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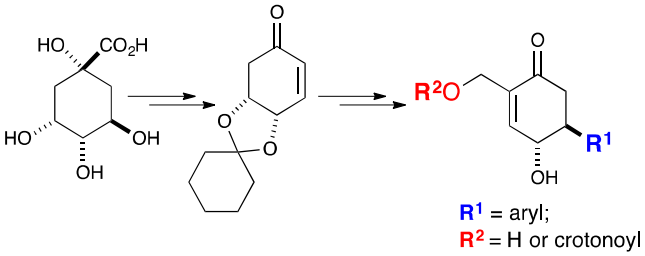
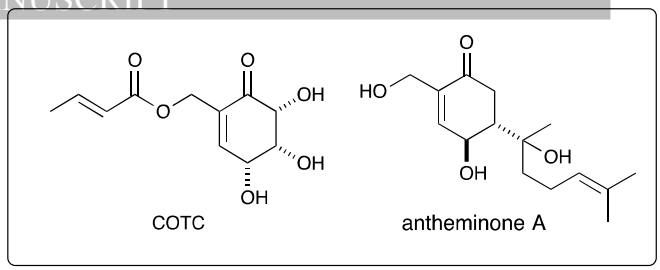


R^1 = aryl;
R^2 = H or crotonoyl



Synthesis of Hybrid Natural Product Analogues with Anti-tumour Properties

Stephania Christou,[a] Alyn C. Edwards,[a] Robin G. Pritchard,[a] Peter Quayle,[a] Yiwei Song,[a] Ian J. Stratford,[b] Katharine F. Williams,[a] Roger C. Whitehead[a]*

[a]*School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK*

[b]*Manchester Pharmacy School, University of Manchester, Oxford Road, Manchester, M13 9PL, UK*

High yielding and diastereoselective conjugate addition reactions of a (-)-quinic acid derived enone have provided access to a small library of hybrid analogues of the anti-tumour natural products antheminone A and COTC. The novel compounds were assessed for their antiproliferative activities towards the A549 non-small-cell lung cancer cell line revealing some useful structure-activity relationships.

Keywords: anti-tumour; natural product analogue; conjugate addition; transition metal; catalysis; rhodium.

1. Introduction

The α-oxyalkylcyclohex-2-enone moiety is a common structural feature of many natural products including poly-oxygenated metabolites (*e.g.* COTC **1**),[1] carvotacetone derivatives such as **2**[2] and terpenoid derivatives exemplified by phorbasin B (**3**)[3] and antheminone A (**4**).[4] A number of these compounds have been found to display notable biological activities: for example, both **1** and **4** show significant toxicity towards a variety of different cancer cell lines.[4,5]

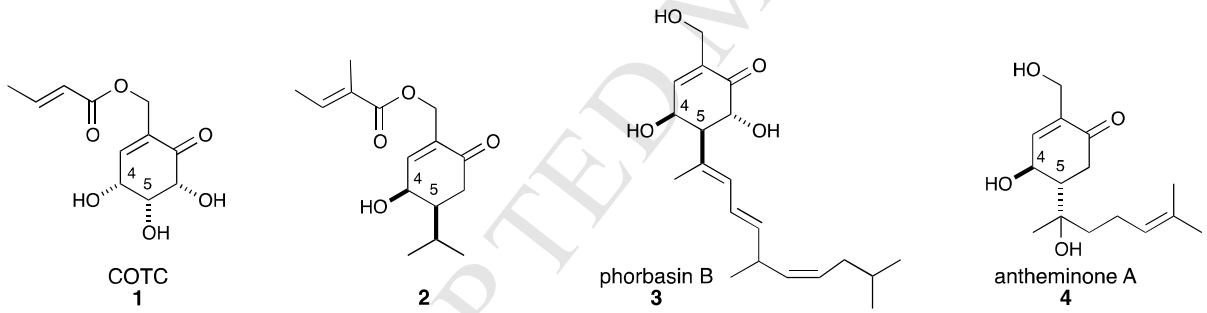


Figure 1 Natural products containing the α-oxyalkylcyclohex-2-enone moiety.

During the course of our investigations into the anti-tumour properties of a variety of α-oxyalkylcyclohex-2-enones, we had cause to focus our attention on compounds bearing a carbon-linked substituent at C5 (*i.e.* analogues of **2**, **3**, and **4**).[6] We describe, herein, a synthetic approach to compounds of this type (general structure **5**), which utilises (⁻)-quinic acid (**6**) as starting material (**Figure 2**). The results of assays of the anti-proliferative activities of the novel analogues towards the A549 non-small-cell lung cancer cell line are also provided.

* Corresponding author. Tel: +44-161-275-7856; Fax: +44-161-275-4939; e-mail: roger.whitehead@manchester.ac.uk

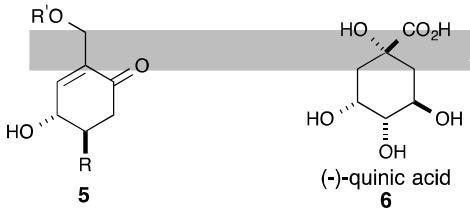
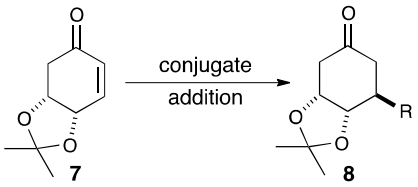


Figure 2 Generic structure of target compounds and the structure of (-)-quinic acid.

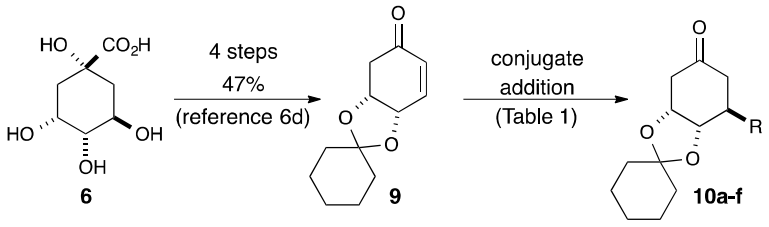
2. Results and Discussion

A number of previous literature reports have described conjugate addition reactions to the isopropylidene protected dioxygenated cyclohexenone **7**, some of which report poor to average yields due, in part, to the lability of enone **7** and/or adducts **8** towards the reaction conditions (**Scheme 1**).[7,8] Bräse and co-workers, for example, reported that treatment of **7** with $Ph_2CuMgBr.S(CH_3)_2$ in THF furnished adduct **8** (R = Ph) in just 27% yield, while reaction with $(2\text{-propyl})_2CuMgBr.S(CH_3)_2$ furnished no isolable quantities of the corresponding conjugate adduct (**8**, R = 2-propyl).[8]



Scheme 1

It was envisaged that a compound possessing the functionality of enone **7** would represent a versatile intermediate for the synthesis of α-oxyalkylcyclohexenones bearing a carbon-linked substituent at C5 and an *anti*-stereochemical relationship between substituents at C4 and C5, as proposed for the structure of antheminone A. An investigation was carried out, therefore, into the use of cyclohexenone **9** as a Michael acceptor with a variety of organometallic reagents. Compound **9**, which can be prepared expediently and on a preparative scale from (-)-quinic acid (**6**),[6d] possesses a cyclohexylidene ketal moiety which was predicted to offer greater resilience to the reaction conditions for conjugate addition than its isopropylidene counterpart **7**. Gratifyingly, exposure of enone **9** to a range of organometallic reagents under either stoichiometric or catalytic conditions, resulted in formation of adducts **10a-f** in good to excellent yields (**Scheme 2** and **Table 1**).



Scheme 2

Entry	Reaction Conditions	Product	Yield / %
1	2-propylMgBr (3 eq.), $ZnCl_2$.TMEDA (1 eq.), $(CH_3)_3SiCl$ (3.3 eq.) , THF, –50 ^oC	**10a**	82
2	PhMgBr (2 eq.), CuI (1 eq.), THF, 0 ^oC	**10b**	73
3	$PhB(OH)_2$, $[RhCl(cod)]_2$ (5 mol%), 1,4-dioxane:water (10:1), Et_3N, rt	**10b**	93
4	4-$(CH_3O)PhB(OH)_2$, $[Rh(\mu\text{-}OH)(cod)]_2$ (5 mol%), 1,4-dioxane:water (10:1), Et_3N, rt	**10c**	93
5	4-$(Br)PhB(OH)_2$, $[RhCl(cod)]_2$ (5 mol%), 1,4-dioxane:water (10:1), Et_3N, rt	**10d**	87
6	2-naphthyl$B(OH)_2$, $[RhCl(cod)]_2$ (5 mol%), 1,4-dioxane:water (10:1), Et_3N, rt	**10e**	83
7	4-biphenyl$B(OH)_2$, $[Rh(\mu\text{-}OH)(cod)]_2$ (5 mol%), 1,4-dioxane:water (10:1), Et_3N, rt	**10f**	78

Table 1 Isolated yields of conjugate addition reactions to enone **9**.

Thus, use of the appropriate tri-organozincate reagent allowed access to 2-propyl substituted compound **10a** (entry 1)[9] whereas aryl substituents could be readily introduced using Gilman cuprates derived from the corresponding Grignard reagents and CuI (entry 2) or alternatively using rhodium catalysis ($[RhCl(cod)]_2$ or $[Rh(\mu\text{-}OH)(cod)]_2$ and the appropriate arylboronic acid (entries 3 to 7).[10a,b] In the latter case, 5 mol % of transition metal catalyst was routinely employed however loadings as low as 2 mol % were also used successfully without significant detrimental effect to isolated yields or reaction times.

Only a single diastereoisomer was obtained from each of these reactions which, in the first instance, was presumed to have arisen from addition of the organometallic reagent to the sterically more accessible "convex" face of enone **9**. Initial evidence to support this conjecture was the observation of nOe's between C(4)H of **10e** and both C(1')H and C(3')H of the naphthalene substituent: analogous enhancements were also observed for the biphenyl adduct **10f**. In both cases, there was no observable transannular nOe between C(3)H and C(5)H. Unambiguous structural confirmation was ultimately made possible by X-ray analysis of a crystalline sample of the biphenyl adduct **10f** (**Figure 2**).[11]

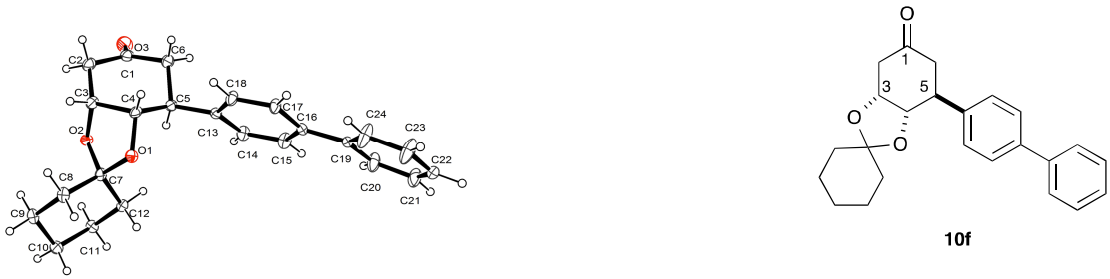
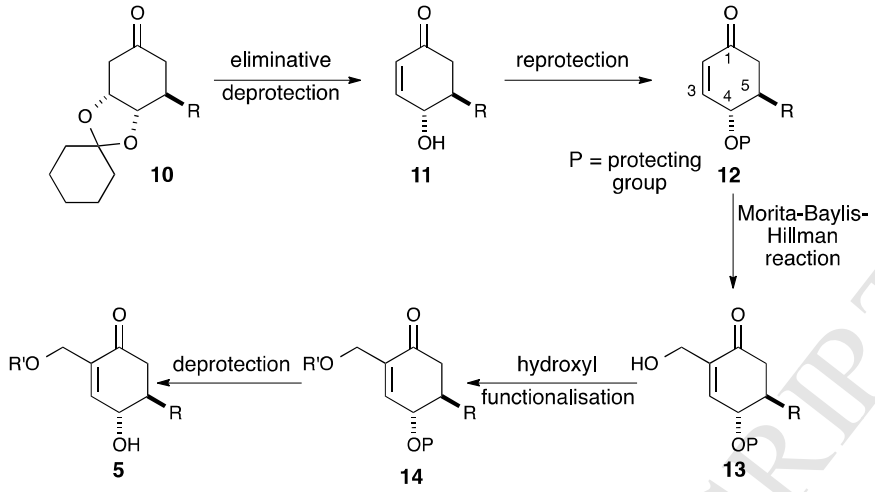


Figure 2 Crystal structure of biphenyl adduct **10f** with ellipsoids at 50% probability

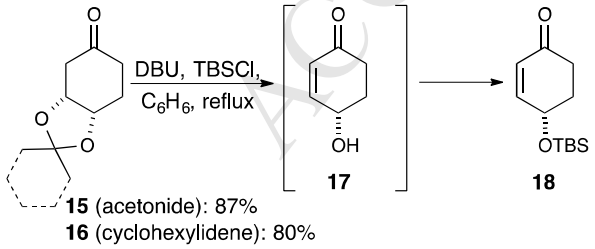
Studies carried out recently on an enantiomeric series of α-oxyalkylcyclohex-2-enones indicated that an aromatic substituent at C5 was an important requirement for good anti-proliferative activity towards lung cancer cell lines.[6e] Efforts were focussed, therefore, on the preparation of a range of aryl-substituted hybrid

analogues of antheminone A and COTC (generic structure **5**, R = aryl) using the synthetic approach outlined in **Scheme 3**.

