H_{18}O_4$ requires (M^+) 310.1205. Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found C, 73.22; H 5.95% and the minor enol tautomer of the 2,6 *cis* isomer:

9b ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50–7.30 (10H, m, Ph), 5.55 (1H, dd, J = 2.3, 1.9 Hz, H-2), 4.78 (1H, dd, J = 10.7, 2.7 Hz, H-6), 3.50 (3H, s, OMe), 2.79 (1H, ddd, J = 17.2, 10.7, 2.3 Hz, H-5), 2.61 (1H, ddd, J = 17.2, 2.7, 1.9 Hz, H-5) ppm.

(2*R, 6*R**)-4-Hydroxy-2,6-diphenyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6b.** White solid. Mp: 118–120 °C; ν_{max} (film) 2955, 2918, 2849, 1745 (C=O), 1662, 1443, 1269, 1219, 1063, 698 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.38 (1H, s, OH), 7.57–7.28 (10H, m, Ph), 5.80 (1H, d, J = 1.0 Hz, H2), 4.59 (1H, dd, J = 10.8, 3.9 Hz, H-6), 3.67 (3H, s, OMe), 2.73 (1H, ddd, J = 18.1, 10.8, 1.0 Hz, H-5), 2.60 (1H, dd, J = 18.1, 3.9 Hz, H-5) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.2, 165.8, 141.0, 140.8, 128.8, 128.4, 128.0, 127.9, 126.9, 126.0, 98.7, 73.7, 68.3, 52.2, 35.6 ppm; m/z (CI+) 310 (50%, M^+), 279 (10%, $M^+ - OMe$), 233 (77%, $M^+ - Ph$); HRMS: found (M^+), 310.1205. $C_{19}H_{18}O_4$ requires (M^+), 310.1205. Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found C, 73.32; H 5.75%.

(2*R, 6*R**)-4-Hydroxy-6-(2-methyl-ethyl)-2-propyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6c.** Colourless oil. ν_{max} (film) 2954, 2873, 1723 (C=O), 1663, 1624, 1271, 1220, 1065 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.05 (1H, s, OH), 4.46 (1H, d, J = 10.3 Hz, H-2), 3.76 (3H, s, OMe), 3.47 (1H, ddd, J = 9.3, 7.3, 4.9 Hz, H-6), 2.25 (1H, dd, J = 17.6, 9.3 Hz, H-5), 2.19 (1H, dd, J = 17.6, 4.9 Hz, H-5), 1.68 (1H, dq, J = 7.3, 6.8 Hz, H-7), 1.6–1.3 (4H, m, H-10 + H-11), 0.99 (3H, d, J = 6.8 Hz, H-8 or 9), 0.93 (3H, t, J = 7.3 Hz, H-12), 0.92 (3H, d, J = 6.8 Hz, H-8 or 9); ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 203.2, 168.8, 81.8, 78.1, 63.3, 52.1, 44.6, 37.2, 33.4, 18.7, 18.2, 18.0, 13.8 ppm; m/z (ES+) 306 (100%, $M^+ + Na + CH_3CN$), 265 (38%, $M^+ + Na$), 243 (37%, $M^+ + H$), 171 (63%, $M^+ + H - C_3H_7CHO$); HRMS: found ($M^+ + Na + CH_3CN$), 306.1673. $C_{13}H_{22}O_4$ requires ($M^+ + Na + CH_3CN$), 306.1681.

(2*S, 3*R**, 6*R**)-6-(2-Methyl-ethyl)-4-oxo-2-propyl-tetrahydro-pyran-3-carboxylic acid methyl ester 5c.** Colourless oil. ν_{max} (film) 2961, 2933, 2873, 1748 (C=O), 1717(C=O), 1260, 1123 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.48 (1H, ddd, J = 10.5, 8.7, 2.6 Hz, H-2), 3.77 (3H, s, OMe), 3.34 (1H, ddd, J = 11.6, 6.7, 2.4 Hz, H-6), 3.23 (1H, dd, J = 10.5, 0.8 Hz, H-2), 2.51 (1H, dd, J = 14.2, 2.4 Hz, H-5), 2.25 (1H, ddd, J = 14.2, 11.6, 0.8 Hz), 1.80 (1H, dseptets, J = 6.7, 6.7 Hz, H-7), 1.55 (4H, m, H-10,11), 1.00 (3H, d, J = 6.7 Hz, H-8 or 9), 0.92 (3H, d, J = 6.8 Hz, H-8 or 9), 0.91 (3H, t, J = 7.2 Hz, H-12); ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 203.2 (s), 168.8 (s), 81.8 (d), 78.1 (d), 63.3 (d), 52.1 (q), 44.6 (t), 37.2 (t), 33.4 (d), 18.7 (t), 18.2 (q), 18.0 (q), 13.8 (q); m/z (ES+) 260 (100%, $M^+ + NH_4$), 243 (22%, $M^+ + H$); HRMS: found ($M^+ + NH_4$), 260.1863. $C_{13}H_{22}O_4$ requires ($M^+ + NH_4$), 260.1862.

(2*R, 6*R**)-4-Hydroxy-6-(2-methyl-ethyl)-2-hexyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6d.** Colourless oil. ν_{max} (film) 2951, 2861, 1663 (C=O), 1624, 1443, 1270, 1221 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.04 (1H, s, OH), 4.44 (1H, d, J = 9.6, 2.7 Hz, H-2), 3.76 (3H, s, OMe), 3.47 (1H, ddd, J = 9.3, 7.3, 4.4 Hz, H-6), 2.25 (1H, dd, J = 17.6, 9.3 Hz, H-5), 2.18 (1H, dd, J = 17.6, 4.4 Hz, H-5), 1.67 (1H, dseptets, J = 7.3, 6.9 Hz, H-7), 1.65–1.20 (10H, m, H-10–14), 0.99 (3H, d, J = 6.9 Hz, H-8 or 9), 0.92 (3H, d, J = 6.9 Hz, H-8 or 9), 0.89 (3H, t, J = 7.4 Hz, H-15); ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.1 (s), 169.9 (s), 101.5 (s), 71.1 (d), 70.8 (d), 51.4 (q), 33.2 (t), 33.0 (t), 32.7 (d), 32.2 (t), 28.9 (t), 26.0 (t), 22.6 (t), 18.7 (q), 18.2 (q), 14.1 (q); m/z (CI+) 285 (39%, $M^+ + H$), 267 (37%, $M^+ - OH$), 199 (100%, $M^+ - C_6H_{13}$); HRMS: found ($M^+ + H$), 285.2055. $C_{16}H_{28}O_4$, requires 285.2066.

(2*S, 3*R**, 6*R**)-6-(2-Methyl-ethyl)-2-hexyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 5d.** Colourless oil. ν_{max} (film) 2957, 2929, 1749 (C=O), 1718 (C=O), 1463, 1362, 1262, 1121 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.83 (1H, m, H-2), 3.77 (3H, s, OMe), 3.34 (1H, ddd, J = 11.7, 6.8, 2.4 Hz, H-6), 3.23 (1H, dd, J = 10.5, 0.8 Hz, H-3), 2.52 (1H, dd, J = 14.2, 2.4 Hz, H-5eq), 2.26 (1H, ddd, J = 14.2, 11.7, 0.8 Hz, H-5ax), 1.79 (1H, m, H-7), 1.56 (4H, m, H-10,11), 1.29 (6H, m, H-12,13,14), 0.95 (9H, m, H-8,9,15); ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 203.3 (s), 168.9 (s), 81.9 (d), 78.5 (d), 63.5 (d), 52.2 (q), 44.7 (t), 35.2 (t), 33.5 (d), 31.8 (t), 29.0 (t), 25.4 (t), 22.7 (t), 18.3 (q), 18.2 (q), 14.1 (q) ppm; m/z (CI+) 285 (62%, $M^+ + H$), 214 (100%, $M^+ - C_5H_{11}$), 199 (20%, $M^+ - C_6H_{13}$); HRMS: found ($M^+ + H$), 285.2059. $C_{16}H_{28}O_4$ requires ($M^+ + H$) 285.2066.

