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Studies Toward the Synthesis of Natural and Unnatural Dienediynes. Part 2: A Practical Approach to Functionalised Cyclopentenones

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Abstract—The dienediyne natural products contain a functionalised dihydroxylated cyclopentane motif. A critical evaluation of the methods for the preparation and rearrangements of pyranones to give 4,5-dihydroxylated cyclopentenones is presented.

Introduction

The dienediyne chromoprotein antibiotics have been the subject of significant scientific interest.[1] In particular, interest in these molecules arises from their unusual synthetically challenging, molecular structure and their potent biological activity.[2] Members of this class include Neocarzinostatin (NCS), Kedarcidin, C-1027 and Maduropeptin which are all isolated from natural sources, and each comprise a 1:1 complex of an apoprotein and a chromophore.[3] The structures of the chromophores are depicted in Scheme 1. Much effort has been directed toward the chemical synthesis of natural and unnatural dienediyne chromophores and numerous elegant studies have been described including the first completed synthesis of a dienediyne chromoprotein natural product (NCS Chrom).[4]

Our own work in this area has focused on NCS and Kedarcidin, and in particular we have been interested in designing synthetic approaches to compounds which can find common use in total synthesis and provide functionalised analogues.[5] From our perspective, a particularly attractive and compelling synthetic objective was the identification of a suitable cyclopentane building block which could be readily prepared on large scale. This paper describes in full a study we have carried out which has led to the identification of a practical procedure for the preparation of functionalised cyclopentenone derivatives which we have routinely used as starting materials for our work in this area.

Keywords: cyclopentenones; diynes; isomerisation; pyrones; rearrangement.

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Background

Our first synthetic objective became the synthesis of a dihydroxylated cyclopentenone derivative which could be used to prepare both functionalised monocyclic NCS analogues[6] and the natural product chromophores (Scheme 2).

Despite numerous methods available for the synthesis of cyclopentane derivatives we felt that very few offered the simplicity and practicality required for our work. The result of our studies led us to identify and optimise a rearrangement reaction which delivers large quantities of cyclopentenone **1** in good yield.

Results and Discussion

Formation of 6-acetoxy-2,3-dihydro-6H-pyrano-3-one 4

The classical approach for the preparation of 6-acetoxy-2,3-dihydro-6*H*-pyran-3-ones is through the preparation of the α,α'-dimethoxydihydroderivative **2** by treating furfuryl alcohol with an excess of bromine in methanol.[7] This reaction has shown great utility for our work as the furan can be formed in up to 100 g quantities (Scheme 3).

Mild hydrolysis of **2** brings about the cleavage of the acetal bonds, leading to the formation of **3**. This hydroxypyranone derivative exhibits low stability in aqueous solutions at ambient temperatures and undergoes rapid decomposition under basic conditions, but can be stored at reduced temperatures without significant decomposition. The workup procedure for this reaction is laborious and problematic. The reaction conditions require an aqueous

