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†

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6-Substituted-2H-dihydropyran-4-one products of the Maitland–Japp reaction have been converted into tetrahydropyrans 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 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 cyclisations9 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 ion11,12 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 psymberin13 (an inhibitor of cancer cell proliferation), zincochlorin14 (an antibiotic), aspergillide B15 (cytotoxicity against mouse lymphocytic leukemia cells) and diospongin B16 (anti-osteoporotic activity) (Fig. 1).

![Fig. 1 2,6-trans-Tetrahydropyran-containing natural products.](image-url)
We recently reported the synthesis of substituted dihydro-
pyran-4-ones (DHPs), by extension of the Maitland–Japp reac-
tion,\textsuperscript{17} a method which is complementary to the Diels–Alder route  
popularised by Danishfesky.\textsuperscript{18} We then converted  
these DHPs into 2,6-cis-THPs.\textsuperscript{17} This strategy enabled us to complete  
syntheses of “Civet” and a fully functionalised model A-ring of  
laasonolide A. Given the dearth of methods for the construction  
of 2,6-trans-THPs we turned our attention to the develop-
ament 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 nuclo-
phile 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 ortho-
amide or orthoester in toluene),\textsuperscript{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 poss-
ible 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 equi-

Table 1 Synthesis of DHPs

\begin{table}
\begin{center}
\begin{tabular}{c|c|c}
DHP & R & Crude mass balance (%) \\
\hline
a & 2-Furyl & 92 \\
b & Ph & 96 \\
c & Pr & 91 \\
d & i-Pr & 97 \\
e & CH\textsubscript{2}OTIPS & 88 \\
f & CH=CHCH\textsubscript{2} & 87 \\
g & CH=CHPh & 97 \\
h & 2-Methyloxazole & 77 \\
\end{tabular}
\end{center}
\end{table}

the addition of BF\textsubscript{3}·OEt\textsubscript{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).

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 substitu-
ts could be incorporated 5b, 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 alco-
hol 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\textsubscript{2}CuLi, Me\textsubscript{2}CuLi and Bu\textsubscript{2}CuLi 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  
ketone-forms 8/9 (Table 2). Addition of Ph\textsubscript{2}CuLi generated the  
2,6-trans-THPs exclusively as the enol tautomer 8. However,  
use of Me\textsubscript{2}CuLi and Bu\textsubscript{2}CuLi 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\textsubscript{2}O, 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
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 Ac₂O, 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 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 CH₃ 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.

**Conversion of dihydroxyran-4-ones to 3,6-disubstituted and 3,3,6-trisubstituted tetrahydroxyran-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 Ac₂O, 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.

![Image](Image.png)

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

| DHP   | R       | Yield₁ 11 (%) | Ratio<sup>a,b</sup> | Yield₂ 12 (%) |
|-------|---------|---------------|---------------------|---------------|
| a     | 2-Furyl | 44            | 1 : 0.4             | 58            |
| b     | Ph      | 74            | 1 : 0.2             | 68            |
| c     | Pr      | 89            | 1 : 0.2             | 51            |
| d     | CH<sub>2</sub>OTIPS | 65        | 1 : 0.2             | 65            |
| e     | CH<sub>2</sub>CHPh | 51        | 1 : 0.4             | 56            |

<sup>a</sup> After flash column chromatography.  <sup>b</sup> Determined by integration of the <sup>1</sup>H NMR.
which probably reflects the inherent stability of the β-ketoester’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. 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-dimethylformamide. 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% (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. 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.

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

| THP 13 | R   | R₁   | Yield* 13 (%) |
|--------|-----|------|-------------|
| a      | Ph  | Me   | 59          |
| b      | CH=CHPh | Me | 53          |
| c      | CH₂OTIPS | Me | 57          |
| d      | Pr   | Me   | 58          |
| e      | Ph   | CH₂CH=CH₂ | 52        |
| f      | CH=CHPh | CH₂CH=CH₂ | 83        |
| g      | CH₂OTIPS | CH₂CH=CH₂ | 57        |
| h      | Pr   | CH₂CH=CH₂ | 52          |
| i      | Ph   | Bn   | 65          |
| j      | CH=CHPh | Bn | 51          |
| k      | CH₂OTIPS | Bn | 62          |
| l      | Pr   | Bn   | 62          |

* Isolated yield after column chromatography.