(2*S, 3*R**, 6*R**)-6-Octyl-2-phenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 5e.** Colourless oil. ν_{max} ($CHCl_3$) 2928, 2856, 1744 (C=O), 1715 (C=O), 1657, 1456, 1346, 1124, 1065, 992 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.22 (5H, m, Ph), 4.90 (1H, d, J = 10.4 Hz, H-2), 3.85 (1H, dddd, J = 11.6, 7.3, 6.1, 2.4 Hz, H-6), 3.61 (3H, s, OMe), 3.59 (1H, 1H, d, J = 10.4 Hz, H-3), 2.57 (1H, dd, J = 14.6, 2.4 Hz, H-5eq), 2.42 (1H, dd, J = 14.6, 11.6 Hz, H-5ax), 1.74 (1H, m, H-7), 1.60 (1H, m, H-7), 1.43–1.20 (12 H, m, H-8–13), 0.87 (3H, t, J = 7.3 Hz, H-14) ppm; ^{13}C NMR (65 MHz; $CDCl_3$) δ 202.0, 168.0, 138.9, 128.6, 127.9, 126.7, 80.7, 76.3, 64.5, 52.0, 47.0, 36.2, 31.8, 29.7, 29.4, 29.2, 25.2, 22.6, 14.1 ppm; m/z (CI+) 346 (55%, M^+), 315 (23%, $M^+ - OMe$), 287 (100%, $M^+ - CO_2Me$), 269 (81%, $M^+ - Ph$); HRMS: found (M^+) 346.2145. $C_{21}H_{30}O_4$ requires (M^+) 346.2144.

(2*S, 3*R**, 6*R**)-6-Heptyl-2-propyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 5f.** ν_{max} (film) 2956, 2932, 1747 (C=O), 1718 (C=O), 1458, 1436, 1339, 1260, 1128, 1032 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.86 (1H, ddd, J = 10.5, 8.5, 2.6 Hz, H-2), 3.77 (3H, s, OMe), 3.62 (1H, dddd, J = 11.4, 8.2, 4.1, 2.3 Hz, H-6), 3.22 (1H, dd, J = 10.5, 0.8 Hz, H-3), 2.46 (1H, dd, J = 14.3, 2.3 Hz, H-5eq), 2.25 (1H, ddd, J = 14.3, 11.4, 0.8 Hz, H-5ax), 1.70–1.21 (14H, m, H-7 to H-11–13 + H-14) 0.92 (6H, m, H-12 + H-15) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 203.6, 169.7, 79.1, 64.2, 53.0, 48.2, 38.1, 37.1, 32.6, 29.9, 26.1, 23.5, 19.6, 14.9, 14.7 ppm; m/z (CI+) 302 (100%, $M^+ + NH_4$), 285 (33%, $M^+ + H$); HRMS: found ($M^+ + NH_4$), 285.2063. $C_{16}H_{28}O_4$ requires ($M^+ + NH_4$), 285.2066.

2,6 Bisphenyl pyran-4-one 7 and 8. To a solution of 2,6-bisphenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester **5b** and 4-hydroxy-2,6-diphenyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester **5b** (310 mg, 1.00 mmol) in THF–H_2O (10 mL, 4 : 1) was added hydrogen peroxide (450 µL, 4.00 mmol) followed by lithium hydroxide (38 mg, 1.60 mmol). The reaction vessel was fitted with a reflux condenser and heated at 80 °C for 4 days. The colourless solution was diluted with

EtOAc (30 mL) and washed with sodium metabisulfite (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 10 EtOAc–petroleum ether) gave pyran products **7** and **8** as an inseparable mixture (204 mg, 82%) the data of which matched that previously reported.

7 ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.48–7.31 (10H, m, Ph), 4.86 (2H, dd, J = 10.3, 3.4 Hz, H-2 + H-6), 2.68 (2H, dd, J = 13.7, 3.4 Hz, H-3eq + H-5eq), 2.68 (2H, dd, J = 13.7, 10.3 Hz, H-3ax + H-5ax) ppm.

8 ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.48–7.31 (10H, m, Ph), 5.14 (2H, dd, J = 6.4, 5.4 Hz, H-2 + H-6), 2.93 (2H, ddd, J = 14.7, 6.4, 1.0 Hz, H-3 + H-5), 2.85 (2H, ddd, J = 14.7, 5.4, 1.0 Hz, H-3 + H-5) ppm.

General procedure for the one-pot Maitland–Japp reaction. The titanium tetrachloride promoted reaction

To a solution of aldehyde (1.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added titanium tetrachloride (111 μL, 1.00 mmol). The black solution was stirred for 2 min and then Chan's diene (570 μL, 2.00 mmol) was added over a 1 min period. The black solution was stirred at −78 °C for 1 h and then trifluoroacetic acid (308 μL 4 mmol) was added. After 2 min the second aldehyde (1.20 mmol) was added and the solution was allowed to warm to room temperature over a 5 min period. The black solution was stirred at room temperature for 2 h and was then diluted with EtOAc (40 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL), 5% sodium metabisulfite (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 19 EtOAc–petroleum ether) gave the pyran products **5** and **6**.

General procedure for the one-pot Maitland–Japp reaction. The ytterbium triflate promoted reaction

To a suspension of ytterbium(III) triflate (620 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added aldehyde (1 mmol) followed by Chan's diene (570 μL, 2.00 mmol). The white mixture was stirred at −78 °C for 40 min and then trifluoroacetic acid (308 μL, 4 mmol) was added followed by the second aldehyde (1.2 mmol). The mixture was warmed to room temperature over 5 min and then stirred at room temperature for 2 h. The mixture was then diluted with EtOAc (40 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 19 EtOAc–petroleum ether) gave pyran products **5** and **6**, which were spectroscopically identical to those made *via* the titanium tetrachloride method.

(2*R, 6*R**)-4-Hydroxy-6-(2-methyl-ethyl)-2-phenyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6g.** White solid. Mp: 57–58 °C; ν_{max} (film) 2957, 1661, 1624, 1442, 1269, 1223 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.32 (1H, s, OH), 7.38–7.30 (5H, m, Ph), 5.65 (1H, s, H-2), 3.65 (3H, s, OMe), 3.14 (1H, ddd, J = 10.8, 6.8, 3.9 Hz, H-6), 2.38 (1H, dd, J = 18.1, 10.8 Hz, H-5ax), 2.25 (1H, dd, J = 18.1, 3.9 Hz, H-5eq), 1.63 (1H, oct, J = 6.8 Hz, H-7), 0.83 (3H, d, J = 6.8 Hz, H-8 or 9), 0.80 (3H, d, J = 6.8 Hz, H-8 or 9) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.8, 171.0, 140.9, 128.4, 127.9, 127.6, 98.5, 72.5, 71.4, 51.5, 32.6, 32.2, 18.3, 17.7 ppm; m/z (CI+) 276 (65%, M$^+$), 199 (100%, M$^+$ − Ph), 167 (82%); HRMS: found (M$^+$), 276.1360. $C_{16}H_{20}O_4$ requires (M$^+$), 276.1362.

(2*R, 3*R**, 6*S**)-6-(2-Methyl-ethyl)-4-oxo-2-phenyl-tetrahydro-pyran-3-carboxylic acid methyl ester 5g.** White solid. Mp: 59–61 °C; ν_{max} (film) 3031, 2964, 1746, 1717, 1250 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40–7.29 (5H, m, Ph), 4.90 (1H, d, J = 10.4 Hz, H-2), 3.62 (1H, ddd, J = 11.6, 6.7, 2.4 Hz, H-6), 3.61 (3H, s, OMe), 3.57 (1H, d, J = 10.4 Hz, H-3), 2.57 (1H, dd, J = 14.0, 11.6 Hz, H-5ax), 2.45 (1H, dd, J = 14.0, 2.4 Hz, H-5eq), 1.91 (1H, octet, J = 6.7 Hz, H-7), 0.99 (3H, d, J = 6.7 Hz, H-8 or 9), 0.97 (3H, d, J = 6.7 Hz, H-8 or 9) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.6 (s), 168.1 (s), 139.2 (s), 128.6 (d), 128.6 (d), 126.7 (d), 81.9 (d), 80.6 (d), 52.1 (q), 43.9 (t), 33.1 (d), 18.8 (q), 17.8 (q) ppm; m/z (CI+) 276 (72%, M$^+$), 199 (100%, M$^+$ − Ph), 167 (75%); HRMS: found (M$^+$), 276.1359. $C_{16}H_{20}O_4$ requires (M$^+$), 276.1362.