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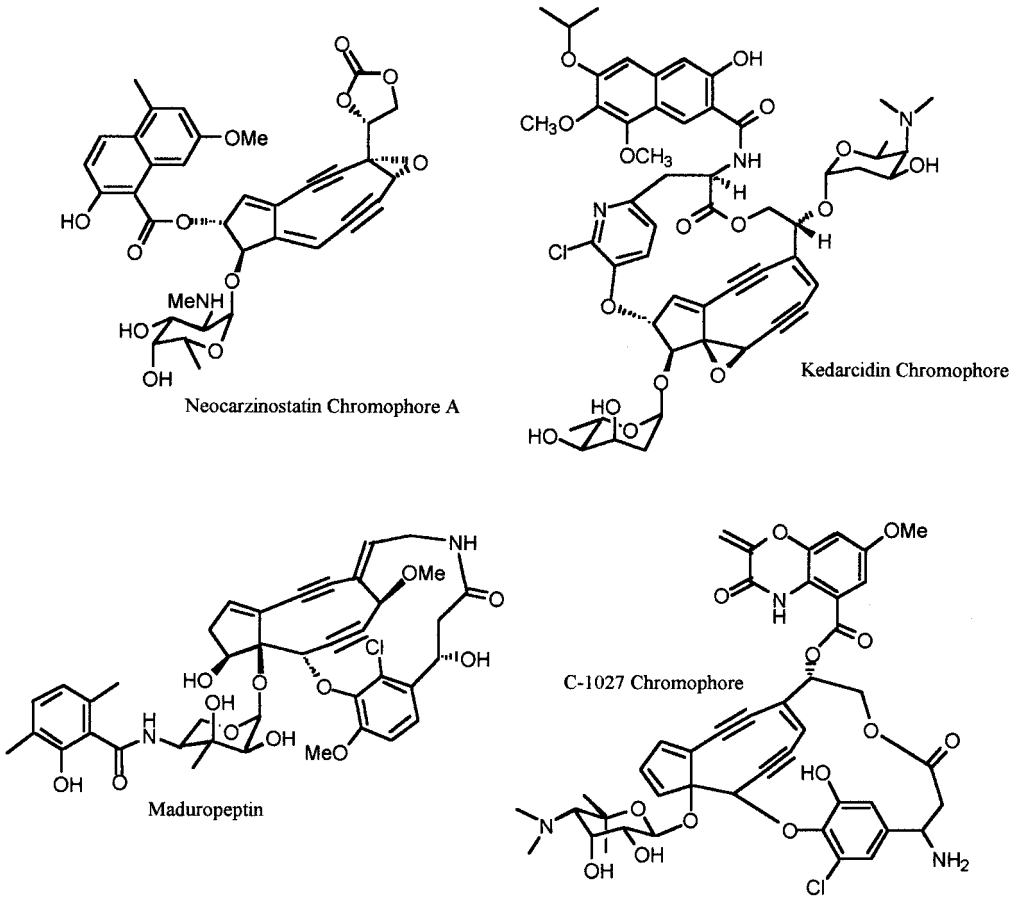
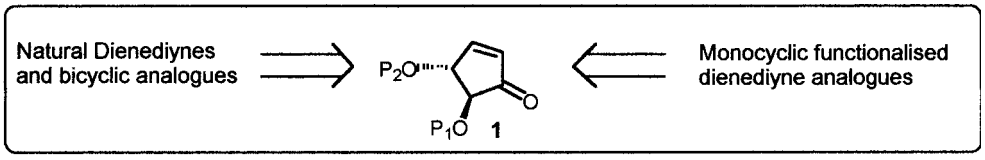


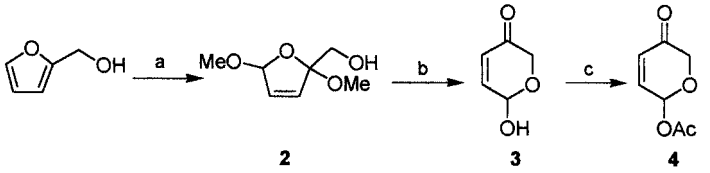
Scheme 1.



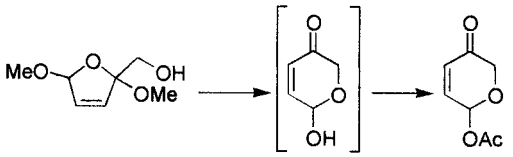
Scheme 2.

solution of sulfuric acid, which must be removed at the end of the reaction in vacuo maintaining a water bath temperature below 30°C. Following the removal of the water a standard aqueous extraction with ethyl acetate may be carried out. Although this route yields the required pyranone in good yield (80% from furfuryl alcohol), this workup procedure, and the instability of the isolated intermediates limits the scale on which the reaction can be carried out. Activation of the hemiacetal hydroxy functionality was achieved through formation of the acetoxypyranone **4** with acetic anhydride and sodium acetate affording the corresponding acetate in 60–70% yield. This activation step was deemed necessary as the corresponding hydroxypyranone **3** is unreactive to ring contraction conditions.

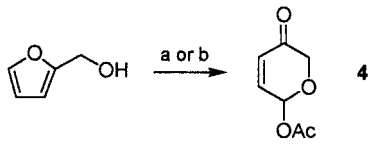
An alteration to the above method involves addition of a catalytic amount of trifluoromethane sulfonic acid to the furan intermediate **2** (Scheme 4).[8] This alteration removes the need for the laborious aqueous extraction as the reaction is carried out in wet THF. A further advantage of this route



Scheme 3. *Reagents and conditions:* (a) Br_2, MeOH:Et_2O, −40°C; NH_3 −40°C—rt; (b) 2% H_2SO_4, $NaHCO_3$, rt, 4 h; (c) Ac_2O, NaOAc, 0°C—rt 18 h.



