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Synthesis of 2,6-*trans*- and 3,3,6-trisubstituted tetrahydropyran-4-ones from Maitland–Japp derived 2*H*-dihydropyran-4-ones: a total synthesis of diospongin B†

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6-Substituted-2*H*-dihydropyran-4-one products of the Maitland–Japp reaction have been converted into tetrahydropyrans containing uncommon substitution patterns. Treatment of 6-substituted-2*H*-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-2*H*-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 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.[1,2] 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 oxy-Michael reactions,[3,4] Diels–Alder reactions,[5] Prins rearrangements,[6,7] reduction of cyclic oxocarbenium ions,[8] metal mediated cyclisations[9] and the Maitland–Japp reaction.[10] Conversely, construction of the 2,6-*trans*-THP ring is almost exclusively limited to either nucleophilic addition to cyclic hemiacetals *via* an oxocarbenium ion[11,12] or kinetically controlled oxy-Michael reactions,[3,4] 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[13] (an inhibitor of cancer cell proliferation), zincophorin[14] (an antibiotic), aspergillide B[15] (cytotoxicity against mouse lymphocytic leukemia cells) and diospongin B[16] (anti-osteoporotic activity) (Fig. 1).

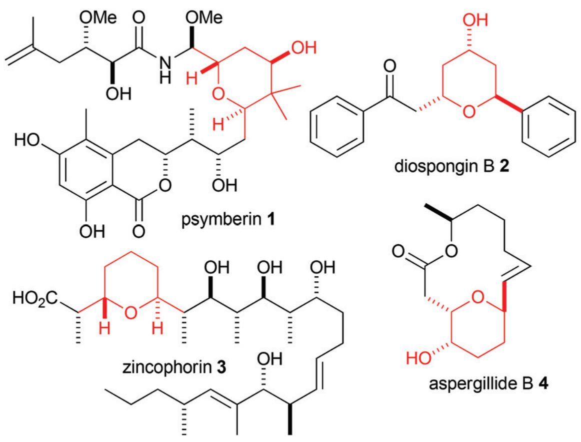

Fig. 1 2,6-*trans*-Tetrahydropyran-containing natural products.

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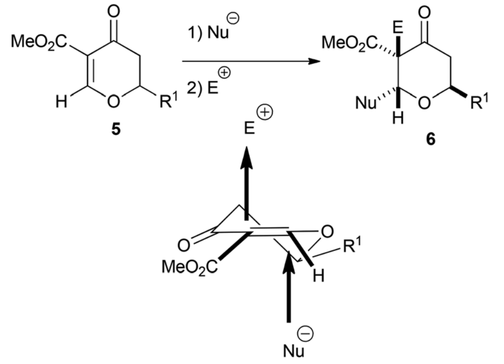


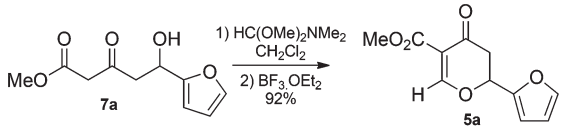
Fig. 2 Stereoelectronic preference for axial addition of nucleophiles leading to 2,6-*trans*-THPS.

We recently reported the synthesis of substituted dihydropyran-4-ones (DHPs), by extension of the Maitland–Japp reaction,[17] a method which is complementary to the Diels–Alder route popularised by Danishfesky.[18] We then converted these DHPs into 2,6-*cis*-THPs.[17] 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 (Fig. 2).

Results and discussion

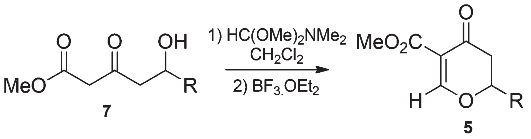
Synthesis of dihydropyran-4-ones

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),[17] 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 CH_2Cl_2, rather than PhMe, followed by the addition of $BF_3{\cdot}OEt_2$ 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.

Table 1 Synthesis of DHPs



DHP 5	R	Crude mass balance (%)
a	2-Furyl	92
b	Ph	96
c	Pr	91
d	i-Pr	97
e	CH_2OTIPS	88
f	$CH{=}CHCH_3$	87
g	$CH{=}CHPh$	97
h	2-Methyloxazole	77

These conditions proved general for the synthesis of a range of C2-unsubstituted, C6-substituted DHPs **5** (Table 1). In addition to the 2-furyl group **5a**, other heteroaromatic substituents could be incorporated **5h**, as well as phenyl **5b**. *n*-Alkyl and branched alkyl substituents are readily tolerated **5c** and **5d**, along with alkene-containing side chains **5f** and **5g**. Perhaps the most encouraging, as it allows further elaboration of the C6-side chain, is the realisation that TIPS-protected alcohols can also be incorporated **5e**.

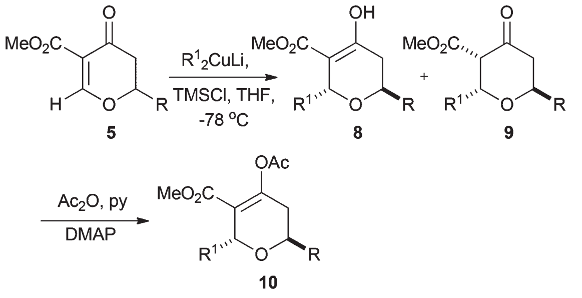
With a range of DHPs to hand we were now in a position to study to formation of 2,6-*trans*-substituted THPs.

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

When DHPs **5** were treated with a range of Gilman cuprates, Ph_2CuLi, Me_2CuLi and Bu_2CuLi 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 Ph_2CuLi generated the 2,6-*trans*-THPs exclusively as the enol tautomer **8**. However, use of Me_2CuLi and Bu_2CuLi 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 Ac_2O, pyridine and DMAP.

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

Table 2 Synthesis of 2,6-*trans*-THPs



THP	R	R^1	Ratio[a] 8 : 9	Yield[b] 8/9 (%)	Yield[b] 10 (%)
a	Ph	Ph	1 : 0	70	N/A
b	Pr	Ph	1 : 0	56	N/A
c	i-Pr	Ph	1 : 0	73	N/A
d	CH_2OTIPS	Ph	1 : 0	48	N/A
e	$CH{=}CHCH_3$	Ph	1 : 0	64	N/A
f	CH=CHPh	Ph	1 : 0	91	N/A
g	2-furyl	Me	1 : 0.4	50	82
h	Ph	Me	1 : 0.2	64	74
i	Pr	Me	1 : 0.4	64	64
j	i-Pr	Me	1 : 0.3	88	77
k	CH_2OTIPS	Me	1 : 0.4	76	81
l	$CH{=}CHCH_3$	Me	1 : 0.5	53	56
m	Ph	Bu	1 : 0.3	82	48
n	Pr	Bu	1 : 0.5	58	62
o	i-Pr	Bu	1 : 0.2	48	79
p	CH_2OTIPS	Bu	1 : 0.5	24	70

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

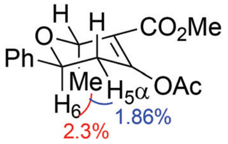


Fig. 3 NOE correlations confirming the 2,6-*trans*-stereochemical configuration of **10h**.

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_2O, pyridine and DMAP to form enol acetates **10**, where the 2,6-*trans*-THP stereochemical configuration was confirmed by analysis of the ^1H NMR and NOE data (Fig. 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 H5α of 1.86%.

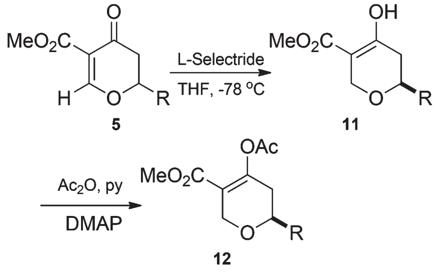
Conversion of dihydropyran-4-ones to 3,6-disubstituted and 3,3,6-trisubstituted tetrahydropyran-4-ones

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_2O, 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.

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).

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 R^1 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 CH_2 group, indicating that these were both axial (Fig. 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,

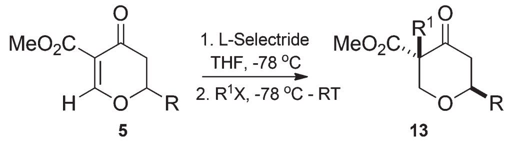
Table 3 Synthesis of 3,6-disubstituted-THPs



DHP 5	R	Yield[a] 11 (%)	Ratio[a,b] enol : keto	Yield[a] 12 (%)
a	2-Furyl	44	1 : 0.4	58
b	Ph	74	1 : 0.2	68
c	Pr	89	1 : 0.2	51
e	CH_2OTIPS	65	1 : 0.2	65
g	CH=CHPh	51	1 : 0.4	56

[a] After flash column chromatography. [b] Determined by integration of the ^1H NMR.