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

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-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-products with uncommon substitution patterns which are accessed by the conjugate addition of L-Selectride, while 3,3,6-substitution pattern are accessed by trapping the enolate formed on addition of t-Selectride with a carbon electrophile. The utility of these procedures was demonstrated by their use in the total synthesis of diospongion 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 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 benzoate 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 layers 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. ν max/cm−1 2953, 1738, 1704, 1579, 1436, 1383, 1296, 1133, 1013, 816, 732 cm−1; δH (400 MHz, CDCl3) 8.27 (1H, s), 7.44 (1H, dd, J = 1.8, 0.6 Hz), 6.45 (1H, dd, 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; 6C (100 MHz, CDCl3) 186.8, 170.5, 170.4, 163.8, 148.7, 134.9, 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)+, C11H10NaO5 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 (96%), orange solid. ν max/cm−1 2955, 1738, 1661, 1572, 1372, 1290, 1244, 1146, 1047, 845, 761, 500 cm−1; δH (400 MHz, 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, d, J = 16.0, 4.0 Hz) ppm; 6C (100 MHz, CDCl3) 186.8, 171.3, 164.2, 136.9, 129.4, 129.0, 126.2, 111.2, 82.3, 52.1 and 43.1 ppm; m/z (ESI+ 255 (M + Na)+, 233 (M + H)+, (Found 255.0631 (M + Na)+, C12H12NaO5 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. ν max/cm−1 2958, 2874, 1741, 1700, 1582, 1435, 1380, 1300, 1147, 1074, 799, 506 cm−1; δH (400 MHz, C6D6) 7.99 (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; 6C (100 MHz, C6D6) 187.6, 171.5, 165.4, 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)+, C11H12NaO4 requires; 221.0790).

Methyl 2-isopropyl-4-oxo-3,4-dihydro-2H-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, C6D6) 8.53 (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; 6C (100 MHz, C6D6) 187.5, 171.6, 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)+, C11H12NaO4 requires; 221.0790).

Methyl 4-oxo-2-((trisopropylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-5-carboxylate 5e. δ-Hydroxy-β-ketoester 7e (0.033 g, 0.204 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, C6D6) 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 1.10–0.94 (2H, m) ppm; 6C (100 MHz, C6D6) 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)+, C17H25NaO5Si requires; 365.1760).
Methyl 4-oxo-2-(prop-1-en-1-yl)-3,4-dihydro-2H-pyran-5-carboxylate 5f. δ-Hydroxy-β-betetosser 7f (0.300 g, 1.612 mmol), yielded 0.274 g (87%), light yellow oil. ν max/cm⁻¹ (film) 2952, 2919, 1740, 1701, 1579, 1435, 1380, 1297, 1135, 1053, 965 cm⁻¹; δH (400 MHz, CDCl3) 8.01 (1H, s), 5.28 (1H, m), 5.08 (1H, m), 4.20 (1H, dd, J = 8.6, 7.0 Hz), 3.51 (3H, s), 2.08 (2H, m) and 1.31 (3H, d, J = 6.5 Hz) ppm; δC (100 MHz, CDCl3) 181.2, 169.9, 164.3, 131.7, 125.0, 111.5, 80.9, 51.3, 41.8 and 17.5 ppm; m/z (ESI⁺) 219 [M + Na]+ (Found 219.0629 [M + Na]+). C₇H₁₂N₂O₄ requires; 219.0628.

Methyl 4-oxo-2-styryl-3,4-dihydro-2H-pyran-5-carboxylate 5g. δ-Hydroxy-β-betetosser 7g (0.106 g, 0.427 mmol), yielded 0.107 g (97%), orange solid. ν max/cm⁻¹ 2951, 2951, 1693, 1569, 1436, 1369, 1260, 1295, 1060, 966, 747, 692 cm⁻¹; δH (400 MHz, 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 Hz, 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]+). C₁₅H₂₀N₂O₄ requires; 281.0784.

Methyl 2-(2-methylxazol-4-yl)-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate 5h. δ-Hydroxy-β-betetosser 7h (0.078 g, 0.343 mmol), yielded 0.062 g (77%), yellow light oil. ν max/cm⁻¹ 2953, 1738, 1704, 1579, 1436, 1383, 1296, 1133, 1013, 816, 732 cm⁻¹; δH (400 MHz, 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, 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]+). C₁₁H₁₄N₂O₄ requires; 260.0535.

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

Addition of Pb₂CuCl₂. 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. NH₄Cl (2.50 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 × 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 5f (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, 1095, 880, 681 cm⁻¹; δH (400 MHz, CDCl3) 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 (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]+). C₂₃H₂₆NaO₄S requires; 443.2224.

(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. ν max/cm⁻¹ (film) 2941, 2861, 1660, 1623, 1442, 1280, 1264, 1095, 880, 681 cm⁻¹; δH (400 MHz, CDCl3) 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 (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]+). C₂₃H₂₆NaO₄S requires; 443.2224.
3.829 mmol), yielded 1.170 g (91%), light yellow solid. ν max/cm⁻¹ (film) 3028, 2925, 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, 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, CDCl₃) 171.1, 170.9, 140.8, 136.4, 131.4, 128.6, 128.5, 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]⁺). C₁₂H₁₀NaO₆ requires; 359.1254.