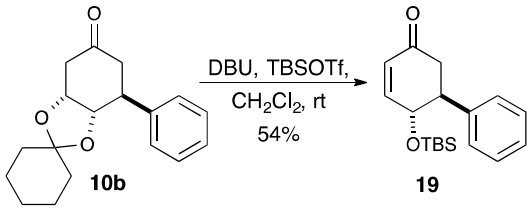


Scheme 3

In a first generation approach, attention was focused on the phenyl adduct **10b** which could be prepared in excellent yield from enone **9** *via* the rhodium catalysed conjugate addition of phenylboronic acid. The first goal was the development of efficient and high yielding conditions for eliminative removal of the cyclohexylidene moiety of **10b** followed by reprotection of the resulting allylic alcohol (γ-hydroxycyclohexenones of this type are known to undergo quite facile base-catalysed tautomerism to cyclohexan-1,4-diones making this a non-trivial transformation). In this context, Danishefsky and co-workers previously reported that acetonide-protected compound **15** could be converted to γ-silyloxy-enone **18** by reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the presence of TBSCl at elevated temperature (**Scheme 4**).[12] In our hands, and under similar reaction conditions, cyclohexylidene ketal **16** also underwent clean conversion to **18** in comparable yield.[6d] Unfortunately, exposure of phenyl-substituted cyclohexanone **10b** to these reaction conditions met with little success, however replacement of the silyl trapping reagent with TBSOTf and conducting the reaction at room temperature ultimately allowed isolation of the desired product **19** in an acceptable yield (**Scheme 5**).



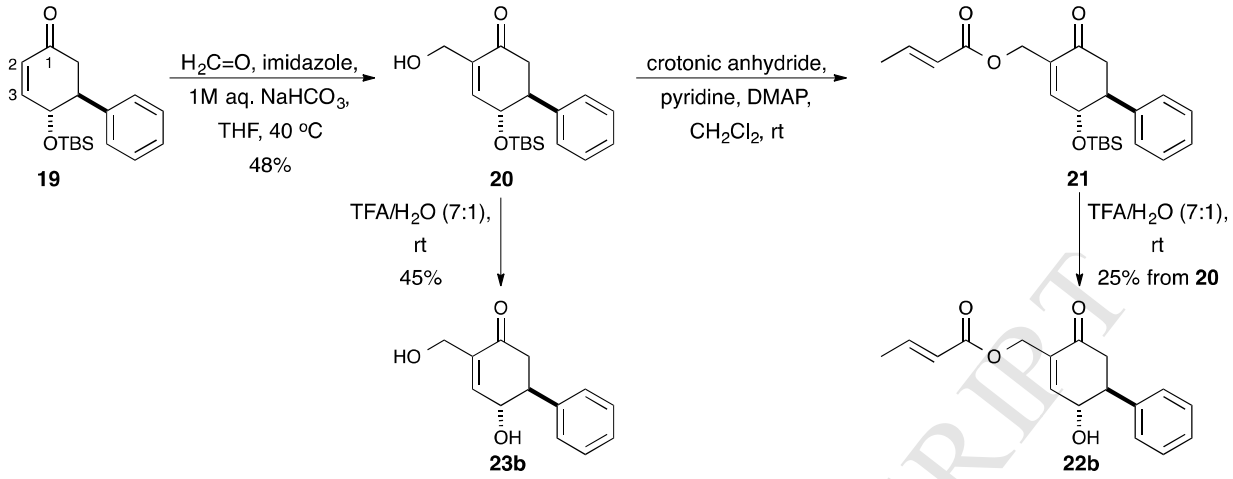
Scheme 4



Scheme 5

Incorporation of a hydroxymethyl group at C2 of enone **19** was accomplished in moderate yield using an imidazole-catalysed Morita-Baylis-Hillman reaction to give primary alcohol **20**.[13a,b] Subsequent esterification with crotonic anhydride gave crotonate **21**, which after partial purification by silica

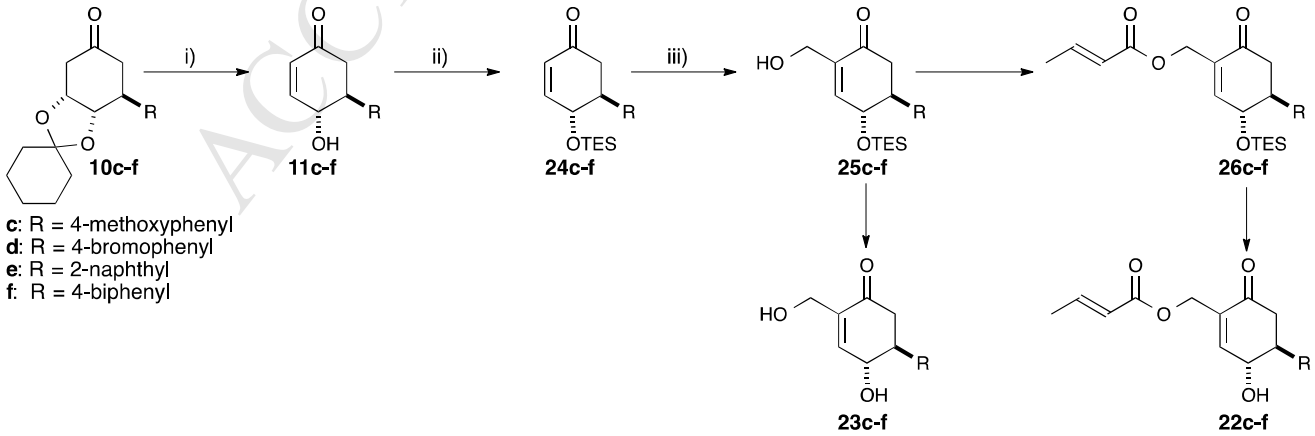
chromatography, was subjected to acid-mediated deprotection conditions to give the hybrid analogue **22b**. Similar deprotection of hydroxymethyl compound **20** gave antheminone A analogue **23b** (**Scheme 6**).



Scheme 6

Although successful for the preparation of **22b** and **23b**, the approach outlined above proved unreliable for the synthesis of target compounds bearing alternative aromatic substituents, particularly with regard to the eliminative deprotection/reprotection sequence and the Morita-Baylis-Hillman reaction. A more robust 'second generation' approach was developed, therefore, for the preparation of the remaining target compounds wherein the deprotection/reprotection sequence was carried out in two discrete synthetic operations.

Accordingly, exposure of the conjugate adducts **10c-f** to either DBU in dichloromethane or a catalytic quantity of aqueous sodium hydroxide in THF (for ~ 4 hours) furnished the γ-hydroxycyclohexenones **11c-f** in good to excellent yields.[14] Subsequent reprotection of the liberated C4-hydroxyl group as its triethylsilyl (TES) ether proved to be surprisingly problematic due mostly to competitive silylenol ether formation. This difficulty was ultimately overcome, however, by pre-mixing TES-triflate and 2,6-lutidine in dichloromethane (to neutralise residual triflic acid) prior to stirring very briefly with the substrate at -78 °C. Under these conditions, TES ethers **24c-f** were obtained in yields greater than 70% (**Scheme 7**).



Reagents and Conditions: i) DBU, CH_2Cl_2, rt, 2 h or 0.5M aq NaOH (cat.), THF, 4 h, 67-87%; ii) TESOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 10 min. 75-89%; iii) DMAP, formaldehyde (37% in H_2O), sodium dodecyl sulfate, rt, 22 h, 30-75%; crotonylation and deprotection conditions as in **Scheme 6**.

Scheme 7

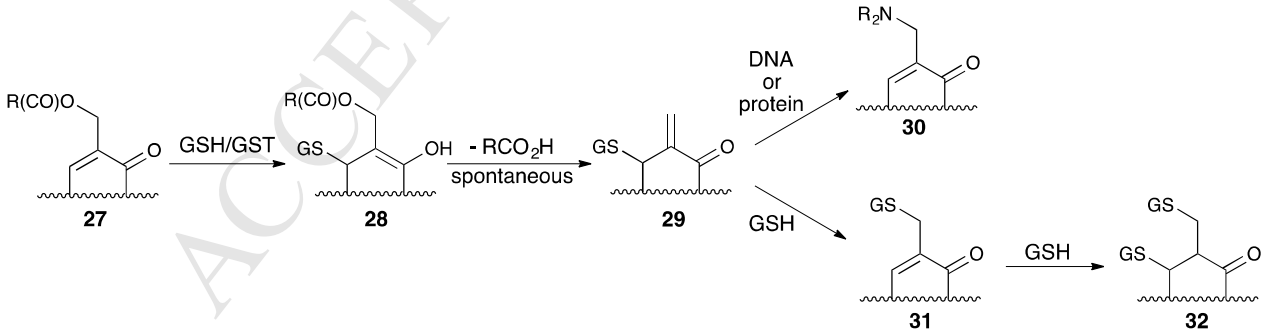
The ambiphilic nature of intermediates **24c-f** prompted an investigation of surfactant conditions for the problematic Morita-Baylis-Hillman reaction and pleasingly, using the SDS-mediated procedure reported by Williams and co-workers,[15] hydroxymethyl compounds **25c-f** could be prepared in yields generally in excess of 60% (with the exception of a disappointingly low yield of 30% for biphenyl compound **25f**). These adducts were then converted to hybrid analogues **22c-f** and antheminone A analogues **23c-f** using similar conditions to those described above for **22b** and **23b**.

Analogues **22b-f** and **23b-f** were initially selected as synthetic targets as they possess variable hydrophobicities (as indicated by their predicted logP (miLogP[16]) values) and assessment of their bioactivity was expected to provide useful structure activity relationship information. A549 non-small-cell lung cancer cells were exposed, therefore, to varying concentrations of each of the compounds for 96 h and their anti-proliferative activities were assessed using the MTT assay (**Table 2**).[17]

Compound	IC_{50} (μM)	miLogP[16]	Compound	IC_{50} (μM)	miLogP[16]
22b	2.3±0.8	2.25	**23b**	90±48	0.86
22c	3.2±0.2	2.31	**23c**	75±11	0.92
22d	3.0±0.2	3.06	**23d**	16.5±1.6	1.67
22e	2.5±0.3	3.44	**23e**	15.3±0.2	2.04
22f	3.3±0.4	4.05	**23f**	28.0±2.5	2.66

Table 2 Predicted log P (miLogP[16]) values and values of IC_{50} (the concentration required to reduce proliferation by 50%) of hybrid analogues of antheminone A and COTC towards non-small-cell lung cancer cell line A549. Toxicity experiments were repeated in triplicate and data within individual experiments were derived from four separate observations: average values are given in the table.

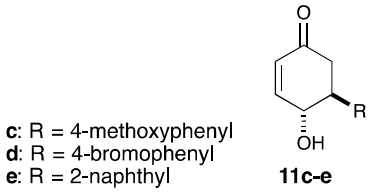
The biological mode of action of COTC and related compounds is generally accepted to be mediated by the detoxification enzyme *glutathione transferase* (GST) and requires a 'reasonable leaving group' attached to the methylene side-chain which undergoes conjugate displacement by the tri-peptide glutathione (GSH) (**27→28→29**) (**Scheme 8**). The ensuing highly reactive exocyclic enone **29** is then believed to alkylate DNA/vital proteins, or deplete intracellular stores of GSH, leading to cell death.[18]

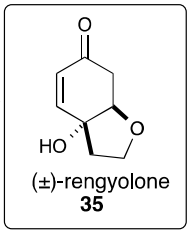


Scheme 8

To a degree, the cytotoxicity data in **Table 2** are in accord with this proposal as compounds **22b-g**, which possess a carboxylate leaving group, are all more potent than their non-esterified counterparts **23b-g**. It is noteworthy, however, that the moderate toxicity of some of the less polar diols (e.g. **23c** and **23d**) indicates that the requirement for a 'reasonable leaving group' is not absolute. In order to throw some light on this observation, three of the γ-hydroxyenone intermediates **11c-e**, which are simple Michael acceptors and are

unable to generate an exocyclic enone, were subjected to MTT assays. These compounds can be viewed as analogues of the plant-derived cyclohexenone (±)-rengyolone (**35**)[19] which has previously been shown to demonstrate weak toxicity towards the A549 cell line (IC_{50} = 16.2±0.8 μg/mL / 105±5 μM).[20] All three enones displayed significantly better antiproliferative activities than the corresponding diols **23c-e** as well as the natural product **35**. Furthermore, the 2-naphthyl substituted compound **11e** showed slightly improved potency compared with *all* of the crotonylated compounds **22b-f** (**Table 3**).





Compound	IC_{50} (μM)	miLogP[16]
11c	7.0±0.3	1.61
11d	5.5±0.5	2.37
11e	1.9±0.4	2.74

Table 3 Predicted log P (miLogP[16]) values and values of IC_{50} (the concentration required to reduce proliferation by 50%) of γ-hydroxyenones **11c-e** towards non-small-cell lung cancer cell line A549. Toxicity experiments were repeated in triplicate and data within individual experiments were derived from four separate observations: average values are given in the table.

These findings raise some questions as to the mode of antiproliferative activity of the COTC/antheminone A analogues described herein and some doubt as to the validity of the assumption that they operate in a similar manner to COTC. This is further emphasised by the finding that phenyl substituted compound **22b** is very similar in potency to its optical antipode (***ent*-22b**: IC_{50} = 1.3 ±02 μM)[6e] which is surprising for an enzyme mediated mode of biological activity. Investigations are now underway in our laboratories to elucidate the most likely mechanism(s) of action, the findings of which will be reported in due course.

3. Acknowledgements

NMR spectrometer and X-ray support for this work was funded by the Engineering and Physical Sciences Research Council (grant number EP/K039547/1) who we also acknowledge, with thanks, for providing financial support for K.F.W. and S.C.

4. Experimental Section

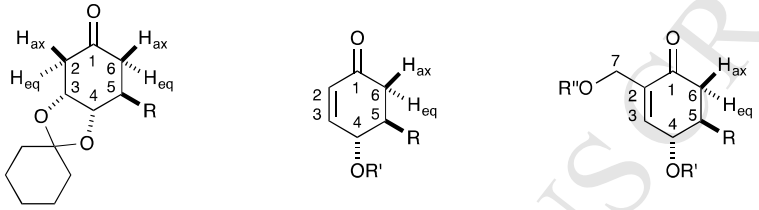
4.1 General

All reagents were purchased from Sigma-Aldrich, Alfa-Aesar or Fisher Scientific. Dichloromethane was dried over and distilled from calcium hydride under an atmosphere of nitrogen. THF was distilled from sodium-benzophenone ketyl under an atmosphere of nitrogen. All other solvents were used as supplied. Flash chromatography was performed using technical grade silica gel (pore size 60Å 230-240, mesh 40-63 μm). IR spectra were recorded on an AT1-Mattson Genesis Series FTIR spectrometer or a Bruker Alpha FT-

IR spectrometer or a Thermo Scientific Nicolet iS5 FT-IR spectrophotometer. ^{1}H, ^{13}C and ^{19}F spectra were recorded on Bruker Avance 300 MHz, Bruker Avance III 400 MHz or Bruker Avance II+ 500 MHz spectrometers. Chemical shifts are referenced to the residual solvent peak. Mass spectra were recorded on a Waters SQD2 (electrospray) spectrometer. Melting points were recorded using a Sanyo Gallenkamp MPD350 heater and are uncorrected. Optical rotations were recorded using an automatic AA-10 polarimeter with sodium D light (λ=589 nm) and values are given in 10^{-1} deg g^{-1} cm^2.