Table 4 Synthesis of 3,3,6-trisubstituted THPs



THP **13**	R	R_1	Yield[a] **13** (%)
a	Ph	Me	59
b	$CH{=}CHPh$	Me	53
c	CH_2OTIPS	Me	57
d	Pr	Me	58
e	Ph	$CH_2CH{=}CH_2$	52
f	$CH{=}CHPh$	$CH_2CH{=}CH_2$	83
g	CH_2OTIPS	$CH_2CH{=}CH_2$	57
h	Pr	$CH_2CH{=}CH_2$	52
i	Ph	Bn	65
j	$CH{=}CHPh$	Bn	51
k	CH_2OTIPS	Bn	62
l	Pr	Bn	62

[a] Isolated yield after column chromatography.

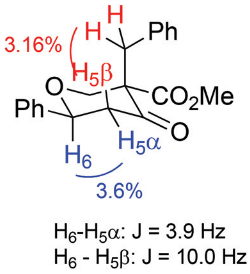


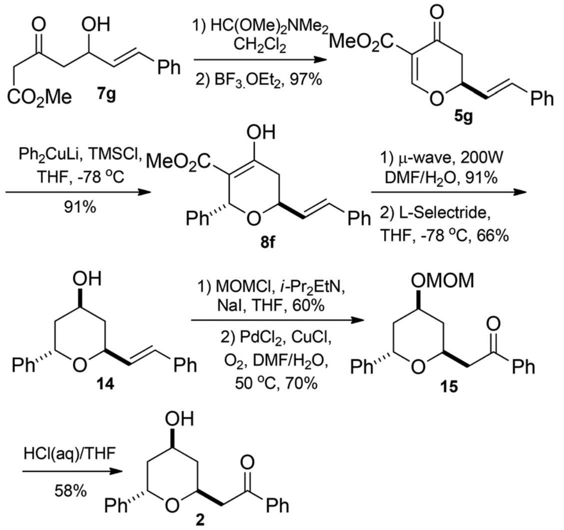
Fig. 4 NOE correlations and coupling constants confirming the stereochemical configuration of **13i**.

which probably reflects the inherent stability of the β-keto-ester's enolate anion.

Synthesis of diospongin B

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.[16] 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.[19]

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 Ph_2CuLi to **5g** yielded 2,6-*trans*-THP **8f** in 91%. Microwave-mediated decarboxylation in wet DMF generated the desired tetrahydropyran-4-one,[20] 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% (Fig. 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.[19f] The final step was the removal of the MOM protecting group, which was achieved by the action of aqueous HCl[19f] 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.[19]



Scheme 2 Synthesis of Diospongin B.

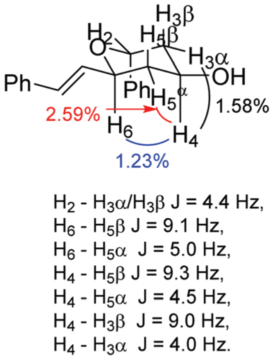


Fig. 5 NOE correlations and coupling constants confirming the stereochemical configuration of **14**.

Conclusions

We have developed a modification of the Maitland–Japp reaction using orthoamides which provides access to a range of 6-substituted-2*H*-dihydropyran-4-ones in good yields. These 2*H*-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-2*H*-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 with a carbon electrophile. The utility of these procedures was demonstrated by their use in the total synthesis of diospongin B, a natural product with potent anti-osteoperotic activity. This work provides a new route to uncommon tetrahydropyran substitution patterns and may ease the synthesis of a significant number of natural products containing these units.

Experimental

General methods

Thin layer chromatography was performed on aluminium plates coated with Merck silica gel 60 F_{254}. 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 Et_2O 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. ^{1}H NMRs were recorded at ambient temperature at either 400 MHz or 500 MHZ and ^{13}C 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-2*H*-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, $BF_3{\cdot}OEt_2$ (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. $NaHCO_3$ (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 $MgSO_4$ 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-2*H*-pyran-5-carboxylate 5a. δ-Hydroxy-β-ketoester **7a** (0.698 g, 3.292 mmol), yielded 0.674 g (92%), light yellow oil. ν max/cm^{-1} 2953, 1738, 1704, 1579, 1436, 1383, 1296, 1133, 1013, 816, 732 cm^{-1}; δH (400 MHz, $CDCl_3$) 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, $CDCl_3$) 186.8, 170.5, 170.4, 163.8, 148.7, 143.9, 110.8, 110.6, 74.7, 51.9 and 39.3 ppm; *m*/*z* (ESI$^+$) 245 (M + Na)$^+$, 223 (M + H)$^+$, (Found 245.0423 (M + Na)$^+$. $C_{11}H_{10}NaO_5$ requires; 245.0426).

Methyl 4-oxo-2-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate 5b. δ-Hydroxy-β-ketoester **7b** (0.050 g, 0.204 mmol), yielded 0.045 g (96%), orange solid. ν max/cm^{-1} 2955, 1738, 1661, 1572, 1372, 1290, 1244, 1146, 1047, 845, 761, 698, 500 cm^{-1}; δH (400 MHz, $CDCl_3$) 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, d, *J* = 16.0, 4.0 Hz) ppm; δC (100 MHz, $CDCl_3$) 186.8, 171.3, 164.2, 136.9, 129.4, 129.0, 126.2, 111.2, 82.3, 52.1 and 43.1 ppm; *m*/*z* (ESI$^+$) 255 (M + Na)$^+$, 233 (M + H)$^+$, (Found 255.0631 (M + Na)$^+$. $C_{13}H_{12}NaO_4$ requires; 255.0633).

Methyl 4-oxo-2-propyl-3,4-dihydro-2*H*-pyran-5-carboxylate 5c. δ-Hydroxy-β-ketoester **7c** (0.052 g, 0.276 mmol), yielded 0.049 g (91%), light yellow oil. ν max/cm^{-1} 2958, 2874, 1741, 1700, 1582, 1435, 1380, 1300, 1147, 1074, 799, 506 cm^{-1}; δH (400 MHz, C_6D_6) 7.97 (1H, s), 3.71–3.64 (1H, m), 3.52 (3H, s), 1.97 (1H, dd, *J* = 16.2, 4.1 Hz), 1.89 (1H, dd, *J* = 16.2, 12.4 Hz), 1.24–0.98 (2H, m), 0.98–0.86 (2H, m) and 0.64 (3H, t, *J* = 7.2 Hz) ppm; δC (100 MHz, C_6D_6) 187.6, 171.5, 164.5, 116.9, 81.3, 51.9, 41.6, 36.0, 17.9 and 13.7 ppm; *m*/*z* (ESI$^+$) 221 (M + Na)$^+$, 199 (M + H)$^+$, (Found 221.0782 (M + Na)$^+$. $C_{10}H_{14}NaO_4$ requires; 221.0790).

Methyl 2-isopropyl-4-oxo-3,4-dihydro-2*H*-pyran-5-carboxylate 5d. δ-Hydroxy-β-ketoester **7d** (0.750 g, 3.780 mmol), yielded 0.713 g (88%), light yellow oil. ν max/cm^{-1} 2962, 1741, 1699, 1633, 1583, 1435, 1383, 1295, 1122, 1047, 771, 593 cm^{-1}; δH (400 MHz, $CDCl_3$) 8.33 (1H, s), 4.28–4.22 (1H, m), 3.76 (3H, s), 2.55 (1H, dd, *J* = 16.3, 13.6 Hz), 2.46 (1H, dd, *J* = 16.3, 3.8 Hz), 2.05–1.97 (1H, m), 0.97 (3H, d, *J* = 6.8 Hz) and 0.99 (3H, d, *J* = 6.8 Hz) ppm; δC (100 MHz, $CDCl_3$) 187.8, 171.8, 164.2, 110.6, 85.7, 51.9, 39.0, 31.7, 17.8 and 17.6 pm; *m*/*z* (ESI$^+$) 221 (M + Na)$^+$, 199 (M + H)$^+$, (Found 221.0786 (M + Na)$^+$. $C_{10}H_{14}NaO_4$ requires; 221.0790).

Methyl 4-oxo-2-(((triisopropylsilyl)oxy)methyl)-3,4-dihydro-2*H*-pyran-5-carboxylate 5e. δ-Hydroxy-β-ketoester **7e** (0.033 g, 0.099 mmol), yielded 0.029 g (88%), light orange oil. ν max/cm^{-1} 2953, 1738, 1704, 1579, 1436, 1383, 1296, 1133, 1013, 816, 732 cm^{-1}; δH (400 MHz, C_6D_6) 7.99 (1H, s), 3.81–3.75 (1H, m), 3.49 (3H, s), 3.29–3.25 (1H, m), 2.42 (1H, dd, *J* = 16.2, 13.0 Hz), 2.07 (1H, dd, *J* = 16.2, 3.8 Hz) and 1.10–9.94 (21H, m) ppm; δC (100 MHz, C_6D_6) 187.4, 171.4, 164.3, 110.6, 81.5, 64.2, 52.0, 38.2, 17.9 and 11.9 ppm; *m*/*z* (ESI$^+$) 365 (M + Na)$^+$ (Found 365.1741 (M + Na)$^+$. $C_{17}H_{30}NaO_5Si$ requires; 365.1760).