Addition of Me₂CuLi. Methyl lithium 1.6 M in Et₂O (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 to stir −78 °C. The reaction mixture was stirred at this temperature for 4.5 hours then sat. aq. NH₄Cl (1.70 ml) was added to the mixture, which was stirred rapidly for 30 minutes at rt. The mixture was diluted with H₂O (10.0 ml) extracted with Et₂O (2 × 20.0 ml) and washed with H₂O (20.0 ml) and brine (20.0 ml). The organic layer was dried over MgSO₄ 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 THF 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 Et₂O (30.0 ml) and H₂O (10.0 ml). The organic layer was washed with H₂O (10.0 ml) and brine (10.0 ml), then dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate) gave products 10.(2R,6S*)-Methyl 4-acetoxy-6-(furan-2-yl)-2-methyl-5,6-dihydro-2H-pyran-3-carboxylate 10g. Dihydroxypropan 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, CDCl₃) 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, CDCl₃) 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)⁺). C₁₂H₁₀NaO₆ requires; 303.0845.

(2R,6S*)-Methyl 4-acetoxy-2-methyl-6-(((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-3-carboxylate 10k. Dihydroxypropan 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, CDCl₃) 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, CDCl₃) 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)⁺). C₁₂H₁₀NaO₂S requires; 423.2179.

(2R,6S*)-Methyl 4-acetoxy-2-methyl-6-(((E)-prop-1-en-1-yl)-5,6-dihydro-2H-pyran-3-carboxylate 10l. Dihydroxypropan 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, CDCl₃) 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 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, CDCl₃) 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)⁺). C₁₂H₁₀NaO₂S requires; 277.1046.

Addition of n-Bu₂CuLi. n-Butyl lithium 2.5 M in hexane solution (0.26 ml, 0.66 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. NH4Cl (1.0 mL) and allowed to warm to rt with vigorous stirring. The mixture was diluted further with sat. aq. NaHCl (10.0 mL) and extracted with EtOAc (5 × 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 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), yielded 0.037 g (35% 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, CDCl3) δ 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, CDCl3) 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]± C23H42NaO5Si requires; 465.2643).

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

A 1.0 M solution of t-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 EtO (10.0 mL) and quenched with sat. aq. NaHCl (10.0 mL). The layers were separated and the azeotropic layer was extracted with EtO (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 as a mixture of enol/keto tautomers.

Methyl 6-(furan-2-yl)-4-hydroxy-5,6-dihydro-2H-pyran-carbonyl oxylate 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, 1267, 1442, 1275, 1066, 1011, 739, 598 cm−1; 1H NMR (400 MHz, CDCl3): 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), 3.44 (3H, s, keto) 2.86 (1H, d, 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, CDCl3) 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)± C11H12NaO5 requires 247.0577).

Methyl 6-propyl-4-hydroxy-5,6-dihydro-2H-pyran-3-carbonyl oxylate 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; 1H 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, 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, CDCl3) 170.5, 168.8, 168.0 (keto), 140.8, 140.0 (keto), 128.9 (keto), 128.7, 128.3 (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)± C13H14NaO5 requires 257.0784).
Methyl 4-hydroxy-5,6-dihydro-2H-pyran-3-carboxylate 11c. Dihydropyran 5e (0.095 g, 0.277 mmol), yielded 0.062 g (65%) oil. υ max/cm⁻¹ (film) 2952, 2865, 1774, 1729, 1709, 1148, 1057, 881, 787, 691 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 11.78 (OH, s), 6.89–6.46 (2H, m, keto), 4.43 (1H, d, J = 13.9), 4.29 (1H, d, J = 13.9), 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, CDCl₃): 170.5, 169.5, 97.1, 79.2 (keto), 74.6, 68.2 (keto), 66.6, 63.2, 57.3 (keto), 52.4 (ketol), 51.5, 44.2 (keto), 131.3, 18.8, 12.0 ppm; m/z (ESI⁺) 367 (M + Na⁺). (Found 367.1905 (M + Na⁺). C₁₇H₁₈NaO₅ requires 367.1911).

(E)-Methyl 4-hydroxy-5,6-dihydro-2H-pyran-3-carboxylate 11g. Dihydropyran 5g (0.100 g, 0.387 mmol), yielded 0.051 g (51%) oil. υ max/cm⁻¹ (film) 2953, 2839, 1665, 1626, 1441, 1263, 1211, 1059, 965, 795, 746, 692 cm⁻¹; ¹H 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; δC (100 MHz, CDCl₃): 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 33.4 ppm; m/z (ESI⁺) 283 (M + Na⁺). (Found 283.0934 (M + Na⁺). C₁₃H₁₂NaO₄ 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 Et₂O (30.0 mL) and H₂O (10.0 mL). The organic layer was washed with H₂O (10.0 mL) and brine (10.0 mL), then dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate) gave the product.