Minor enol tautomer **9g**, constituting 20% of the purified sample by ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40–7.28 (5H, m, Ph), 5.30 (1H, dd, J = 2.6, 1.8 Hz, H-2), 3.46 (3H, s, OMe), 3.38 (1H, ddd, J = 10.6, 6.7, 2.9 Hz, H-6), 2.46 (1H, ddd, J = 17.2, 10.6, 2.6 Hz, H-5), 2.31 (1H, ddd, J = 17.2, 2.9, 1.8 Hz, H-5), 1.77 (1H, octet, J = 6.7 Hz, H-7), 0.96 (3H, d, J = 6.7 Hz, H-8 or 9), 0.79 (3H, d, J = 6.7 Hz, H-8 or 9) ppm. Upon standing in chloroform this gave the *cis* keto isomer above.

(2*S, 3*R**, 6*R**)-6-(2-Methyl-ethyl)-4-oxo-2-(pent-5-ene)-tetrahydro-pyran-3-carboxylic acid methyl ester 5h.** Colourless oil. ν_{max} (film) 2961, 2876, 1747 (C=O), 1660 (C=O), 1344, 1268, 1222, 1130, 1038, 913 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.75 (1H, dddd, J = 17.1, 10.3, 7.3, 6.4 Hz, H-12), 4.98 (1H, ddt, J = 17.1, 3.4, 2.0 Hz, H-13*trans*), 4.93 (1H, ddt, J = 10.3, 3.4, 1.5 Hz, H-13*cis*), 3.80 (1H, ddd, J = 10.8, 9.3, 2.9 Hz, H-2), 3.70 (3H, s, OMe), 3.28 (1H, ddd, J = 11.7, 6.8, 2.0 Hz, H-6), 3.19 (1H, dd, J = 10.8, 1.0 Hz, H-3), 2.45 (1H, dd, J = 14.2, 2.0 Hz, H-5eq), 2.23 (1H, ddd, J = 14.2, 11.7, 1.0 Hz, H-5ax), 2.22 (2H, m, H-10), 1.76 (1H, octet, J = 6.8 Hz, H-7), 1.62 (2H, m, H-11), 0.99 (3H, d, J = 6.8 Hz, H-8 or 9), 0.90 (3H, d, J = 6.8 Hz, H-8 or 9) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.7, 168.6, 137.6, 115.1, 81.7, 77.4, 63.1, 52.0, 44.6, 34.1, 33.4, 29.5, 18.2, 18.1 ppm; m/z (ES+) 318 (68%, M$^+$ + Na + CH_3CN), 277 (100%, M$^+$ + Na), 171 (98%, M$^+$ + H–CH_2=$CH(CH_2)_2CHO$); HRMS: found (M$^+$ + Na), 277.1425. $C_{14}H_{22}O_4$ requires (M$^+$ + Na) 277.1416.

(2*R, 6*R**)-4-Hydroxy-6-(2-methyl-ethyl)-4-oxo-2-(pent-5-ene)-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6h.** Colourless oil. ν_{max} (film) 2956, 1748, 1662 (C=O), 1623, 1443, 1365, 1270, 1221, 1067 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.04 (1H, s, OH), 5.85 (1H, ddt, J = 17.2, 10.3, 6.8 Hz, H-12), 5.07 (1H, ddt, J = 17.2, 1.5, 1.5 Hz, H-13*cis*), 4.97 (1H, ddt, J = 10.3, 1.5, 1.5 Hz, H-13*trans*), 4.46 (1H, d, J = 6.8 Hz, H-2), 3.75 (3H, s, OMe), 3.46 (1H, ddd, J = 12.7, 7.3, 5.4 Hz, H-6), 2.22 (4H, m, H-5 + H-10), 1.69 (3H, m, H-7 + H-11), 1.00 (3H, d, J = 6.8 Hz, H-8 or 9), 0.92 (3H, d, J = 6.8 Hz, H-8 or 9) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ (67.8 MHz; $CDCl_3$) 171.0 (s), 170.1 (s), 138.3 (d), 114.5 (t), 101.1 (s), 70.9 (d), 70.5 (d), 51.4 (q), 33.1 (d), 32.1 (t), 31.8 (t), 30.2 (t), 18.7 (q), 18.2 (q) ppm; m/z (ES+) 318 (48%, M$^+$ + Na + CH_3CN), 277 (100%, M$^+$ + Na), 255 (12%, M$^+$ + H), 171 (98%, M$^+$ + H–CH_2=$CH(CH_2)_2CHO$); HRMS: found (M$^+$ + Na + CH_3CN), 318.1681. $C_{14}H_{22}O_4$ requires (M$^+$ + Na + CH_3CN) 318.1674.

(2*R, 6*S**)-4-Hydroxy-2-(2-benzyloxy)-methyl-6-propyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6i.** Colourless oil. ν_{max} (film) 2957, 2872, 1661 (C=O), 1622, 1443, 1290, 1217, 1074 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.15 (1H, s, OH), 7.35–7.26 (5H, m, Ph), 4.73 (1H, dd, J = 7.8, 2.0 Hz, H-2), 4.62 (1H, d, J = 12.2 Hz, H-11), 4.55 (1H, 12.2 Hz, H-11), 3.91 (1H, m, H-6), 3.70 (3H, s, OMe), 3.64 (1H, dd, J = 10.8, 7.8 Hz, H-10), 3.54 (1H, dd, J = 10.8, 2.0 Hz, H-10), 2.20 (2H, m, H-5), 1.60 (2H, m, H-7), 1.44 (2H, m, H-8), 0.94 (3H, t, J = 7.3, Hz, H-9) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.5, 170.7, 138.4, 128.3, 127.7, 127.5, 96.8, 72.9, 71.0, 69.7, 66.7, 51.4, 37.8, 34.2, 18.5, 14.0 ppm; m/z (ES+) 343 (100% M$^+$ + Na), 335 (38%); HRMS: found, (M$^+$ + Na) 343.1529. $C_{18}H_{24}O_5$ requires (M$^+$ + Na) 343.1521.

(2*R, 3*R**, 6*R**)-2-(2-Benzyloxy)-methyl-6-propyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 5i.** ν_{max} (film) 2957, 2872, 1746 (C=O), 1716 (C=O), 1622, 1438, 1348, 1264, 1128 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35–7.28 (5H, m, Ph), 4.64 (1H, d, J = 12.3 Hz, H-11), 4.50 (1H, d, J = 12.3 Hz,

H-11), 4.11 (1H, ddd, $J = 10.5, 4.1, 3.2$ Hz, H-2), 3.68 (1H, m, H-6), 3.66 (1H, dd, $J = 10.5, 0.9$ Hz, H-3), 3.66 (3H, s, OMe), 3.62 (1H, dd, $J = 10.8, 3.2$ Hz, H-10), 3.58 (1H, dd, $J = 10.8, 4.1$ Hz, H-10), 2.47 (1H, dd, $J = 14.3, 2.4$ Hz, H-5eq), 2.30 (1H, dd, $J = 14.3, 11.4$ Hz, H-5ax), 1.70 (1H, m, H-7), 1.45 (3H, m, H-7 + H-8), 0.93 (3H, t, $J = 7.3$ Hz, H-9) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 202.5 (s), 168.3 (s), 137.7 (s), 128.3 (d), 127.7 (d), 127.7 (d), 77.7 (d), 77.0 (d), 73.5 (t), 70.6 (t), 59.1 (d), 52.0 (q), 47.0 (t), 38.1 (t), 18.4 (t), 13.8 (q) ppm; *m/z* (ES+) 343 (100% $M^+ + Na$), 335 (38%); HRMS: found, ($M^+ + Na$) 343.1552. $C_{18}H_{24}O_5$ requires ($M^+ + Na$) 343.1521.