Methyl 4-oxo-2-(prop-1-en-1-yl)-3,4-dihydro-2*H*-pyran-5-carboxylate 5f. δ-Hydroxy-β-ketoester **7f** (0.300 g, 1.612 mmol), yielded 0.274 g (87%), light orange oil. *ν* max/cm^{-1} 2952, 2919, 1740, 1701, 1579, 1435, 1380, 1297, 1135, 1053, 965 cm^{-1}; δH (400 MHz, $CDCl_3$) 8.01 (1H, s), 5.28 (1H, m), 5.08 (1H, m), 4.20 (1H, ddd, *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; δC (100 MHz, $CDCl_3$) 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)$^+$. $C_{10}H_{12}NaO_4$ requires; 219.0628).

Methyl 4-oxo-2-styryl-3,4-dihydro-2*H*-pyran-5-carboxylate 5g. δ-Hydroxy-β-ketoester **7g** (0.106 g, 0.427 mmol), yielded 0.107 g (97%), orange solid. *ν* max/cm^{-1} 2951, 1693, 1569, 1436, 1369, 1260, 1295, 1060, 966, 747, 692 cm^{-1}; δH (400 MHz, $CDCl_3$) 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, ddd, *J* = 9.1, 6.9, 6.8 Hz), 3.53 (3H, s) and 2.12 (2H, m) ppm; δC (100 MHz, $CDCl_3$) 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)$^+$. $C_{15}H_{14}NaO_4$ requires; 281.0784).

Methyl 2-(2-methyloxazol-4-yl)-4-oxo-3,4-dihydro-2*H*-pyran-5-carboxylate 5h. δ-Hydroxy-β-ketoester **7h** (0.078 g, 0.343 mmol), yielded 0.062 g (77%), light yellow oil. *ν* max/cm^{-1} 2953, 1738, 1704, 1579, 1436, 1383, 1296, 1133, 1013, 816, 732 cm^{-1}; δH (400 MHz, $CDCl_3$) 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; δC (100 MHz, $CDCl_3$) 198.7, 167.7, 160.1, 137.2, 63.0, 52.6, 49.6, 45.5, 31.5, 30.1 and 14.2 ppm; *m*/*z* (ESI$^+$) 260 (M + Na)$^+$ (Found 260.0523 (M + Na)$^+$. $C_{11}H_{11}NNaO_5$ requires; 260.0535).

General procedure for the synthesis 2,6-*trans*-tetrahydropyran-4-ones 8/9

Addition of Ph_2CuLi. Phenyl lithium 1.9 M 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. NH_4Cl (2.50 mL) and allowed to warm to rt with vigorous stirring. The mixture was diluted with sat. aq. NH_4Cl (10.0 mL) and extracted with EtOAc (5 × 15.0 mL). The combined organic extracts were washed with H_2O (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 product as a mixture of enol/keto tautomers **8/9**.

(2*R,6*S**)-Methyl 4-hydroxy-2,6-diphenyl-5,6-dihydro-2*H*-pyran-3-carboxylate 8a.** Dihydropyran **5b** (0.088 g, 0.379 mmol), yielded 0.082 g (70%), light brown oil. *ν* max/cm^{-1} (film) 2955, 2931, 2872, 1768, 1723, 1710, 1435, 1363, 1254, 1177, 1149, 1055, 875, 480 cm^{-1}; δH (400 MHz, $CDCl_3$) 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; δC (100 MHz, $CDCl_3$) 193.0, 171.2, 140.7, 128.6, 128.3, 128.0, 127.9, 126.0, 98.6, 73.3, 68.4, 51.8, 41.1, 35.6, 31.1 ppm; *m*/*z* (ESI$^+$) 333 (M + Na)$^+$ (Found 333.1108 (M + Na)$^+$. $C_{19}H_{18}NaO_4$ requires; 333.1103).

(2*R,6*R**)-Methyl 4-hydroxy-2-phenyl-6-propyl-5,6-dihydro-2*H*-pyran-3-carboxylate 8b.** Dihydropyran **5c** (0.045 g, 0.227 mmol), yielded 0.035 g (56%), oil. *ν* max/cm^{-1} (film) 2955, 2927, 2875, 1658, 1621, 1441, 1288, 1262, 1216, 1043, 775, 698 cm^{-1}; δH (400 MHz, $CDCl_3$) 12.29 (1H, s), 7.37–7.27 (5H, m), 5.59 (1H, 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; δC (100 MHz, $CDCl_3$) 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)$^+$. $C_{16}H_{20}NaO_4$ requires; 299.1254).

(2*R,6*S**)-Methyl 4-hydroxy-6-isopropyl-2-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate 8c.** Dihydropyran **5d** (0.060 g, 0.303 mmol), yielded 0.060 g (73%), light yellow oil. *ν* max/cm^{-1} (film) 2924, 2852, 1946, 1739, 1661, 1365, 1268, 1222, 1060, 841 cm^{-1}; δH (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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)$^+$. $C_{16}H_{20}NaO_4$ requires; 299.1254).

(2*R,6*S**)-Methyl 4-hydroxy-2-phenyl-6-(((triisopropylsilyl)-oxy)methyl)-5,6-dihydro-2*H*-pyran-3-carboxylate 8d.** Dihydropyran **5e** (0.073 g, 0.213 mmol), yielded 0.043 g (48%), light yellow oil. *ν* max/cm^{-1} (film) 2941, 2861, 1660, 1623, 1442, 1280, 1264, 1215, 1095, 880, 681 cm^{-1}; δH (400 MHz, C_6D_6) 12.90 (1H, s), 7.38–7.36 (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 (21H, m) ppm; δC (100 MHz, C_6D_6) 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)$^+$. $C_{23}H_{36}NaO_5Si$ requires; 443.2224).

(2*R,6*S**)-Methyl 4-hydroxy-2-phenyl-6-((*E*)-prop-1-en-1-yl)-5,6-dihydro-2*H*-pyran-3-carboxylate 8e.** Dihydropyran **5f** (0.055 g, 0.280 mmol), yielded 0.049 g (64%), light yellow oil. *ν* max/cm^{-1} (film) 3028, 2952, 2896, 1662, 1618, 1437, 1325, 1243, 1205, 1181, 1051, 958, 740, 690 cm^{-1}; δH (400 MHz, $CDCl_3$) 12.30 (1H, s), 7.40–7.27 (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, ddd, *J* = 12.0, 4.0, 4.0 Hz), 3.62 (3H, s), 2.47 (1H, 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, $CDCl_3$) 171.1, 140.9, 130.4, 128.6, 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)$^+$. $C_{16}H_{18}NaO_4$ requires; 297.1097).

(2*R,6*S**)-Methyl 4-hydroxy-2-phenyl-6-((*E*)-styryl)-5,6-dihydro-2*H*-pyran-3-carboxylate 8f.** Dihydropyran **5g** (0.988 g, 3.829 mmol), yielded 1.170 g (91%), light yellow solid. ν max/cm^{-1} (film) 3028, 2952, 2896, 1662, 1618, 1437, 1325, 1243, 1205, 1181, 1051, 958, 740, 690 cm^{-1}; δH (400 MHz, $CDCl_3$) 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, ddd, *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, $CDCl_3$) 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)$^+$. $C_{21}H_{20}NaO_4$ requires; 359.1254).

Addition of Me_2CuLi. Methyl lithium 1.6 M in Et_2O (0.56 ml, 0.72 mmol) was added to a suspension of copper iodide (0.069 g, 0.36 mmol) in THF (2.00 mL) at 0 °C. The mixture was stirred at this temperature for 20 minutes after which chlorotrimethylsilane (0.14 ml, 0.54 mmol) then DHP **5** (0.10 mmol) in THF (2.00 mL) were added at −78 °C. The reaction mixture was stirred at this temperature for 4.5 hours then sat. aq. NH_4Cl (1.70 mL) was added to the mixture, which was stirred rapidly for 30 minutes at rt. The mixture was diluted with H_2O (10.0 mL) extracted with Et_2O (2 × 20.0 mL) and washed with H_2O (20.0 mL) and brine (20.0 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane–ethyl acetate 7 : 1 to 3 : 1) 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_2O (30.0 mL) and H_2O (10.0 mL). The organic layer was washed with H_2O (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**.