4.2 Atom numbering

For simplicity and consistency the numbering systems illustrated below have been employed for the assignment of NMR spectroscopic data.



4.3 Procedures and Analytical Data

(3a*S*,4*S*,7a*R*)-4-isopropyltetrahydrospiro[benzo[*d*][1,3]dioxole-2,1'-cyclohexan]-6(3a*H*)-one (**10a**)

To a solution of $ZnCl_2$.TMEDA (564 mg, 2.23 mmol) in THF (9 mL) was added *iso*-propylmagnesium chloride (2M in diethyl ether, 2.8 mL, 5.6 mmol) at 0 °C under an atmosphere of N_2. The solution was stirred at 0 °C for 15 min, cooled to –50 °C and chlorotrimethylsilane (0.8 mL, 6.3 mmol) was added followed by a solution of enone **9** (387 mg, 1.86 mmol) in THF (16 mL). The reaction mixture was stirred at –50 °C for 2 h when it was quenched by the addition of a saturated aqueous ammonium chloride/ammonium hydroxide solution (9:1, 30 mL) and allowed to warm to room temperature over 45 min. The organic material was extracted into ethyl acetate (2 x 50 mL) and the combined organic extracts were washed with water (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an orange liquid. This liquid was re-dissolved in THF (4 mL), a 1M aqueous solution of hydrochloric acid (0.2 mL) was added and the solution was stirred at room temperature for 15 min. The solution was neutralised by the addition of a saturated aqueous solution of sodium bicarbonate (4 mL) and, after dilution with water (10 mL), organic material was extracted into ethyl acetate (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as an orange oil which was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:9) to yield **10a** as a colourless oil (386 mg, 82%). R_f (ethyl acetate:40-60 petroleum ether, 1:9) 0.32; $[\alpha]_D^{26}$ -67.1 (*c* 0.98 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2934s (C-H), 2867m (C-H), 1716s (C=O); δ_H (400 MHz; $CDCl_3$) 0.90 (3H, d, *J* 6.7, CH(C<u>H</u>$_3$)), 1.00 (3H, d, *J* 6.7, CH(C<u>H</u>$_3$)), 1.38-1.67 (10H, m, 5 x C<u>H</u>$_2$ of cyclohexane), 1.79 (1H, octet, *J* 6.7, C<u>H</u>(CH$_3$)$_2$), 1.89 (1H, dtd, *J* 10.2, 6.7, 3.9, C(5)<u>H</u>), 2.02 (1H, dd, *J* 17.1, 10.2, C(6)<u>H</u>$_{ax}$), 2.42 (1H, dd, *J* 17.1, 3.9, C(6)<u>H</u>$_{eq}$), 2.62 (2H, ~d,

J 5.8, C(2)$\underline{H}_2$), 4.25 (1H, ~t, *J* 6.7, C(4)$\underline{H}$), 4.47 (1H, dt, *J* 6.7, 5.8, C(3)$\underline{H}$); δ_C (100 MHz; $CDCl_3$) 18.7 (CH($\underline{C}H_3$)), 20.9 (CH($\underline{C}H_3$)), 23.6, 24.0 & 25.1 (3 x $\underline{C}H_2$ of cyclohexane), 28.3 ($\underline{C}H(CH_3)_2$), 34.0 & 37.2 (2 x $\underline{C}H_2$ of cyclohexane), 37.8 ($\underline{C}(6)H_2$), 42.6 ($\underline{C}(2)H_2$), 43.3 ($\underline{C}(5)H$), 72.0 ($\underline{C}(3)H$), 74.7 ($\underline{C}(4)H$), 109.2 (ketal $\underline{C}$), 209.8 ($\underline{C}$=O); *m/z* (+ES) 275 ($[M+Na]^+$, 100%); (Found 275.1613, $C_{15}H_{24}NaO_3$ ($[M+Na]^+$) requires 275.1623).

(3a*S*,4*S*,7a*R*)-4-phenyltetrahydrospiro[benzo[*d*][1,3]dioxole-2,1'-cyclohexan]-6(3a*H*)-one (**10b**).

To a stirred suspension of copper(I) iodide (100 mg, 0.53 mmol) in THF (1 mL) at 0 °C, was added phenylmagnesium bromide (3M in Et_2O) (0.35 mL, 1.06 mmol) and the reaction mixture was stirred for 1 h at 0 °C under an atmosphere of N_2. A solution of enone **9** (100 mg, 0.48 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of a saturated aqueous ammonium chloride/ammonium hydroxide solution (9:1, 10 mL). The two layers were separated and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:9) to give the title compound **10b** as a pale yellow oil (98 mg, 73%). R_f (ethyl acetate:40-60 petroleum ether, 1:9) 0.18; $[\alpha]_D^{28}$ -42.8 (*c* 1.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2934w (C-H), 2883w (C-H), 1712s (C=O); δ_H (400MHz; $CDCl_3$) 1.37-1.76 (10H, m, 5 x $\underline{C}H_2$ of cyclohexane), 2.60-2.66 (2H, m, one of C(2)$\underline{H}_2$ & one of C(6)$\underline{H}_2$), 2.73 (1H, dd, *J* 16.7, 4.4, one of C(2)$\underline{H}_2$), 2.79 (1H, dd, *J* 17.6, 4.8, one of C(6)$\underline{H}_2$), 3.44 (1H, d~t, *J* 8.5, 4.8, C(5)$\underline{H}$), 4.57-4.68 (2H, m, C(3)$\underline{H}$ and C(4)$\underline{H}$), 7.23-7.28 (3H, m, 3 x aryl-$\underline{H}$), 7.33-7.37 (2H, m, 2 x aryl-$\underline{H}$); δ_C (100MHz; $CDCl_3$) 23.6, 24.0, 25.1, 33.7 & 36.9 (5 x cyclohexane $\underline{C}H_2$), 40.7 ($\underline{C}(6)H_2$), 42.3 ($\underline{C}(5)H$), 42.7 ($\underline{C}(2)H_2$), 72.2 ($\underline{C}(3)H$ or $\underline{C}(4)H$), 76.7 ($\underline{C}(3)H$ or $\underline{C}(4)H$), 109.3 (ketal $\underline{C}$), 127.0, 127.5 & 128.8 (aryl-$\underline{C}H$), 140.2 (aryl-$\underline{C}$), 208.9 ($\underline{C}$=O); *m/z* (+ES) 309 ($[M+Na]^+$, 100%); (Found 309.1461, $C_{18}H_{22}NaO_3$ ($[M+Na]^+$) requires 309.1467).

*Representative procedure for the rhodium catalysed conjugate addition of an arylboronic acid to enone **9**.*

(3a*S*,4*S*,7a*R*)-4-(4-methoxyphenyl)tetrahydrospiro[benzo [d][1,3] dioxole-2,1'-cyclohexan]-6(3a*H*)-one (**10c**)

To a solution of enone **9** (365 mg, 1.75 mmol) in dioxane:water (10:1, 4.0 mL) was added 4-methoxyphenylboronic acid (800 mg, 5.26 mmol) and $[Rh(\mu\text{-}OH)(cod)]_2$ (44 mg, 5 mol%), followed by Et_3N (0.23 mL, 1.75 mmol). The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 6.5 h when the solvents were removed *in vacuo* to give an orange residue. This residue was dissolved in CH_2Cl_2 (10 mL) and washed with brine (10 mL). Removal of the CH_2Cl_2 *in vacuo* gave a crude product which was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:12) to give the adduct **10c** as a pale yellow solid (516 mg, 93%). mp 109.8-111.1 °C; R_f (ethyl acetate:40-60

petroleum ether, 1:5) 0.25; $[\alpha]_D^{27}$ -60.3 (*c* 0.50 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2935s (C-H), 2856s (C-H), 1718s (C=O); δ_H (400MHz; $CDCl_3$) 1.35-1.75 (10H, m, 5 x C$\underline{H}_2$ of cyclohexane), 2.59 (1H, dd, *J* 17.5, 8.4, C(6)$\underline{H}_{ax}$), 2.62 (1H, dd, *J* 17.2, 4.6, one of C(2)$\underline{H}_2$), 2.73 (1H, dd, *J* 17.2, 4.6, one of C(2)$\underline{H}_2$), 2.75 (1H, dd, *J* 17.5, 4.6, C(6)$\underline{H}_{eq}$), 3.38 (1H, d~t, *J* 8.4, 4.6, C(5)$\underline{H}$), 3.80 (3H, s, OC$\underline{H}_3$), 4.54-4.60 (1H, m, C(3)$\underline{H}$ and C(4)$\underline{H}$), 6.88 (2H, d, *J* 8.6, aryl-$\underline{H}$), 7.16 (2H, d, *J* 8.6, aryl-$\underline{H}$); δ_C (100MHz; $CDCl_3$) 23.6, 23.9, 25.1, 33.7 & 36.9 (5 x cyclohexane $\underline{C}H_2$), 40.9 ($\underline{C}(2)H_2$), 41.8 ($\underline{C}(5)H$), 42.3 ($\underline{C}(6)H_2$), 55.2 (O$\underline{C}H_3$), 72.1 ($\underline{C}(3)H$ or $\underline{C}(4)H$), 77.4 ($\underline{C}(3)H$ or $\underline{C}(4)H$), 109.3 (ketal $\underline{C}$), 114.1 & 128.4 (aryl-$\underline{C}H$), 132.0 & 158.4 (aryl-$\underline{C}$), 209.0 ($\underline{C}$=O); *m/z* (+ES) 339 ($[M+Na]^+$, 100%); (Found 339.1584, $C_{19}H_{24}NaO_4$ ($[M+Na]^+$) requires 339.1572).

(3a*S*,4*S*,7a*R*)-4-(4-bromophenyl)tetrahydrospiro[benzo[d][1,3] dioxole-2,1'-cyclohexan]-6(3a*H*)-one (**10d**)
Using a similar procedure to that described above (replacing $[Rh(\mu\text{-}OH)(cod)]_2$ with $[RhCl(cod)]_2$), enone **9** (370 mg, 1.78 mmol) was converted to adduct **10d** (a viscous white oil, 567 mg, 87%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.24; $[\alpha]_D^{29}$ -77.0 (*c* 1.00 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2931s (C-H), 2857m (C-H), 1715s (C=O); δ_H (400 MHz; $CDCl_3$) 1.28-1.75 (10H, m, 5 × C$\underline{H}_2$ of cyclohexane), 2.55 (1H, dd, *J* 17.1, 9.6, C(6)$\underline{H}_{ax}$), 2.62-2.69 (2H, m, C(6)$\underline{H}_{eq}$ & C(2)$\underline{H}_{ax}$), 2.75 (1H, dd, *J* 16.9, 5.1, C(2)$\underline{H}_{eq}$), 3.35 (1H, ddd, *J* 9.6, 6.7, 4.5, C(5)$\underline{H}$), 4.50 (1H, t, *J* 6.7, C(4)$\underline{H}$), 4.57 (1H, d~t, *J* 6.7, 5.1, C(3)$\underline{H}$), 7.12 (2H, d, *J* 8.9, aryl-$\underline{H}$), 7.47 (2H, d, J 8.9, aryl-$\underline{H}$); δ_C (100 MHz; $CDCl_3$) 23.6, 24.0, 25.1, 33.9 & 37.1 (5 × $\underline{C}H_2$ of cyclohexane), 41.0 ($\underline{C}(2)H_2$), 41.2 ($\underline{C}(5)H$), 42.5 ($\underline{C}(6)H_2$), 72.1 ($\underline{C}(3)H$), 77.4 ($\underline{C}(4)H$), 109.7 (ketal $\underline{C}$), 121.0 (aryl-$\underline{C}$), 129.2 ($\underline{C}(3')H$ & $\underline{C}(5')H$), 131.9 ($\underline{C}(2')H$ & $\underline{C}(6')H$), 139.3 (aryl-$\underline{C}$), 208.2 ($\underline{C}$=O); *m/z* (+ES) 389 ($[M(^{81}Br)+Na]^+$, 50%), 387 ($[M(^{79}Br)+Na]^+$, 50%), 367 ($[M(^{81}Br)+H]^+$, 50%), 365 ($[M(^{79}Br)+H]^+$, 50%), 160 (100%); (Found 387.0566, $C_{18}H_{21}{}^{79}BrNaO_3$ ($[M+Na]^+$) requires 387.0572).