(2*R, 6*R**)-4-Hydroxy-6-cyclohexyl-4-oxo-2-phenyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6j.** White solid. Mp: 89–91 °C; ν_{max} (film) 2924, 2852, 1661 (C=O), 1624, 1443, 1361, 1277, 1242, 1218, 1051 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.28 (1H, s, OH), 7.35–7.28 (5H, m, Ph), 5.60 (1H, s, H-2), 3.63 (3H, s, OMe), 3.14 (1H, ddd, $J = 10.8, 7.3, 3.9$ Hz, H-6), 2.36 (1H, dd, $J = 17.6, 10.8$ Hz, H-5), 2.23 (1H, dd, $J = 17.6, 3.9$ Hz, H-5), 1.86 (1H, m, H-7), 1.70–1.47 (4H, m, H-8 + 9), 1.36–1.01 (4H, m, H-8 + 9), 0.85 (1H, ddd, $J = 24.5, 12.7, 3.9$ Hz, H-10), 0.66 (1H, ddd, $J = 24.5, 12.7, 3.9$ Hz, H-10) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.9 (s), 140.9 (s), 128.5 (d), 127.9 (d), 127.6 (d), 98.5 (s), 72.5 (d), 70.6 (d), 51.5 (q), 42.3 (d), 32.3 (t), 28.6 (t), 26.3 (t), 25.9 (t), 25.6 (t) ppm; *m/z* (CI+) 334 (100%, $M^+ + NH_4$), 317 (55%, $M^+ + H$); HRMS: found ($M^+ + NH_4$), 334.2013. $C_{19}H_{24}O_4$ requires ($M^+ + NH_4$) 334.2013. Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found C, 71.93; H 7.72%.

(2*S, 3*R**, 6*R**)-6-Cyclohexyl-4-oxo-6-propyl-tetrahydro-pyran-3-carboxylic acid methyl ester 5j.** White solid. Mp: 92–94 °C; ν_{max} (film) 2927, 2854, 1748 (C=O), 1716 (C=O), 1453, 1338, 1136, 1066, 1030, 760, 699 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.30 (5H, m, Ph), 4.89 (1H, d, $J = 10.5$ Hz, H-2), 3.63 (1H, ddd, $J = 11.4, 6.1, 2.6$ Hz, H-6), 3.61 (3H, s, OMe), 3.57 (1H, dd, $J = 10.5, 0.6$ Hz, H-3), 2.58 (1H, dd, $J = 14.0, 2.6$ Hz, H-5eq), 2.46 (1H, ddd, $J = 14.0, 11.4, 0.6$ Hz, H-5ax), 1.91 (1H, m, H-7), 1.80–1.55 (5H, m, H-7–11), 1.27 (5H, m, H-7–11) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 202.7 (s), 168.1 (s), 139.2 (s), 128.7 (d), 128.6 (d), 126.8 (d), 81.5 (d), 80.7 (d), 64.9 (d), 52.1 (q), 44.4 (t), 43.0 (d), 28.6 (t), 28.2 (t), 26.4 (t), 26.0 (t) ppm; *m/z* (ES+) 380 (100%, $M^+ + Na + CH_3CN$), 339 (77%, $M^+ + Na$), 211 (46%); HRMS: found ($M^+ + Na + CH_3CN$), 380.1866. $C_{19}H_{24}O_4$ requires ($M^+ + Na + CH_3CN$) 380.1838. Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found C, 72.12; H 7.72%.

(2*R, 6*R**)-4-Hydroxy-2-(4-methoxyphenyl)-6-propyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 6k.** Colourless oil. ν_{max} (film) 3417, 2932, 1661 (C=O), 1623, 1510, 1443, 1247, 1218, 823 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.28 (1H, s, OH), 7.24 (2H, d, $J = 8.8$ Hz, Ph), 6.87 (2H, d, $J = 8.8$ Hz, Ph), 5.58 (1H, d, $J = 1,0$ Hz, H-2), 3.83 (3H, s, OMe), 3.64 (3H, s, OMe), 3.48 (1H, m, H-6), 2.32 (1H, ddd, $J = 18.1, 10.3, 1.0$ Hz, H-5), 2.24 (1H, dd, $J = 18.1, 4.4$ Hz, H-5), 1.52–1.13 (4H, m, H-7 + H-8), 0.76 (3H, t, $J = 6.9$ Hz, H-9) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.4, 171.1, 159.0, 133.2, 129.5, 113.2, 98.8, 72.1, 65.8, 55.1, 51.5, 37.6, 34.7, 18.2, 13.7 ppm; *m/z* (CI+) 306 (84%, M^+), 275 (50%, $M^+ - OMe$), 247 (80%, $M^+ - CO_2Me$); HRMS: found (M^+), 306.1454. $C_{17}H_{22}O_5$ requires (M^+) 306.1467.

(2*S, 3*R**, 6*R**)-2-(4-Methoxyphenyl)-4-oxo-6-propyl-tetrahydro-pyran-3-carboxylic acid methyl ester 5k.** Colourless oil. ν_{max} (film) 2958, 2872, 1747 (C=O), 1715 (C=O), 1614, 1515, 1251, 1034 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.31 (2H, d, $J = 8.8$ Hz, Ph), 6.87 (2H, d, $J = 8.8$ Hz, Ph), 4.84 (1H, d, $J = 10.6$ Hz, H-2), 3.84 (1H, dddd, $J = 11.7, 9.5, 5.1, 2.2$ Hz, H-6), 3.79 (3H, s, OMe), 3.59 (1H, dd, $J = 10.6, 0.7$ Hz, H-3), 2.55 (1H, dd, $J = 14.3, 2.2$ Hz, H-5eq), 2.41 (1H, ddd, $J = 14.3, 11.7, 0.7$ Hz, H-5ax), 1.71 (1H, dddd, $J = 15.7, 9.9, 7.0, 5.1$ Hz, H-7), 1.56 (1H, dddd, $J = 15.7, 9.9, 9.5, 5.9$ Hz, H-7), 1.43 (2H, m, H-8), 0.92 (3H, t, $J = 7.3$ Hz, H-9) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 202.1 (s), 168.0 (s), 159.6 (s), 131.0 (s), 128.0 (d), 113.9 (d), 80.4 (d), 77.0 (d), 64.5 (d), 55.2 (q), 51.9 (q), 46.9 (t), 38.2 (t), 18.2 (t), 13.8 (q) ppm; *m/z* (ES+) 370 (90%, $M^+ + Na + CH_3CN$), 329 (100%, $M^+ + Na$); HRMS: found ($M^+ + Na$), 329.1355. $C_{17}H_{22}O_5$ requires ($M^+ + Na$) 329.1365.

(2*S, 3*R**, 6*R**)-2-(2-Methyl-ethyl)-6-phenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 5l.** White solid. Mp: 99–101 °C; ν_{max} (film) 2966, 2934, 1746 (C=O), 1715 (C=O), 1454, 1361, 1132, 1073 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.43–7.32 (5H, m, Ph), 4.73 (1H, dd, $J = 11.7, 2.5$ Hz, H-6), 4.00 (1H, dd, $J = 10.8, 2.9$ Hz, H-2), 3.79 (3H, s, OMe), 3.53 (1H, dd, $J = 10.8, 1.0$ Hz, H-3), 2.75 (1H, dd, $J = 14.2, 2.5$ Hz, H-5eq), 2.52 (1H, ddd, $J = 14.2, 11.7, 1.0$ Hz, H-5ax), 1.84 (1H, dseptets, $J = 6.8, 2.9$ Hz, H-11), 1.10 (3H, d, $J = 6.8$ Hz, H-12 or 13), 1.05 (3H, d, $J = 6.8$ Hz, H-12 or 13) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 202.4, 168.6, 140.8, 128.5, 127.9, 125.2, 82.3, 77.9, 60.5, 52.1, 48.8, 31.5, 19.7, 15.3 ppm; *m/z* (CI+) 276 (5%, M^+), 233 (100%, $M^+ - (CH_3)_2CH$); HRMS: found (M^+) 276.1360. $C_{16}H_{20}O_4$ requires (M^+) 276.1362.

