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Synthesis of 2,6-trans- and 3,3,6-Trisubstituted Tetrahydropyran-4-ones from Maitland-Japp Derived 2H-Dihydropyran-4-ones: A Total Synthesis of Diospongin B

Paul A. Clarke,* Nadiah Mad Nasir, Philip B. Sellars, Alejandra M. Peter, Connor A. Lawson and James L. Burroughs

6-Substituted-2H-dihydropyran-4-one products of the Maitland-Japp reaction have been converted into tetrahydropyran rings containing uncommon substitution patterns. Treatment of 6-substituted-2H-dihydropyran-4-ones with carbon nucleophiles led to the formation of tetrahydropyran rings with the 2,6-trans-stereochemical arrangement. Reaction of the same 6-substituted-2H-dihydropyran-4-ones with L-Selectride led to the formation of 3,6-disubstituted tetrahydropyran rings, while trapping of the intermediate enolate with carbon electrophiles in turn led to the formation of 3,3,6-trisubstituted tetrahydropyran rings. The relative stereochemical configuration of the new substituents was controlled by the stereoelectronic preference for pseudo-axial addition of the nucleophile and trapping of the enolate from the opposite face. Application of these methods led to a synthesis of the potent anti-osteoporotic diarylheptanoid natural product diospongin B.

Introduction

Substituted tetrahydropyran (THP) rings are present in a large number of biologically active natural products, and as such their synthesis has received much attention over the years. On inspection of these THP rings it is clear that some substitution patterns occur more often than others, and this has resulted in a greater amount of synthetic effort being directed towards their synthesis compared to the synthesis of other substitution patterns. The consequences of those efforts are that these common substitution patterns can now be accessed readily, while the more uncommon substitution patterns still require greater synthetic effort. For example, 2,6-cis-THP rings can be accessed by a wide variety of methods, including thermodynamically controlled oxo-Michael reactions, Diels-Alder reactions, Prins rearrangements, reduction of cyclic oxocarbenium ions, metal mediated cyclisations and the Maitland-Japp reaction. Conversely, construction of the 2,6-trans-THP ring is almost exclusively limited to either nucleophilic addition to cyclic hemiacetals via an oxocarbenium ion or kinetically controlled oxo-Michael reactions, though in the latter case the trans-selectivity is often only moderate.

A survey of THP-containing natural products shows that a sizable number do contain the 2,6-trans-THP ring, for example psymberin (an inhibitor of cancer cell proliferation), zincophorin (an antibiotic), aspergillide B (cytotoxicity against mouse lymphocytic leukemia cells) and diospongin B (anti-osteoporotic activity) (Figure 1).

We recently reported the synthesis of substituted dihydropyran-4-ones (DHPs), by extension of the Maitland-Japp reaction, a method which is complementary to the Diels-Alder route popularised by Danishfesky. We then converted these DHPs into 2,6-cis-THPs. This strategy enabled us to complete syntheses of “Civet” and a fully...
functionalised model A-ring of lasonolide A. Given the dearth of methods for the construction of 2,6-trans-THP rings we turned our attention to the development of a new method for the selective synthesis of 2,6-trans-THPs. We envisaged that 2,6-trans-THPs could be formed from the conjugate addition of a carbon nucleophile to the double bond of Maitland-Japp DHPs such as 5. We rationalised that the stereoelectronic preference for axial addition of a nucleophile to the double bond would generate a 2,6-trans-THP with the opportunity to trap the resultant enolate, which would allow for further functionalisation of the THP-ring (Figure 2).

Figure 2: Stereoelectronic preference for axial addition of nucleophiles leading to 2,6-trans-THPs

Results and Discussion

Synthesis of dihydropyran-4-ones

In order to investigate the formation of 2,6-trans-THPs we had to prepare DHPs 5. To this end we employed the conditions we had used for the synthesis of C2-substituted DHPs (an orthoamide or orthoester in toluene), however, when we used the dimethyl acetal of N,N-dimethylformamide and δ-hydroxy-β-ketoesters 7, complex mixtures of products resulted. Our initial results suggested that there was an inherent instability in the DHPs 5 that was not apparent in their C2-substituted counterparts, this was particularly noticeable during attempted isolation by chromatography on silica gel (2D TLC showed multiple interconverting spots). However, if the crude reaction mixture was exposed to a Gilman cuprate, it was possible to isolate some 2,6-trans THP with the exception of 7a which gave a moderate isolated yield of DHP 5a. Following considerable investigation we realised that the Knoevenagel-like condensation of the orthoamide occurred but the oxy-Michael cyclisation to give the DHP did not. This issue could be rectified by performing the reaction with only one equivalent of orthoamide in CH₂Cl₂, rather than PhMe, followed by the addition of BF₃·OEt₂ to promote cyclisation, resulting in a 92% crude mass balance of 5a which could be used crude, without the need for purification (Scheme 1).

Scheme 1: Formation of C2-unsubstituted DHPs

With a range of DHPs to hand we were now in a position to study the formation of 2,6-trans-substituted THPs.

Conversion of dihydropyran-4-ones to 2,6-trans-tetrahydropyran-4-ones

When DHPs 5 were treated with a range of Gilman cuprates, Ph₂CuLi, Me₂CuLi and Bu₂CuLi in the presence of TMSCl at -78 °C in THF, it was found that conjugate addition occurred smoothly to yield the 2,6-trans-THPs in a mixture of enol and keto-forms 8/9 (Table 2). Addition of Ph₂CuLi generated the 2,6-trans-THPs exclusively as the enol tautomer 8. However, use of Me₂CuLi and Bu₂CuLi generated mixtures of enol-keto tautomers 8 and 9 of the 2,6-trans-THPs. For the purposes of characterisation, these tautomers were converted into enol acetates 10 by the action of Ac₂O, pyridine and DMAP.

Table 1: Synthesis of DHPs

<table>
<thead>
<tr>
<th>DHP 5</th>
<th>R</th>
<th>Crude Mass Balance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-furyl</td>
<td>92</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>96</td>
</tr>
<tr>
<td>c</td>
<td>Pr</td>
<td>91</td>
</tr>
<tr>
<td>d</td>
<td>i-Pr</td>
<td>97</td>
</tr>
<tr>
<td>e</td>
<td>CH₂OTIPS</td>
<td>88</td>
</tr>
<tr>
<td>f</td>
<td>CH=CHCH₃</td>
<td>87</td>
</tr>
<tr>
<td>g</td>
<td>CH=CHPh</td>
<td>97</td>
</tr>
<tr>
<td>h</td>
<td>2-methylxazole</td>
<td>77</td>
</tr>
</tbody>
</table>
Table 2: Synthesis of 2,6-trans-THPs

<table>
<thead>
<tr>
<th>THP</th>
<th>R</th>
<th>R'</th>
<th>Ratio(^a) 8:9</th>
<th>Yield(^b) 8/9 (%)</th>
<th>Yield(^b) 10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>Ph</td>
<td>1:0</td>
<td>70</td>
<td>N/A</td>
</tr>
<tr>
<td>b</td>
<td>Pr</td>
<td>Ph</td>
<td>1:0</td>
<td>56</td>
<td>N/A</td>
</tr>
<tr>
<td>c</td>
<td>i-Pr</td>
<td>Ph</td>
<td>1:0</td>
<td>73</td>
<td>N/A</td>
</tr>
<tr>
<td>d</td>
<td>CH(_2)OTIPS</td>
<td>Ph</td>
<td>1:0</td>
<td>48</td>
<td>N/A</td>
</tr>
<tr>
<td>e</td>
<td>CH=CHCH(_3)</td>
<td>Ph</td>
<td>1:0</td>
<td>64</td>
<td>N/A</td>
</tr>
<tr>
<td>f</td>
<td>CH=CHPh</td>
<td>Ph</td>
<td>1:0</td>
<td>91</td>
<td>N/A</td>
</tr>
<tr>
<td>g</td>
<td>2-furyl</td>
<td>Me</td>
<td>1:0.4</td>
<td>50</td>
<td>82</td>
</tr>
<tr>
<td>h</td>
<td>Ph</td>
<td>Me</td>
<td>1:0.2</td>
<td>64</td>
<td>74</td>
</tr>
<tr>
<td>i</td>
<td>Pr</td>
<td>Me</td>
<td>1:0.4</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>j</td>
<td>i-Pr</td>
<td>Me</td>
<td>1:0.3</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>k</td>
<td>CH(_2)OTIPS</td>
<td>Me</td>
<td>1:0.4</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>l</td>
<td>CH=CHCH(_3)</td>
<td>Me</td>
<td>1:0.5</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>m</td>
<td>Ph</td>
<td>Bu</td>
<td>1:0.3</td>
<td>82</td>
<td>48</td>
</tr>
<tr>
<td>n</td>
<td>Pr</td>
<td>Bu</td>
<td>1:0.5</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>o</td>
<td>i-Pr</td>
<td>Bu</td>
<td>1:0.2</td>
<td>48</td>
<td>79</td>
</tr>
<tr>
<td>p</td>
<td>CH(_2)OTIPS</td>
<td>Bu</td>
<td>1:0.5</td>
<td>24</td>
<td>70</td>
</tr>
</tbody>
</table>

\(^a\) Ratio obtained by integration of H-3 and OH resonances in the \(^1\)H NMR of the crude reaction mixture. \(^b\) Isolated yield after column chromatography.