(2*R,6*S**)-Methyl 4-acetoxy-6-(furan-2-yl)-2-methyl-5,6-dihydro-2*H*-pyran-3-carboxylate 10g.** Dihydropyran **5a** (0.028 g, 0.126 mmol), yielded 0.015 g (42% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2955, 2924, 2854, 1766, 1720, 1435, 1364, 1253, 1176, 1144, 1052, 742, 598 cm^{-1}; δH (400 MHz, $CDCl_3$) 7.41 (1H, s), 6.37–6.35 (2H, m), 5.04 (1H, dd, *J* = 9.2, 4.2 Hz), 4.85 (1H, q, *J* = 6.5 Hz), 3.74 (3H, s), 2.79 (1H, dd, *J* = 17.9, 9.2 Hz), 2.53 (1H, dd, *J* = 17.9, 4.2 Hz,), 2.22 (3H, s) and 1.48 (3H, d, *J* = 6.5 Hz) ppm; δC (100 MHz, $CDCl_3$) 168.5, 164.0, 157.5, 152.6, 142.9, 121.6, 110.4, 108.0, 69.0, 63.4, 51.9, 32.6, 21.1 and 19.3 ppm; *m*/*z* (ESI$^+$) 303 (M + Na)$^+$ (Found 303.0827 (M + Na)$^+$. $C_{14}H_{16}NaO_6$ requires; 303.0845).

(2*R,6*S**)-Methyl 4-acetoxy-2-methyl-6-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate 10h.** Dihydropyran **5b** (0.254 g, 1.094 mmol), yielded 0.149 g (47% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2945, 2931, 1766, 1720, 1708, 1664, 1365, 1247, 1174, 1053, 758, 698 cm^{-1}; δH (400 MHz, C_6D_6) 7.30–7.23 (2H, m), 7.17–7.16 (1H, m), 7.14–7.05 (2H, m), 5.13 (1H, q, *J* = 6.6 Hz), 4.83 (1H, dd, *J* = 9.7, 4.1 Hz), 3.26 (3H, s), 2.40 (1H, dd, *J* = 17.9, 9.7 Hz), 2.31 (1H, dd, *J* = 17.9, 4.1 Hz), 1.88 (3H, s) and 1.39 (3H, d, *J* = 6.6 Hz) ppm; NOE C2(Me) – H6 2.3% and C2(Me) – H5α 1.86%; δC (100 MHz, C_6D_6) 193.5, 167.8, 163.9, 154.1, 141.0, 128.6, 126.7, 121.7, 69.5, 68.8, 51.1, 36.9, 20.5 and 19.5 ppm; *m*/*z* (ESI$^+$) 313 (M + Na)$^+$ (Found 313.1040 (M + Na)$^+$. $C_{16}H_{18}NaO_5$ requires; 313.1052).

(2*R,6*R**)-Methyl 4-acetoxy-2-methyl-6-propyl-5,6-dihydro-2*H*-pyran-3-carboxylate 10i.** Dihydropyran **5c** (0.030 g, 0.151 mmol), yielded 0.015 g (40% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2955, 2931, 2872, 1768, 1723, 1710, 1435, 1363, 1254, 1177, 1149, 1055, 875, 480 cm^{-1}; δH (400 MHz, C_6D_6) 5.02 (1H, q, *J* = 6.5 Hz), 3.73–3.67 (1H, m), 3.25 (3H, s), 2.09–2.02 (2H, m), 1.90 (3H, s), 1.50–1.39 (2H, m), 1.35 (3H, d, *J* = 6.5 Hz), 1.31–1.12 (2H, m) and 0.82 (3H, t, *J* = 7.2 Hz) ppm; δC (100 MHz, C_6D_6) 193.3, 168.0, 163.9, 154.4, 121.8, 68.9, 66.4, 51.0, 37.6, 35.4, 20.7, 18.8 and 14.0 ppm; *m*/*z* (ESI$^+$) 279 (M + Na)$^+$ (Found 279.1202 (M + Na)$^+$. $C_{13}H_{20}NaO_5$ requires; 279.1208).

(2*R,6*S**)-Methyl 4-acetoxy-6-isopropyl-2-methyl-5,6-dihydro-2*H*-pyran-3-carboxylate 10j.** Dihydropyran **5d** (0.713 g, 3.330 mmol), yielded 0.660 g (67% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2959, 2927, 2875, 1768, 1723, 1710, 1435, 1367, 1249, 1177, 1142, 1058, 875, 783 cm^{-1}; δH (400 MHz, C_6D_6) 5.00 (1H, q, *J* = 6.5 Hz), 3.45–3.40 (1H, m), 3.24 (3H, s), 2.17 (1H, dd, *J* = 17.7, 10.1 Hz), 2.02 (1H, dd, *J* = 17.7, 3.4 Hz), 1.92 (3H, s), 1.60–1.53 (1H, m), 1.34 (3H, d, *J* = 6.5 Hz), 0.93 (3H, d, *J* = 6.5 Hz) and 0.73 (3H, d, *J* = 6.5 Hz) ppm; δC (100 MHz, C_6D_6) 193.5, 168.3, 164.1, 155.0, 121.8, 71.4, 69.0, 50.8, 33.0, 20.6, 19.3, 18.4 and 18.0 ppm; *m*/*z* (ESI$^+$) 279 (M + Na)$^+$ (Found 279.1199 (M + Na)$^+$. $C_{13}H_{20}NaO_5$ requires; 279.1208).

(2*R,6*S**)-Methyl 4-acetoxy-2-methyl-6-(((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-3-carboxylate 10k.** Dihydropyran **5e** (0.057 g, 0.166 mmol), yielded 0.040 g (61% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2941, 2866, 1771, 1725, 1712, 1365, 1246, 1177, 1149, 1055, 880, 681 cm^{-1}; δH (400 MHz, C_6D_6) 5.04 (1H, q, *J* = 6.5 Hz), 4.03–3.97 (1H, m), 3.76 (1H, dd, *J* = 10.2, 5.1 Hz), 3.63 (1H, dd, *J* = 10.2, 5.2 Hz), 3.23 (3H, s), 2.44 (1H, dd, *J* = 17.8, 10.0 Hz), 2.25 (1H, dd, *J* = 17.8, 3.8 Hz), 1.87 (3H, s), 1.39 (3H, d, *J* = 6.5 Hz) and 1.09 (21H, m) ppm; δC (100 MHz, C_6D_6) 168.0, 163.8, 154.4, 121.8, 69.1, 68.1, 66.4, 51.1, 32.0, 20.6, 19.4, 18.3 and 12.2 ppm; *m*/*z* (ESI$^+$) 423 (M + Na)$^+$ (Found 423.2160 (M + Na)$^+$. $C_{20}H_{36}NaO_6Si$ requires; 423.2179).

(2*R,6*S**)-Methyl 4-acetoxy-2-methyl-6-((*E*)-prop-1-en-1-yl)-5,6-dihydro-2*H*-pyran-3-carboxylate 10l.** Dihydropyran **5f** (0.050 g, 0.255 mmol), yielded 0.019 g (29% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2952, 2930, 1767, 1721, 1664, 1436, 1366, 1245, 1212, 1176, 1046, 1050, 985 cm^{-1}; δH (400 MHz, $CDCl_3$) 5.78 (1H, dd, *J* = 16.0, 4.0 Hz), 5.52 (1H, dq, *J* = 16.0, 4.0 Hz), 4.85 (1H, q, *J* = 8.0 Hz), 4.37 (1H, ddd, *J* = 8.0, 4.0, 4.0 Hz), 3.72 (3H, s), 2.30 (2H, m), 2.20 (3H, s), 1.71 (2H, d, *J* = 4.0 Hz) and 1.42 (3H, d, *J* = 8.0 Hz) ppm; δC (100 MHz, $CDCl_3$) 168.7, 164.1, 153.3, 130.2, 129.2, 121.3, 68.8, 67.9, 51.9, 34.8, 21.0, 19.6 and 17.9 ppm; *m*/*z* (ESI$^+$) 277 (M + Na)$^+$ (Found 277.1047 (M + Na)$^+$. $C_{13}H_{18}NaO_5$ requires; 277.1046).

Addition of *n*-Bu_2CuLi. *n*-Butyl lithium 2.5 M 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_4Cl (1.50 mL) and allowed to warm to rt with vigorous stirring. The mixture was diluted further with sat. aq. NH_4Cl (10.0 mL) and extracted with EtOAc (5 × 15.0 mL). The combined organic extracts were washed with H_2O (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_2O (30.0 mL) and H_2O (10.0 mL). The organic layer was washed with H_2O (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**.

(2*R,6*S**)-Methyl 4-acetoxy-2-butyl-6-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate 10m.** Dihydropyran **5g** (0.100 g, 0.431 mmol), yielded 0.056 g (39% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2953, 2860, 1764, 1721, 1248, 1174, 1055, 698 cm^{-1}; δH (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; δC (100 MHz, $CDCl_3$) 168.9, 164.1, 153.2, 141.0, 128.6, 128.0, 126.0, 121.2, 73.2, 68.4, 51.8, 36.0, 32.2, 28.3, 22.4, 21.0 and 14.0 ppm; *m*/*z* (ESI$^+$) 355 (M + Na)$^+$ (Found 355.1509 (M + Na)$^+$. $C_{19}H_{24}NaO_5$ requires; 355.1516).