5-Hydroxy-8-methyl-2-methylmethanoate-3-oxo-1-phenyl-non-1,2-ene-8-ene 13. To a solution of 5-hydroxy-3-oxo-8-ene-nonanoic acid methyl ester **12** (200 mg, 0.93 mmol) in CH_2Cl_2 (5 ml) at room temperature was added ethylene diamine diacetate (10 mg, 0.06 mmol) and benzaldehyde (101 mg, 1.10 mmol). The reaction mixture was stirred at room temperature for 20 h at which point TLC analysis still showed the presence of starting material. More ethylene diamine diacetate (10 mg, 0.06 mmol) and benzaldehyde (101 mg, 1.10 mmol) was added to the reaction. After a further 48 h the reaction mixture was taken up in EtOAc (25 ml), washed with 5% sodium metabisulfite (5 × 20 ml), water (2 × 20 ml) and brine (2 × 20 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 19 EtOAc–petroleum ether) gave the title compound **13** as a mixture of geometrical isomers and as a colourless oil. Isomer 1: oil. (150 mg, 56%) ν_{max} (film) 3438, 2956, 2957, 1727, 1620, 1449, 1379, 1269, 1124, 1073, 1039 cm^{-1}; ^{1}H NMR isomer 1 (400 MHz; $CDCl_3$) δ 7.75 (1H, s, H-1), 7.40 (5H, m, Ph), 4.70 (1H, s, H-9), 4.65 (1H, s, H-9), 4.12 (1H, m, H-5), 3.85 (3H, s, OMe), 2.97, (1H, s, OH), 2.77 (1H, dd, $J = 18.1, 3.0$ Hz, H-4), 2.69 (1H, dd, $J = 18.1, 8.5$ Hz, H-4), 2.10 (2H, m, H-6), 1.62 (2H, m, H-7), 1.71 (3H, s, H-10) ppm; ^{1}H NMR Isomer 2 (400 MHz; CDCl3) δ 7.65 (1H, s, H-1), 7.43 (5H, m, Ph), 4.78 (1H, s, H-9), 4.73 (1H, s, H-9), 4.12 (1H, m, H-5), 3.86 (3H, s, OMe), 3.03 (1H, s, OH), 2.94 (1H, dd, $J = 17.5, 3.0$ Hz, H-4), 2.85 (1H, dd, $J = 17.5, 8.6$ Hz, H-4), 2.16 (2H, m, H-6), 1.76 (2H, m, H-7), 1.67 (3H, s, H-10) ppm; ^{13}C NMR isomer 1 (100 MHz; $CDCl_3$) δ 206.5, 165.2, 145.5, 141.9, 133.2, 132.9, 131.0, 130.0, 129.3, 110.4, 67.6, 52.9, 50.4, 34.3, 33.8, 22.7 ppm; ^{13}C NMR isomer 2 (100 MHz; $CDCl_3$) δ 207.1, 168.3, 145.5, 142.3, 141.9, 131.0, 130.0, 129.8, 129.2, 110.5, 67.6, 52.9, 45.6, 34.5, 33.9, 22.7 ppm; *m/z* (CI+) 303 (100%, $M^+ + H$), 302 (50%, M^+), 199; HRMS: found ($M^+ + H$), 303.1599. $C_{18}H_{22}O_4$ requires ($M^+ + H$) 303.1596.

(2*R, 6*R**)-6-(4-Ene-butyl)-4-hydroxy-2-phenyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 14.** To a solution of 5-hydroxy-8-methyl-2-methylmethanoate-3-oxo-1-phenyl-non-1,2-ene-8-ene **13** (50 mg, 0.17 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added boron trifluoride etherate (37 mg, 0.26 mmol). After 1 min the reaction was quenched with water (2 ml). The reaction mixture was taken up in EtOAc (15 ml) and washed with brine (2 × 10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 19 EtOAc–petroleum ether) gave **14** as a coloured solid. Mp: 58–60 °C; (46 mg 92%) ν_{max} (film) 2915, 2869, 1658 (C=O), 1628, 1442, 1355, 1286, 1271, 1219 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35–7.30 (5H, m, Ph), 5.62 (1H, s, H-2), 4.56 (1H,

d, J = 0.7 Hz, H-10), 4.40 (1H, d, J = 0.7 Hz, H-10) 3.63 (3H, s, OMe), 3.47 (1H, dddd, J = 10.4, 8.3, 4.2, 4.2 Hz, H-6), 2.35 (1H, dd, J = 18.0, 10.4 Hz, H-5), 2.26 (1H, dd, J = 18.0, 4.2 Hz, H-5), 2.04 (1H, m, H-7), 1.78 (1H, m, H-7), 1.57 (2H, m, H-8), 1.56 (3H, s, H-11) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.8, 171.5, 144.8, 140.8, 128.4, 128.0, 127.7, 110.1, 98.2, 72.7, 66.0, 51.5, 34.7, 33.5, 33.0, 22.3 ppm; m/z (CI+) 320 (80%, $M^+ + NH_4$), 303 (90%, $M^+ + H$), 231 (43%), 224 (52%), 205 (100%), 177 (85%); HRMS: found ($M^+ + H$), 303.1595. $C_{18}H_{22}O_4$ requires ($M^+ + H$) 303.1596.

2-(2-Methylester-3-oxo-1-phenyl-but-3,4-ene)-5,5-dimethyl-furan 15. To a solution of 5-hydroxy-2-methylester-3-oxo-1-phenyl-non-1,2-ene-8-ene **13** (20 mg, 0.07 mmol) in CH_2Cl_2 (4 ml) at 0 °C was added boron trifluoride etherate (15 mg, 0.11 mmol). After 20 min the reaction mixture was warmed to room temperature. The reaction mixture was stirred for a further 24 h at room temperature and was then quenched with water (2 ml). The reaction mixture was taken up in ethyl acetate (20 ml) and washed with water (3 × 10 ml) and brine (2 × 10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 19 EtOAc–petroleum ether) gave **15** as an oil as two geometric isomers: (16 mg 80%) ν_{max} (film) 2968, 1724, 1704, 1666, 1622, 1576, 1495, 1455, 1392, 1367, 1317, 1266, 1134, 1096, 1048, 1001, 870, 838 cm^{-1}; ^{1}H NMR isomer 2 (400 MHz; $CDCl_3$) δ 7.64 (1H, s, H-11), 7.52–7.36 (5H, m, Ph), 4.43 (1H, m, H-2), 3.85 (3H, s, OMe), 3.18 (1H, dd, J = 16.3, 5.2 Hz, H-8), 2.72 (1H, dd, J = 16.3, 7.6 Hz, H-8), 2.25 (1H, m, H-3), 1.79 (2H, m, H-4), 1.67 (1H, m, H-3), 1.27 (3H, s, H-6 or 7), 1.25 (3H, s, H-6 or 7) ppm; ^{13}C NMR isomer 1 (100 MHz; $CDCl_3$) δ 206.5, 165.2, 145.5, 141.9, 133.0, 131.0, 130.0, 129.3, 110.4, 67.6, 52.9, 50.4, 34.3, 33.8, 22.7 ppm; ^{13}C NMR isomer 2 (100 MHz; $CDCl_3$) δ 207.1, 168.3, 145.5, 142.3, 131.0, 130.0, 129.8, 129.2, 110.5, 67.6, 52.9, 45.6, 34.5, 33.9, 22.7 ppm; m/z (ES+) 303 (75%, $M^+ + H$), 302 (85%, M^+), 243 (65%, $M^+ - CO_2Me$); HRMS: found ($M^+ + H$), 303.1596. $C_{18}H_{22}O_4$ requires ($M^+ + H$) 303.1599.

Bis (5-hydroxy-3-oxo-5-phenyl-pentanoic acid methyl ester) 16. To a solution of benzaldehyde (102 μL, 1.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added titanium tetrachloride (111 μL, 1.00 mmol). The black solution was stirred for 2 min and then Chan's diene (570 μL, 2.00 mmol) was added over a 1 min period. The black solution was stirred at −78 °C for 1 h and then trifluoroacetic acid (308 μL 4 mmol) was added. After 15 min, the solution was raised to 40 °C and stirred at this temperature for 75 min and was then diluted with Et_2O (40 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 10 EtOAc–petroleum ether) gave the dimer **16** as a yellow oil (81 mg, 73%) ν_{max} (film) 3032, 2953, 1747, 1719, 1654, 1494, 1437, 1330, 1265, 1200, 695 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.42–7.29 (10 H, m, Ph), 5.38 (2H, dd, J = 8.3, 5.4 Hz, H-5), 3.72 (6H, s, OMe), 3.48 (2H, dd, J = 17.2, 8.3, Hz, H-4), 3.48 (4H, s, H-2), 3.23 (2H, dd, J = 17.2, 5.4 Hz, H-4) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 198.4 (s), 166.9 (s), 140.3 (s), 128.8 (d), 128.7 (d), 126.9 (d), 56.7 (d), 52.4 (q), 52.1 (t), 49.5 (t) ppm; m/z (EI+) 449 (85%, M^+ + Na), 431 (100%); HRMS: found (M^+ + Na), 449.1584. $C_{24}H_{26}O_7$ requires (M^+ + Na) 449.1576.