We rationalise that 2,6-trans-THPs exist as a mixture of keto/enol tautomers because either the C2 or C6 substituent must be axial. The penalty for having an axial substituent may be partly relieved by enolisation as this allows for the formation of an intramolecular H-bond and the reduction of a 1,3-diaxial interaction for the axial group. Therefore, in order to definitively characterise the 2,6-trans-THP products the keto/enol mixture was treated with Ac\(_2\)O, pyridine and DMAP to form enol acetates 10, where the 2,6-trans-THP stereochemical configuration was confirmed by analysis of the \(^1\)H NMR and NOE data (Figure 3). In the representative case of 10h there was a strong NOE correlation between C2 methyl group and H6 of 2.3% and a NOE correlation between C2 methyl group and H5\(\alpha\) of 1.86%.

Figure 3: NOE correlations confirming the 2,6-trans-stereochemical configuration of 10h

Table 3: Synthesis of 3,6-disubstituted-THPs

<table>
<thead>
<tr>
<th>DHP 5</th>
<th>R</th>
<th>Yield(^a) 11 (%)</th>
<th>Ratio(^b) (^c) enol:keto</th>
<th>Yield(^b) 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-furyl</td>
<td>44</td>
<td>1:0.4</td>
<td>58</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>74</td>
<td>1:0.2</td>
<td>68</td>
</tr>
<tr>
<td>c</td>
<td>Pr</td>
<td>89</td>
<td>1:0.2</td>
<td>51</td>
</tr>
<tr>
<td>e</td>
<td>CH(_2)OTIPS</td>
<td>65</td>
<td>1:0.2</td>
<td>65</td>
</tr>
<tr>
<td>g</td>
<td>CH=CHPh</td>
<td>51</td>
<td>1:0.4</td>
<td>56</td>
</tr>
</tbody>
</table>

\(^a\) After flash column chromatography. \(^b\) Determined by integration of the \(^1\)H NMR.

Conversion of dihydropyran-4-ones to 3,6-disubstituted and 3,3,6-trisubstituted tetrahydropyran-4-ones

With the development of a successful strategy for the synthesis of 2,6-trans-THPs we sought to extend the scope for the conversion of DHPs 5 into THPs with other substitution patterns. We considered the possibility that 3,6-disubstituted-THPs could be accessed by the conjugate reduction of the C2-C3 double bond. When DHPs 5 were treated with L-Selectride at -78 °C and quenched, a range of 3,6-disubstituted THPs 11 were formed in good yields; the enol tautomer was the major product in all cases, with small amounts of the keto-tautomer present. In order to aid characterisation the product mixture was converted into the enol acetate 12 by the action of Ac\(_2\)O, pyridine and DMAP (Table 3). In all cases studied we could not detect products from reduction of either the ketone or the ester carbonyl groups.

Table: Synthesis of 3,6-disubstituted-THPs

<table>
<thead>
<tr>
<th>DHP 5</th>
<th>R</th>
<th>Yield(^a) 11 (%)</th>
<th>Ratio(^b) (^c) enol:keto</th>
<th>Yield(^b) 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-furyl</td>
<td>44</td>
<td>1:0.4</td>
<td>58</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>74</td>
<td>1:0.2</td>
<td>68</td>
</tr>
<tr>
<td>c</td>
<td>Pr</td>
<td>89</td>
<td>1:0.2</td>
<td>51</td>
</tr>
<tr>
<td>e</td>
<td>CH(_2)OTIPS</td>
<td>65</td>
<td>1:0.2</td>
<td>65</td>
</tr>
<tr>
<td>g</td>
<td>CH=CHPh</td>
<td>51</td>
<td>1:0.4</td>
<td>56</td>
</tr>
</tbody>
</table>

\(^a\) After flash column chromatography. \(^b\) Determined by integration of the \(^1\)H NMR.

The addition of L-Selectride to DHPs 5 initially generated an enolate which was quenched upon workup to give 3,6-disubstituted THPs 11. We wondered if it would be possible to intercept the enolate with a carbon electrophile to form 3,3,6-trisubstituted THPs. Alkyl halides methyl iodide, allyl bromide and benzyl bromide were investigated (Table 4).
Table 4: Synthesis of 3,3,6-trisubstituted THPs

<table>
<thead>
<tr>
<th>THP 13</th>
<th>R</th>
<th>R₁</th>
<th>Yield 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>Me</td>
<td>59</td>
</tr>
<tr>
<td>b</td>
<td>CH=CHPh</td>
<td>Me</td>
<td>53</td>
</tr>
<tr>
<td>c</td>
<td>CH₂OTIPS</td>
<td>Me</td>
<td>57</td>
</tr>
<tr>
<td>d</td>
<td>Pr</td>
<td>Me</td>
<td>58</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>CHCH₂CH₃</td>
<td>52</td>
</tr>
<tr>
<td>f</td>
<td>CH=CHPh</td>
<td>CHCH₂CH₃</td>
<td>83</td>
</tr>
<tr>
<td>g</td>
<td>CH₂OTIPS</td>
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<td>57</td>
</tr>
<tr>
<td>h</td>
<td>Pr</td>
<td>CHCH₂CH₃</td>
<td>52</td>
</tr>
<tr>
<td>i</td>
<td>Ph</td>
<td>Bn</td>
<td>65</td>
</tr>
<tr>
<td>j</td>
<td>CH=CHPh</td>
<td>Bn</td>
<td>51</td>
</tr>
<tr>
<td>k</td>
<td>CH₂OTIPS</td>
<td>Bn</td>
<td>62</td>
</tr>
<tr>
<td>l</td>
<td>Pr</td>
<td>Bn</td>
<td>62</td>
</tr>
</tbody>
</table>

a) Isolated yield after column chromatography

We reasoned that delivery of hydride would occur from the pseudo-axial trajectory and the electrophilic quenching would occur from the opposite face of the THP ring. This should deliver THP products with a quaternary stereocenter at C3, in which the R and R₁ groups are cis to each other. No other diastereomer was detected in the ¹H NMR of the crude reaction mixture. The THP products 13 were characterised, and the relative stereochemical configuration confirmed, by ¹H NMR and NOE correlations. For example, in the representative case of 13i there was a clear NOE of 3.6% between H₆ and H₅α when H₆ was irradiated. When H₅α was irradiated a NOE to H₆ of 2.26% was seen. There was a NOE of 3.16% between H₅β and the benzyl CH₂ group, indicating that these were both axial (Figure 4). The protocol gave the desired functionalisation with the halide electrophiles but, to our disappointment, we were unable to intercept the enolate with aldehyde electrophiles, which probably reflects the inherent stability of the β-ketoester’s enolate anion.

With procedures developed for the synthesis of highly substituted THP-rings, especially the less common and synthetically more challenging 2,6-trans-THP, we sought to demonstrate the utility of the approach by completing the total synthesis of the anti-osteoporotic 2,6-trans-THP-containing natural product diospongin B 2. Diospongin B is a diaryl heptanoid natural product which was isolated in 2003 from the rhizomes of Dioscorea spongiosa and was shown to exhibit potent inhibitory activity on bone resorption induced by parathyroid hormone. The activity of diospongin B is comparable to calcitonin, a drug currently used to treat osteoporosis, and this has led to a number of total syntheses being reported for it and its 2,6-cis-diastereomer, diospongin A.