(2*R,6*R**)-Methyl 4-acetoxy-2-butyl-6-propyl-5,6-dihydro-2*H*-pyran-3-carboxylate 10n.** Dihydropyran **5c** (0.070 g, 0.353 mmol), yielded 0.037 g (35% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2956, 2932, 2872, 1767, 1722, 1241, 1177, 1053, 900 cm^{-1}; δH (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; δC (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, 22.3, 21.0, 18.8 and 14.1 ppm; *m*/*z* (ESI$^+$) 321 (M + Na)$^+$ (Found 321.1681 (M + Na)$^+$. $C_{16}H_{26}NaO_5$ requires; 321.1672).

(2*R,6*S**)-Methyl 4-acetoxy-2-butyl-6-isopropyl-5,6-dihydro-2*H*-pyran-3-carboxylate 10o.** Dihydropyran **5d** (0.037 g, 0.186 mmol) yielded 0.020 g (37% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2955, 2929, 1767, 1724, 1712, 1435, 1365, 1249, 1202, 1177, 1056, 490 cm^{-1}; δH (400 MHz, C_6D_6) 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 (1H, m), 1.37–1.24 (4H, m), 0.96 (3H, d, *J* = 6.7 Hz), 0.88 (3H, t, *J* = 7.3 Hz) and 0.74 (3H, d, *J* = 6.8 Hz) ppm; δC (100 MHz, C_6D_6) 167.9, 164.0, 154.4, 121.4, 72.8, 71.4, 51.0, 33.0, 32.9, 32.2, 28.7, 22.6, 20.6, 18.6, 18.3 and 14.2 ppm; *m*/*z* (ESI$^+$) 321 (M + Na)$^+$ (Found 321.1669 (M + Na)$^+$. $C_{16}H_{26}NaO_5$ requires; 321.1672).

(2*R,6*S**)-Methyl 4-acetoxy-2-butyl-6-(((triisopropylsilyl)oxy)-methyl)-5,6-dihydro-2*H*-pyran-3-carboxylate 10p.** Dihydropyran **5e** (0.056 g, 0.163 mmol), yielded 0.012 g (16% after 2 steps), light yellow oil. ν max/cm^{-1} (film) 2941, 2865, 1770, 1725, 1712, 1364, 1247, 1192, 1177, 1146, 1094, 1052, 881, 786, 681, 659 cm^{-1}; δH (400 MHz, C_6D_6) 4.89 (1H, d, *J* = 9.6 Hz), 3.99–3.93 (1H, m), 3.75 (1H, dd, *J* = 10.3, 5.6 Hz), 3.61 (1H, dd, *J* = 10.3, 4.8 Hz), 3.27 (3H, s), 2.35 (1H, dd, *J* = 17.9, 10.0 Hz), 2.21 (1H, dd, *J* = 17.9, 3.9 Hz), 1.87 (3H, s), 1.73–1.59 (2H, m), 1.49–1.39 (2H, m), 1.38–1.23 (2H, m), 1.10 (21H, m) and 0.89 (3H, t, *J* = 7.3 Hz) ppm; δC (100 MHz, C_6D_6) 167.9, 163.9, 154.0, 121.5, 72.8, 67.9, 66.5, 51.0, 32.4, 31.8, 28.5, 22.6, 20.6, 18.2, 14.2 and 12.2 ppm; *m*/*z* (ESI$^+$) 465 (M + Na)$^+$ (Found 465.2625 (M + Na)$^+$. $C_{23}H_{42}NaO_6Si$ requires; 465.2643).

General procedure for the synthesis of 3,6-disubstituted-tetrahydropyran-4-ones 11

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 −78 °C then diluted with Et_2O (10.0 mL) and quenched with sat. aq. $NHCl_4$ (10.0 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10.0 mL). The combined organic extracts were washed with brine (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane–ethyl acetate) afforded the product as a mixture of enol/keto tautomers.

Methyl 6-(furan-2-yl)-4-hydroxy-5,6-dihydro-2*H*-pyran-3-carboxylate 11a. Dihydropyran **5a** (0.098 g, 0.439 mmol), yielded 0.043 g (44%) oil. ν max/cm^{-1} (film) 2954, 2927, 2868, 1737, 1667, 1627, 1442, 1275, 1066, 1011, 739, 598 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 11.81 (OH, s), 7.42 (1H, m), 7.38 (1H, m, *keto*) 6.37–6.33 (2H, m), 6.28–6.27 (2H, m, *keto*), 5.08 (1H, dd, *J* = 11.6, 2.9 Hz, *keto*), 4.88 (1H, dd, *J* = 10.0, 3.6 Hz, *keto*), 4.73 (1H, dd, *J* = 9.9, 3.9 Hz), 4.50 (2H, m), 4.44 (1H, d, *J* = 14.0), 4.37 (1H, d, *J* = 14.0 Hz), 3.77 (3H, s), 3.70 (3H, s, *keto*), 2.86 (1H, dd, *J* = 17.8, 9.9 Hz), 2.80 (1H, m, *keto*), 2.53 (1H, dd, *J* = 17.8, 3.8 Hz), 2.08 (1H, m, *keto*) ppm; δC (100 MHz, $CDCl_3$): 170.4, 168.2, 152.7, 143.0, 110.4, 107.9, 106.2 (*keto*), 97.1, 72.9 (*keto*), 68.9, 67.7 (*keto*), 62.9, 51.6, 31.9 and 26.1 (*keto*) ppm; *m*/*z* (ESI$^+$) 247 (M + Na)$^+$. (Found 247.0575 (M + Na)$^+$. $C_{11}H_{12}NaO_5$ requires 247.0577).

Methyl 4-hydroxy-6-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate 11b. Dihydropyran **5b** (0.100 g, 0.427 mmol), yielded 0.074 g (74%). oil. ν max/cm^{-1} (film) 2952, 2922, 2852, 1664, 1622, 1445, 1269, 1209, 1066, 1027, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *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, d, *J* = 14.0), 4.39 (1H, d, *J* = 14.0 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; δC (100 MHz, $CDCl_3$): 170.5, 168.8, 168.0 (*keto*), 140.8, 140.0 (*keto*), 128.9 (*keto*), 128.7, 128.5 (*keto*), 128.1, 125.9, 125.7 (*keto*), 97.2, 80.4 (*keto*), 75.6, 68.3 (*keto*), 63.5, 57.3 (*keto*), 53.0 (*keto*), 51.6, 49.5 (*keto*), 48.7 (*keto*) and 35.8 ppm; *m*/*z* (ESI$^+$) 257 (M + Na)$^+$. (Found 257.0782 (M + Na)$^+$. $C_{13}H_{14}NaO_4$ requires 257.0784).

Methyl 4-hydroxy-6-propyl-5,6-dihydro-2*H*-pyran-3-carboxylate 11c. Dihydropyran **5c** (0.100 g, 0.505 mmol), yielded 0.089 g, (89%). oil. ν max/cm^{-1} (film) 2957, 2871, 1666, 1626, 1441, 1213, 1074, 807 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): 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, t, *J* = 7.2 Hz) ppm; δC (100 MHz, C_6D_6): 200.8 (*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)$^+$. $C_{10}H_{16}NaO_4$ requires 223.0941).

Methyl 4-hydroxy-6-(((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-3-carboxylate 11e. Dihydropyran **5e** (0.095 g, 0.277 mmol), yielded 0.062 g, (65%) oil. ν max/cm^{-1} (film) 2924, 2865, 1774, 1729, 1709, 1148, 1057, 881, 787, 681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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; δC (100 MHz, $CDCl_3$): 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)$^+$. $C_{17}H_{32}NaO_5Si$ requires 367.1911).

(*E*)-Methyl 4-hydroxy-6-styryl-5,6-dihydro-2*H*-pyran-3-carboxylate 11g. Dihydropyran **5g** (0.100 g, 0.387 mmol), yielded 0.051 g, (51%) oil. ν max/cm^{-1} (film) 2953, 2839, 1665, 1626, 1441, 1263, 1211, 1059, 965, 795, 746, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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; δC (100 MHz, $CDCl_3$): 170.5, 168.5, 136.4, 136.0 (*keto*), 132.3 (*keto*), 131.8, 128.7, 128.2, 128.1, 126.8 (*keto*), 126.7, 97.2, 74.0, 68.0 (*keto*), 62.9, 52.4 (*keto*), 51.6, 47.7 (*keto*) and 34.3 ppm; *m*/*z* (ESI$^+$) 283 (M + Na)$^+$. (Found 283.0934 (M + Na)$^+$. $C_{15}H_{16}NaO_4$ requires 283.0941).

General procedure for the acylation of 3,6-disubstituted-tetrahydropyran-4-ones 11, formation of enol acetates 12

The THP keto/enol **11** mixture (0.03 mmol), acetic anhydride (0.10 mL, 0.1 mmol) and DMAP (2 mg.) were stirred in pyridine (0.47 mL) at 40 °C for 40 minutes. The mixture was cooled to room temperature, concentrated *in vacuo* and partitioned between Et_2O (30.0 mL) and H_2O (10.0 mL). The organic layer was washed with H_2O (10.0 mL) and brine (10.0 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane–ethyl acetate) gave the product.