(3a*S*,4*S*,7a*R*)-4-(naphthalen-2-yl)tetrahydrospiro [benzo [d][1,3] dioxole-2,1'-cyclohexan]-6(3a*H*)-one (**10e**)
Using a similar procedure to that described above (replacing $[Rh(\mu\text{-}OH)(cod)]_2$ with $[RhCl(cod)]_2$), enone **9** (100 mg, 0.48 mmol) was converted to adduct **10e** (a colourless crystalline solid, 134 mg, 83%). mp 83.3-85.3 °C; R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.32; $[\alpha]_D^{24}$ -74.4 (*c* 1.00 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3047w (C-H), 3017w (C-H), 2933s (C-H), 2861s (C-H), 1718s (C=O); δ_H (400MHz; $CDCl_3$) 1.35-1.80 (10H, m, 5 x C$\underline{H}_2$ of cyclohexane), 2.68 (1H, dd, *J* 17.2, 5.1, one of C(2)$\underline{H}_2$), 2.76 (1H, dd, *J* 17.6, 8.0, C(6)$\underline{H}_{ax}$), 2.77 (1H, dd, *J* 17.2, 5.1, one of C(2)$\underline{H}_2$), 2.87 (1H, dd, *J* 17.7, 5.1, C(6)$\underline{H}_{eq}$), 3.60 (1H, dt, *J* 8.0, 5.1, C(5)$\underline{H}$), 4.64 (1H, dt, *J* 6.5, 5.1, C(3)$\underline{H}$), 4.75 (1H, ~t, *J* 6.0, C(4)$\underline{H}$), 7.43 (1H, dd, *J* 8.7, 1.9, C(3´)$\underline{H}$), 7.46-7.53 (2H, m, C(6´)$\underline{H}$ and C(7´)$\underline{H}$), 7.62 (1H, s, C(1´)$\underline{H}$), 7.78-7.86 (3H, m, C(4´)$\underline{H}$, C(5´)$\underline{H}$ & C(8´)$\underline{H}$); δ_C (100MHz; $CDCl_3$) 23.6, 23.9, 25.1, 33.7 & 36.9 (5 x cyclohexane $\underline{C}H_2$), 40.6 ($\underline{C}(2)H_2$), 42.3 ($\underline{C}(6)H_2$), 42.8 ($\underline{C}(5)H$), 72.2 ($\underline{C}(3)H$), 77.1 ($\underline{C}(4)H$), 109.3 (ketal $\underline{C}$), 125.8, 125.9, 126.0, 126.4, 127.6, 127.8 & 128.6 (aryl-$\underline{C}H$), 132.3, 133.4 & 137.6 (aryl-$\underline{C}$), 208.8 ($\underline{C}$=O); *m/z* (+ES) 359 ($[M+Na]^+$, 100%); (Found 359.1616, $C_{22}H_{24}O_3Na$ ($[M+Na]^+$) requires 359.1623).

(3a*S*,7a*R*)-4-([1,1'-biphenyl]-4-yl)tetrahydrospiro[benzo[d][1,3]dioxole-2,1'-cyclohexan]-6(3a*H*)-one (**10f**)

Using a similar procedure to that described above, enone **9** (0.250 g, 1.20 mmol) was converted to adduct **10f** (an off-white solid, 0.340 g, 78 %). m.p. 103.7-104.3 °C; $[\alpha]_D^{28}$ -70.8 (*c* 1.3 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2943s (C-H), 2900s (C-H), 1716s (C=O); δ_H (400 MHz; C_6D_6) 1.48-1.77 (10H, m, 5 x C$\underline{H}_2$, cyclohexane), 2.26 (1H, dd, *J* 17.3, 10.1, C(6)$\underline{H}_{ax}$), 2.36 (1H, dd, *J* 16.9, 5.3, one of C(2)$\underline{H}_2$), 2.56 (1H, dd, *J* 17.3, 4.6, C(6)$\underline{H}_{eq}$), 2.61 (1H, dd, *J* 16.9, 5.3, one of C(2)$\underline{H}_2$), 3.15 (1H, ddd, *J* 10.1, 6.7, 4.6, C(5)$\underline{H}$), 4.02 (1H, dt, *J* 6.7, 5.3, C(3)$\underline{H}$), 4.15 (1H, t, *J* 6.7, C(4)$\underline{H}$), 7.02-7.50 (9H, m, aryl-$\underline{H}$); δ_C (100 MHz; C_6D_6) 24.3, 24.7, 25.9, 34.7 & 37.9 (5 x cyclohexane $\underline{C}H_2$), 41.6 ($\underline{C}(2)H_2$), 43.0 ($\underline{C}(6)H_2$), 43.3 ($\underline{C}(5)H$), 72.9 ($\underline{C}(3)H$), 78.2 ($\underline{C}(4)H$), 109.6 (ketal $\underline{C}$), 127.7, 128.0, 128.3, 128.5 & 129.4 (aryl-$\underline{C}H$) 140.5, 140.6 & 141.6 (aryl-$\underline{C}$), 206.5 ($\underline{C}$=O); *m/z* (+ES) 385 ($[M+Na]^+$, 100 %); (Found 385.1770, $C_{24}H_{26}NaO_3$ ($[M+Na]^+$) requires, 385.1780).

First generation synthesis

(1*S*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**19**)

TBSOTf (50 μL mL, 0.22 mmol) and DBU (40 μL, 0.27 mmol) were added sequentially to a solution of conjugate adduct **10b** (57 mg, 0.199 mmol) in dichloromethane (2.2 mL) and the reaction mixture was stirred at room temperature under an atmosphere of N_2 for 4.5 h. A second portion of DBU (10 μL, 0.067 mmol) was then added and the reaction mixture was stirred for a further 1 h at room temperature. The reaction mixture was diluted with dichloromethane (10 mL) and washed sequentially with water (10 mL), a 1M aqueous solution of hydrochloric acid (10 mL), a saturated aqueous solution of sodium bicarbonate (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a yellow oil (92 mg). Purification by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:19) gave the title compound as a yellow crystalline solid (33 mg, 54%). R_f (ethyl acetate:40-60 petroleum ether, 1:19) 0.13; m.p. 75.2-76.7 °C [Lit. m.p. 74-75 °C]; $[\alpha]_D^{36}$ -132.0 (*c* 0.85 in CH_2Cl_2) [Lit. $[\alpha]_D^{20}$ -158 (*c* 0.5 in $CHCl_3$)]; ν_{max} (film)/cm^{-1} 3031w (C-H), 2951m (C-H), 2928m (C-H), 2894w (C-H), 2854m (C-H), 2817m (C-H), 1681s (C=O); δ_H (400 MHz; $CDCl_3$) -0.50 (3H, s, Si(C$\underline{H}_3$)), -0.13 (3H, s, Si(C$\underline{H}_3$)), 0.76 (9H, s, SiC(C$\underline{H}_3$)$_3$), 2.67 (1H, ddd, *J* 16.4, 4.3, 1.4, C(6)$\underline{H}_{eq}$), 2.78 (1H, dd, *J* 16.4, 13.7, C(6)$\underline{H}_{ax}$), 3.27 (1H, ddd, *J* 13.7, 9.4, 4.3, C(5)$\underline{H}$), 4.53 (1H, d~t, *J* 9.4, 2.0, C(4)$\underline{H}$), 6.03 (1H, ddd, *J* 10.4, 2.0, 1.4, C(2)$\underline{H}$), 6.85 (1H, dd, *J* 10.4, 2.0, C(3)$\underline{H}$), 7.24-7.36 (5H, m, aryl-$\underline{H}$); δ_C (100 MHz; $CDCl_3$) -5.9 (Si($\underline{C}H_3$)), -5.2 (Si($\underline{C}H_3$)), 17.9 (Si$\underline{C}$(CH$_3$)$_3$), 25.6 (SiC($\underline{C}$H$_3$)$_3$), 42.6 ($\underline{C}(6)H_2$), 50.7 ($\underline{C}(5)H$), 73.0 ($\underline{C}(4)H$), 127.3, 128.2, 128.4 & 128.5 (aryl-$\underline{C}$H & $\underline{C}(2)H$), 140.6 (aryl-$\underline{C}$), 153.9 ($\underline{C}(3)H$), 198.5 ($\underline{C}$=O); *m/z* (+ES) 357 ($[M+Na+CH_3OH]^+$, 100%), 325 ($[M+Na]^+$, 85); (Found 325.1591, $C_{18}H_{26}NaO_2Si$ ($[M+Na]^+$) requires 325.1600).

(1*S*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-4-(hydroxymethyl)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**20**)

Formaldehyde (37%) (20 μL, 0.27 mmol) and imidazole (1.4 mg, 0.02 mmol) were added to a solution of enone **19** (61 mg, 0.20 mmol) in a mixture of THF (1.2 mL) and 1M aqueous sodium bicarbonate (0.6 mL). After stirring at room temperature under N_2 for 5 days, further portions of formaldehyde (37%) (15 μL, 0.20 mmol) and imidazole (1.4 mg, 0.02 mmol) were added. After a further 3 days, additional formaldehyde (37%) (15 μL, 0.20 mmol) and imidazole (1.4 mg, 0.02 mmol) were added. After a total reaction time of 12 days, the reaction was quenched with a 1M aqueous solution of hydrochloric acid (1 mL) and diluted with water (10 mL). The organic material was extracted into dichloromethane (3 x 10 mL) then washed sequentially with brine (15 mL) and a saturated aqueous solution of sodium bicarbonate (15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a pink oil (84 mg). This residue was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:5) to give the title compound as a colourless oil (32 mg, 48%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.19; $[\alpha]_D^{30}$ -126.7 (*c* 0.55 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3436br (O-H), 2954m (C-H), 2928m (C-H), 2890w (C-H), 2855m (C-H), 1675s (C=O); δ_H (400 MHz; $CDCl_3$) -0.51 (3H, s, Si(C$\underline{H}_3$)), -0.12 (3H, s, Si(C$\underline{H}_3$)), 0.76 (9H, s, SiC(C$\underline{H}_3$)$_3$), 2.39 (1H, ~t, *J* 6.4, $CH_2O\underline{H}$), 2.71 (1H, dd, *J* 16.5, 4.3, C(6)$\underline{H}_{eq}$), 2.81 (1H, dd, *J* 16.5, 13.6, C(6)$\underline{H}_{ax}$), 3.26 (1H, ddd, *J* 13.6, 9.5, 4.3, C(5)$\underline{H}$), 4.28 (1H, br dd, *J* 13.5, 6.4, C(7)$H_a\underline{H}_b$), 4.39 (1H, br dd, *J* 13.5, 6.4, C(7)$\underline{H}_aH_b$), 4.56 (1H, d~q, *J* 9.5, 1.5, C(4)$\underline{H}$), 6.77 (1H, dm, *J* 1.5, C(3)$\underline{H}$), 7.24-7.26 (5H, m, aryl-$\underline{H}$); δ_C (100 MHz; $CDCl_3$) -5.9 (Si($\underline{C}H_3$)), -5.1 (Si($\underline{C}H_3$)), 17.8 (Si$\underline{C}$(CH$_3$)$_3$), 25.6 (SiC($\underline{C}$H$_3$)$_3$), 42.9 ($\underline{C}$(6)H_2), 50.8 ($\underline{C}$(5)H), 61.3 ($\underline{C}$(7)H_2), 73.0 ($\underline{C}$(4)H), 127.4, 128.2 & 128.5 (aryl-$\underline{C}$H), 136.9 ($\underline{C}$(2)), 140.4 (aryl-$\underline{C}$), 149.7 ($\underline{C}$(3)H), 199.2 ($\underline{C}$=O); *m/z* (+ES) 355 ($[M+Na]^+$, 100%); (Found 355.1711, $C_{19}H_{28}NaO_3Si$ ($[M+Na]^+$) requires 355.1705).

((1*S*,6*R*)-6-hydroxy-3-oxo-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)methyl (*E*)-but-2-enoate (**22b**)

Crotonic anhydride (70 μL, 0.47 mmol), DMAP (2.8 mg, 0.02 mmol) and pyridine (160 μL, 1.98 mmol) were added sequentially to a solution of hydroxymethyl compound **20** (76 mg, 0.23 mmol) in dichloromethane (1.3 mL) under an atmosphere of N_2. The reaction mixture was stirred at room temperature for 45 min when it was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (1.5 mL). Water (10 mL) was added and the organic material was extracted into dichloromethane (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a brown oil (171 mg). This residue was partially purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:19) to give a colourless oil (59 mg). δ_H (400 MHz; $CDCl_3$) -0.46 (3H, s, Si(C$\underline{H}_3$)), -0.14 (3H, s, Si(C$\underline{H}_3$)), 0.76 (9H, s, SiC(C$\underline{H}_3$)$_3$), 1.91 (3H, dd, *J* 7.0, 1.6, CH=CHC$\underline{H}_3$), 2.72 (1H, dd, *J* 16.4, 4.3, C(6)$\underline{H}_{eq}$), 2.82 (1H, dd, *J* 16.4, 13.6, C(6)$\underline{H}_{ax}$), 3.28 (1H, ddd, *J* 13.6, 9.4, 4.3, C(5)$\underline{H}$), 4.58 (1H, d~q, *J* 9.4, 1.5, C(4)$\underline{H}$), 4.84 (1H, dm, *J* 14.0, C(7)$H_a\underline{H}_b$), 4.91 (1H, d~t, *J* 14.0, 1.5, C(7)$\underline{H}_aH_b$), 5.91 (1H, dq, *J* 15.6, 1.6, C$\underline{H}$=CHCH$_3$), 6.80 (1H, ~q, *J* 1.5, C(3)$\underline{H}$), 7.05 (1H, dq, *J* 15.6, 7.0, CH=C$\underline{H}$CH$_3$), 7.24-7.36 (5H, m, aryl-$\underline{H}$); δ_C (100 MHz; $CDCl_3$) -5.8 (Si($\underline{C}H_3$)), -5.3 (Si($\underline{C}H_3$)), 17.9 (Si$\underline{C}$(CH$_3$)$_3$), 18.0 (CH=CH$\underline{C}$H$_3$), 25.6 (SiC($\underline{C}$H$_3$)$_3$), 42.8 ($\underline{C}$(6)H_2), 50.7

(C(5)H), 60.3 (C(7)H_2), 70.0 (C(4)H), 122.2 (CH=$CHCH_3$), 127.4, 128.1 & 128.5 (aryl-CH), 133.4, 140.4 (aryl-C & C(2)), 145.4 (CH=$CHCH_3$), 150.2 (C(3)H), 165.9 (C=O, ester), 196.8 (C=O, enone).