Our synthesis (Scheme 2) began with the Maitland-Japp formation of DHP 5g in 97% yield using the dimethylacetal of N,N-dimethyl formamide. Conjugate addition of Ph₂CuLi to 5g yielded 2,6-trans-THP 8f in 91%. Microwave-mediated decarboxylation in wet DMF generated the desired tetrahydropyran-4-one, which was in turn reduced with L-Selectride to give THP 14 as the major diastereomer (9:1) with the correct relative stereochemical configuration for diospongin B. The stereochemical configuration of 14 was confirmed by H₂ being coupled to both H₃α and H₃β with J = 4.4 Hz indicating its equatorial position, H₆ was coupled to H₅β J = 9.1 Hz and H₅α J = 5.0 Hz, indicating its axial position while H₄ was coupled to H₅β J = 9.3 Hz, H₅α J = 4.5 Hz, H₃β J = 9.0 Hz and H₃α J = 4.0 Hz indicating its axial orientation. Additionally, H₂ only had NOE correlations to H₃α of 1.33% and to H₃β of 1.89%, H₄ had NOE correlations to H₆ of 1.23%, to H₃α of 1.58% and to H₅α of 2.59% (Figure 5). The synthesis was completed by MOM-protection of the free hydroxyl in 60% yield, and Wacker oxidation of the double bond to give 15 in 70% yield. The final step was the removal of the MOM protecting group, which was achieved by the action of aqueous HCl and generated diospongin B 2 in 58% yield.

Spectroscopic data for our sample of diospongin B 2 were identical to those reported in the literature.

Synthesis of Diospongin B

![Figure 4: NOE correlations and coupling constants confirming the stereochemical configuration of 13i](image-url)
Conclusions

We have developed a modification of the Maitland-Japp reaction using orthoamides which provides access to a range of 6-substituted-2H-dihydropyran-4-ones in good yields. These 2H-dihydropyran-4-ones can be converted into tetrahydropyran products with uncommon substitution patterns which are found in a number of biologically active natural products. 2,6-trans-Tetrahydropyran-4-ones are obtained by the stereoselective addition of Gilman cuprates to 6-substituted-2H-dihydropyran-4-ones. Tetrahydropyrans with the 3,6-substitution pattern are accessed by the conjugate addition of L-Selectride, while 3,3,6-substitution pattern are obtained by trapping the enolate formed on addition of L-Selectride to the stereoselective addition of Gilman cuprates to 6-substituted-2H-dihydropyran-4-ones. The aqueous layer was extracted with EtOAc (15.0 mL) and the combined organic extracts were washed with brine (10.0 mL) and dried over MgSO₄ and concentrated in vacuo to give the crude DHP 5. No further purification was carried out on the products and they were used crude in all subsequent reactions.

Experimental

General Methods

Thin layer chromatography was performed on aluminium plates coated with Merck silica gel 60 F₂₅₄. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate or ethanolic anisaldehyde. Flash column chromatography was performed with the solvent systems indicated in the appropriate experimental procedure. The stationary phase was silica gel 60 (220–240 mesh), unless stated otherwise. Dichloromethane was distilled from calcium hydride; THF and Et₂O were distilled from sodium–benzophenone ketyl radical; toluene was dried over sodium wire; hexane was distilled prior to use. All other solvents and reagents were used as received from commercial suppliers. ¹H NMRs were recorded at ambient temperature at either 400 MHz or 500 MHz and ¹³C NMRs were recorded at ambient temperature at either 100 MHz or 125 MHz. Mass spectrometry was performed using ES ionisation.

General Procedure for the Synthesis of 6-substituted-2H-dihydropyran-4-ones 5.

N,N-Dimethylformamide dimethyl acetal (0.03 mL, 0.20 mmol) was added to a stirred solution of δ-hydroxy-β-ketoester 7 (0.2 mmol) in dry dichloromethane (2 mL) at room temperature. After stirring at this temperature for 45 minutes, BF₃·OEt₂ (0.03 mL, 0.20 mmol) was added. The reaction was stirred at room temperature and monitored by TLC (hexane − ethyl acetate). Upon completion the mixture was diluted with EtOAc (40.0 mL) and washed with sat. aq. NaHCO₃ (10.0 mL). The aqueous layer was extracted with EtOAc (15.0 mL) and the combined organic extracts were washed with brine (10.0 mL), dried over MgSO₄ and concentrated in vacuo to give the crude DHP 5. No further purification was carried out on the products and they were used crude in all subsequent reactions.

Methyl 2-(furan-2-yl)-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate 5a

δ-Hydroxy-β-ketoester 7a (0.698 g, 3.292 mmol), yielded 0.674 g (92 %), light yellow oil. v max/cm⁻¹ 2953, 1738, 1704, 1579, 1436, 1383, 1296, 1133, 1013, 816, 732 cm⁻¹; ¹H (400MHz, CDCl₃) 8.27 (1H, s), 7.44 (1H, dd, J = 1.8, 0.6 Hz), 6.45 (1H, d, J = 3.3 Hz), 6.36 (1H, dd, J = 3.3, 1.8 Hz), 5.58 (1H, dd, J = 11.5, 4.3 Hz), 3.74 (3H, s), 3.07 (1H, dd, J = 16.6, 11.5 Hz) and 2.79 (1H, dd, J = 16.6, 4.3 Hz) ppm; δC (100 MHz, CDCl₃) 186.8, 170.5, 170.4, 163.8, 143.7, 138.7, 110.9, 110.6, 74.7, 51.9 and 39.3 ppm; m/z (ESI⁺) 245 (M + Na)⁺, 223 (M + H)⁺, (Found C₂₉H₂₂NaO₂ requires; 245.0426).

Methyl 4-oxo-2-phenyl-3,4-dihydro-2H-pyran-5-carboxylate 5b

δ-Hydroxy-β-ketoester 7b (0.050 g, 0.204 mmol), yielded 0.045 g (91 %), orange solid. v max/cm⁻¹ 2955, 2958, 1738, 1661, 1572, 1372, 1290, 1244, 1087, 845, 761, 698, 500 cm⁻¹; ¹H (400MHz, CDCl₃) 8.43 (1H, s), 7.43-7.36 (5H, m), 5.54 (1H, dd, J = 12.0, 4.0 Hz), 3.81 (3H, s), 2.96 (1H, dd, J = 16.0, 4.0 Hz) and 2.76 (1H, dd, J = 16.0, 4.0 Hz) ppm; δC (100 MHz, CDCl₃) 186.8, 171.3, 164.2, 136.9, 129.4, 129.0, 126.2, 111.2, 82.3, 52.1 and 43.1ppm; m/z (ESI⁺) 223 (M + Na)⁺, 211 (M + H)⁺, (Found C₂₉H₁₈NaO₂ requires; 255.0633).

Methyl 4-oxo-2-propyl-3,4-dihydro-2H-pyran-5-carboxylate 5c

δ-Hydroxy-β-ketoester 7c (0.052 g, 0.276 mmol), yielded 0.049 g (91%), light yellow oil. v max/cm⁻¹ 2958, 2874, 1741, 1700, 1582, 1435, 1380, 1300, 1147, 1074, 799, 506 cm⁻¹; ¹H (400MHz, CDCl₃) 7.97 (1H, s), 3.71-3.64 (1H, m), 3.52 (3H, s), 2.98 (1H, dd, J = 16.0, 4.0 Hz) and 2.79 (1H, dd, J = 16.0, 4.0 Hz) ppm; δC (100 MHz, CDCl₃) 187.6, 171.5, 164.5, 116.9, 81.3, 43.1, 39.3 ppm; m/z (ESI⁺) 209 (M + Na)⁺, 187 (M + H)⁺, (Found C₂₉H₂₀NaO₂ requires; 255.0633).

Methyl 4-oxo-2-(furan-2-yl)-3,4-dihydro-2H-pyran-5-carboxylate 5d

δ-Hydroxy-β-ketoester 7d (0.052 g, 0.276 mmol), yielded 0.049 g (91%), light yellow oil. v max/cm⁻¹ 2958, 2874, 1741, 1700, 1582, 1435, 1380, 1300, 1147, 1074, 799, 506 cm⁻¹; ¹H (400MHz, CDCl₃) 7.97 (1H, s), 3.71-3.64 (1H, m), 3.52 (3H, s), 2.98 (1H, dd, J = 16.0, 4.0 Hz) and 2.79 (1H, dd, J = 16.0, 4.0 Hz) ppm; δC (100 MHz, CDCl₃) 187.6, 171.5, 164.5, 116.9, 81.3, 43.1, 39.3 ppm; m/z (ESI⁺) 209 (M + Na)⁺, 187 (M + H)⁺, (Found C₂₉H₂₀NaO₂ requires; 255.0633).