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. υ max/cm⁻¹ (film) 2953, 2847, 1760, 1723, 1706, 1671, 1365, 1253, 1173, 1132, 1059, 1009, 743 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; δC (100 MHz, CDCl₃): 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⁺]. C₁₃H₁₂NaO₄ requires 289.0683).

Methyl 4-acetoxy-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate 12b. Tetrahydropyran-4-one 11b (0.074 g, 0.316 mmol), yielded 0.059 g (68%) solid white. υ max/cm⁻¹ (film) 2949, 2842, 1765, 1718, 1664, 1166, 1131, 1060, 743, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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, CDCl₃): 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⁺]. C₁₃H₁₄NaO₄ requires 299.0890).
(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-allyl-4-oxo-6-phenyltetrahydro-2H-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, 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, 4.6 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; 6C (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, 52.5, 46.2 and 36.1 ppm; m/z (ESI⁺) 297 (M + Na)⁺. (Found 297.1101 (M + Na)⁺. C₂₀H₁₄NaO₅ requires 297.1097).

(3S*,6S*)-Methyl 3-allyl-4-oxo-6-((E)-styryl)tetrahydro-2H-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, CDCl₃): 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, ddd, J = 17.1, 10.1, 7.5, 7.0 Hz), 5.05 (1H, ddd, J = 17.1, 4.4 Hz), 4.99 (1H, ddd, 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; 6C (100 MHz, CDCl₃): 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)⁺. C₂₀H₁₄NaO₅ requires 323.1230).

(3S*,6S*)-Methyl 3-allyl-4-oxo-6-((triisopropylsilyl)oxy)methyltetrahydro-2H-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, CDCl₃): 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, ddd, J = 9.9, 1.8 Hz), 4.17 (1H, d, J = 11.6 Hz), 4.14 (1H, ddd, 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; 6C (100 MHz, CDCl₃): 203.6, 170.1, 132.3, 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 407.2221 (M + Na)⁺. C₂₂H₂₄NaO₅Si requires 407.2224.)
Synthesis of diospongín 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 cinnamic acid (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, 154.0 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 mL) and a 20% w/v citric acid solution (120 mL) was added. The layers were separated and the aqueous layer was extracted with Et₂O (2 × 50 mL). The combined organic extracts were washed with brine (2 × 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%).

ν 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, 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; 13C (100 MHz, CDCl₃): 201.9, 167.3, 137.2, 131.0, 130.2, 128.8, 127.8, 126.8, 85.8, 51.8, 49.7 and 49.6 ppm; m/z (ESI⁺) 271 (M + Na⁺). Found 271.0937 (M + Na⁺). C₁₉H₁₂₄NaO₄ requires 271.0941.

(2S,4S,6S*)-2-Phenyl-6-((E)-styryl)tetrahydro-2H-pyran-4-ol 14. A solution of 8f (0.059 g, 0.175 mmol) in DMF (0.92 mL) and H₂O (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 H₂O (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 MgSO₄ and concentrated in vacuo to give 0.044 g (91%) of a dark yellow oil. ν max/cm⁻¹ (film) 2978, 2881, 2871, 1230, 1204, 966, 753, 737, 695 cm⁻¹; 6H (400 MHz, CDCl₃) 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, 3.8 Hz), 2.78–2.88 (4H, m) ppm; NOE H₂ – H₃α 1.33% H₂ – H₇β 1.89%, H₄ – H₆ 1.23%, H₄ – H₃α 1.58%, H₄ – H₅α 2.59%; 13C (100 MHz, CDCl₃) 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⁺). C₁₉H₁₂₃NaO₄ requires 301.1199.

A 1.0 M solution of 3-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 Et₂O (20.0 mL) and sat. aq. NH₄Cl (20.0 mL) and the layers separated. The aqueous layer was washed with Et₂O (20.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over MgSO₄ 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; 6H (400 MHz, CDCl₃) 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, dd, J = 13.5, 4.4, 4.0 Hz), 2.31 (1H, m, minor), 2.19 (1H, m, minor), 2.08 (1H, dddd, J = 12.6, 5.0, 4.5 Hz), 1.96 (1H, dddd, 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; 13C (100 MHz, CDCl₃) 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)⁺). C₇₊H₁₂Na₂O₄ requires 303.1356. Data in agreement with that previously reported.²⁹

2-((2S*,4S*,6S*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethane 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 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 0.010 g (70%) as a light yellow oil.

The mixture was heated at 80 °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 diospongin B, 0.006 g (58%) as a light yellow oil.

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