Partially purified ester **21** (59 mg) was stirred in TFA/H_2O (7:1) (1.6 mL) under an atmosphere of N_2 at 0 °C for 45 min and the solution was then concentrated *in vacuo* to give a brown oil (32 mg). This residue was partially purified by flash silica chromatography (ethyl acetate:40−60 petroleum ether, 1:5) to give a colourless oil (30 mg) which was further purified by preparative HPLC (ethyl acetate:hexane, 2:3) to yield the title compound as a colourless oil (16 mg, 25% from **20**). R_f (ethyl acetate:40-60 petroleum ether, 1:2) 0.24; $[\alpha]_D^{28}$ -71.7 (*c* 0.82 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3445br (O-H), 3060w (C-H), 3029w (C-H), 2956w (C-H), 1718s (C=O, ester), 1676s (C=O, enone); δ_H (400 MHz; $CDCl_3$) 1.91 (3H, dd, *J* 6.9, 1.7, CH=CHCH_3), 2.03 (1H, br s, OH), 2.71-2.80 (2H, m, C(6)H_2), 3.22-3.29 (1H, m, C(5)H), 4.72 (1H, br d, *J* 9.8, C(4)H), 4.86 (1H, d~t, *J* 14.3, 1.7, C(7)H_aH_b), 4.91 (1H, ddd, *J* 14.3, 2.2, 1.7, C(7)H_aH_b), 5.91 (1H, dq, *J* 15.5, 1.7, CH=$CHCH_3$), 6.96 (1H, ~q, *J* 1.7, C(3)H), 7.05 (1H, dq, *J* 15.5, 6.9, CH=CHCH_3), 7.29-7.36 (3H, m, aryl-H), 7.39-7.43 (2H, m, aryl-H); δ_C (100 MHz; $CDCl_3$) 18.1 (CH=CHCH_3), 43.2 (C(6)H_2), 50.6 (C(5)H), 60.2 (C(7)H_2), 71.9 (C(4)H), 122.1 (CH=$CHCH_3$), 127.7, 128.0 & 129.2 (aryl-CH), 134.2, 139.2 (aryl-C & C(2)), 145.7 (CH=$CHCH_3$), 148.1 (C(3)H), 165.9 (C=O, ester), 196.3 (C=O, enone); *m/z* (+ES) 595 ($[2M+Na]^+$, 100%), 309 ($[M+Na]^+$, 40), 287 ($[M+H]^+$, 20); (Found 309.1087, $C_{17}H_{18}NaO_4$ ($[M+Na]^+$) requires 309.1098).

(1*S*,6*R*)-6-hydroxy-4-(hydroxymethyl)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**23b**)

Hydroxymethyl compound **20** (27 mg, 0.081 mmol) was stirred in a mixture of TFA and H_2O (7:1, 0.8 mL) at 0 °C under an atmosphere of N_2. After 5 h the reaction mixture was allowed to warm to room temperature when it was concentrated *in vacuo* to give a brown oil (26 mg). The residue was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 2:1) to yield the title compound as a colourless crystalline solid (7.9 mg, 45%). (Found: C, 71.2; H, 6.5. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%); m.p. 103.1-104.4 °C; R_f (ethyl acetate:40-60 petroleum ether, 2:1) 0.24; $[\alpha]_D^{28}$ -93.6 (*c* 1.2 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3375br (O-H), 2959w (C-H), 2916m (C-H), 2845w (C-H), 1668s (C=O); δ_H (400 MHz; $CDCl_3$) 1.96 (1H, d, *J* 3.9, C(4)OH), 2.35 (1H, ~t, *J* 6.2, CH_2OH), 2.72 (1H, dd, *J* 16.9, 6.6, C(6)H_{eq}), 2.77 (1H, dd, *J* 16.9, 11.5, C(6)H_{ax}), 3.26 (1H, ddd, *J* 11.5, 9.9, 6.6, C(5)H), 4.32 (1H, ddm, *J* 13.7, 6.2, C(7)H_aH_b), 4.39 (1H, ddm, *J* 13.7, 6.2, C(7)H_aH_b), 4.73 (1H, dd~q, *J* 9.9, 3.9, 1.7, C(4)H), 6.96 (1H, d, *J* 1.7, C(3)H), 7.30-7.37 (3H, m, aryl-H), 7.40-7.44 (2H, m, aryl-H); δ_C (100 MHz; $CDCl_3$) 43.3 (C(6)H_2), 50.8 (C(5)H), 61.2 (C(7)H_2), 71.8 (C(4)H), 127.7, 128.0 & 129.2 (aryl-CH), 137.7 & 139.2 (aryl-C & C(2)), 147.7 (C(3)H), 198.5 (C=O); *m/z* (+ES) 241 ($[M+Na]^+$, 100%), 219 ($[M+H]^+$, 55%); (Found 241.0824, $C_{13}H_{14}NaO_3$ ($[M+Na]^+$) requires 241.0836).

Second generation synthesis

Representative procedure for eliminative deprotection using DBU

(4*R*,5*S*)-4-hydroxy-5-(naphthalen-2-yl)cyclohex-2-enone (**11e**)

To a stirred solution of **10e** (70 mg, 0.21 mmol) in dichloromethane (4 mL), under an atmosphere of nitrogen, was added DBU (30 μL, 0.23 mmol). The reaction mixture was stirred at room temperature for 2 h 45 mins when it was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The two layers were separated and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a brown gum. Purification by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:2) gave the title compound as a viscous oil (37 mg, 75%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.04; $[\alpha]_D^{33}$ -88.5 (*c* 0.40 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3393br (O-H), 3051w (C-H), 2962w (C-H), 2931w (C-H), 2901w (C-H), 2874w (C-H), 1667s (C=O); δ_H (400MHz; $CDCl_3$) 1.95 (1H, d, *J* 3.8, O<u>H</u>), 2.77 (1H, ddd, *J* 16.8, 4.8, 1.2, C(6)<u>H</u>$_{eq}$), 2.85 (1H, dd, *J* 16.8, 13.4, C(6)<u>H</u>$_{ax}$), 3.44 (1H, ddd, *J* 13.4, 9.7, 4.8, C(5)<u>H</u>), 4.83 (1H, ddt, *J* 9.7, 3.8, 2.2, C(4)<u>H</u>), 6.12 (1H, ddd, *J* 10.3, 2.2, 1.2, C(2)<u>H</u>), 7.05 (1H, dd, *J* 10.3, 2.2, C(3)<u>H</u>), 7.45 (1H, dd, *J* 8.4, 1.9, C(3´)<u>H</u>), 7.49-7.56 (2H, m, C(6´)<u>H</u> and C(7´)<u>H</u>), 7.77 (1H, s, C(1´)<u>H</u>), 7.84-7.88 (2H, m, C(5´)<u>H</u> and C(8´)<u>H</u>), 7.91 (1H, d, *J* 8.4 C(4´)<u>H</u>); δ_C (100 MHz; $CDCl_3$) 43.1 (<u>C</u>(6)H_2), 50.9 (<u>C</u>(5)H), 71.8 (<u>C</u>(4)H), 125.0, 126.3, 126.7, 127.0 & 127.8 (aryl-<u>C</u>H), 129.1 (<u>C</u>(2)H), 129.2 (aryl-<u>C</u>H), 132.9, 133.5 & 136.7 (aryl-<u>C</u>), 152.0 (<u>C</u>(3)H), 197.8 (<u>C</u>=O); *m/z* (-ES) 237 ([M-H]$^-$, 100%); (Found 237.0916, $C_{16}H_{13}O_2$ ([M-H]$^-$) requires 237.0916).

(1*S*,6*R*)-6-hydroxy-4'-methoxy-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**11c**)

Using a similar method to that described above ketone **10c** (508 mg, 1.61 mmol) was converted to enone **11c** (a white solid, 236 mg, 67%). mp. 119.3-121.7 ºC; R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.03; $[\alpha]_D^{26}$ -134 (*c* 0.9, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3494br (O-H), 2961w (C-H), 2895w (C-H), 1665s (C=O), 1650s (C=C); δ_H (400MHz; $CDCl_3$) 2.62-2.73 (2H, m, C(6)<u>H</u>$_2$), 3.20 (1H, td, *J* 10.0, 7.8, C(5)<u>H</u>), 3.83 (3H, s, OC<u>H</u>$_3$), 4.62 (1H, dt, *J* 10.0, 2.1, C(4)<u>H</u>), 6.06 (1H, dd, *J* 10.3, 2.1, C(2)<u>H</u>), 6.94 (2H, d, *J* 8.6, 2 x aryl-<u>H</u>), 7.01 (1H, dd, *J* 10.3, 2.1, C(3)<u>H</u>), 7.23 (2H, d, *J* 8.6, 2 x aryl-<u>H</u>); δ_C (100MHz; $CDCl_3$) 43.3 (<u>C</u>(6)H_2), 50.0 (<u>C</u>(5)H), 55.4 (O<u>C</u>H_3), 72.1 (<u>C</u>(4)H), 114.6 & 128.7 (aryl-<u>C</u>H), 129.0 (<u>C</u>(2)H), 131.3 (aryl-<u>C</u>), 152.1 (<u>C</u>(3)H), 159.2 (aryl-<u>C</u>), 198.2 (<u>C</u>=O); *m/z* (+ES) 241 ([M+Na]$^+$, 100%); (Found 241.0836, $C_{13}H_{14}O_3Na$ ([M+Na]$^+$) requires 241.0841).

Representative procedure for eliminative deprotection using sodium hydroxide

(1*S*, 6*R*)-6-hydroxy-1,6-dihydro-[1,1':4',1''-terphenyl]-3(2*H*)-one (**11f**)

A stirred solution of ketone **10f** (100 mg, 0.28 mmol) in THF (4 mL) at 0 °C was treated with four aliquots of a 0.5 M aqueous sodium hydroxide solution (30 μL, 0.015 mmol) at equally spaced intervals over a period of 4 h. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product which was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:1) to give the title compound as colourless crystals (58 mg, 79%). m.p. 108.6-109.2 °C; $[\alpha]_D^{24}$ -106.5 (*c* 1.3 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3423br (O-H), 3028m (C-H), 2932s (C-H), 2855s (C-H), 1682s (C=O); δ_H (300 MHz; $CDCl_3$) 2.05 (1H, br s, O<u>H</u>), 2.69-2.81 (2H, m, C(6)<u>H</u>$_2$), 3.31 (1H, td, *J* 10.1, 7.4, C(5)<u>H</u>), 4.72 (1H, dd, *J* 10.1, 2.0, C(4)<u>H</u>), 6.09 (1H, dd, *J* 10.1, 2.0, C(2)<u>H</u>), 7.03 (1H, dd, *J* 10.1, 2.0, C(3)<u>H</u>), 7.35-7.64 (9H, m, 9 x aryl-<u>H</u>); δ_C (75 MHz; $CDCl_3$) 43.0 (<u>C</u>(6)H_2), 50.4 (<u>C</u>(5)H), 71.9 (<u>C</u>(4)H), 127.0, 127.5, 127.9, 128.1, 128.9 & 129.0 (aryl-<u>C</u>H and <u>C</u>(2)H), 138.4, 140.4 & 140.9 (aryl-<u>C</u>), 152.1 (<u>C</u>(3)H), 197.9 (<u>C</u>=O); *m/z* (-ES) 301 ($[M+^{37}Cl]^-$, 7 %), 299 ($[M+^{35}Cl]^-$, 20 %).

(1*S*,6*R*)-4'-bromo-6-hydroxy-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**11d**)

Using a similar method to that described above method ketone **10d** (567 mg, 1.55 mmol) was converted to enone **11d** (a viscous oil, 358 mg, 87%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.04; $[\alpha]_D^{29}$ -105.1 (*c* 0.50 in CH_3OH); ν_{max} (film)/cm^{-1} 3388br (O-H), 2953w (C-H), 2846w (C-H), 1665s (C=O); δ_H (400 MHz; $CDCl_3$) 1.96 (1H, s, O<u>H</u>), 2.67 (2H, d, *J* 9.3, C(6)<u>H</u>$_2$), 3.23 (1H, q, *J* 9.3, C(5)<u>H</u>), 4.65 (1H, dt, *J* 9.3, 2.0, C(4)<u>H</u>), 6.08 (1H, dd, *J* 10.2, 2.0, C(2)<u>H</u>), 6.99 (1H, dd, *J* 10.2, 2.0, C(3)<u>H</u>), 7.20 (2H, d, *J* 8.4, aryl-<u>H</u>), 7.53 (2H, d, *J* 8.4, aryl-<u>H</u>); δ_C (100 MHz; $CDCl_3$) 42.8 (<u>C</u>(6)H_2), 50.1 (<u>C</u>(5)H), 71.7 (<u>C</u>(4)H), 121.8 (aryl-<u>C</u>), 129.1 & 129.4 (aryl-<u>C</u>H), 132.3 (<u>C</u>(2)H), 138.5 (aryl-<u>C</u>), 151.9 (<u>C</u>(3)H), 197.5 (<u>C</u>=O); *m/z* (+ES) 291 ($[M(^{81}Br)+Na]^+$, 100%), 289 ($[M(^{79}Br)+Na]^+$, 100%); (Found 288.9843, $C_{12}H_{11}{}^{79}BrNaO_2$ ($[M+Na]^+$) requires 288.9840).

Representative procedure for preparation of TES-ethers

(4*R*,5*S*)-5-(naphthalen-2-yl)-4-((triethylsilyl)oxy)cyclohex-2-enone (**24e**)

To a solution of 2,6-lutidine (0.24 mL, 2.09 mmol) in dry dichloromethane (5 mL), at -78 °C under an atmosphere of nitrogen, was added TESOTf (0.44 mL, 1.94 mmol) followed, a few minutes later, by dropwise addition of a solution of alcohol **11e** (170 mg, 0.71 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred at -78 °C for 35 min when it was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL) and allowed to warm to room temperature. The two layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:19) to give the title compound as a viscous oil

(224 mg, 89%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.60; $[\alpha]_D^{29}$ -82.4 (*c* 0.50 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2955w (C-H), 2877s (C-H), 1683s (C=O); δ_H (400MHz; $CDCl_3$) 0.16-0.38 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.69 (9H, t, *J* 8.1, $Si(CH_2C\underline{H}_3)_3$), 2.77 (1H, ddd, *J* 16.6, 4.1, 1.2, C(6)$\underline{H}_{eq}$), 2.88 (1H, dd, *J* 16.6, 13.6, C(6)$\underline{H}_{ax}$), 3.45 (1H, ddd, *J* 13.6, 9.3, 4.1, C(5)$\underline{H}$), 4.64 (1H, d~t, *J* 9.3, 2.0, C(4)$\underline{H}$), 6.07 (1H, d~t, *J* 10.3, 2.0, C(2)$\underline{H}$), 6.89 (1H, dd, *J* 10.3, 2.0, C(3)$\underline{H}$), 7.41 (1H, dd, *J* 8.6, 1.8, C(3´)$\underline{H}$), 7.45-7.52 (2H, m, C(6´)$\underline{H}$ and C(7´)$\underline{H}$), 7.70 (1H, s, C(1´)$\underline{H}$), 7.80-7.85 (3H, m, C(4´)$\underline{H}$, C(5´)$\underline{H}$ & C(8´)$\underline{H}$); δ_C (100MHz; $CDCl_3$) 4.4 ($Si(\underline{C}H_2CH_3)_3$), 6.5 ($Si(CH_2\underline{C}H_3)_3$), 42.8 ($\underline{C}(6)H_2$), 50.8 ($\underline{C}(5)H$), 72.6 ($\underline{C}(4)H$), 125.7, 126.2, 127.1, 127.6, 127.7 & 128.2 (aryl-$\underline{C}H$), 128.5 ($\underline{C}(2)H$), 132.7, 133.4 & 138.0 (aryl-$\underline{C}$), 153.8 ($\underline{C}(3)H$), 198.4 ($\underline{C}$=O); *m/z* (+ES) 375 ($[M+Na]^+$, 100%); (Found 353.1947, $C_{22}H_{29}O_2Si$ ($[M+H]^+$) requires 353.1937).