Methyl 4-acetoxy-6-(furan-2-yl)-5,6-dihydro-2*H*-pyran-3-carboxylate 12a. Tetrahydropyran-4-one **11a** (0.043 g, 0.191 mmol), yielded 0.029 g, (58%) oil. ν max/cm^{-1} (film) 2953, 2847, 1760, 1723, 1706, 1671, 1365, 1253, 1173, 1132, 1059, 1009, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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; δC (100 MHz, $CDCl_3$): 168.4, 163.1, 153.5, 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)$^+$. (Found 289.0692 (M + Na)$^+$. $C_{13}H_{14}NaO_6$ requires 289.0683).

Methyl 4-acetoxy-6-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate 12b. Tetrahydropyran-4-one **11b** (0.074 g, 0.316 mmol), yielded 0.059 g (68%) solid white. ν max/cm^{-1} (film) 2949, 2842, 1765, 1718, 1664, 1166, 1131, 1060, 743, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (5H, m), 6.69 (1H, d, *J* = 16.0 Hz), 4.67 (1H, m), 4.49 (1H, d, *J* = 16.0, 4.0 Hz), 3.74 (3H, s), 2.63 (1H, m), 2.47 (1H, m) and 2.24 (3H, s) ppm; δC (100 MHz, $CDCl_3$): 168.4, 163.3, 154.1, 140.4, 128.7, 128.2, 125.9, 116.5, 75.5, 64.9, 51.7, 36.5 and 21.0 ppm; *m*/*z* (ESI$^+$) 299 (M + Na)$^+$. (Found 299.0894 (M + Na)$^+$. $C_{15}H_{16}NaO_5$ requires 299.0890).

Methyl 4-acetoxy-6-propyl-5,6-dihydro-2*H*-pyran-3-carboxylate 12c. Tetrahydropyran-4-one **11c** (0.090 g, 0.450 mmol), yielded 0.056 g (51%) oil. ν max/cm^{-1} (film) 2957, 2872, 1768, 1726, 1250, 1212, 1177, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 4.53 (1H, dd, *J* = 15.0 Hz), 4.31 (1H, dd, *J* = 15.0 Hz), 3.70 (3H, s), 3.60 (1H, m), 2.30–2.14 (2H, m), 2.23 (3H, s) 1.64–1.50 (5H, m) and 0.93 (3H, t, *J* = 7.2 Hz) ppm; δC (100 MHz, $CDCl_3$): 168.4, 163.5, 154.5, 116.3, 73.5, 64.6, 51.7, 37.4, 35.0, 21.0, 18.5 and 14.1 ppm; *m*/*z* (ESI$^+$) 265 (M + Na)$^+$. (Found 265.1052 (M + Na)$^+$. $C_{12}H_{18}NaO_5$ requires 265.1046).

Methyl 4-acetoxy-6-(((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-3-carboxylate 12e. Tetrahydropyran-4-one **11e** (0.040 g, 0.116 mmol), yielded 0.029 g (65%) oil. ν max/cm^{-1} (film) 2924, 2865, 1774, 1729, 1709, 1148, 1057, 881, 787, 681 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): 4.70 (1H, dd, *J* = 15.5, 2.0 Hz), 4.33 (1H, dd, *J* = 15.5, 3.4 Hz), 3.82 (1H, dd, *J* = 10.0, 5.0 Hz), 3.70 (1H, dd, *J* = 10.0, 5.0 Hz), 3.65 (1H, m), 3.30 (3H, s), 2.59 (1H, m), 2.27 (1H, m), 2.02 (3H, s) and 1.18–1.17 (21H, m) ppm; δC (100 MHz, C_6D_6): 167.7, 163.0, 154.9, 116.7, 74.7, 66.1, 64.8, 50.8, 32.0, 20.6, 18.1 and 12.2 ppm; *m*/*z* (ESI$^+$) 409 (M + Na)$^+$. (Found 409.2022 (M + Na)$^+$. $C_{19}H_{34}NaO_6Si$ requires 409.2017).

(*E*)-Methyl 4-acetoxy-6-styryl-5,6-dihydro-2*H*-pyran-3-carboxylate 12g. Tetrahydropyran-4-one **11g** (0.015 g, 0.057 mmol), yielded 0.010 g (56%) oil. ν max/cm^{-1} (film) 3026, 2951, 2844, 1761, 1723, 1705, 1248, 1172, 1142, 1051, 748, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.23 (5H, m), 6.68 (1H, d, *J* = 16.0 Hz), 6.23 (1H, dd, *J* = 16.0, 6.1 4.1 Hz), 4.63 (1H, d, *J* = 15.0 Hz), 4.43 (1H, d, *J* = 15.0 Hz), 4.33 (1H, m), 3.72 (3H, s) 2.52 (1H, m), 2.37 (1H, m) and 2.24 (3H, s) ppm; δC (100 MHz, $CDCl_3$): 168.4, 163.3, 153.8, 136.3, 132.1, 128.7, 128.1, 127.6, 126.7, 116.5, 73.9, 64.3, 51.8, 34.9 and 21.0 ppm; *m*/*z* (ESI$^+$) 325 (M + Na)$^+$. (Found 325.1053 (M + Na)$^+$. $C_{17}H_{18}NaO_5$ requires 325.1046).

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 Et_2O (10.0 mL) and quenched with sat. aq. $NHCl_4$ (10.0 mL). The layers were separated and aqueous layer was extracted with Et_2O (10.0 mL). The combined organic extracts were washed with brine (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane–ethyl acetate) to afforded the product.

(3*S,6*S**)-Methyl 3-methyl-4-oxo-6-phenyltetrahydro-2*H*-pyran-3-carboxylate 13a.** Dihydropyran **5b** (0.100 g, 0.431 mmol), yielded 0.063 g (59%) oil. ν max/cm^{-1} (film) 3032, 2953, 2877, 1736, 1710, 1268, 1233, 1095, 1075, 699, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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; δC (100 MHz, $CDCl_3$): 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)$^+$. $C_{14}H_{16}NaO_4$ requires 271.0941).

(3*S,6*S**)-Methyl 3-methyl-4-oxo-6-((*E*)-styryl)tetrahydro-2*H*-pyran-3-carboxylate 13b.** Dihydropyran **5g** (0.120 g, 0.465 mmol), yielded 0.068 g (53%) oil. ν max/cm^{-1} (film) 3026, 2952, 2875, 1733, 1713, 1232, 1264, 1114, 1088, 967, 748, 693 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 7.18–7.02 (5H, m), 6.44 (1H, d, *J* = 16.0 Hz), 5.94 (1H, 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, C_6D_6): 203.2, 171.9, 136.6, 132.2, 128.9, 128.1, 127.9, 126.9, 77.7, 72.1, 58.7, 52.0, 43.9 and 18.1 ppm; *m*/*z* (ESI$^+$) 297 (M + Na)$^+$. (Found 297.1095 (M + Na)$^+$. $C_{16}H_{18}NaO_4$ requires 297.1097).

(3*S,6*S**)-Methyl 3-methyl-4-oxo-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3-carboxylate 13c.** Dihydropyran **5d** (0.097 g, 0.280 mmol), yielded 0.057 g (57%) oil. ν max/cm^{-1} (film) 2942, 2866, 1738, 1715, 1105, 881, 681, 659 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): 4.13 (1H, d, *J* = 11.4 Hz), 3.73 (1H, d, *J* = 11.4 Hz), 3.58 (1H, dddd, *J* = 10.0, 3.8, 3.8, 3.5 Hz), 3.45 (1H, dd, *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 1.05–104 (21H, m) ppm; δC (100 MHz, C_6D_6): 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)$^+$. $C_{18}H_{34}NaO_5Si$ requires 381.2068).

(3*S,6*R**)-Methyl 3-methyl-4-oxo-6-propyltetrahydro-2*H*-pyran-3-carboxylate 13d.** Dihydropyran **5c** (0.100 g, 0.505 mmol), yielded 0.063 g (58%) oil. ν max/cm^{-1} (film) 2956, 2929, 2872, 1738, 1714, 1263, 1100, 782 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): 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, t, *J* = 7.3 Hz) ppm; δC (100 MHz, C_6D_6): 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)$^+$. $C_{11}H_{18}NaO_4$ requires 237.1097).

(3*S,6*S**)-Methyl 3-allyl-4-oxo-6-phenyltetrahydro-2*H*-pyran-3-carboxylate 13e.** Dihydropyran **5b** (0.100 g, 0.431 mmol), yielded 0.061 g (52%) oil. ν max/cm^{-1} (film) 3065, 2952, 2875, 1736, 1711, 1227, 1076, 763, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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, 4.6 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, $CDCl_3$): 203.8, 170.2, 139.9, 132.1, 128.8, 128.4, 126.0, 119.9, 79.6, 70.1, 62.5, 52.5, 46.2 and 36.1 ppm; *m*/*z* (ESI$^+$) 297 (M + Na)$^+$. (Found 297.1101 (M + Na)$^+$. $C_{16}H_{18}NaO_4$ requires 297.1097).