(*E*) and (*Z*) 2-acetyl-1-phenyl-prop-1,2-enoic acid methyl ester 17 and 18. To a stirred solution of the methyl acetoacetate (540 μL. 5.00 mmol) in benzene (25 mL), was added benzaldehyde (508 μL, 5.00 mmol), glacial acetic acid (50 μL, 0.89 mmol), and piperidine (50 μL, 0.51 mmol). The solution was heated at reflux for 4 h and then allowed to cool to room temperature, then diluted with EtOAc (40 mL) and washed with 1M HCl (30 mL), 5% $NaHCO_3$ (30 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc–petroleum ether) gave **17** and **18**. Isomer 1 (190 mg, 19%) ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.69 (1H, s, H-1), 7.42–7.40 (5H, m, Ph), 3.84 (3H, s, OMe), 2.34 (3H, s, H-4) ppm. Isomer 2 (450 mg, 45%) ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.58 (1H, s, H-1), 7.45–7.39 (5H, m, Ph), 3.84 (3H, s, OMe), 2.43 (3H, s, H-4) ppm.

General method for the *tert*-butyl one-pot pyran

To a solution of aldehyde (1.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added titanium tetrachloride (111 μL, 1.00 mmol). The black solution was stirred for 2 min and then the diene **19** (454 mg, 1.50 mmol) was added over a 1 min period. The black solution was stirred at −78 °C for 40 min and then trifluoroacetic acid (231 μL, 3.0 mmol) was added followed by pyridine (160 μL, 2 mmol). After 2 min the second aldehyde (1.20 mmol) was added and the solution was allowed to warm to room temperature over a 5 min period. The black solution was stirred at room temperature for 90 min and was then diluted with Et_2O (40 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL), 5% $CuSO_4$ (3 × 30 mL), 5% sodium metabisulfite (3 × 30 mL), brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 10 EtOAc–petroleum ether) gave the pyran products **20** and **21**.

(2*S, 3*R**, 6*R**)-6-(2-Methyl-ethyl)-2-propyl-4-oxo-tetrahydro-pyran-3-carboxylic acid *tert*-butyl ester 20a.** Colourless oil. ν_{max} (film) 2962, 2875, 1738 (C=O), 1716 (C=O), 1368, 1344, 1256, 1165, 1121 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.76 (1H, ddd, J = 10.6, 8.4, 2.6 Hz, H-2), 3.30 (1H, ddd, J = 11.7, 7.0, 2.6 Hz, H-6), 3.06 (1H, dd, J = 10.6, 0.7 Hz, H-3), 2.46 (1H, dd, J = 14.3, 2.6 Hz, H-5eq), 2.21 (1H, ddd, J 14.3, 11.7, 0.7 Hz, H-5ax), 1.76 (1H, octet, J = 6.6 Hz, H-7), 1.65–1.55 (2H, m, H-10), 1.47 (11H, m, H-15 + H-11), 0.99 (3H, d, J = 6.6 Hz, H-8 or H-9), 0.92 (3H, t, J = 7.3 Hz, H-12), 0.90 (3H, d, J = 6.6 Hz, H-8 or H-9) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 203.7, 167.6, 81.8, 78.2, 78.2, 64.2, 44.8, 37.1, 33.5, 28.1, 18.7, 18.3, 18.2, 13.9 ppm; m/z (ES+) 348 (60%, $M^+ + Na + CH_3CN$), 307 (100%, $M^+ + Na$), 251 (30%), 157 (50%); HRMS: found ($M^+ + Na + CH_3CN$), 348.2154. $C_{16}H_{28}O4$ requires ($M^+ + Na + CH_3CN$), 348.2151.

(2*S, 3*R**, 6*R**)-2,6-Bisphenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid *tert*-butyl ester 20b.** White solid. Mp: 131–133 °C; ν_{max} (film) 3034, 2979, 1732 (C=O), 1715 (C=O), 1456, 1348, 1159 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.51–7.30 (10H, m, Ph), 5.05 (1H, d, J = 11.0 Hz, H-2), 4.93 (1H, dd, J = 11.6, 3.0 Hz, H-6), 3.63 (1H, d, J = 11.0 Hz, H-3), 2.82 (1H, dd, J = 14.6, 3.0 Hz, H-5eq), 2.74 (1H, dd, J = 14.6, 11.6 Hz, H-5ax), 1.34 (9H, s, H-21) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 201.7, 166.5, 140.2, 138.7, 128.7, 128.7, 128.6, 128.3, 127.2, 125.7, 82.1, 81.3, 79.0, 65.3, 49.1, 27.9 ppm; m/z (EI+) 352 (7%, M^+), 296 (59%, $M^+ - O^tBu$), 251 (15%, $M^+ - CO_2{}^tBu$), 219 (42%, $M^+ - {}^tBu$–Ph) 205 (30%), 201, 104.1 (77%) 77 (31%, Ph), 71 (49%); HRMS: found (M^+), 352.1666. $C_{22}H_{24}O_4$ requires (M^+) 352.1675. Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found C, 74.83; H, 6.81%.

(2*R, 6*R**)-4-Hydroxy-2,6-diphenyl-2,3-dihydro-2*H*-pyran-3-carboxylic acid *tert*-butyl ester 21b.** White solid. Mp: 120–122 °C; ν_{max} (film) 2977, 2923, 1659 (C=O), 1621, 1454, 1394, 1281, 1153 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.49 (1H, s, OH), 7.41–7.26 (10H, m, Ph), 5.67 (1H, s, H-2), 4.63 (1H, dd, J = 10.4, 3.7 Hz, H-6), 2.71 (1H, ddd, J = 17.7, 10.4, 1.2 Hz, H-5), 2.57 (1H, dd, J = 17.7, 3.7 Hz, H-5), 1.27 (9H, s, H-21) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.4 (s), 170.0 (s), 141.1 (s), 141.1 (s), 128.6 (d), 128.5 (d), 128.0 (d), 127.8 (d), 126.0 (d), 126.0 (d), 99.9 (s), 81.8 (s), 73.8 (d), 68.4 (d), 35.6 (t), 28.0 (q) ppm; m/z (ES+) 416 (40%, $M^+ + Na + CH_3CN$), 375 (100%, $M^+ + Na$); HRMS: found ($M^+ + Na$), 375.1562. $C_{22}H_{24}O_4$ requires ($M^+ + Na$) 375.1572.

(2*S, 3*R**, 6*R**)-2-Cyclohexyl-6-bisphenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid *tert*-butyl ester 20c.** White solid.

Mp: 91–93 °C; ν_{max} (film) 2977, 2930, 2855, 1738 (C=O), 1715 (C=O), 1452, 1368, 1351, 1252, 1157, 1126, 988 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41–7.29 (5H, m, Ph), 4.68 (1H, dd, J = 11.7, 2.6 Hz, H-6), 3.91 (1H, dd, J = 10.8, 2.6 Hz, H-2), 3.43 (1H, dd, J = 10.8, 0.9 Hz, H-3), 2.70 (1H, dd, J = 14.3, 2.6 Hz, H-5eq), 2.48 (1H, ddd, J = 14.3, 11.7, 0.9 Hz, H-5ax), 1.94–1.64 (5H, m, Cy), 1.60 (9H, s, ^{t}Bu), 1.17–1.41 (5H, m, Cy) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 203.3, 167.6, 140.9, 128.6, 128.0, 125.4, 82.6, 82.0, 78.1, 61.0, 49.1, 41.7, 30.3, 28.1, 26.6, 26.5, 26.4, 26.2 ppm; m/z (ES+) 422 (75%, M^+ + Na + CH_3CN), 381 (100%, M^+ + Na), 287 (81%, M^+ − O^{t}Bu); HRMS: found (M^+ + Na), 381.2025. $C_{22}H_{30}O_4$ requires (M^+ + Na) 381.2041.