(1*S*,6*R*)-4'-methoxy-6-((triethylsilyl)oxy)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**24c**)

Using a similar method to that described above, alcohol **11c** (80 mg, 0.37 mmol) was converted to TES-ether **24c** (a yellow oil, 105 mg, 86%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.58; $[\alpha]_D^{26}$ -149.6 (*c* 0.50, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2957m (C-H), 2908m (C-H), 2874m (C-H), 1684s (C=O); δ_H (400MHz; $CDCl_3$) 0.25-0.44 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.79 (9H, t, *J* 8.1, $Si(CH_2C\underline{H}_3)_3$), 2.66 (1H, ddd, *J* 16.4, 4.8, 1.0, C(6)$\underline{H}_{eq}$), 2.73 (1H, dd, *J* 16.4, 13.4, C(6)$\underline{H}_{ax}$), 3.21 (1H, ddd, *J* 13.4, 9.7, 4.8, C(5)$\underline{H}$), 3.82 (3H, s, $OC\underline{H}_3$), 4.51 (1H, dt, *J* 9.7, 1.9, C(4)$\underline{H}$), 6.02 (1H, ddd, *J* 10.2, 1.9, 1.0, C(2)$\underline{H}$), 6.84 (1H, dd, *J* 10.2, 1.9, C(3)$\underline{H}$), 6.88 (2H, d, *J* 8.6, 2 x aryl-$\underline{H}$), 7.17 (2H, d, *J* 8.6, 2 x aryl-$\underline{H}$); δ_C (100MHz; $CDCl_3$) 4.4 ($Si(\underline{C}H_2CH_3)_3$), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 43.0 ($\underline{C}(6)H_2$), 49.8 ($\underline{C}(5)H$), 55.4 ($O\underline{C}H_3$), 72.9 ($\underline{C}(4)H$), 113.8 (aryl-$\underline{C}H$), 128.4 ($\underline{C}(2)H$), 128.9 (aryl-$\underline{C}H$), 132.9 (aryl-$\underline{C}$), 153.9 ($\underline{C}(3)H$), 158.8 (aryl-$\underline{C}$), 198.7 ($\underline{C}$=O); *m/z* (+ES) 355 ($[M+Na]^+$, 100%); (Found 355.1692, $C_{19}H_{28}O_3NaSi$ ($[M+Na]^+$) requires 355.1705).

(1*S*,6*R*)-4'-bromo-6-((triethylsilyl)oxy)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**24d**)

Using a similar method to that described above, alcohol **11d** (133 mg, 0.50 mmol) was converted to TES-ether **24d** (a pale yellow oil, 190 mg, 81%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.57; $[\alpha]_D^{29}$ -91.7 (*c* 0.50 in CH_3OH); ν_{max} (film)/cm^{-1} 3040w (ArC-H), 2953m (C-H), 2910w (C-H), 2873m (C-H), 1685s (C=O); δ_H (500 MHz; $CDCl_3$) 0.20-0.36 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.79 (9H, t, *J* 8.0, $Si(CH_2C\underline{H}_3)_3$), 2.63 (1H, ddd, *J* 17.0, 4.6, 1.0, C(6)$\underline{H}_{eq}$), 2.70 (1H, dd, *J* 17.0. 13.1, C(6)$\underline{H}_{aq}$), 3.23 (1H, ddd, *J* 13.1, 9.2, 4.6, C(5)$\underline{H}$), 4.52 (1H, dt, *J* 9.2, 2.0, C(4)$\underline{H}$), 6.04 (1H, ddd, *J* 10.1, 2.0, 1.0, C(2)$\underline{H}$), 6.83 (1H, dd, *J* 10.1, 2.0, C(3)$\underline{H}$), 7.14 (2H, d, *J* 8.3, 2 x aryl-$\underline{H}$), 7.47 (2H, d, *J* 8.3, 2 x aryl-$\underline{H}$); δ_C (100 MHz; $CDCl_3$) 4.5 ($Si(\underline{C}H_2CH_3)_3$), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 42.5 ($\underline{C}(6)H_2$), 50.1 ($\underline{C}(5)H$), 72.6 ($\underline{C}(4)H$), 121.1 (aryl-$\underline{C}$), 128.4 ($\underline{C}(2)H$), 129.7 & 131.5 (aryl-$\underline{C}H$), 139.7 (aryl-$\underline{C}$), 153.6 ($\underline{C}(3)H$), 197.9 ($\underline{C}$=O); *m/z* (+ES) 405 ($[M(^{81}Br)+Na]^+$, 100%), 403 ($[M(^{79}Br)+Na]^+$, 100%); (Found, 403.0706 $C_{18}H_{25}{}^{79}BrNaO_2$ ($[M+Na]^+$) requires 403.0705).

(1*S*,6*R*)-6-((triethylsilyl)oxy)-1,6-dihydro-[1,1':4',1''-terphenyl]-3(2*H*)-one (**24f**)

Using a similar method to that described above, alcohol **11f** (100 mg, 0.39 mmol) was converted to TES-ether **24f** (a yellow oil, 110 mg, 75 %). $[\alpha]_D^{24}$ -109.3 (*c* 0.6 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3028m (C-H), 2954s (C-H), 2874s (C-H), 1691s (C=O); δ_H (300 MHz; $CDCl_3$) 0.24-0.46 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.78 (9H, t, *J* 7.9, $Si(CH_2C\underline{H}_3)_3$), 2.73 (1H, ddd, *J* 16.7, 4.9, 0.8, C(6)$\underline{H}_{eq}$), 2.80 (1H, dd, *J* 16.7, 13.5, C(6)$\underline{H}_{ax}$), 3.32 (1H, ddd, *J* 13.5, 9.4, 4.9, C(5)$\underline{H}$), 4.60 (1H, dt, *J* 9.4, 1.6 C(4)$\underline{H}$), 6.05 (1H, dt, *J* 10.3, 1.6 C(2)$\underline{H}$), 6.87 (1H, dt, *J* 10.3, 1.6 C(3)$\underline{H}$), 7.27-7.61 (9H, m, 9 x aryl-$\underline{H}$). δ_C (75 MHz; $CDCl_3$) 4.5 ($Si(\underline{C}H_2CH_3)_3$), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 42.7 ($\underline{C}(6)H_2$), 50.3 ($\underline{C}(5)H$), 72.8 ($\underline{C}(4)H$), 127.1, 127.2, 127.3, 128.4 & 128.8 (aryl-$\underline{C}H$ & $\underline{C}(2)H$), 139.8, 140.4 & 140.9 (aryl-$\underline{C}$), 153.8 ($\underline{C}(3)H$), 198.4 ($\underline{C}$=O); *m/z* (+ES) 401 ($[M+Na]^+$, 100 %).

Representative procedure for surfactant mediated Morita-Baylis-Hillman reactions

(4*R*,5*S*)-2-(hydroxymethyl)-5-(naphthalen-2-yl)-4-((triethylsilyl)oxy)cyclohex-2-enone (**25e**)

To a suspension of compound **24e** (50 mg, 0.14 mmol) in water (0.4 mL) was added SDS (12 mg, 0.04 mmol) and DMAP (17 mg, 0.14 mmol). The reaction mixture was stirred for 5 min at room temperature and then formaldehyde 37% (0.19 mL, 1.96 mmol) was added. The resulting mixture was stirred at room temperature for 22 h. The reaction was quenched by the addition of brine (2 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a waxy solid which was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:6) to furnish hydroxymethyl compound **25e** as an oil (35 mg, 64 %). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.12; $[\alpha]_D^{29}$ -103.3 (*c* 1.2 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3420br (O-H), 2955s (C-H), 2910s (C-H), 2874s (C-H), 1672s (C=O); δ_H (400MHz; $CDCl_3$) 0.16-0.37 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.69 (9H, t, *J* 7.6, $Si(CH_2C\underline{H}_3)_3$), 2.78 (1H, dd, *J* 16.4, 4.2, C(6)$\underline{H}_{eq}$), 2.91 (1H, dd, *J* 16.4, 13.6, C(6)$\underline{H}_{ax}$), 3.44 (1H, ddd, *J* 13.6, 9.5, 4.2, C(5)$\underline{H}$), 4.30 (1H, d, *J* 13.6, C(7)$\underline{H}_aH_b$), 4.42 (1H, d, *J* 13.6, C(7)$H_a\underline{H}_b$), 4.73 (1H, dd, *J* 9.5, 0.8, C(4)$\underline{H}$), 6.82 (1H, s, C(3)$\underline{H}$), 7.40 (1H, dd, *J* 8.8, 1.5, C(3´)$\underline{H}$), 7.45-7.51 (2H, m, C(6´)$\underline{H}$ & C(7´)$\underline{H}$), 7.70 (1H, s, C(1´)$\underline{H}$), 7.80-7.85 (3H, m, C(4´)$\underline{H}$, C(5´)$\underline{H}$ & C(8´)$\underline{H}$); δ_C (100MHz; $CDCl_3$) 4.4 ($Si(\underline{C}H_2CH_3)_3$), 6.5 ($Si(CH_2\underline{C}H_3)_3$), 43.1 ($\underline{C}(6)H_2$), 50.9 ($\underline{C}(5)H$), 61.3 ($\underline{C}(7)H_2$), 72.6 ($\underline{C}(4)H$), 125.7, 125.8, 126.2, 127.1, 127.6, 127.6 & 128.2 (aryl-$\underline{C}H$), 132.7, 133.3, 136.8 & 137.7 (aryl-$\underline{C}$ & $\underline{C}(2)$), 149.8 ($\underline{C}(3)H$), 199.2 ($\underline{C}$=O); *m/z* (+ES) 383 ($[M+H]^+$, 100%); (Found 383.2048, $C_{23}H_{31}O_3Si$ ($[M+H]^+$) requires 383.2042).

(1*S*,6*R*)-4-(hydroxymethyl)-4'-methoxy-6-((triethylsilyl)oxy)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**25c**)

Using a similar method to that described above, TES-ether **24c** (177 mg, 0.53 mmol) was converted to hydroxymethyl compound **25c** (a colourless oil, 146 mg, 75 %). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.11; $[\alpha]_D^{26}$ -91.2 (*c* 0.50, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3423br (O-H), 2955s (C-H), 2911m (C-H), 2876m (C-H), 1674s (C=O); δ_H (400MHz; $CDCl_3$) 0.25-0.44 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.79 (9H, t, *J* 7.8, $Si(CH_2C\underline{H}_3)_3$), 2.68 (1H, dd, *J* 16.7, 4.8, C(6)$\underline{H}_{eq}$), 2.75 (1H, dd, *J* 16.7, 13.4, C(6)$\underline{H}_{ax}$), 3.20 (1H, ddd, *J* 13.4, 9.3, 4.8, C(5)$\underline{H}$), 3.81 (3H, s, $OC\underline{H}_3$), 4.25 (1H, dt, *J* 13.5, 1.4, C(7)$\underline{H}_aH_b$), 4.38 (1H, dt, *J* 13.5, 1.4, C(7)$H_a\underline{H}_b$), 4.54

(1H, dq, *J* 9.3, 1.4, C(4)H), 6.76 (1H, q, *J* 1.4, C(3)H), 6.88 (2H, d, *J* 8.6, 2 x aryl-H), 7.17 (2H, d, *J* 8.6, 2 x aryl-H); δ_C (100MHz; $CDCl_3$) 6.4 ($Si(\underline{C}H_2CH_3)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 43.5 ($\underline{C}(6)H_2$), 50.0 ($\underline{C}(5)H$), 55.3 ($O\underline{C}H_3$), 61.2 ($\underline{C}(7)H_2$), 72.0 ($\underline{C}(4)H$), 114.5 (aryl-CH), 128.7 (aryl-CH), 131.0 & 137.6 (aryl-C & C(2)), 147.8 ($\underline{C}(3)H$), 159.2 (aryl-C), 198.8 ($\underline{C}$=O); *m/z* (+ES) 385 ($[M+Na]^+$, 100%); (Found 363.1989, $C_{20}H_{31}O_4Si$ ($[M+H]^+$) requires 363.1992).

(1*S*,6*R*)-4'-bromo-4-(hydroxymethyl)-6-((triethylsilyl)oxy)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**25d**)

Using a similar method to that described above, TES-ether **24d** (195 mg, 0.513 mmol) was converted to hydroxymethyl compound **25d** (a colourless oil, 120 mg, 55%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.11; $[\alpha]_D^{30}$ -74.7 (*c* 0.50 in CH_3OH); ν_{max} (film)/cm^{-1} 3341br (O-H), 2959m (C-H), 2907m (C-H), 2871m (C-H), 1675s (C=O); δ_H (400 MHz; $CDCl_3$) 0.25-0.46 (6H, m, $Si(\underline{C}H_2CH_3)_3$), 0.79 (9H, t, *J* 8.0, $Si(CH_2C\underline{H}_3)_3$), 2.32 (1H, t, *J* 6.0, O<u>H</u>), 2.65 (1H, dd, *J* 16.2, 5.1, $C(6)\underline{H}_{eq}$), 2.73 (1H, dd, *J* 16.2, 13.0, $C(6)\underline{H}_{ax}$), 3.22 (1H, ddd, *J* 13.0, 9.5, 5.1, C(5)H), 4.26 (1H, dd, *J* 13.9, 6.0, $C(7)\underline{H}_aH_b$), 4.38 (1H, dd, *J* 13.9, 6.0, $C(7)H_a\underline{H}_b$), 4.55 (1H, dd, *J* 9.5, 1.6, C(4)H), 6.77 (1H, d, *J* 1.6, C(3)H), 7.14 (2H, d, *J* 8.4, 2 × aryl-H), 7.48 (2H, d, *J* 8.4, 2 × aryl-H); δ_C (100 MHz; $CDCl_3$) 4.5 ($Si(\underline{C}H_2CH_3)_3$), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 42.8 ($\underline{C}(6)H_2$), 50.2 ($\underline{C}(5)H$), 61.2 ($\underline{C}(7)H_2$), 72.6 ($\underline{C}(4)H$), 121.2 (aryl-C), 129.7 & 131.6 (aryl-CH), 137.1 & 139.5 (aryl-C & C(2)), 149.2 ($\underline{C}(3)H$), 198.6 ($\underline{C}$=O); *m/z* (+ES) 435 ($[M(^{81}Br)+Na]^+$, 100%), 433 ($[M(^{79}Br)+Na]^+$, 100%); (Found 433.0825, $C_{18}H_{25}{}^{79}BrNaO_2$ ($[M+Na]^+$) requires 433.0811).