Scheme 4. *Reagents and conditions:* TfOH (15%), THF:H_2O, Ac_2O, NaOAc.



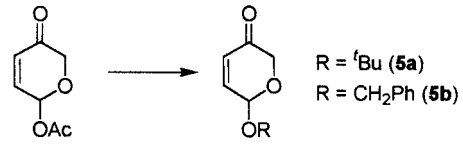
Scheme 5. *Reagents and conditions:* (a) NBS, $NaHCO_3$, THF:H_2O, Ac_2O; (b) *m*CPBA, DCM, 0°C, AcCl, pyridine, 2 h.

is that the highly unstable hydroxypyranone **3** is never isolated as the reaction is carried out in the presence of acetic anhydride and sodium acetate, which yields the required acetoxypyranone **4** in 70% yield from furfuryl alcohol.

The instability of the intermediates in the synthesis of 6-acetoxy-2,3-dihydro-6*H*-pyrano-3-one **4** makes the idea of a one-pot synthesis very appealing (Scheme 5). One such method utilises *N*-bromosuccinimide in the presence of sodium bicarbonate and acetic anhydride to functionalise furfuryl alcohol.[9] Although this self-indicating reaction affords the required acetoxypyranone **4** in moderate yield (57%) from furfuryl alcohol, problems are encountered during scale-up. Whereas the acid hydrolysis reactions can both be carried out using 70 g of furfuryl alcohol, the NBS cannot be effectively carried out above 20 g scale.

Although the yield of the reaction was reduced in comparison to the two acid catalysed reactions, the NBS method is simple and, unlike the acid hydrolysis routes does not involve the bromine addition step which is highly sensitive to temperature. An interesting point to note is that if the reaction is carried out over two steps with isolation of the intermediate hydroxypyranone **3**, the limiting step in this sequence is found to be the acetylation reaction which occurs in 48% yield.

Alternatively, it is possible to form acetoxypyranone **4** via a *m*CPBA mediated ring expansion.[10] Again, this method avoids the temperamental low temperature bromine addition. The *m*-chloroperoxybenzoic acid is added to furfuryl alcohol in portions at reduced temperature yielding hydroxypyranone **3**. A by-product from this reaction is benzoic acid, the removal of which is problematic. Filtration



Scheme 6. *Reagents and conditions:* $SnCl_4$ (5 mol%), $ClCH_2CH_2Cl$, ROH, rt.

can be used to remove some of the benzoic acid, which is only sparingly soluble in dichloromethane. The remaining benzoic acid persists and co-elutes with acetoxypyranone **4** on silica-gel. The incorporation of an aqueous extraction can remove the residual benzoic acid. However, the instability of hydroxypyranone **3** to aqueous and basic conditions precludes the incorporation of such conditions.

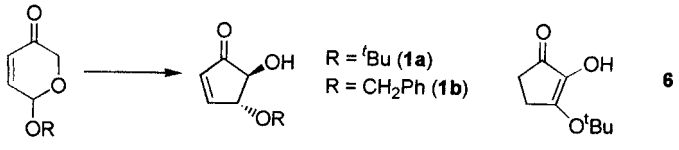
In conclusion, our method of choice for the production of acetoxypyranones is the triflic acid mediated hydrolysis and ring expansion procedure. Although the NBS and *m*CPBA mediated reactions appear to offer simple procedures they produce less of the required acetoxypyranone. Moreover, the Lewis acid mediated reactions are sensitive to impurities which are difficult to remove from the acetoxypyranone **4** derived from these procedures.

Ring contraction to polyfunctionalised cyclopentenones

There are relatively few procedures for the conversion of a hemiacetal hydroxy of **3** into its corresponding glycosidic function, and many methods are unsuitable for our purpose due to scale up problems. One report efficiently demonstrated the conversion via acetate **4** into various ethers using catalytic Lewis acid conditions.[11] Using these conditions we were able to effectively transform acetate **4** into the corresponding *tert*-butyl **5a** and benzyl **5b** derivatives in 89 and 82% yield respectively (Scheme 6).