(3*S,6*S**)-Methyl 3-allyl-4-oxo-6-((*E*)-styryl)tetrahydro-2*H*-pyran-3-carboxylate 13f.** Dihydropyran **5f** (0.100 g, 0.387 mmol), yielded 0.097 g (83%) oil. ν max/cm^{-1} (film) 2952, 1736, 1712, 1226, 1073, 1031, 966, 748, 693 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 7.19–7.02 (5H, m), 6.45 (1H, dd, *J* = 16.0, 1.2 Hz), 5.95 (1H, dd, *J* = 16.0, 5.4 Hz), 5.88 (1H, dddd, *J* = 17.1, 10.1, 7.5, 7.0 Hz), 5.05 (1H, dd, *J* = 17.1, 4.4 Hz), 4.99 (1H, dd, *J* = 10.1, 4.4 Hz), 4.16 (1H, d, *J* = 11.8 Hz), 4.03 (1H, dddd, *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, C_6D_6): 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)$^+$. $C_{16}H_{21}NaO_4$ requires 323.1230).

(3*S,6*S**)-Methyl 3-allyl-4-oxo-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3-carboxylate 13g.** Dihydropyran **5e** (0.096 g, 0.280 mmol), yielded 0.061 g (57%) oil. ν max/cm^{-1} (film) 2943, 2866, 1739, 1715, 1231, 1124, 1083, 881, 680, 660 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 6.05 (1H, dddd, *J* = 16.8, 9.9, 7.1, 7.0 Hz), 5.29 (1H, dd, *J* = 16.8, 1.8 Hz), 5.14 (1H, dd, *J* = 9.9, 1.8 Hz), 4.17 (1H, d, *J* = 11.6 Hz), 4.14 (1H, d, *J* = 11.6 Hz), 3.70 (1H, m), 3.50 (2H, m), 3.47 (3H, s), 2.90 (1H, dd, *J* = 13.6, 7.0 Hz), 2.79 (1H, dd, *J* = 13.6, 7.1 Hz), 2.73 (1H, dd, *J* = 15.0, 8.0 Hz) and 2.33 (1H, dd, *J* = 15.0, 3.2 Hz) and 1.16–1.14 (21H, m) ppm; δC (100 MHz, C_6D_6): 203.6, 170.1, 133.2, 119.4, 78.7, 70.3, 65.8, 62.7, 51.8, 41.0, 36.0, 18.1 and 12.2 ppm; *m*/*z* (ESI$^+$) 407 (M + Na)$^+$. (Found 407.2211 (M + Na)$^+$. $C_{20}H_{36}NaO_5Si$ requires 407.2224).

(3*S,6*R**)-Methyl 3-allyl-4-oxo-6-propyltetrahydro-2*H*-pyran-3-carboxylate 13h.** Dihydropyran **5c** (0.100 g, 0.505 mmol), yielded 0.063 g (52%) oil. ν max/cm^{-1} (film) 2958, 2873, 1737, 1712, 1229, 1081, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.76 (1H, dddd, *J* = 17.4, 10.2, 7.3, 7.2 Hz), 5.18 (1H, dd, *J* = 17.4, 1.4 Hz), 5.10 (1H, dd, *J* = 10.2, 1.4 Hz), 4.05 (1H, d, *J* = 11.8 Hz), 4.01 (1H, d, *J* = 11.8 Hz), 3.74 (3H, s), 3.74 (1H, m), 2.69 (1H, dd, *J* = 13.8, 7.3 Hz), 2.64 (1H, dd, *J* = 13.8, 7.2 Hz), 2.45 (1H, dd, *J* = 14.8, 3.6 Hz), 2.36 (1H, *J* = 14.8, 10.0 Hz), 1.51–1.34 (4H, m, H-7) and 0.93 (1H, t, *J* = 7.0 Hz) ppm; δC (100 MHz, $CDCl_3$): 204.6, 170.3, 132.3, 119.7, 78.1, 70.1, 62.5, 52.4, 45.2, 37.7, 36.0, 18.4 and 13.9 ppm; *m*/*z* (ESI$^+$) 263 (M + Na)$^+$. (Found 263.1264 (M + Na)$^+$. $C_{13}H_{20}NaO_4$ requires 263.1254).

(3*S,6*S**)-Methyl 3-benzyl-4-oxo-6-phenyltetrahydro-2*H*-pyran-3-carboxylate 13i.** Dihydropyran **5b** (0.050 g, 0.215 mmol), yielded 0.045 g (65%) oil. ν max/cm^{-1} (film)

2948, 2920, 1710, 1207, 1073, 767, 702, 597 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.24 (10H, m), 4.89 (1H, dd, J = 10.0, 3.9 Hz), 4.13 (1H, d, J = 12.4 Hz), 4.10 (1H, d, J = 12.4 Hz), 3.76 (3H, s), 3.40 (1H, d, J = 13.4 Hz), 3.33 (1H, d, J = 13.4 Hz), 2.96 (1H, dd, J = 15.1, 10.0 Hz) and 2.78 (1H, dd, J = 15.1, 3.9 Hz) ppm; NOE H6 – H5α 3.6%, H5α – H6 2.26%, H5β – benzyl–CH_2 3.16%; δC (100 MHz, $CDCl_3$): 203.9, 169.7, 140.1, 135.0, 130.8, 128.9, 128.6, 128.5, 127.3, 126.0, 80.0, 69.1, 63.9, 52.4, 46.0 and 37.0 ppm; *m*/*z* (ESI+) 347 (M + Na)+. (Found 347.1252 (M + Na)+. $C_{20}H_{20}NaO_4$ requires 347.1254).

(3*S,6*S**)-Methyl 3-benzyl-4-oxo-6-((*E*)-styryl)tetrahydro-2*H*-pyran-3-carboxylate 13j.** Dihydropyran **5g** (0.096 g, 0.372 mmol), yielded 0.066 g (51%) oil. ν max/cm^{-1} (film) 2958, 2860, 1734, 1712, 1209, 1070, 742, 703, 597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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, dddd, 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), 3.73 (3H, s), 3.34 (1H, d, J = 13.5 Hz), 3.20 (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; δC (100 MHz, $CDCl_3$): 204.0, 169.8, 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)$^+$. (Found 373.1401 (M + Na)$^+$. $C_{22}H_{22}NaO_4$ requires 373.1410).

(3*S,6*S**)-Methyl 3-benzyl-4-oxo-6-(((triisopropylsilyl)oxy)-methyl)tetrahydro-2*H*-pyran-3-carboxylate 13k.** Dihydropyran **5e** (0.100 g, 0.292 mmol), yielded 0.078 g (62%) oil. ν max/cm^{-1} (film) 2942, 2865, 1736, 1713, 1121, 1074, 881, 682, 660 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): 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; δC (100 MHz, C_6D_6): 203.7, 169.6, 135.9, 131.2, 128.6, 128.1, 127.9, 127.3, 79.0, 69.2, 65.8, 64.2, 51.7, 40.5, 36.6, 18.1 and 12.2 ppm; *m*/*z* (ESI$^+$) 457 (M + Na)$^+$. (Found 457.2388 (M + Na)$^+$. $C_{24}H_{38}NaO_5Si$ requires 457.2381).

(3*S,6*R**)-Methyl 3-benzyl-4-oxo-6-propyltetrahydro-2*H*-pyran-3-carboxylate 13l.** Dihydropyran **5c** (0.050 g, 0.252 mmol), yielded 0.045 g (62%) oil. ν max/cm^{-1} (film) 2956, 2932, 2872, 1734, 1711, 1262, 1206, 1077, 1016, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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; δC (100 MHz, $CDCl_3$): 204.7, 169.8, 135.2, 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)$^+$. (Found 313.1416 (M + Na)$^+$. $C_{17}H_{22}NaO_4$ requires 313.1410).

Synthesis of diospongin B 2

(*E*)-Methyl 5-hydroxy-3-oxo-7-phenylhept-6-enoate 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 CH_2Cl_2 (104 mL) at −78 °C. After 5 minutes, methanol (6.24 mL, 154.0 mmol) was added and the mixture was stirred at −20 to −10 °C for 1.5 hours. The reaction mixture was diluted with Et_2O (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 Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane–ethyl acetate, 3 : 2) gave the product as an oil, isolated yield 7.33 g (76%). ν max/cm^{-1} (film) 3423, 3026, 2953, 1740, 1710, 1436, 1319, 1266, 1149, 1070, 967, 747, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.05 (5H, m), 6.57 (1H, d, J = 16.0 Hz), (1H, 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), 2.31 (1H, dd, J = 16.8, 3.6 Hz) ppm; δC (100 MHz, $CDCl_3$): 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)$^+$. $C_{14}H_{16}NaO_4$ requires 271.0941).