Methyl 4-oxo-2-(furan-2-yl)-3,4-dihydro-2H-pyran-5-carboxylate 5f

δ-Hydroxy-β-ketoester 7f (0.052 g, 0.276 mmol), yielded 0.049 g (91%), light yellow oil. v max/cm⁻¹ 2958, 2874, 1741, 1700, 1582, 1435, 1380, 1300, 1147, 1074, 799, 506 cm⁻¹; ¹H (400MHz, CDCl₃) 7.97 (1H, s), 3.71-3.64 (1H, m), 3.52 (3H, s), 2.98 (1H, dd, J = 16.0, 4.0 Hz) and 2.79 (1H, dd, J = 16.0, 4.0 Hz) ppm; δC (100 MHz, CDCl₃) 187.6, 171.5, 164.5, 116.9, 81.3, 43.1, 39.3 ppm; m/z (ESI⁺) 209 (M + Na)⁺, 187 (M + H)⁺, (Found C₂₉H₂₀NaO₂ requires; 255.0633).
Methyl 4-oxo-2-[(trisopropylsilyloxy)methyl]-3,4-dihydro-2H-pyran-5-carboxylate 5f

δ-Hydroxy-β-ketoester 7f (0.30 g, 1.612 mmol), yielded 0.274 g (87%), light orange oil. u max/cm⁻¹: 2952, 2919, 1740, 1579, 1436, 1381, 1297, 1135, 1053, 965 cm⁻¹; 6H (400MHz, CDCl₃) 8.01 (1H, s), 5.28 (1H, m), 5.08 (1H, m), 4.20 (1H, dd, J = 8.6, 7.0, 7.0 Hz), 3.51 (3H, s), 2.08 (2H, m) and 1.31 (3H, d, J = 6.5 d) ppm; 6C (100 MHz, CDCl₃) 181.2, 169.9, 164.3, 131.5, 127.0, 111.5, 80.9, 51.3, 41.8 and 17.5 ppm; m/z (ESI⁺) 219 (M + Na⁺) (Found 219.0629 (M + Na⁺)). C₁₈H₃₀NaO₄ requires; 365.1760.

Methyl 4-oxo-2-styryl-3,4-dihydro-2H-pyran-5-carboxylate 5g

δ-Hydroxy-β-ketoester 7g (0.107 g, 0.427 mmol), yielded 0.107g (97%), orange solid. u max/cm⁻¹: 2951, 1693, 1569, 1436, 1369, 1260, 1295, 1060, 966, 747, 692 cm⁻¹; 8H (400MHz, CDCl₃) 8.04 (1H, s), 7.10-7.03 (5H, m), 6.19 (1H, dd, J = 16.0, 1.1 Hz), 5.73 (1H, dd, J = 16.0, 6.8 Hz), 4.26 (1H, dd, J = 9.1, 6.9, 6.8 Hz), 3.53 (3H, s) and 2.12 (2H, m) ppm; 6C (100 MHz, CDCl₃) 193.2, 184.9, 169.9, 164.9, 135.6, 134.3, 128.9, 127.1, 124.2, 111.8, 81.0, 51.5 and 42.0 ppm; m/z (ESI⁺) 281 (M + Na⁺) (Found 281.0781 (M + Na⁺)). C₁₃H₁₂NaO₄ requires; 281.0784.

Methyl 2-(2-methylazol-4-yl)-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate 5h

δ-Hydroxy-β-ketoester 7h (0.078 g, 0.343 mmol), yielded 0.062 g (77%), light yellow oil. u max/cm⁻¹: 2953, 1738, 1704, 1579, 1436, 1383, 1296, 1133, 1013, 816, 732 cm⁻¹; 6H (400MHz, CDCl₃) 8.34 (1H, s), 7.61 (1H, s), 5.55 (1H, dd, J = 12.0, 4.0 Hz), 3.80 (3H, s), 3.10 (1H, dd, J = 16.7, 12.0 Hz), 2.81 (1H, dd, J = 16.7, 4.0 Hz) and 2.48 (3H, s) ppm; 6C (100 MHz, CDCl₃) 198.7, 167.7, 160.1, 137.2, 145.3, 92.6, 49.6, 35.5, 31.5, 30.1 and 14.2 ppm; m/z (ESI⁺) 260 (M + Na⁺) (Found 260.0523 (M + Na⁺)). C₁₂H₁₂NaO₄ requires; 260.0535.

General Procedure for the Synthesis 2,6-trans-tetrahydropyran-4-ones 8/9.

Addition of Ph₃CuLi:
Phenyl lithium 1.9M in dibutyl ether solution (0.58 mL, 0.90 mmol) was added to a suspension of copper iodide (86.3 mg, 0.45 mmol) in THF (3.00 mL) at 0 °C. The mixture was stirred at this temperature for 20 minutes then cooled to -78 °C. Addition of chlorotrimethylsilane (0.18 mL, 1.4 mmol) was followed by addition of DHP (0.28 mmol) in THF (2.00 mL) at -78 °C. The reaction mixture was stirred at this temperature for 30 minutes then at 0 °C for 1.5 hours. The reaction was quenched with sat. aq. NH₄Cl (2.5 mL) and allowed to warm to rt with vigorous stirring. The mixture was diluted with sat. aq. NH₄Cl (10.0 mL) and extracted with EtOAc (5 x 15.0 mL). The combined organic extracts were washed with H₂O (15.0 mL) and brine (15.0 mL), then dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (hexane – ethyl acetate) afforded the product as a mixture of enol/keto tautomers 8/9.

(2R*,6S*)-Methyl 4-hydroxy-2,6-diphenyl-5,6-dihydro-2H-pyran-3-carboxylate 8a

Dihydropyran 5b (0.088g, 0.379 mmol), yielded 0.082 g (70 %), light brown oil. u max/cm⁻¹ (film) 2955, 2931, 2872, 1768, 1723, 1710, 1435, 1363, 1254, 1177, 1149, 1055, 875, 480 cm⁻¹; 6H (400MHz, CDCl₃) 12.4 (1H, s), 7.41-7.24 (10H, m). 5.8 (1H, s), 4.56 (1H, dd, J = 10.8, 4.0 Hz), 3.66 (3H, s). 2.73 (1H, dd, J = 18.1, 10.8 Hz), 2.59 (1H, dd, J = 18.1, 4.0 Hz) ppm; 6C (100 MHz, CDCl₃) 193.0, 171.2, 140.7, 128.6, 128.3, 128.0, 127.9, 126.0, 98.6, 73.3, 68.4, 51.8, 41.5, 35.6, 31.1 ppm; m/z (ESI⁺) 333 (M + Na⁺) (Found 333.1108 (M + Na⁺)). C₁₈H₁₈NaO₄ requires; 333.1103.

(2R*,6R*)-Methyl 4-hydroxy-2-phenyl-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate 8b

Dihydropyran 5c (0.045g, 0.227 mmol), yielded 0.035g (56 %), oil. u max/cm⁻¹ (film) 2955, 2927, 2875, 1658, 1621, 1441, 1288, 1262, 1216, 1043, 775, 698 cm⁻¹; 6H (400MHz, CDCl₃) 12.29 (1H, s), 7.37-7.27 (5H, m), 5.59 (3H, s), 3.63 (3H, s), 3.47-3.41 (1H, m). 2.32 (1H, dd, J = 18.0, 10.0 Hz), 2.23 (1H, dd, J = 18.0, 4.2 Hz), 1.05-1.43 (2H, m), 1.37-1.28 (2H, m) and 0.72 (3H, t, J = 7.2 Hz) ppm; 6C (100 MHz, CDCl₃) 171.7, 171.2, 141.1, 128.5, 128.1, 127.8, 98.6, 72.2, 66.3, 51.7, 37.8, 35.0, 18.3 and 13.8 ppm; m/z (ESI⁺) 299 (M + Na⁺) (Found 299.1255 (M + Na⁺)). C₁₈H₁₆NaO₄ requires; 299.1254.
Dihydropyran 5d (0.060 g, 0.303 mmol), yielded 0.060 g (73 %), light yellow oil. u max/cm⁻¹ (film) 2924, 2852, 1946, 1739, 1661, 1365, 1268, 1222, 1060 841 cm⁻¹; δH (400 MHz, CDCl₃) 12.30 (1H, s), 7.37-7.27 (5H, m), 5.62 (1H, s), 3.63 (3H, s), 3.10 (1H, dd, J = 10.8, 3.9 Hz), 2.36 (1H, dd, J = 18.0, 10.8 Hz), 2.23 (1H, dd, J = 18.0, 3.9 Hz), 1.64-1.56 (1H, m), 0.80 (3H, d, J = 6.8 Hz) and 0.77 (3H, d, J = 6.8 Hz) ppm; δC (100 MHz, CDCl₃) 193.2, 141.5, 128.6, 128.0, 127.7, 98.5, 72.6, 71.6, 51.2, 41.3, 32.8, 32.3, 18.4 and 17.8 ppm; m/z (ESI⁺) 299 (M + Na)⁺ (Found 299.1245 (M + Na)⁺). C₁₈H₂₁NaO₃ requires; 299.1254.