The isomerisation reaction of pyranones to a give a dihydroxylated cyclopentenone has previously been reported using a palladium catalysed procedure.[12] We were able to devise a modified procedure which could be carried out on preparative scale (ca. 50 g) without the requirement of metal catalysts, instead using an amine base to give cyclopentenones **1a** and **1b**. (Scheme 7).[13]

It can be seen from Table 1 that the isomerisation reaction occurs under a variety of basic conditions. A study on the rearrangement of pyranone **5a** is presented in Table 1. As previously reported by this group, the optimum conditions involve treatment of the pyranone **5a** or **5b** with 5 equiv. of triethylamine in hot DMF over a 24 h period which leads to cyclopentenone **1a** and **1b** in good yield.[14] More importantly, the reaction is stereoselective, forming exclusively the 1,2-*trans* product.



Scheme 7. *Reagents and conditions:* NEt_3, DMF, 80°C, 24 h.

Table 1. Variation of basic conditions in the isomerisation reaction of pyranone **5a**

Entry	Base	Solvent	Temperature °C	Yield %
1	Et_3N[a]	DMF	80	54
2	Et_3N[b]	DMF	80	76
3	$^iPr_2Net$[a]	DMF	80	16
4	$^iPr_2Net$[b]	DMF	80	29
5	Pyridine[a]	DMF	80	11
6	Pyridine[b]	DMF	80	11
7	DBN[a]	CH_2Cl_2	30	11
8	DBN[b]	CH_2Cl_2	30	–
9	DBU[a]	CH_2Cl_2	30	19
10	DBU[b]	CH_2Cl_2	30	10
11	Et_3N[b]	MeOH	70	37 (**6**)

[a] Method a: 1.5 equiv. base.
[a] Method b: 5 equiv. base.

These results are noteworthy because it can be seen that we can deliver good quantities of substituted cyclopentenones under basic conditions (entry 2). The conditions used for this transformation are similar to those used by a number of workers to generate oxidopyrilium species from related acetoxy pyranone derivatives (i.e. **4**).[15] It is clear that the reactivity of a pyranone is sensitive to substrate structure and/or reaction conditions and we found that the nature of the amine base can have a profound and detrimental impact on the reactivity of pyranone **5a** (entry 3 onwards). Solvent can also play a role and in particular we found that when we carried out the reaction in methanol we isolated 3-*t*-butoxy-2-hydroxy-cyclopent-2-enone **6** which we assume is derived from isomerisation of the initially formed cyclopentenone **5a**. In order to further support this assumption we stirred cyclopentenone **5a** with Et_3N and obtained **6** (entry 11).

In conclusion, we have devised a new practical procedure for the preparation of functionalised cyclopentenones. This method relies on a new base mediated isomerisation reaction which proceeds in good yield on large scale. However, this methodology is limited to availability of precursors and after extensive evaluation we have identified what we believe to be the optimum method for the preparation of pyranone precursors in good yield on large scale. We believe that these features make this procedure attractive to synthetic chemists and we have found this methodology ideal for our work in the dienediyne area.

Experimental

General

All glassware was oven or flame dried prior to use. All reagents and solvents were purchased from commercial sources and used as supplied or purified using standard methods. Preparations were performed under an inert atmosphere unless stated otherwise. ^1H NMR spectra were recorded on a Bruker spectrometer at 300 MHz operating at ambient probe temperature. Coupling constants were measured in hertz (Hz). ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ using residual $CHCl_3$ as internal reference. Infra red spectra were recorded on a Perkin–Elmer 1710 FTIR spectrometer as thin films, solutions or KBr discs. Mass spectra were recorded on a Kratos MS25 spectrometer. Analytical thin layer chromatography was carried out using SIL G/UV_{254} plates and visualised using standard procedures. Melting points are uncorrected.

2-Hydroxymethyl-2,5-dimethoxy-3,4-dihydrofuran (2).[7,16] A solution of bromine (136.9 g, 0.86 mol) in methanol (239 mL) was slowly added via addition funnel to a stirred solution of distilled furfuryl alcohol (70.4 g, 0.718 mol) in dry diethyl ether (239 mL) and methanol (239 mL) maintaining an internal temperature between −35 and −45°C. Upon addition completion, stirring was continued for a further 2 h at reduced temperature. The resulting light yellow solution was saturated with gaseous ammonia to pH 8 and allowed to warm to an ambient temperature. The resulting yellow suspension was filtered, removing ammonium bromide and concentrated in vacuo. Further filtration removed the white solid formed upon concentration of the yellow oil. The oil was diluted in benzene (500 mL) and filtered through neutral alumina. Evaporation of the solvent yielded a yellow oil (102.6 g, 90.4%) which was seen to be of sufficient purity for use in further stages. ν_{max} 3473, 2988, 2837, 1632, 1266, 995 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.95 (1H, br s), 3.09 (3H, s), 3.38 (3H, s), 3.52–3.69 (2H, m), 5.48 (1H, d J=0.9 Hz), 5.93 (1H, d J=4.7 Hz), 6.04 (1H, d J=4.7 Hz); δ_C (75 MHz, $CDCl_3$) 50.4, 56.2, 66.6, 107.3, 112.9, 131.3, 132.2; HRMS (EI) $[M-OH]^+$, found 143.0699. $C_7H_{11}O_3$ requires 143.0708.