(2*S,4*S**,6*S**)-2-Phenyl-6-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol 14.** A solution of **8f** (0.059 g, 0.175 mmol) in DMF (0.92 mL) and H_2O (0.02 mL) was submitted to 200 W microwave radiation in a sealed tube at 160 °C for 10 minutes. The solution was cooled to rt and taken up in EtOAc (30.0 mL). The mixture was washed with H_2O (2 × 20.0 mL). The aqueous layer was extracted with EtOAc (30.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give 0.044 g (91%) of a dark yellow oil. ν max/cm^{-1} (film) 2978, 2881, 1721, 1230, 1047, 966, 753, 737, 695 cm^{-1}; δH (400 MHz, $CDCl_3$) 7.34–7.17 (10H, m), 6.53 (1H, dd, J = 16.3, 1.3 Hz), 6.23 (1H, dd, J = 16.3, 5.1 Hz), 5.12 (1H, dd, J = 7.7, 4.8 Hz), 4.82 (1H, ddd, J = 10.5, 5.2, 5.1 Hz), 2.78–2.68 (4H, m) ppm; NOE H2 – H3α 1.33%, H2 – H3β 1.89%, H4 – H6 1.23%, H4 – H3α 1.58%, H4 – H5α 2.59%; δC (100 MHz, $CDCl_3$) 205.9, 140.5, 135.7, 133.5, 128.8, 128.7, 128.3, 128.2, 127.9, 126.7, 126.5, 73.6, 72.9, 47.8, 45.4 ppm; *m*/*z* (ESI$^+$) 301 (M + Na)$^+$. (Found 301.1196 (M + Na)$^+$. $C_{19}H_{18}NaO_2$ requires 301.1199). A 1.0 M solution of L-Selectride® in THF (0.73 mL) was added to a stirred solution of the crude decarboxylated product (0.079 g, 0.28 mmol) in THF (3.5 mL) at −78 °C. The mixture was stirred at this temperature for 15 minutes then warmed to room temperature. Upon completion, the mixture was diluted with Et_2O (20.0 mL) and sat. aq. NH_4Cl (20.0 mL) and the layers separated. The aqueous layer was washed with Et_2O (20.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give **14** as a light yellow oil, 0.052 g (66%), dr 9 : 1. ν max/cm^{-1} (film) 3374, 2925, 1448, 1364, 1052, 695 cm^{-1}; δH (400 MHz, $CDCl_3$) 7.47–7.22 (10H, m), 6.64 (1H, dd, J = 16.1, 1.1 Hz), 6.37 (1H, dd, J = 16.1, 5.8 Hz), 5.31 (1H, t, J = 4.4 Hz), 4.98 (1H, m, minor), 4.74 (1H, m, minor), 4.27 (1H, dddd, J = 9.1, 5.8, 5.0, 1.1 Hz), 4.19 (1H, m, minor), 4.07 (1H, dddd, J = 9.3, 9.0, 4.5, 4.0 Hz), 2.54 (1H, ddd, J = 13.5, 4.4, 4.0 Hz), 2.31 (1H, m, minor), 2.19 (1H, m, minor), 2.08 (1H, ddd, J = 12.6, 5.0, 4.5 Hz), 1.96 (1H, ddd, J = 13.5, 9.0, 4.4 Hz), 1.89 (1H, m, minor), 1.64 (1H, ddd, J = 12.6, 9.3, 9.1 Hz) and 1.64 (1H, bs) ppm; δC (100 MHz, $CDCl_3$) 140.7, 136.8, 130.6, 129.9, 128.8, 128.7, 127.8, 127.3, 126.6, 126.4, 72.2, 70.6, 64.7, 40.5 and 37.0 ppm; *m*/*z* (ESI$^+$) 303 (M + Na)$^+$. (Found 303.1361 (M + Na)$^+$. $C_{19}H_{20}NaO_2$ requires 303.1356). Data in agreement with that previously reported.[19f]

2-((2*S,4*S**,6*S**)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-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** (0.078 g, 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 H_2O (20 mL) and extracted with EtOAc (20 mL). The extract was washed with brine and dried over $MgSO_4$ and concentrated *in vacuo* to give the product 0.054 g (60%) as a light yellow oil. ν max/cm^{-1} (film) 2923, 2854, 1145, 1033, 695 cm^{-1}; δH (400 MHz, $CDCl_3$) 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, dddd, *J* = 9.2, 6.0, 4.6, 1.2 Hz), 3.96 (1H, dddd, *J* = 9.4, 9.2, 5.0, 4.0 Hz), 3.41, (3H, s), 2.54 (1H, dddd, *J* = 13.4, 4.4, 4.0, 1.5 Hz), 2.09 (1H, ddd, *J* = 12.8, 5.0, 4.6, 1.5 Hz), 2.03 (1H, ddd, *J* = 13.4, 9.4, 4.4 Hz), 1.67 (1H, ddd, *J* = 12.8, 9.2, 9.2 Hz) ppm; δC (100 MHz, $CDCl_3$) 140.6, 136.9, 130.5, 129.9, 128.7, 128.6, 127.7, 127.3, 126.6, 126.4, 94.9, 72.3, 70.8, 69.8, 55.4, 37.9 and 34.6 ppm; *m*/*z* (ESI$^+$) 347 (M + Na)$^+$. (Found 347.1618 (M + Na)$^+$. $C_{21}H_{24}NaO_3$ requires 347.1618).

$PdCl_2$ (0.004 g, 0.02 mmol) and CuCl (0.006 g, 0.06 mmol) were added to a stirred solution of crude MOM-protected alcohol (0.014 g, 0.04 mmol) in DMF (0.5 mL) and H_2O (0.5 mL) at room temperature. The mixture was heated at 50 °C for 3 days under an oxygen atmosphere, after which the solvent was removed *in vacuo* to give **15** 0.010 g (70%) as a light yellow oil. ν max/cm^{-1} (film) 2921, 1682, 1445, 1036, 690 cm^{-1}; δH (400 MHz, $CDCl_3$) 7.97 (2H, dd, *J* = 7.0, 1.0 Hz), 7.57 (1H, tt, *J* = 7.4, 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, dddd, *J* = 9.3, 7.0, 5.9, 3.0 Hz), 3.91 (1H, dddd, *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, 9.3 Hz) ppm; δC (100 MHz, $CDCl_3$) 198.1, 140.4, 137.2, 133.2, 128.7, 128.3, 127.2, 126.4, 95.2, 72.4, 69.5, 67.5, 55.4, 44.4, 38.1, 34.7 and 30.0 ppm; *m*/*z* (ESI$^+$) 363 (M + Na)$^+$. (Found 363.1559 (M + Na)$^+$. $C_{21}H_{24}NaO_4$ requires 363.1567). Data in agreement with those previously reported.[19f]

Diospongin B 2

A solution of THP **15** (0.013 mg, 0.04 mmol) and 30% HCl (0.68 mL) was stirred in THF (2.1 mL) at room temperature for 2 hours, after which water was added and the mixture neutralized with $NaHCO_3$ before being extracted with EtOAc (30.0 mL). The organic extract was washed with H_2O (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give diospongin B, 0.006 g (58%) as a light yellow oil. ν max/cm^{-1} (film) 3375, 2916, 2846, 1557, 1411, 1129 cm^{-1}; δH (400 MHz, $CDCl_3$)) 7.98 (2H, dd, *J* = 8.0, 1.7 Hz), 7.58 (1H, tt, *J* = 7.1, 1.3 Hz), 7.47 (2H, td, *J* = 7.6, 2.2 Hz), 7.37–7.3 (5H, m), 5.19 (1H, t, *J* = 4.3 Hz), 4.23 (1H, dddd, *J* = 9.5, 7.1, 6.0, 3.0 Hz), 4.03 (1H, dddd, *J* = 9.9, 9.5, 5.5, 4.5 Hz), 3.46 (1H, dd, *J* = 15.8, 7.1 Hz), 3.18 (1H, dd, *J* = 15.8, 6.0 Hz), 2.52 (1H, ddd, *J* = 13.4, 5.5, 4.3 Hz), 2.06 (1H, ddd, *J* = 12.4, 4.5, 3.0 Hz), 1.92 (1H, ddd, *J* = 13.4, 9.9, 4.3 Hz), 1.51 (1H, ddd, *J* = 12.4, 9.5, 9.5 Hz) ppm; δC (100 MHz, $CDCl_3$) 198.5, 140.4, 137.2, 133.3, 128.7, 128.6, 128.4, 127.2, 126.4, 72.5, 67.0, 64.3, 44.7, 40.3 and 36.8 ppm; *m*/*z* (ESI$^+$) 319 (M + Na)$^+$. (Found 319.1300 (M + Na)$^+$. $C_{19}H_{20}NaO_3$ requires 319.1305). Data in agreement with those previously reported.[19]

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