(2R*,6S*)-Methyl 4-hydroxy-2-phenyl-6-((E)-styryl)-5,6-dihydro-2H-pyran-3-carboxylate 8d

Dihydropyran 5e (0.073 g, 0.213 mmol), yielded 0.043 g (48 %), light yellow oil. u max/cm⁻¹ (film) 2941, 2861, 1660, 1623, 1442, 1280, 1264, 1215, 1095, 880, 681 cm⁻¹; δH (400 MHz, CDCl₃) 12.90 (1H, s), 7.38-7.64 (2H, m), 7.18-7.08 (3H, m) 5.79 (1H, s), 3.65-3.60 (1H, m), 3.55-3.46 (2H, m), 3.05 (3H, s), 2.59 (1H, dd, J = 18.1, 10.8 Hz), 2.18 (1H, dd, J = 18.1, 2.8 Hz) and 1.01 (2H, m) ppm; δC (100 MHz, CDCl₃) 172.3, 171.3, 141.5, 128.9, 128.4, 127.9, 99.0, 73.1, 67.9, 66.3, 51.0, 31.4, 81.1 and 12.2 ppm; m/z (ESI⁺) 443 (M + Na)⁺ (Found 443.2209 (M + Na)⁺). C₂₃H₂₆NaO₄Si requires; 443.2224.

(2R*,6S*)-Methyl 4-hydroxy-2-phenyl-6-((E)-styryl)-5,6-dihydro-2H-pyran-3-carboxylate 8e

Dihydropyran 5f (0.055 g, 0.280 mmol), yielded 0.049 g (64 %), light yellow oil. u max/cm⁻¹ (film) 3028, 2952, 2896, 1662, 1618, 1437, 1325, 1243, 1205, 1181, 1051, 958, 740, 690 cm⁻¹; δH (400 MHz, CDCl₃) 12.30 (1H, s), 7.50-7.77 (5H, m), 5.62 (1H, s), 5.56 (1H, d, J = 16.0, 4.0 Hz), 5.44 (1H, dd, J = 16.0, 4.0 Hz), 3.97 (1H, dd, J = 12.0, 4.0, 4.0 Hz), 3.62 (3H, s), 2.16 (2H, dd, J = 16.0, 12.0 Hz), 2.32 (1H, dd, J = 16.0, 4.0 Hz) and 1.65 (1H, d, J = 4.0 Hz) ppm; δC (100 MHz, CDCl₃) 171.1, 140.9, 130.8, 126.8, 128.5, 128.2, 127.9, 127.1, 98.6, 73.0, 67.1, 51.6, 34.4 and 17.9 ppm; m/z (ESI⁺) 297 (M + Na)⁺ (Found 297.1091 (M + Na)⁺). C₁₉H₁₉NaO₄ requires; 297.1097.

(2R*,6S*)-Methyl 4-hydroxy-2-phenyl-6-((E)-styryl)-5,6-dihydro-2H-pyran-3-carboxylate 8f

Dihydropyran 5g (0.988g, 3.822 mmol), yielded 1.170 g (91 %), light yellow solid. u max/cm⁻¹ (film) 3028, 2952, 2896, 1662, 1618, 1437, 1325, 1243, 1205, 1181, 1051, 958, 740, 690 cm⁻¹; δH (400 MHz, CDCl₃) 12.32 (1H, s), 7.46-7.20 (10H, m), 6.49 (1H, d, J = 16.1 Hz), 6.15 (1H, dd, J = 16.1, 5.7 Hz), 5.70 (1H, s), 4.24 (1H, dd, J = 10.5, 5.7, 4.1 Hz), 3.64 (3H, s), 2.58 (1H, dd, J = 18.0, 10.5 Hz) and 2.46 (1H, dd, J = 18.0, 4.1 Hz) ppm; δC (100 MHz, CDCl₃) 171.1, 170.9, 140.8, 136.4, 131.4, 128.6, 128.5, 128.3, 128.0, 127.9, 126.6, 115.4, 98.3, 73.0, 67.4, 51.8 and 34.5 ppm; m/z (ESI⁺) 359 (M + Na)⁺ (Found 359.1249 (M + Na)⁺). C₂₁H₂₃NaO₄ requires; 359.1254.

Addition of Me₂CuLi.
Addition of n-Bu$_3$CuLi:

n-Butyl lithium 2.5M in hexane solution (0.26 ml, 0.6 mmol) was added to a suspension of copper iodide (57.2 mg, 0.3 mmol) in THF (1.70 ml) at 0 °C. The mixture was stirred at this temperature for 20 minutes. After this time the mixture was cooled to -78 °C and chlorotrimethylsilane (0.12 ml, 0.9 mmol) was added, followed by addition of DHP 5 (0.2 mmol) in THF (1.80 ml) at -78 °C. The reaction mixture was stirred at -78 °C for 4 hours then quenched with sat. aq. NH$_4$Cl (1.50 ml) and allowed to warm to rt with vigorous stirring. The mixture was diluted further with sat. aq. NH$_4$Cl (10.0 ml) and extracted with EtOAc (5 x 15.0 ml). The combined organic extracts were washed with H$_2$O (15.0 ml) and brine (15.0 ml), then dried over MgSO$_4$ and concentrated in vacuo. Flash column chromatography (hexane – ethyl acetate) afforded the products as an inseparable mixture of enol and ketone tautomers 8/9, which were then subjected to acylation. The THP mixture 8/9 (0.03 mmol), acetic anhydride (0.10 ml, 0.10 mmol) and DMAP (2 mg) were stirred in pyridine (0.47 ml) at 40 °C for 40 minutes. The mixture was cooled to rt, concentrated in vacuo and partitioned between Et$_2$O (30.0 ml) and H$_2$O (10.0 ml). The organic layer was washed with H$_2$O (10.0 ml) and brine (10.0 ml), then dried over MgSO$_4$ and concentrated in vacuo. Flash column chromatography (hexane – ethyl acetate) gave products 10.

(2R,6S*)-Methyl 4-acetoxy-2-butyl-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate 10m

Dihydropyran 5g (0.100 g, 0.431 mmol), yielded 0.056 g (39 % after 2 steps), light yellow oil. u max/cm$^{-1}$ (film) 2953, 2860, 1764, 1721, 1248, 1174, 1055, 698 cm$^{-1}$; $\delta$ (400 MHz, CDCl$_3$) 7.40-7.29 (5H, m), 4.92 (1H, dd, J = 9.0, 5.0 Hz), 4.79 (1H, d, J = 10.1 Hz), 3.75 (3H, s), 2.69-2.47 (2H, m), 2.21 (3H, s), 1.88-1.24 (6H, m), 0.89 (3H, t, J = 7.3 Hz) ppm; $\delta$ (100 MHz, CDCl$_3$) 168.9, 164.1, 153.2, 141.0, 128.6, 128.0, 4.0 ppm; m/z (ESI$^+$) 355 (M + Na)$^+$ (Found 355.1509 (M + Na)$^+$). C$_{28}$H$_{26}$NaO$_3$ requires; 355.1516.

(2R,6S*)-Methyl 4-acetoxy-2-butyl-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate 10n

Dihydropyran 5h (0.070 g, 0.353 mmol), yielded 0.037 g (35 % after 2 steps), light yellow oil. u max/cm$^{-1}$ (film) 2956, 2932, 2872, 1767, 1722, 1241, 1177, 1053, 900 cm$^{-1}$; $\delta$ (400 MHz, CDCl$_3$) 4.61 (1H, d, J = 10.3 Hz), 2.84 (1H, m), 3.71 (3H, s), 2.22-2.16 (2H, m), 2.18 (3H, s), 1.74-1.25 (10H, m), 0.95-0.88 (6H, m) ppm; 6C (100 MHz, CDCl$_3$) 168.6, 164.3, 153.9, 121.1, 77.3, 72.5, 66.2, 51.8, 37.7, 35.0, 32.0, 28.2, 23.8, 21.0, 18.8 and 14.1 ppm; m/z (ESI$^+$) 321 (M + Na)$^+$ (Found 321.1681 (M + Na)$^+$). C$_{27}$H$_{26}$NaO$_3$ requires; 321.1672.