6-Hydroxy-2,3-dihydro-6*H*-pyrano-3-one (3).[17] To **2** (102.6 g, 0.64 mol) was added a 2% v:v solution of aqueous sulfuric acid (200 mL, 2 mL/g). The reaction was stirred at ambient temperature for 4 h. whereupon solid sodium hydrogen carbonate was added until the solution reached pH 4. The residue was extracted into ethyl acetate (3×750 mL), dried over $MgSO_4$, filtered and concentrated in vacuo maintaining the water bath temperature below 35°C to yield the title compound as a yellow oil (65.3 g, 89.5%). ν_{max} 3417, 3055, 1708, 1630, 1266, 978 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.49 (bs, 1H), 4.14 (1H, d J=17 Hz), 4.58 (1H, d J=17 Hz), 5.64 (1H, dd J=5.4, 3.0 Hz), 6.17 (1H, d J=10.4 Hz), 6.97 (1H, dd J=10.4, 1.5 Hz); δ_C (75 MHz, $CDCl_3$) 66.5, 88.1, 127.7, 146.1, 194.8; HRMS (EI) $[M]^+$, found 114.0306. $C_5H_6O_3$ requires 114.0316.

6-Acetoxy-2,3-dihydro-6*H*-pyrano-3-one 4 from (3).[18] To a cold solution (0°C) of **3** (65.3 g, 0.57 mol) in THF (600 mL) was added acetic anhydride (234 g, 2.29 mol) and sodium acetate (188 g, 2.29 mol). The slurry was stirred for 18 h at ambient temperature, following which, the resulting orange solution was filtered under pressure to remove any residual solid and concentrated in vacuo. The reaction was quenched by addition of saturated sodium bicarbonate solution (1 L) and additional solid sodium hydrogen carbonate until effervescence ceased. The organic portions were extracted into diethyl ether (2×1 L), dried over $MgSO_4$, filtered and concentrated in vacuo (cold bath) to yield an orange oil. Purification of this oil was achieved by column chromatography on silica gel with petrol: diethyl ether (1:4 v:v) as the eluent to give the required product as a yellow oil (59.6 g, 67%); ν_{max} 2979, 1707, 1700, 1630, 1264, 998 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.15 (3H, s), 4.23 (1H, d J=1.7 Hz), 4.51 (1H, d J=17 Hz), 6.18 (1H, d J=11 Hz), 6.47 (1H, d J=3.6 Hz), 6.95 (1H, dd J=11, 3.6 Hz); δ_C

(75 MHz, $CDCl_3$) 21.3, 67.8, 87.0, 129.2, 142.7, 169.9, 193.8; HRMS (EI) $[M]^+$, found 156.0419, $C_7H_8O_4$ requires 156.0422.

6-Acetoxy-2,3-dihydro-6*H*-pyrano-3-one (4) from (2). To **2** (71.4 g, 0.717 mol) in THF (700 mL) and water (25 mL) cooled to 0°C was added triflic acid (16.6 g, 0.107 mol) producing a dark colouration. The reaction mixture was stirred at 0°C for 3 h, after which acetic anhydride (292 g, 2.87 mol) and sodium acetate (235 g, 2.87 mol) were added. The reaction was allowed to warm to room temperature for 18 h, after which the solid was removed via filtration under reduced pressure. The resulting brown liquid was washed with saturated sodium bicarbonate solution (500 mL) and the organic layer was extracted into ethyl acetate (3×400 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting brown liquid was passed through a short plug of silica with petrol:ethyl acetate (5:1 v:v) as the eluent to yield the title compound as a yellow low melting point solid (77.4 g, 69%).