(2*S, 3*R**, 6*R**)-2-(2-Methyl-ethyl)-6-phenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid *tert*-butyl ester 20d.** White solid. Mp: 84–86 °C; ν_{max} (film) 2970, 1727 (C=O), 1708 (C=O), 1368, 1344, 1132 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40–7.30 (5H, m, Ph), 4.71 (1H, dd, J = 11.5, 2.6 Hz, H-6), 3.94 (1H, dd, J = 10.7, 2.6 Hz, H-2), 3.38 (1H, d, J = 10.7 Hz, H-3), 2.72 (1H, dd, J = 14.5, 2.6 Hz, H-5eq), 2.49 (1H, dd, J = 14.5, 11.5 Hz, H-5ax), 1.87 (1H, dseptet, J = 6.8, 2.6 Hz, H-13), 1.51 (9H, s, H-18), 1.10 (3H, d, J = 6.8 Hz, H-14 or 15), 1.07 (3H, d, J = 6.8 Hz, H-14 or 15) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 203.1 (s), 167.5 (s), 140.8 (s), 128.5 (d), 127.9 (d), 125.3 (d), 82.4 (d), 81.9 (s), 77.8 (d), 61.4 (d), 49.0 (t), 31.5 (d), 28.0 (q), 19.9 (q), 15.5 (q) ppm; m/z (EI+) 318 (2%, M^+), 275 (10%, $M^+ - C_3H_7$), 261 (69%, M^+ − O^{t}Bu), 219 (80%) 173 (40%); HRMS: found (M^+), 318.1831. $C_{19}H_{26}O_4$ requires (M^+), 318.1831. Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found C, 71.55; H, 8.12%.

General method for the decarboxylative reaction

To a solution of aldehyde (1.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added titanium tetrachloride (111 μL, 1.00 mmol). The black solution was stirred for 2 min and then the diene **19** (454 mg, 1.50 mmol) was added over a 1 min period. The black solution was stirred at −78 °C for 40 min and then trifluoroacetic acid (231 μL, 3.0 mmol) was added followed by pyridine (160 μL, 2 mmol). After 2 min the second aldehyde (1.20 mmol) was added and the solution was allowed to warm to room temperature over a 5 min period. The black solution was stirred at room temperature for 90 min and then trifluoroacetic acid (770 μL 10 mmol) was added. The solution was stirred at room temperature for a further 12 h and then pyridine (800 μL, 10 mmol) was added and the solution was heated at a vigorous reflux for 2 h. The solution was cooled to room temperature and diluted with Et_2O (40 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL), 5% $CuSO_4$ (3 × 30 mL), 5% sodium metabisulfite (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (1 : 10 EtOAc–petroleum ether) gave pyran products **22** and **23**.

(2*S, 6*R**)-2-(2-Methyl-ethyl)-6-phenyl-4-oxo-tetrahydro-pyran 22d.** Colourless oil. ν_{max} (film) 3031, 2963, 1717 (C=O), 1347, 1252, 1153, 1065 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.31–7.16 (5H, m, Ph), 4.51 (1H, dd, J = 11.5, 2.6 Hz, H-6), 3.39 (1H, ddd, J = 11.5, 6.0, 2.6 Hz, H-2), 2.53 (1H, ddd, J = 14.5, 2.6, 2.1 Hz, H-5eq), 2.40 (1H, dd, J = 14.5, 11.5 Hz, H-5ax), 2.35 (1H, ddd, J = 14.1, 2.6, 2.1 Hz, H-3eq), 2.28 (1H, dd, J = 14.1, 11.5 Hz, H-3ax), 1.81 (1H, octet J = 6.8 Hz, H-13), 0.92 (3H, d, J = 6.8 Hz, H-14 or 15), 0.88 (3H, d, J = 6.8 Hz, H-14 or 15) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 207.6 (s), 141.1 (s), 128.5 (d), 127.8 (d), 125.4 (d), 81.9 (d), 78.2 (t), 49.7 (t), 44.6 (t), 33.2 (d), 18.2 (q), 17.9 (q) ppm; m/z (CI+) 218 (59%, M^+), 175 (16%, $M^+ - C_3H_7$), 131 (100%), 104.1 (77%) 77 (31%, Ph), 71 (49%); HRMS: found (M^+), 218.1307. $C_{14}H_{18}O_2$ requires (M^+), 218.1307.

(2*R, 6*R**)-2-(2-Methyl-ethyl)-6-phenyl-4-oxo-tetrahydro-pyran 23d.** Colourless oil. ν_{max} (film) 3031, 2962, 1717 (C=O), 1450, 1366, 1256, 1061 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.38–7.28 (5H, m, Ph), 5.30 (1H, dd, J = 6.0, 5.1 Hz, H-6), 3.46 (1H, ddd, J = 8.5, 6.8, 4.7 Hz, H-2), 2.91 (1H, ddd, J = 14.9, 5.1, 1.3 Hz, H-5), 2.83 (1H, ddd, J = 14.9, 6.0, 0.9 Hz, H-5), 2.48 (1H, ddd, J = 14.5, 4.7, 1.3 Hz, H-3), 2.43 (1H, ddd, J = 14.5, 8.5, 0.9 Hz, H-3), 1.80 (1H, octet, J = 6.8 Hz, H-13), 0.96 (3H, d, J = 6.8 Hz, H-14 or 15), 0.87 (3H, d, J = 6.8 Hz, H-14 or 15) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 208.0 (s), 140.0 (s), 128.7 (d), 128.0 (d), 127.1 (d), 76.6 (d), 73.9 (d), 45.3 (t), 44.9 (t), 32.1 (d), 18.4 (q), 18.4 (q) ppm; m/z (CI+) 218 (59%, M^+ + H), 175 (16%, $M^+ - C_3H_7$), 131 (100%), 104.1 (77%) 77 (31%, Ph), 71 (49%); HRMS: found (M^+ + H), 218.1307. $C_{14}H_{17}O_2$ requires (M^+ + H) 218.1307.

(2*S, 6*R**)-6-Octyl-2-phenyl-4-oxo-tetrahydro-pyran 22e.** Colourless oil. ν_{max} (film) 2928, 2856, 1603 (C=O), 1497, 1410, 1348, 1312, 1286, 1207, 1145, 1059, 814; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.28–7.40 (5H, m, Ph), 4.64 (1H, dd, J = 3.0, 11.6 Hz, H-2), 3.76 (1H, dddd, J = 11.6, 7.3, 4.9, 2.4 Hz, H-6), 2.64 (1H, ddd, J = 14.6, 3.0, 1.8 Hz, H-3eq), 2.54 (1H, d, J = 14.6, 11.6, Hz, H-3ax), 2.47 (1H, ddd, J = 14.6, 2.4, 1.8 Hz, H-5eq), 2.37 (1H, dd, J = 14.6, 11.6 Hz, H-5ax), 1.77 (1H, m, H-7), 1.61 (1H, m, H-7), 1.49 (1H, m, H-8), 1.40 (1H, m, H-8), 1.35–1.18 (10H, m, H-9–13), 0.89 (3H, t, J = 6.7 Hz, H-14); ^{13}C NMR (100 MHz; $CDCl_3$) δ 207.2, 141.0, 128.6, 127.9, 125.6, 78.5, 77.4, 49.6, 47.8, 36.4, 31.8, 29.5, 29.4, 25.2, 25.2, 22.6 ppm; m/z 288 (88%, M^+), 211 (6%, M^+ − Ph), 175 (10%, $M^+ - C_8H_{17}$), 147 (100%, M^+ + H–$C_9H_{18}O$); HRMS: found (M^+), 288.2102. $C_{10}H_{14}O_3$ requires (M^+) 288.2089.