(2R,6S*)-Methyl 4-acetoxy-2-butyl-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate 10o

Dihydropyran 5d (0.037g, 0.186 mmol) yielded 0.020 g (37 % after 2 steps), light yellow oil. u max/cm$^{-1}$ (film) 2955, 2929, 1767, 1724, 1712, 1435, 1365, 1249, 1202, 1177, 1056, 490 cm$^{-1}$; $\delta$ (400 MHz, CDCl$_3$) 4.89 (1H, d, J = 10.0 Hz), 3.43-3.38 (1H, m), 3.28 (3H, s), 2.15 (1H, dd, J = 17.7, 9.6 Hz), 2.07 (1H, dd, J = 17.7, 4.3 Hz), 1.92 (3H, s), 1.74-1.53 (2H, m), 1.48-1.39 mmol) in THF (1.70 ml) at 0 °C. The mixture was stirred at this temperature for 20 minutes. After this time the mixture was cooled to -78 °C and chlorotrimethylsilane (0.12 ml, 0.9 mmol) was added, followed by addition of DHP 5 (0.2 mmol) in THF (1.80 ml) at -78 °C. The reaction mixture was stirred at -78 °C for 4 hours then quenched with sat. aq. NH$_4$Cl (1.50 ml) and allowed to warm to rt with vigorous stirring. The mixture was diluted further with sat. aq. NH$_4$Cl (10.0 ml) and extracted with EtOAc (5 x 15.0 ml). The combined organic extracts were washed with H$_2$O (15.0 ml) and brine (15.0 ml), then dried over MgSO$_4$ and concentrated in vacuo. Flash column chromatography (hexane – ethyl acetate) afforded the products as an inseparable mixture of enol and ketone tautomers 8/9, which were then subjected to acylation. The THP mixture 8/9 (0.03 mmol), acetic anhydride (0.10 ml, 0.10 mmol) and DMAP (2 mg) were stirred in pyridine (0.47 ml) at 40 °C for 40 minutes. The mixture was cooled to rt, concentrated in vacuo and partitioned between Et$_2$O (30.0 ml) and H$_2$O (10.0 ml). The organic layer was washed with H$_2$O (10.0 ml) and brine (10.0 ml), then dried over MgSO$_4$ and concentrated in vacuo. Flash column chromatography (hexane – ethyl acetate) gave products 10.
**Dihydropyran 5e** (0.056 g, 0.163 mmol), yielded 0.012 g (16 %). H NMR (400 MHz, CDCl₃): δ 11.29 (OH, s), 7.43-7.29 (5H, m), 4.70 (1H, m, keto) 4.67 (1H, dd, J = 10.48, 3.71 Hz), 4.59 (1H, m, keto), 4.55-4.36 (2H, m, keto), 4.44 (1H, dd, J = 14.00), 4.39 (1H, dd, J = 14.00 Hz), 3.81 (3H, s), 3.80 (3H, s, keto), 3.02-2.68 (2H, m, keto) and 2.67-2.49 (2H, m) ppm; m/z (ESI⁺) 257 (M + Na⁺). (Found 257.0782 (M + Na)⁺. C₁₇H₁₄NaO₃ requires 257.0784).

**Methyl 4-hydroxy-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate 11c**

Dihydropyran 5c (0.100 g, 0.505 mmol), yielded 0.089 g, (89 %). H NMR (400 MHz, CDCl₃): δ 12.09 (OH, s), 4.50 (1H, d, J = 13.7), 4.40 (1H, m, keto), 4.11 (1H, d, J = 13.7 Hz), 4.05 (1H, m, keto), 3.22 (3H, s), 3.21 (3H, s, keto), 3.20 (1H, m), 3.05 (1H, m, keto), 2.12 (2H, m, keto), 2.08 (1H, m), 1.94 (1H, m), 1.47-0.96 (4H, m) and 0.79 (3H, s, J = 7.2 Hz) ppm; 8C (100 MHz, CDCl₃): 208.0 (keto), 170.8, 170.0, 168.0 (keto), 97.5, 78.2 (keto), 73.5, 68.1 (keto), 63.2, 57.5 (keto), 51.6 (keto), 50.9, 47.7 (keto), 38.3 (keto), 37.9, 34.6, 18.7, 18.5 (keto), 14.1 and 14.0 (keto) ppm; m/z (ESI⁺) 223 (M + Na)⁺. (Found 223.0938 (M + Na)⁺. C₁₇H₁₄NaO₃ requires 223.0941).

**Methyl 4-hydroxy-6-(((trisopropysilyloxy)methyl)5,6-dihydro-2H-pyran-3-carboxylate 11e**

Dihydropyran 5e (0.095 g, 0.277 mmol), yielded 0.062 g, (65 %). H NMR (400 MHz, CDCl₃): δ 11.78 (OH, s), 4.69-4.66 (2H, m, keto), 4.43 (1H, d, J = 13.9), 4.22 (1H, d, J = 13.9 Hz), 3.93 (1H, m, keto), 3.88 (1H, m), 3.83-3.79 (2H, m), 3.76 (3H, s, keto), 3.75 (3H, s), 3.62-3.59 (2H, m, keto), 2.82 (1H, m, keto), 2.61-2.28 (2H, m), 2.31 (1H, m, keto) and 1.06-1.05 (21H, m) ppm; 8C (100 MHz, CDCl₃): 170.5, 169.5, 97.1, 79.2 (keto), 74.6, 68.2 (keto), 66.0, 63.2, 57.3 (keto), 52.4 (keto), 51.5, 44.2 (keto), 31.3, 18.8, 12.0 ppm; m/z (ESI⁺) 367 (M + Na)⁺. (Found 367.1905 (M + Na)⁺. C₁₇H₁₄NaO₃ requires 367.1911).

**E)-Methyl 4-hydroxy-6-styryl-5,6-dihydro-2H-pyran-3-carboxylate 11g**

Dihydropyran 5g (0.100 g, 0.387 mmol), yielded 0.051 g, (51 %). H NMR (400 MHz, CDCl₃): δ 11.78 (OH, s), 7.41-7.23 (5H, m), 6.65 (1H, d, J = 16.0 Hz), 6.58 (1H, m, keto), 6.23 (1H, dd, J = 16.0, 6.0 Hz), 6.19 (1H, m, keto), 4.48 (1H, d, J = 13.9), 4.47 (1H, m, keto), 4.32 (1H, d, J = 13.9 Hz), 4.28 (1H, m), 4.26 (1H, m, keto), 3.79 (3H, s, keto), 3.77 (3H, s), 2.84 (1H, m, keto), 2.67 (1H, m, keto) and 2.69-2.38 (2H, m) ppm; 8C (100 MHz, CDCl₃): 170.5, 168.5, 136.4 (keto), 132.3 (keto), 131.8, 128.7, 128.2, 128.1, 126.8 ppm; m/z (ESI⁺) 367 (M + Na)⁺. (Found 367.1905 (M + Na)⁺. C₁₇H₁₄NaO₃ requires 367.1911).
Methyl 4-acetoxy-6-furan-2-yl)-5,6-dihydro-2H-pyran-3-carboxylate 12a

Tetrahydropyran-4-one 11a (0.043 g, 0.191 mmol), yielded 0.029 g (58 %) oil. u max/cm−1 (film) 3025, 2953, 2844, 1761, 1723, 1705, 1248, 1172, 1142, 1051, 748, 693 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.41 (1H, s), 6.41 (1H, m), 6.35 (1H, m), 4.80 (1H, dd, J = 9.0, 4.1 Hz), 4.51-4.48 (2H, m), 3.72 (3H, s) 2.89 (1H, m), 2.55 (1H, m) and 2.52 (3H, s) ppm; 6C (100 MHz, CDCl3): 168.4, 163.4, 151.3, 152.2, 143.0, 116.5, 110.4, 108.3, 68.7, 64.0, 51.8, 32.4 and 21.0 ppm; m/z (ESI)+ 289 (M + Na)+.

General Procedure for the Synthesis of 3,3,6-trisubstituted tetrahydropyran-4-ones 13.

A 1.0 M solution of L-Selectride in THF (0.04 mL, 0.04 mmol) was added to a stirred solution of DHP (0.04 mmol) in THF (1.00 mL) at -78 °C. The mixture was stirred for 1 hour at this temperature before addition of the electrophile (0.4 mmol). The reaction mixture was stirred at room temperature until completion then diluted with Et2O (10.0 mL) and quenched with sat. aq. NH4Cl (10.0 mL). The layers were separated and aqueous layer was extracted with Et2O (10.0 mL). The combined organic extracts were washed with brine (20.0 mL), dried over MgSO4 and concentrated in vacuo. Purification by flash column chromatography (hexane – ethyl acetate) afforded the product.