6-Acetoxy-2,3-dihydro-6*H*-pyrano-3-one (4) from furfuryl alcohol using *m*-CPBA

To a cooled solution of furfuryl alcohol (20 g, 0.21 mol) in dichloromethane (800 mL) was added 3-chloroperoxybenzoic acid† (53 g, 0.31 mol) in 5 g portions. The reaction mixture was allowed to stir at 0°C for 6 h, during which a white solid was generated. The white solid was removed by filtration leaving a yellow liquid, which upon concentration yielded more of the white solid. The residual oil was diluted with dichloromethane (300 mL) and cooled to 0°C, whereupon pyridine (28 mL, 0.35 mol) and acetyl chloride (25 mL, 0.35 mol) were added and stirring continued for 2 h. The resulting brown liquid was poured into saturated sodium bicarbonate solution (150 mL) and the organics were extracted into dichloromethane (2×100 mL). The organics were washed with saturated copper sulfate solution (2×50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to yield a brown oil. Purification of this oil was attempted using chromatography on silica gel with diethyl ether:petrol (4:1 v:v) as the eluent to yield the title compound as a yellow solid contaminated with residual benzoic acid (24.27 g, 74%)

6-Acetoxy-2,3-dihydro-6*H*-pyran-3-one (4) from furfuryl alcohol using NBS

To a stirring solution of furfuryl alcohol (26 g, 0.27 mmol) in THF:water (104 mL:26 mL) cooled to 0°C, was added portion wise a finely ground mixture of NBS (52 g, 0.29 mol) and sodium bicarbonate (44 g, 0.53 mol). To the resulting solution was added acetic anhydride (54 g, 0.53 mol) and stirring was continued at ambient temperature for 18 h. To the resulting orange solution was added enough solid sodium bicarbonate and saturated sodium bicarbonate solution to neutralise the solution. The organics were extracted from ethyl acetate (5×100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to yield the title compound as an orange oil. Yield (24.25 g, 57%).

† 57–85% in water.

6-*t*-Butoxy-2,3-dihydro-6*H*-pyrano-3-one (5a).[19] A solution of tin (IV) chloride (6 mL of a 1 M in dichloromethane, 5.6 mmol) was slowly added to a stirred solution of **4** (17.6 g, 0.113 mol) in dichloroethane (10 mL) and *tert*-butanol (53 mL, 0.55 mol). Stirring was continued at ambient temperature for 5 h, after which, the reaction was quenched with saturated sodium bicarbonate solution (150 mL) and the resulting oil was extracted into ethyl acetate (500 mL). The organics were washed with saturated sodium bicarbonate solution (50 mL) and water (40 mL), dried ($MgSO_4$), filtered under reduced pressure and concentrated in vacuo to yield an orange oil which, was purified by chromatography on silica with petrol:ethyl acetate (7:1 v:v) as the eluent to yield the title compound as a colourless liquid (17.1 g, 89%). ν_{max} 3056, 2979, 1707, 1630, 1392, 1266, 998 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.17 (9H, s), 3.91 (1H, d J=16.9 Hz), 4.39 (1H, d J=16.9 Hz), 5.33 (1H, d J=3.4 Hz), 5.95 (1H, d J=10.2 Hz), 6.64 (1H, dd J=10.2, 3.4 Hz); δ_C (75 MHz, $CDCl_3$) 28.9, 66.5, 88.3, 127.6, 146.6, 195.9; HRMS (EI) $[M-CH_3]^+$ found 155.0703. $C_8H_{11}O_3$ requires 155.0708.

6-Benzyloxy-2,3-dihydro-6*H*-pyrano-3-one (5b).[17–19] A solution of tin (IV) chloride (3.46 mL of a 1 M in dichloromethane, 5.6 mmol) was slowly added to a stirred solution of **4** (10.8 g, 69.2 mmol) in 1,2-dichloroethane (180 mL) and benzyl alcohol (8.59 mL, 83 mmol). Stirring was continued at ambient temperature for 5 h, after which, the reaction was quenched with saturated sodium bicarbonate solution (150 mL) and the resulting oil was extracted into ethyl acetate (500 mL). The organics were washed with saturated sodium bicarbonate solution (50 mL) and water (40 mL), dried ($MgSO_4$), filtered under reduced pressure and concentrated in vacuo to yield an orange oil which, was purified by chromatography on silica with petrol: ethyl acetate (7:1 v:v) as the eluent to yield the title compound as a colourless liquid (11.65 g, 82%). ν_{max} 3064, 2881, 1707, 1630, 1265, 854 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.13 (1H, d, J=16.8 Hz), 4.50 (1H, d, J=16.8 Hz), 4.68 (1H, d, J=11.7 Hz), 4.87 (1H, d, J=11.7 Hz), 5.30 (1H, d, J=3.6 Hz), 6.16 (1H, d, J=10.3 Hz), 6.91 (1H, dd, J=10.3, 3.4 Hz), 7.30–7.39 (5H, m); δ_{CH} (75 MHz, $CDCl_3$) 66.3, 70.7, 92.1, 127.9, 128.1, 128.4, 128.5, 136.8, 144.3, 194.7; HRMS (EI) $[M]^+$, found 204.0795. $C_{12}H_{12}O_3$ requires 204.0786.