Starting with enantio-pure β-hydroxy ketoesters

(*R*)-5-Hydroxy-3-oxo-hexanoic acid *tert*-butyl ester 26[20]. To a solution of diisopropylamine (4.15 mL, 29.6 mmol) in THF (45 mL) at −78 °C was added ^{n}BuLi (11.86 mL, 29.65 mmol, 2.5 M hexanes) followed by *tert*-butylacetate (3.44 mL, 25.4 mmol). After 1 min, (*S*)-3-hydroxy-butanoate (1.00 g, 8.47 mmol) was added dropwise over a 5 min period. The solution was stirred at −50 °C for 90 min and was then left to stand at −15 °C for 15 min. The reaction was quenched by pouring on to ice water (30 mL) and was then extracted with Et_2O (40 mL) and washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc–pet. ether) gave **26** (950 mg, 72%), the data for which was in agreement with the published literature values. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.23 (1H, m, H-5), 3.38 (1H, d, J = 15.8 Hz, H-2), 3.34 (1H, d, J = 15.8 Hz, H-2), 2.98 (1H, d, J = 3.0 Hz, OH), 2.71 (1H, dd, J = 17.5, 3.0 Hz, H-4), 2.61 (1H, dd, J = 17.5, 8.5 Hz, H-4), 1.44 (9H, s, ^{t}Bu), 1.17 (3H, d, J = 6.4,Hz, H-6) ppm; $[\alpha]_D$ ($CHCl_3$, c = 1), −28.7.

(*R*)-3-Hydroxy-butanoic acid methyl ester 27[22]. To a solution of diisopropylamine (1.34 mL, 9.55 mmol) in THF (15 mL) at −78 °C was added ^{n}BuLi (3.82 mL, 9.55 mmol, 2.5 M hexanes) followed by *tert*-butylacetate (1.12 mL, 8.32 mmol). After 10 min, methyl (*R*)-3-hydroxy-3-phenylpropanoate (0.50 g, 2.77 mmol) was added dropwise over a 5 min period. The solution was stirred at −50 °C for 1 h and then −5 °C for 1 h. The reaction was quenched by pouring on to ice water (30 mL) and was then extracted with Et_2O (40 mL) and washed with brine (30 mL), dried ($MgSO_4$) and gave **27** (290 mg, 55%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41 (2H, d, J = 7.3 Hz, H-8), 7.35 (2H, dd, J = 7.3, 7.3 Hz, H-9), 7.29 (1H, d, J = 7.3 Hz, H-10), 5.11 (1H, dd, J = 11.1, 1.7 Hz, H-2), 4.69 (1H, s, OH), 2.56 (1H, dd, J = 14.9, 11.1 Hz, H-3ax), 2.27 (1H, dd, J = 14.9, 1.7 Hz, H-3eq) ppm; $[\alpha]_D$ ($CHCl_3$, c = 1), −14.7.

(*R*)-5-Hydroxy-3-oxo-5-phenyl-pentanoic acid *tert*-butylester 28. To a solution of diisopropylamine (1.34 mL, 9.55 mmol) in THF (15 mL) at −78 °C was added ^{n}BuLi (3.82 mL, 9.55 mmol, 2.5 M hexanes) followed by *tert*-butylacetate (1.12 mL, 8.32 mmol). After 10 min, methyl (*R*)-3-hydroxy-3-phenylpropanoate (0.50 g, 2.77 mmol) was added dropwise over

a 5 min period. The solution was stirred at −50 °C for 2 h and then was left to stand at −20 °C for 12 h. The reaction was quenched by pouring on to ice water (30 mL) and was then extracted with Et_2O (40 mL) and washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc–pet. ether) gave **28** as a white solid, mp 42–43 °C (600 mg, 82%) ν_{max} (film) 3598 (OH), 2981, 2933, 1732 (C=O), 1710 (C=O), 1455, 1370, 1323, 1144, 1072 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.36–7.23 (5H, m, Ph), 5.18 (1H, dd, $J = 9.4$, 3.4 Hz, H-5), 3.39 (2H, s, H-2), 2.98 (1H, dd, $J = 17.5$, 9.4 Hz, H-4), 2.90 (1H, dd, $J = 17.5$, 3.4 Hz, H-4), 1.46 (9H, s, ^{t}Bu); ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 203.5, 166.1, 142.6, 128.6, 127.8, 125.7, 82.4, 69.8, 51.6, 51.2, 28.0 ppm; *m/z* (CI+) 265 (30%, $M^+ + H$), 247 (22%, $M^+ - OH$), 207 (38%, $M^+ - {}^t$Bu), 191 (100%, $M^+ - O^t$Bu), 149 (21%, $M^+ - CO_2{}^t$Bu); HRMS (CI+): found ($M^+ + H$), 265.1446. $C_{15}H_{20}O_4$ requires ($M^+ + H$) 265.1440. Anal. Calcd. for $C_{15}H_{20}O_4$: C, 67.97; H, 7.46. Found C, 68.16; H 7.63%. $[a]_D$ ($CHCl_3$, $c = 1$), −46.8.

2-(*R*)-Phenyl-6-(*R*)-methyl-4-oxo-tetrahydro-pyran-3-(*S*)-carboxylic acid *tert*-butyl ester 29. To a solution of (*R*)-5-hydroxy-3-oxo-hexanoic acid *tert*-butyl ester **26** (90 mg, 0.45 mmol) in CH_2Cl_2 (5 mL) at room temperature was added pyridine (70 μL, 1 mmol) and benzaldehyde (60 μL, 0.6 mmol) followed by titanium tetrachloride (55 μL, 0.5 mmol). The black solution was stirred at room temperature for 10 min and was quenched by addition of 5% $NaHCO_3$ (5 mL). The solution was diluted with Et_2O (40 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL), 5% $CuSO_4$ (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc–pet. ether) gave **29** as a white solid, mp 88–90 °C (50 mg, 55%) ν_{max} (film) 2978, 2932, 1740 (C=O), 1714 (C=O), 1369, 1288, 1127, cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.43–7.27 (5H, m, Ph), 4.84 (1H, d, $J =$ 10.8 Hz, H-2), 4.00 (1H, ddq, $J = 10.8$, 5.9, 2.9 Hz, H-6), 3.47 (1H, d, $J = 10.8$, 1.0 Hz, H-3), 2.53 (1H, dd, $J = 14.6$, 2.9 Hz, H-5eq), 2.40 (1H, ddd, $J = 14.6$, 10.8, 1.0 Hz, H-5ax), 1.29 (9H,s, H-16), 1.38 (3H, d, $J = 5.9$ Hz, H-7) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 202.3 (s), 166.6 (s), 138.7 (s), 128.7 (d), 128.6 (d), 127.2 (d), 82.0 (s), 81.1 (d), 73.8 (d), 64.9 (d), 48.7 (t), 27.9 (q), 22.2 (q) ppm; *m/z* (ES+) 354 (100%, $M^+ +$ Na + CH_3CN), 313 (82%, $M^+ +$ Na), 298 (38%), 257 (32%); HRMS: found ($M^+ +$ Na), 313.1428. $C_{17}H_{22}O_4$ requires ($M^+ +$ Na) 313.1416; $[a]_D$ ($CHCl_3$, $c = 1$), +4.48. Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found C, 70.18; H, 7.57%.

2-(*S*)-(2-Methyl-ethyl)-6-(*R*)-phenyl-4-oxo-tetrahydro-pyran 22d. To a solution of the (*R*)-5-hydroxy-3-oxo-5-phenyl-pentanoic acid *tert*-butylester **28** (53 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) at room temperature was added pyridine (32 μL, 0.4 mmol) and iso-butyraldehyde (22 μL, 0.24 mmol) followed by titanium tetrachloride (22 μL, 0.2 mmol). The black solution was stirred at room temperature for 90 min and then TFA (154 μL, 2.0 mmol) was added and the black solution was stirred at room temperature for 12 h then pyridine (326 μL, 2 mmol) was added and the solution was then heated at 35 °C for 2 h. The solution was diluted with Et_2O (40 mL) and washed with 5% $NaHCO_3$ (3 × 30 mL), 5% $CuSO_4$ (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc–pet. ether) gave **22d** (32 mg, 70%); the data matched that which had previously been obtained. $[a]_D$ ($CHCl_3$, $c = 1$), +46.8.

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