(3S*,6S*)-Methyl 3-methyl-4-oxo-6-(((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-3-carboxylate 13a

Dihydropyran 5b (0.100 g, 0.431 mmol), yielded 0.063 g (59 %) oil. u max/cm−1 (film) 3032, 2953, 2877, 1736, 1710, 1268, 1233, 1095, 1075, 672 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.41-7.31 (5H, m), 4.89 (1H, dd, J = 9.5, 4.1 Hz), 4.29 (1H, d, J = 11.7 Hz), 3.94 (1H, d, J = 11.7 Hz), 3.79 (3H, s), 2.86 (1H, dd, J = 15.2, 9.5 Hz), 2.75 (1H, dd, J = 15.2, 4.1 Hz) and 1.54 (3H, s) ppm; 6C (100 MHz, CDCl3): 204.9, 171.3, 139.8, 128.8, 128.4, 126.0, 79.5, 72.5, 58.6, 52.6, 45.1 and 18.6 ppm; m/z (ESI)+ 271 (M + Na)+. (Found 271.0936 (M + Na)+).

(3S*,6S*)-Methyl 3-methyl-4-oxo-6-((E)-styryl)tetrahydropyran-3-carboxylate 13b

Dihydropyran 5g (0.120 g, 0.465 mmol), yielded 0.068 g (53 %) oil. u max/cm−1 (film) 3026, 2952, 2875, 1733, 1713, 1232, 1264, 1114, 1088, 967, 748, 693 cm−1; 1H NMR (400 MHz, CD2D2): δ 7.18-7.02 (5H, m), 6.44 (1H, d, J = 16.0 Hz), 5.94 (1H, J = 15.5, 2.0 Hz), 4.33 (1H, dd, J = 10.5, 3.4 Hz), 3.70 (1H, dd, J = 10.0, 5.0 Hz), 2.57 (1H, m), 2.27 (1H, m), 2.02 (3H, s) and 1.18-1.17 (21H, m) ppm; 6C (100 MHz, CD2D2): 167.7, 163.0, 154.9, 116.7, 74.7, 66.1, 45.8, 50.8, 32.0, 20.6, 18.1 and 12.2 ppm; m/z (ESI)+ 409 (M + Na)+. (Found 409.2022 (M + Na)+).


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dd, J = 16.0, 5.3 Hz), 4.19 (1H, d, J = 11.6 Hz), 4.06 (1H, ddd, J = 9.0, 5.3, 4.4 Hz), 3.66 (1H, d, J = 11.6 Hz), 3.36 (3H, s), 2.41 (1H, dd, J = 15.0, 4.4 Hz), 2.29 (1H, dd, J = 15.0, 9.0 Hz) and 1.31 (3H, s) ppm; δC (100 MHz, CD2Cl2): 203.2, 171.9, 136.6, 132.2, 128.9, 128.1, 127.9, 126.9, 77.2, 72.1, 58.7, 52.0, 43.9 and 18.1 ppm; m/z (ESI+) 297 (M + Na)\(^+\). (Found 297.1095 (M + Na)\(^+\). C\(_{12}\)H\(_{12}\)NaO\(_4\) requires 297.1097).

\((3S,6S*)\)-Methyl 3-methyl-4-oxo-6-\((\text{trisopropylsilyl})\text{oxy}\)methyl)tetrahydro-2H-pyran-3-carboxylate 13c

Dihydropyran 5d (0.097 g, 0.280 mmol), yielded 0.057 g (57 %) oil. u. max/cm\(^{-1}\) (film) 2942, 2866, 1738, 1715, 1105, 881, 681,659 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD2Cl2): δ 4.13 (1H, d, J = 11.4 Hz), 3.73 (1H, d, J = 11.4 Hz), 3.58 (1H, ddd, J = 10.0, 3.8, 3.8 Hz), 3.45 (1H, d, J = 8.0, 3.8 Hz), 3.40 (1H, dd, J = 8.0, 3.8 Hz), 3.36 (3H, s), 2.59 (1H, dd, J = 15.1, 10.0 Hz), 2.25 (1H, dd, J = 15.1, 3.5 Hz), 1.43 (3H, s) and 1.05-1.10 (21H, m) ppm; δC (100 MHz, CD2Cl2): 205.0, 171.1, 78.6, 73.0, 65.9, 58.8, 51.9, 40.2, 18.6, 18.1 and 12.2 ppm; m/z (ESI+) 381 (M + Na)\(^+\). (Found 381.2065 (M + Na)\(^+\). C\(_{12}\)H\(_{14}\)NaO\(_4\)Si requires 381.2068).

\((3S,6R*)\)-Methyl 3-allyl-4-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate 13d

Dihydropyran 5e (0.100 g, 0.505 mmol), yielded 0.063 g (58 %) oil. u. max/cm\(^{-1}\) (film) 2956, 2929, 2872, 1738, 1714, 1100, 782 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD2Cl2): δ 4.08 (1H, d, J = 11.5 Hz), 3.62 (1H, d, J = 11.5 Hz), 3.38 (3H, s), 3.24 (1H, m), 2.12 (1H, dd, J = 15.0, 3.6 Hz), 1.99 (1H, dd, J = 15.0, 10.2 Hz), 1.35 (3H, s), 1.32-0.93 (4H, m) and 0.74 (3H, J, t = 7.3 Hz) ppm; δC (100 MHz, CD2Cl2): 204.3, 171.9, 77.8, 72.2, 58.8, 51.8, 44.2, 37.7, 18.7, 18.5 and 14.0 ppm; m/z (ESI+) 237 (M + Na)\(^+\). (Found 237.1100 (M + Na)\(^+\). C\(_{12}\)H\(_{14}\)NaO\(_4\) requires 237.1097).

\((3S,6S*)\)-Methyl 3-allyl-4-oxo-6-phenyltetrahydro-2H-pyran-3-carboxylate 13e

Dihydropyran 5b (0.100 g, 0.431 mmol), yielded 0.061 g (52 %) oil. u. max/cm\(^{-1}\) (film) 3065, 2952, 2875, 1736, 1711, 1227, 1076, 763, 699 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl3): δ 7.42-7.32 (5H, m), 5.80 (1H, m), 5.20 (1H, dd, J = 17.2, 4.4 Hz), 5.15 (1H, dd, J = 10.1, 4.4 Hz), 4.86 (1H, dd, J = 9.3, 4.4 Hz), 4.21 (1H, d, J = 11.8 Hz), 4.12 (1H, d, J = 11.8 Hz), 3.79 (3H, s) and 2.82-2.71 (4H, m) ppm; δC (100 MHz, CDCl3): 203.8, 170.2, 139.9, 132.1, 128.8, 128.4, 126.0, 119.9, 79.6, 70.1, 62.5, 52, 52.5, 46.2 and 36.1 ppm; m/z (ESI+) 297 (M + Na)\(^+\). (Found 297.1101 (M + Na)\(^+\). C\(_{12}\)H\(_{14}\)NaO\(_4\) requires 297.1097).