General method for the ring contraction reaction

Triethylamine (5 equiv.) was added to a stirred solution of the alkoxypyranone (1 equiv.) in DMF (2.5 mL/mmol). The reaction mixture was allowed to stir at 80°C for 24 h, after which, the DMF was removed under reduced pressure to yield a brown oil. This oil was purified by chromatography on silica with petrol:ethyl acetate (2:1 v:v) as the eluent to yield a yellow oil which crystallised on standing to yield the corresponding cyclopentenone as a white solid.

***trans*-4-*t*-Butoxy-5-hydroxy-2-cyclopenten-1-one (1a).**[12,20] The general method was employed for the preparation of **1a**. The quantities of reagents used were as follows: triethylamine (146.1 g, 1.45 mol), **5a** (49.4 g, 0.29 mol), DMF (750 mL). (38.4 g, 78%) mp 61–63°C. ν_{max} 3430, 2979, 1719, 1615, 1393, 1266, 922 cm^{-1}; δ_H (300 MHz,

$CDCl_3$) 1.25 (9H, s), 2.81 (1H, br s), 4.01 (1H, d J=2.3 Hz), 4.53–4.56 (1H, m), 6.17 (1H, d J=6.1 Hz), 7.29 (1H, dd J=6.1, 1.8 Hz); δ_C (75 Hz, $CDCl_3$) 28.2, 75.1, 76.4, 80.7, 131.3, 161.5, 205.0; HRMS (EI) $[M-CH_3]^+$ found 155.0703. $C_8H_{11}O_3$ requires 155.0708.

***trans*-4-Benzyloxy-5-hydroxy-2-cyclopenten-1-one (1b).**[12] The general method was employed for the preparation of **1b**. The quantities of reagents used were as follows: triethylamine (14.4 g, 142 mmol), **5b** (5.8 g, 28.4 mmol), DMF (70 mL). (4.55 g, 78%), mp 55–56°C. ν_{max} 3424, 3056; 2871, 1724, 1627, 896 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.85 (1H, br s), 4.28 (1H, d, J=2.2 Hz), 4.55 (1H, s), 4.74 (1H, d, J=11.7 Hz), 4.88 (1H, d, J=11.7 Hz), 6.30 (1H, d, J=6.1 Hz), 7.32–7.42 (5H, m), 7.48 (1H, d, J=6.1 Hz); δ_C (75 MHz, $CDCl_3$) 72.4, 80.4, 82.5, 128.0, 128.1, 128.5, 132.1, 137.2, 159.0, 204.2; HRMS (EI) $[M]^+$ found 204.0790. $C_{12}H_{12}O_3$ requires 204.0786.

3-*t*-Butoxy-2-hydroxy-cyclopent-2-enone (6). To a stirred solution of *trans*-4-*t*-butoxy-5-hydroxy-2-cyclopenten-1-one (0.3071 g, 1.81 mmol, 1 equiv.) in anhydrous methanol (5 mL), was added NEt_3 (1.26 mL, 9.03 mmol, 5.0 equiv.) via syringe and heated at 60°C for 23 h. The reaction was concentrated in vacuo to give a brown oil. Purification of this oil was achieved by flash chromatography on silica gel eluting with petrol:ethyl acetate (3:1 v:v) as the eluent yielding the title compound as a pale yellow oil (113 mg, 37%). ν_{max} 3306, 2978, 1728, 1615 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.47 (9H, s), 2.31–2.34 (2H, m), 2.38–2.41 (2H, m), 6.38 (1H, br s); δ_C (75 MHz, $CDCl_3$) 25.1, 28.1, 28.7, 81.2, 129.9, 160.0, 200.2; HRMS (EI) $[M]^+$ found 170.0959, $C_9H_{14}O_3$ requires 170.0943.

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