(1*S*, 6*R*)-4-(hydroxymethyl)-6-((triethylsilyl)oxy)-1,6-dihydro-[1,1':4',1''-terphenyl]-3(2*H*)-one (**25f**)

Using a similar method to that described above, TES-ether **24f** (100 mg, 0.26 mmol) was converted to hydroxymethyl compound **25f** (a yellow oil, 25 mg, 30 %). ν_{max} (film)/cm^{-1} 3435br (O-H), 2954m (C-H), 2908m (C-H), 2875m (C-H), 1664s (C=O); δ_H (300 MHz; $CDCl_3$) 0.24-0.46 (6H, m, $Si(\underline{C}H_2CH_3)_3$), 0.78 (9H, t, *J* 7.9, $Si(CH_2C\underline{H}_3)_3$), 2.18 (1H, br, $C(7)H_2O\underline{H}$), 2.74 (1H, dd, *J* 16.6, 4.9, C(6)Heq), 2.83 (1H, dd, *J* 16.6, 13.4, $C(6)\underline{H}_{ax}$), 3.30 (1H, ddd, *J* 13.4, 9.4, 4.9, C(5)H), 4.04 (1H, d, *J* 13.3, $C(7)\underline{H}_aH_b$), 4.17 (1H, d, *J* 13.3, $C(7)H_a\underline{H}_b$), 4.63 (1H, dd, *J* 9.4, 1.4, C(4)H), 6.80 (1H, s, C(3)H), 7.27-7.61 (9H, m, aryl-H); δ_C (75 MHz; $CDCl_3$) 4.5 ($Si(\underline{C}H_2CH_3)_3$), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 43.0 ($\underline{C}(6)H_2$), 50.5 ($\underline{C}(5)H$), 61.3 ($\underline{C}(7)H_2$), 72.8 ($\underline{C}(4)H$), 127.1, 127.2, 127.3, 128.5 & 128.8 (aryl-CH), 137.0, 139.5, 140.5 & 140.9 (aryl-C & C(2)), 149.5 ($\underline{C}(3)H$), 199.1 ($\underline{C}$=O); *m/z* (+ES) 839 ($[2M+Na]^+$, 100 %), 431 ($[M+Na]^+$, 12 %); (Found (-ES) 407.2057, $C_{25}H_{31}O_3Si$ ($[M-H]^-$) requires 407.2042).

Representative procedure for TES deprotection of Morita-Baylis-Hillman adducts

(4*R*,5*S*)-4-hydroxy-2-(hydroxymethyl)-5-(naphthalen-2-yl) cyclohex-2-enone (**23e**)

A solution of hydroxymethyl compound **25e** (25 mg, 0.07 mmol) in TFA:H_2O (7:1, 0.56 mL) was stirred at room temperature for 30 min. The solvents were removed *in vacuo* to give a yellow gum which was purified

by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:2) to furnish the diol **23e** as a colourless oil (18 mg, 93 %). R_f (ethyl acetate:40-60 petroleum ether, 1:1) 0.24; $[\alpha]_D^{28}$ -96.4 (*c* 0.50, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3368br (O-H), 3047w (C-H), 3014w (C-H), 2953w (C-H), 2919w (C-H), 2898w (C-H), 2864w (C-H), 1663s (C=O); δ_H (400MHz; $CDCl_3$) 2.78 (1H, dd, *J* 16.7, 4.8, C(6)$\underline{H}_{eq}$), 2.87 (1H, dd, *J* 16.7, 13.2, C(6)$\underline{H}_{ax}$), 3.42 (1H, ddd, *J* 13.2, 9.8, 4.8, C(5)$\underline{H}$), 4.34 (1H, d, *J* 13.6, C(7)$\underline{H}_aH_b$), 4.40 (1H, d, *J* 13.6, C(7)$H_a\underline{H}_b$), 4.83 (1H, dd, *J* 9.8, 0.9, C(4)$\underline{H}$), 6.99 (1H, s, C(3)$\underline{H}$), 7.43 (1H, d, *J* 8.6, C(3´)$\underline{H}$), 7.49-7.56 (2H, m, C(6´)$\underline{H}$ and C(7´)$\underline{H}$), 7.76 (1H, s, C(1´)$\underline{H}$), 7.84-7.88 (2H, m, C(5´)$\underline{H}$ and C(8´)$\underline{H}$), 7.90 (1H, d, *J* 8.6, C(4´)$\underline{H}$); δ_C (100MHz; $CDCl_3$) 43.3 ($\underline{C}(6)H_2$), 50.9 ($\underline{C}(5)H$), 61.1 ($\underline{C}(7)H_2$), 71.7 ($\underline{C}(4)H$), 124.9, 126.3, 126.6, 127.0, 127.7, 127.8 & 129.1 (aryl-$\underline{C}H$), 132.9, 133.4, 136.5 & 137.7 (aryl-$\underline{C}$ & $\underline{C}(2)$), 147.8 ($\underline{C}(3)H$), 198.5 ($\underline{C}$=O); *m/z* (+ES) 291 ($[M+Na]^+$, 100%); (Found 291.0997, $C_{17}H_{16}O_3Na$ ($[M+Na]^+$) requires 291.0997).

(1*S*,6*R*)-6-hydroxy-4-(hydroxymethyl)-4'-methoxy-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (**23c**)

Using a similar procedure to that described above, hydroxymethyl compound **25c** (40 mg, 0.11 mmol) was converted into diol **23c** (a white solid, 18 mg, 66 %). mp. 108.7-110.9 °C; R_f (ethyl acetate:40-60 petroleum ether, 1:1) 0.14; $[\alpha]_D^{28}$ -97.5 (*c* 0.45, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3367br (O-H), 2926w (C-H), 2901w (C-H), 1668s (C=O); δ_H (400 MHz; $CDCl_3$) 1.97 (1H, s, O$\underline{H}$), 2.32 (1H, br s, O$\underline{H}$), 2.71 (2H, ~d, *J* 9.9, C(6)$\underline{H}_2$), 3.21 (1H, q, *J* 9.9, C(5)$\underline{H}$), 3.83 (3H, s, OC$\underline{H}_3$), 4.31 (1H, d, *J* 13.5, C(7)$\underline{H}_aH_b$), 4.39 (1H, d, *J* 13.5, C(7)$H_a\underline{H}_b$), 4.66 (1H, d, *J* 9.9, C(4)$\underline{H}$), 6.93-6.95 (3H, m, C(3)$\underline{H}$ and 2 x aryl-$\underline{H}$), 7.22-7.24 (2H, m, aryl-$\underline{H}$); δ_C (100MHz; $CDCl_3$) 43.5 ($\underline{C}(6)H_2$), 50.0 ($\underline{C}(5)H$), 55.3 (O$\underline{C}H_3$), 61.2 ($\underline{C}(7)H_2$), 72.0 ($\underline{C}(4)H$), 114.6 & 128.7 (aryl-$\underline{C}H$), 131.0 & 137.6 (aryl-$\underline{C}$ and $\underline{C}(2)$), 147.8 ($\underline{C}(3)H$), 192.0 ($\underline{C}$=O); *m/z* (+ES) 287 ($[M+K]^+$, 30%), 271 ($[M+Na]^+$, 60%), 129 (100%); (Found 271.0939, $C_{14}H_{16}O_4Na$ ($[M+Na]^+$), requires 271.0941).

(*4R, 5S*)-4-hydroxy-2-(hydroxymethyl)-5-(4-bromophenyl)-cyclohex-2-enone (**23d**)

Using a similar procedure to that described above, hydroxymethyl compound **25d** (96 mg, 0.23 mmol) was converted into diol **23d** (off-white wax, 39 mg, 56%). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.03; $[\alpha]_D^{28}$ -86.4 (*c* 0.50 in CH_3OH); ν_{max} (film)/cm^{-1} 3368br (O-H), 2953w (C-H), 2923w (C-H), 2901w (C-H), 2865w (C-H), 1664s (C=O); δ_H (400 MHz; $CDCl_3$) 2.59 (2H, d, *J* 9.2, C(6)$\underline{H}_2$), 3.12 (1H, q, *J* 9.2, C(5)$\underline{H}$), 4.18-4.28 (2H, m, C(7)$\underline{H}_2$), 4.56 (1H, d, *J* 9.2, C(4)$\underline{H}$), 6.84br (1H, s, C(3)$\underline{H}$), 7.10 (2H, d, *J* 8.3, aryl-$\underline{H}$), 7.44 (2H, d, *J* 8.3, aryl-$\underline{H}$); δ_C (100 MHz; $CDCl_3$) 43.2 ($\underline{C}(6)H_2$), 50.0 ($\underline{C}(5)H$), 60.5 ($\underline{C}(7)H_2$), 71.6 ($\underline{C}(4)H$), 121.7 (aryl-$\underline{C}$), 129.4 & 132.2 (aryl-$\underline{C}H$), 137.7 & 138.5 (aryl-$\underline{C}$ & $\underline{C}(2)$), 148.0 ($\underline{C}(3)H$), 198.2 ($\underline{C}$=O); *m/z* (+ES) 321 ($[M(^{81}Br)+Na]^+$, 100%), 319 ($[M(^{79}Br)+Na]^+$, 100%); (Found 318.9954, $C_{13}H_{13}{}^{79}BrNaO_3$ ($[M+Na]^+$) requires 318.9946).

(1*S*,6*R*)-6-hydroxy-4-(hydroxymethyl)-1,6-dihydro-[1,1':4',1''-terphenyl]-3(2*H*)-one (**23f**)

Using a similar procedure to that described above, hydroxymethyl compound **25f** (25 mg, 0.09 mmol) was converted into diol **23f** (a white powder, 6 mg, 23 %). ν_{max} (film)/cm^{-1} 3414br (O-H), 2965w (C-H), 2958m (C-H), 2880w (C-H), 1673s (C=O); δ_H (300 MHz; CD_3OD) 2.54 (1H, dd, *J* 16.3, 3.9, C(6)$\underline{H}_{eq}$), 2.83 (1H, dd, *J* 16.3, 13.9, C(6)$\underline{H}_{ax}$), 3.21 (1H, ddd, *J* 13.9, 9.9, 3.9, C(5)$\underline{H}$), 4.22 (2H, t, *J* 1.8 C(7)H_2), 4.71 (1H, dq, *J* 9.9, 1.8 C(4)$\underline{H}$), 6.96 (1H, q, *J* 1.8 C(3)$\underline{H}$), 7.28 (1H, t, *J* 7.5, aryl-$\underline{H}$), 7.36-7.42 (4H, m, aryl-$\underline{H}$,), 7.57 (4H, d, *J* 7.5, aryl-$\underline{H}$); δ_C (75 MHz; CD_3OD) 45.2 ($\underline{C}$(6)H_2), 51.8 ($\underline{C}$(5)H), 59.6 ($\underline{C}$(7)H_2), 72.4 ($\underline{C}$(4)H), 128.0, 128.3, 128.4, 129.6 & 130.0 (aryl-$\underline{C}$H), 139.2, 141.5, 141.7 & 142.3 (aryl-$\underline{C}$ & $\underline{C}$(2)), 150.2 ($\underline{C}$(3)H), 199.9 (C=O); *m/z* (+ES) 317 ([M+Na]$^+$, 100 %); (Found 317.1137, $C_{19}H_{18}O_3Na$ ([M+Na]$^+$) requires 317.1148).