\((3S,6S*)\)-Methyl 3-4-oxo-6-(\(\alpha\)-styril)tetrahydro-2H-pyran-3-carboxylate 13f

Dihydropyran 5f (0.100 g, 0.387 mmol), yielded 0.097 g (83 %) oil. u. max/cm\(^{-1}\) (film) 2952, 1736, 1712, 1226, 1073, 1031, 966, 748, 693 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD2Cl2): δ 7.19-7.02 (5H, m), 6.45 (1H, d, d, J = 16.0, 1.2 Hz), 5.95 (1H, dd, J = 16.0, 5.4 Hz), 5.88 (1H, ddd, J = 17.1, 10.1, 7.5, 7.0 Hz), 5.05 (1H, dd, J = 17.1, 4.4 Hz), 4.99 (1H, dd, d, J = 10.1, 4.4 Hz), 4.16 (1H, d, J = 11.8 Hz), 4.03 (1H, ddd, J = 9.0, 5.4, 4.2, 1.2 Hz), 3.98 (1H, d, J = 11.8 Hz), 3.36 (3H, s), 2.69 (1H, dd, J = 13.8, 7.0 Hz), 2.52 (1H, dd, J = 13.8, 7.5 Hz), 2.41 (1H, dd, J = 14.7, 4.2 Hz) and 2.31 (1H, dd, J = 14.7, 9.0 Hz) ppm; δC (100 MHz, CD2Cl2): 202.6, 170.2, 136.6, 133.0, 132.1, 128.9, 126.9, 119.4, 77.8, 69.8, 62.7, 51.9, 44.8 and 35.9 ppm; m/z (ESI+) 323 (M + Na)\(^+\). (Found 323.1242 (M + Na)\(^+\). C\(_{12}\)H\(_{12}\)NaO\(_4\) requires 323.1230).
Dihydropyrany 5g (0.096 g, 0.372 mmol), yielded 0.066 g (51 %) oil. u max/cm⁻¹ (film) 2958, 2860, 1734, 1712, 1209, 1070, 742, 703, 597 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.42-7.19 (10H, m), 6.67 (1H, dd, J = 16.1, 1.0 Hz), 6.26 (1H, dd, J = 16.1, 5.7 Hz), 4.59 (1H, ddd, J = 8.6, 5.7, 4.5, 1.0 Hz), 4.11 (1H, d, J = 12.2 Hz), 4.05 (1H, d, J = 12.2 Hz) ppm; 7C (1H, d, J = 13.5 Hz), 3.80 (1H, d, J = 13.5 Hz), 2.83 (1H, dd, J = 14.8, 8.6 Hz) and 2.73 (1H, dd, J = 14.8, 4.5 Hz) ppm; 6C (100 MHz, CDCl₃): 204.3, 196.8, 136.0, 135.1, 132.9, 130.7, 128.8, 128.5, 128.4, 127.4, 127.3, 126.8, 78.1, 68.7, 63.8, 52.5, 44.6 and 36.7 ppm; m/z (ESI⁺) 373 (M + Na⁺). C₂₁H₁ₙNaO₄ requires 373.1410.

(3S*,6S*)-Methyl 3-benzyl-4-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate 13k
Dihydropyrany 5e (0.100 g, 0.292 mmol), yielded 0.078 g (62 %) oil. u max/cm⁻¹ (film) 2942, 2865, 1713, 1121, 1074, 881, 682, 660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.48-7.02 (5H, m), 4.15 (1H, d, J = 12.0 Hz), 3.97 (1H, d, J = 12.0 Hz), 3.64 (1H, m), 3.43 (2H, m), 3.34 (3H, s), 3.42 (1H, d, J = 13.0 Hz), 3.27 (1H, d, J = 13.0 Hz), 2.79 (1H, dd, J = 15.0, 10.6 Hz), 2.22 (1H, dd, J = 15.0, 3.4 Hz) and 1.08-1.00 (21H, m) ppm; NOE H2; requires 373.1410. (Found 373.1401 (M + Na⁺). C₂₂H₂₅NaO₄ requires 373.4281.

(3S*,6S*)-Methyl 3-benzyl-4-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate 13l
Dihydropyrany 5c (0.050 g, 0.252 mmol), yielded 0.045 g (62 %) oil. u max/cm⁻¹ (film) 2956, 2932, 2872, 1734, 1711, 1262, 1206, 1077, 1016, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.27-7.20 (5H, m), 3.99 (1H, d, J = 12.2 Hz), 3.94 (1H, d, J = 12.2 Hz), 3.81 (1H, m), 3.70 (3H, s), 3.31 (1H, d, J = 13.4 Hz), 3.21 (1H, d, J = 13.4 Hz), 2.56 (1H, dd, J = 15.0, 9.8 Hz), 2.48 (1H, dd, J = 15.0, 3.8 Hz), 1.58-1.37 (4H, m) and 0.95 (3H, t, J = 7.16 Hz) ppm; 6C (100 MHz, CDCl₃): 204: 207.7, 204.6, 138.5, 132.9, 130.7, 128.5, 127.7, 78.4, 69.0, 63.9, 52.3, 44.9, 37.7, 36.8, 18.3 and 14.0 ppm; m/z (ESI⁺) 313 (M + Na⁺). C₁₉H₁₉NaO₄ requires 313.2381.


(E)-Methyl 5-hydroxy-3-oxo-7-phenylhept-6-enate 7g
Titanium tetraisopropoxide (11.48 mL, 38.80 mmol) was added to a stirred solution of cinnamaldehyde (4.88 g, 38.80 mmol) and diketene (5.36 mL, 69.60 mmol) in CH₂Cl₂ (104 mL) at -78 °C. After 5 minutes, methanol (6.24 mL, 154.00 mmol) was added and the mixture was stirred at -20 to -10 °C for 1.5 hours. The reaction mixture was diluted with Et₂O (100.0 mL) and a 20 % w/v citric acid solution (120.0 mL) was added. The layers were separated and the aqueous layer was extracted with Et₂O (2 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (Hexane – ethyl acetate, 3:2) gave the product as an oil, isolated yield 7.33 g (76 %). u max/cm⁻¹ (film) 3423, 3026, 2953, 1740, 1710, 1436, 1319, 1266, 1149, 1070, 976, 747, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.28-7.05 (5H, m), 6.57 (1H, d, J = 16.0 Hz), (1H, dd, dd, J = 16.0, 5.4 Hz), 4.62 (1H, m), 3.30 (3H, s), 3.10 (2H, s), 2.49 (1H, dd, J = 16.8, 8.9 Hz) ppm; 6C (100 MHz, CDCl₃): 201.9, 167.3, 137.2, 131.0, 130.2, 128.8, 127.8, 126.8, 68.4, 51.8, 49.7 and 49.6 ppm; m/z (ESI⁺) 271 (M + Na⁺). (Found 271.0937 (M + Na⁺). C₁₉H₁₉NaO₄ requires 271.0941.

(2S*,4S*,6S*)-2-(Ethoxy)methoxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethanone 15
N,N-Diisopropylethylamine (0.6 mL, 3.36 mmol), MOMCl (0.34 mL, 4.48 mmol) and sodium iodide (0.1 g, 0.67 mmol) were added to a stirred solution of 14 (0.078g, 0.28 mmol) in THF (5.0 mL) at room temperature. The mixture was heated at 50 °C for 10 hours, after which the solvent was removed in vacuo. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL). The extract was washed with brine and dried over MgSO₄ and concentrated in vacuo to give the product 0.054 g (60 %) as a light yellow oil. u max/cm⁻¹ (film) 2923, 2854, 1145, 1033, 695 cm⁻¹; δH (400 MHz, CDCl₃) 7.47-7.22 (10H, m), 6.62 (1H, d, J = 16.0 Hz), 6.38 (1H, dd, J = 16.0, 6.0 Hz), 5.29 (1H, t, J = 4.4 Hz), 4.74, (2H, s), 4.26 (1H, ddd, J = 9.2, 6.0, 4.6, 1.2 Hz), 3.96 (1H, ddd, J = 9.4, 9.2, 5.0, 4.0 Hz), 3.41, (3H, s), 2.54 (1H, dddd, J = 9.4, 9.2, 5.0, 4.0 Hz), 1.2 Hz), 7.47 (2H, t, J = 7.3 Hz), 7.35-7.29 (5H, m), 5.16 (1H, t, J = 4.3 Hz), 4.70 (2H, s), 4.24 (1H, ddd, J = 9.3, 7.0, 5.9, 3.0 Hz), 3.91 (1H, ddd, J = 9.8, 9.3, 4.2, 4.1 Hz), 3.42 (1H, dd, J = 15.9, 7.0 Hz), 3.38, (3H, s), 3.18 (1H, dd, J = 15.9, 5.9 Hz), 2.52 (1H, ddd, J = 13.5, 4.3, 4.1 Hz), 2.08 (1H, ddd, J = 12.6, 4.2, 3.0 Hz), 1.98 (1H, ddd, J = 13.5, 9.8, 4.3 Hz), 1.67 (1H, ddd, J = 12.6, 9.3 Hz) ppm; δC (100 MHz, CDCl₃) 198.1, 140.4, 137.2, 133.3, 128.7, 128.6, 128.4, 127.2, 126.4, 72.5, 64.3, 44.7, 40.3 and 36.8 ppm; m/z (ESI⁺) 319 (M + Na)⁺. (Found 319.1300 (M + Na)⁺). C₉H₁₅NO₃ requires 319.1305. Data in agreement with those previously reported.19

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Notes and references
6 For a review on the application of the Prins reaction to THP synthesis see: C. Oiler, M. Kafarani, S. Gastsaldi and M. P Bertrand, Tetrahedron, 2010, 66, 413.