General two-step procedure for the preparation of hybrid analogues

((3*R*, 4*S*)-3-hydroxy-4-(naphthalen-2-yl)-6-oxocyclohex-1-en-1-yl)methyl (*E*)-but-2-enoate (**22e**)

To a solution of alcohol **25e** (88 mg, 0.23 mmol) in dichloromethane (1.8 mL) at room temperature under an atmosphere of nitrogen, was added crotonic anhydride (0.08 mL, 0.51 mmol), followed by DMAP (3 mg, 0.023 mmol) and pyridine (0.16 mL, 2.02 mmol). The reaction mixture was stirred at room temperature for 3 h when it was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2 mL). The mixture was diluted with water (2 mL) and organic material was extracted into dichloromethane (3 x 4 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was partially purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:18) to give a mixture of **26e** and an unknown impurity (60 mg). TFA:H_2O (7:1, 1.20 mL) was added to the mixture at room temperature and the resulting solution was stirred for 1 h when the solvents were removed *in vacuo* to give a brown oil. This material was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 2:7) to give the title compound as a white waxy solid (37 mg, 48% from **25e**). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.09; $[\alpha]_D^{29}$ -57.0 (*c* 0.4 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3426br (O-H), 2962m (C-H), 2915w (C-H), 1722s (C=O, ester), 1682s (C=O, ketone); δ_H (400MHz; $CDCl_3$) 1.92 (3H, dd, *J* 7.0, 1.8, CH=CHC$\underline{H}_3$), 2.81 (1H, dd, *J* 16.6, 5.0, C(6)$\underline{H}_{eq}$), 2.88 (1H, dd, *J* 16.6, 12.9, C(6)$\underline{H}_{ax}$), 3.44 (1H, ddd, *J* 12.9, 9.8, 5.0, C(5)$\underline{H}$), 4.83-4.86 (1H, m, C(4)$\underline{H}$), 4.87 (1H, dt, *J* 14.4, 1.8, C(7)$\underline{H}_a$H$_b$), 4.97 (1H, dt, *J* 14.4, 1.8, C(7)H$_a\underline{H}_b$), 5.92 (1H, dq, *J* 15.5, 1.8, C$\underline{H}$=CHCH$_3$), 7.00 (1H, q, *J* 1.8, C(3)$\underline{H}$), 7.07 (1H, dq, *J* 15.5, 7.0, CH=C$\underline{H}$CH$_3$), 7.43 (1H, dd, *J* 8.4, 2.0, C(3´)$\underline{H}$), 7.50-7.56 (2H, m, C(6´)$\underline{H}$ and C(7´)$\underline{H}$), 7.76 (1H, s, C(1´)$\underline{H}$), 7.84-7.88 (2H, m, C(5´)$\underline{H}$ and C(8´)$\underline{H}$), 7.91 (1H, d, *J* 8.4, C(4´)$\underline{H}$); δ_C (100MHz; $CDCl_3$) 18.1 (CH=CH$\underline{C}$H$_3$), 43.2 ($\underline{C}$(6)H_2), 50.8 ($\underline{C}$(5)H), 60.2 ($\underline{C}$(7)H_2), 71.8 ($\underline{C}$(4)H), 122.2 ($\underline{C}$H=CHCH$_3$), 125.0, 126.3, 126.7, 127.0, 127.7 & 129.2 (aryl-$\underline{C}$H), 133.0, 133.5, 134.3, 136.5 (aryl-$\underline{C}$ & $\underline{C}$(2)), 145.7 (CH=$\underline{C}$HCH$_3$), 148.0 ($\underline{C}$(3)H), 165.9 ($\underline{C}$=O, ester), 196.7 ($\underline{C}$=O, ketone); *m/z* (+ES) 359 ([M+Na]$^+$, 100%); (Found 359.1259, $C_{21}H_{20}NaO_4$ ([M+Na]$^+$) requires 359.1259).

((1*S*,6*R*)-6-hydroxy-4'-methoxy-3-oxo-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)methyl (*E*)-but-2-enoate (**22c**)

Using a similar procedure to that described above, hydroxymethyl compound **25c** (72 mg, 0.198 mmol) was converted to hybrid analogue **22c** (a pale yellow solid, 19 mg, 30 % from **25c**). mp. 99-101 ℃; R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.06; $[\alpha]_D^{27}$ -83.5 (*c* 0.33, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3415br (O-H), 2922w (C-H), 2901w (C-H), 1717s (C=O, ester), 1699s (C=O, ketone); δ_H (400MHz; $CDCl_3$) 1.91 (3H, dd, *J* 6.8, 1.6, CH=CHC$\underline{H}_3$), 2.72 (2H, ~d, *J* 9.3, C(6)$\underline{H}_2$), 3.21 (1H, q, *J* 9.3, C(5)$\underline{H}$), 3.82 (3H, s, OC$\underline{H}_3$) 4.66 (1H, dq, *J* 9.3, 1.8, C(4)$\underline{H}$), 4.87 (1H, dt, *J* 14.4, 1.8, C(7)$\underline{H}_aH_b$), 4.91 (1H, dt, *J* 14.4, 1.8, C(7)$H_a\underline{H}_b$), 5.90 (1H, dq, *J* 15.5, 1.6, C$\underline{H}$=CHCH$_3$), 6.93 (2H, d, *J* 8.5, aryl-$\underline{H}$), 6.96 (1H, q, *J* 1.8, C(3)$\underline{H}$), 7.05 (1H, dq, *J* 15.5, 6.8, CH=C$\underline{H}$CH$_3$), 7.22 (2H, d, *J* 8.5, aryl-$\underline{H}$); δ_C (100MHz; $CDCl_3$) 18.1 (CH=CH$\underline{C}$H$_3$), 43.4 ($\underline{C}$(6)H_2), 49.9 ($\underline{C}$(5)H), 55.3 ($\underline{C}$H$_3$O), 60.2 ($\underline{C}$(7)H_2), 72.1 ($\underline{C}$(4)H), 114.6 (aryl-$\underline{C}$H), 122.1 ($\underline{C}$H=CHCH$_3$), 128.7 (aryl-$\underline{C}$H), 131.0 & 134.2 (aryl-$\underline{C}$ & $\underline{C}$(2)), 145.7 (CH=$\underline{C}$HCH$_3$), 148.1 ($\underline{C}$(3)H), 159.2 (aryl-$\underline{C}$), 165.9 ($\underline{C}$=O, ester), 196.5 ($\underline{C}$=O, ketone); *m/z* (+ES) 339 ($[M+Na]^+$, 100%); (Found 317.1384, $C_{18}H_{21}O_5$ ($[M+H]^+$) requires 317.1389).

((1*S*,6*R*)-4'-bromo-6-hydroxy-3-oxo-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)methyl (*E*)-but-2-enoate (**22d**)

Using a similar procedure to that described above, hydroxymethyl compound **25d** (135 mg, 0.33 mmol) was converted to hybrid analogue **22d** (an off-white oil, 50 mg, 39% from **25d**). R_f (ethyl acetate:40-60 petroleum ether, 1:5) 0.05; $[\alpha]_D^{29}$ -44.0 (*c* 0.53 in CH_3OH); ν_{max} (film)/cm^{-1} 3432br (O-H), 2975w (C-H), 2932w (C-H), 2917w (C-H), 2877w (C-H), 1717s (C=O, ester), 1677s (C=O, ketone); δ_H (400 MHz; $CDCl_3$) 1.91 (3H, dd *J* 7.0, 1.7, CH=CHC$\underline{H}_3$), 2.69-2.73 (2H, m, C(6)$\underline{H}_2$), 3.24 (1H, td, *J* 9.6, 8.1, C(5)$\underline{H}$), 4.68 (1H, dq, *J* 9.6, 1.7, C(4)$\underline{H}$), 4.82 (1H, dt, *J* 14.5, 1.7, C(7)$\underline{H}_aH_b$), 4.91 (1H, dt, *J* 14.5, 1.7, C(7)$H_a\underline{H}_b$), 5.90 (1H, dq, *J* 15.6, 1.7, C$\underline{H}$=CHCH$_3$), 6.93 (1H, d *J* 1.7, C(3)$\underline{H}$), 7.05 (1H, dq, *J* 15.6, 7.0, CH=C$\underline{H}$CH$_3$), 7.19 (2H, d, *J* 8.3, aryl-$\underline{H}$), 7.54 (2H, d, *J* 8.3, aryl-$\underline{H}$); δ_C (100 MHz; $CDCl_3$) 18.1 ($\underline{C}$(11)H_3), 42.9 ($\underline{C}$(6)H_2), 50.0 ($\underline{C}$(5)H), 60.1 ($\underline{C}$(7)H_2), 71.7 ($\underline{C}$(4)H), 121.8 (aryl-$\underline{C}$), 122.0 ($\underline{C}$H=CHCH$_3$), 129.4 & 132.3 (aryl-$\underline{C}$H), 134.3 & 138.2 (aryl-$\underline{C}$ & $\underline{C}$2), 145.9 (CH=$\underline{C}$HCH$_3$), 147.9 ($\underline{C}$(3)H), 165.9 ($\underline{C}$=O, ester), 195.9 ($\underline{C}$=O, ketone); *m/z* (+ES) 389 ($[M(^{81}Br)+Na]^+$, 100%), 387 ($[M(^{79}Br)+Na]^+$, 100%); (Found, 387.0206 $C_{17}H_{17}{}^{79}BrNaO_4$ ($[M+Na]^+$) requires 387.0208).

((1*S*,6*R*)-3-oxo-6-((triethylsilyl)oxy)-1,2,3,6-tetrahydro-[1,1':4',1''-terphenyl]-4-yl)methyl (*E*)-but-2-enoate (**26f**)

To a stirred solution of alcohol **25f** (34 mg, 0.08 mmol) in dichloromethane (0.6 mL) at room temperature under an atmosphere of nitrogen, was added crotonic anhydride (30 μL, 0.18 mmol) followed by DMAP (1 mg, 0.08 mmol) and pyridine (60 μL, 0.73 mmol). The reaction mixture was stirred at room temperature for 2.5 h when it was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was diluted with water (8 mL) and organic material was extracted into dichloromethane (3 x 8 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over magnesium sulphate and concentrated *in vacuo*. The resulting solid was purified by flash silica chromatography (ethyl acetate:40-60

petroleum ether, 1:3) to give crotonate ester **26f** as a sticky white solid (26 mg, 60 %). $[\alpha]_D^{24}$ -47.9 (*c* 1.0 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3029w (C-H), 2953s (C-H), 2909s (C-H), 2875s (C-H), 1723s (C=O, ester), 1680s (C=O, ketone); δ_H (500 MHz; $CDCl_3$) 0.28-0.46 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.78 (9H, t, *J* 8.2 $Si(CH_2C\underline{H}_3)_3$), 1.91 (3H, dd, *J* 6.9, 1.7, $CH=CHC\underline{H}_3$), 2.78 (1H, dd, *J* 16.4, 4.6, $C(6)\underline{H}_{eq}$), 2.79 (1H, dd, *J* 16.4, 13.6, $C(6)\underline{H}_{ax}$), 3.32 (1H, ddd, *J* 13.6, 9.3, 4.6, C(5)H), 4.63 (1H, dd, *J* 9.3, 1.8, C(4)H), 4.84 (1H, dt, *J* 14.2, 1.8, $C(7)\underline{H}_aH_b$), 4.92 (1H, dt, *J* 14.2, 1.8 $C(7)H_a\underline{H}_b$), 5.90 (1H, dq, *J* 15.4, 1.7, $C\underline{H}=CHCH_3$), 6.80 (1H, q, *J* 1.8, C(3)H), 7.05 (1H, dq, *J* 15.4, 6.9, $CH=C\underline{H}CH_3$), 7.32-7.60 (9H, m, aryl-H); δ_C (125 MHz; $CDCl_3$) 4.4 ($Si(\underline{C}H_2CH_3)_3$), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 18.0 ($CH=CH\underline{C}H_3$), 42.8 (C(6)H), 50.3 (C(5)H), 60.3 ($C(7)H_2$), 72.8 (C(4)H), 122.2 ($\underline{C}H=CHCH_3$), 127.1, 127.2, 127.3, 128.4, 128.8 & 133.5 (aryl-CH, aryl-C & C(2) (some signals coincident)), 145.4 ($CH=\underline{C}HCH_3$), 150.0 (C(3)H), 165.9 (C=O, ester), 196.7 (C=O, ketone); *m/z* (+ES) 499 ($[M+Na]^+$, 100%); (Found 499.2283, $C_{29}H_{36}O_4NaSi$ ($[M+Na]^+$) requires 499.2281).

((1*S*,6*R*)-6-hydroxy-3-oxo-1,2,3,6-tetrahydro-[1,1':4',1''-terphenyl]-4-yl)methyl (*E*)-but-2-enoate (**22f**)

A solution of crotonate ester **26f** (26 mg, 0.09 mmol) in TFA:H_2O (7:1, 0.5 mL) was stirred at room temperature for 30 minutes. The solvents were removed *in vacuo* to give a colourless oil which was purified by flash silica chromatography (ethyl acetate:40-60 petroleum ether, 1:3), to furnish hybrid analogue **22f** as a white film (10 mg, 53%). $[\alpha]_D^{24}$ -38.5 (*c* 0.6 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3407 br (O-H), 3020w (C-H), 2958s (C-H), 1720s (C=O, ester), 1685s (C=O, ketone); δ_H (500 MHz; $CDCl_3$) 1.92 (3H, dd, *J* 6.9, 1.8, $CH=CHC\underline{H}_3$), 2.76–2.83 (2H, m, $C(6)\underline{H}_2$), 3.31 (1H, td, *J* 10.1, 7.9, C(5)H), 4.76 (1H, br d, *J* 10.1, C(4)H), 4.88 (1H, dt, *J* 14.4, 1.7, $C(7)\underline{H}_aH_b$), 4.94 (1H, dt, *J* 14.4, 1.7, $CH_a\underline{H}_b$), 5.92 (1H, dq, *J* 15.4, 1.8, $C\underline{H}=CHCH_3$), 6.98 (1H, q, *J* 1.7, C(3)H), 7.06 (1H, dq, *J* 15.4, 6.9, $CH=C\underline{H}CH_3$), 7.27-7.32 (3H, m, aryl-H), 7.38 (2H, t, *J* 7.9, aryl-H), 7.50-7.58 (4H, m, aryl-H); δ_C (125 MHz; $CDCl_3$) 18.1 ($CH=CH\underline{C}H_3$), 43.2 ($\underline{C}(6)H_2$), 50.3 (C(5)H), 60.2 ($\underline{C}(7)H_2$), 71.9 (C(4)H), 122.2 ($\underline{C}H=CHCH_3$), 127.1, 127.5, 127.9, 128.1 & 128.9 (aryl-CH), 134.3, 138.2, 140.4 & 141.0 (aryl-C and C(2)), 145.7 ($CH=\underline{C}HCH_3$), 148.1 (C(3)H), 165.9 (C=O, ester), 196.2 (C=O, ketone); *m/z* (+ES) 385 ($[M+Na]^+$, 100 %).

5. References and Notes

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11) Crystal data for **10f**: $C_{24}H_{26}O_3$, M=362.45, space group P212121, a=5.9418(2), b=8.6600(3), c=36.2709(11) Å, U=1866.36(11) Å3, dcalcd=1.290 Mg/m3. Intensity data were collected using a Bruker X8 Prospector diffractometer; 14846 reflections were collected, of which 2685 were unique including 969 Friedel pairs, Rint= 0.0447. Data processing was carried out using Bruker SAINT and the structure was solved by direct methods using SHELXS97. All non-hydrogen atoms were refined anisotropically, and hydrogens were included in calculated positions, using the riding method. Refinement on F2 was carried out using SHELXL97. Final wR2=0.0913 for all data and R1=0.0417 for data with I>2σ(I). All calculations were carried out using the WinGX package. Crystallographic data (excluding structure factors) have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 950707. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk].

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