

Synthesis of the Germination Stimulant 3-Methyl-2*H*-furo[2,3-*c*]pyran-2-one and Analogous Compounds from Carbohydrates

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An efficacious synthetic route to the recently identified, potent germination stimulant 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one and analogous compounds, using carbohydrate substrates, is described. D-Xylose and D-glucuronic acid γ -lactone were used in the preparation of the parent heterocycle and its 5-methoxycarbonyl analogue, respectively. These compounds were elaborated using various methods to furnish the natural product and a suite of its analogues. The

germination stimulant was thus prepared on a multi-gram scale in nine steps from inexpensive, commercially available 1,2-*O*-isopropylidene-D-xylofuranose in an overall yield of 30 %, vastly improving upon the only method published to date.

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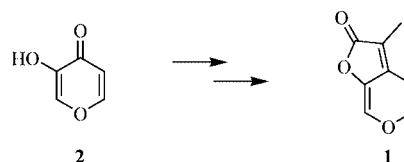
Introduction

Many plant species native to areas frequented by wild-fire have evolved traits allowing them to synchronise many key biological events, such as regrowth, reproduction and germination, with an incidence of fire.^[1] Such adaptations allow these species to capitalise upon the opportunities offered by their post-fire environment. Perhaps the most remarkable of these adaptations is the tendency of some species to germinate readily only after an outbreak of fire.^[2,3] The cue for this post-fire emergence was found to be smoke derived from plant material, the stimulation chemical in origin.^[4,5]

Over the years many attempts at elucidating the nature of the compound(s) in smoke responsible for promoting germination proved to be fruitless, in no small part due to the complexity of the mixture of chemicals that is smoke.^[6] Recently, Flematti et al. isolated and characterised 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one (**1**) from “cellulose-derived” smoke and demonstrated its ability to promote the germination of both “smoke responsive” and “non-smoke responsive” plant species from Africa, Australia and North America.^[7] This remarkable germination stimulant exhibited incredible potency, with effective germination promotion observed at concentrations of less than one part-per-billion. The authors went on to postulate upon the possible benefits **1** could offer the agricultural, horticultural and even mining (environmental rehabilitation) industries.^[7]

Despite these predictions of industrial application, only one synthesis of **1** has been published to date.^[8] This syn-

thesis converts a rather expensive substrate, pyromeconic acid (**2**), into the stimulant **1** in three steps but in a poor overall yield of around 10% (Scheme 1). Further, this method returns still lower yields on larger scales with the isolation of **1** from the complex reaction mixture proving to be laborious, impractical and inefficient.

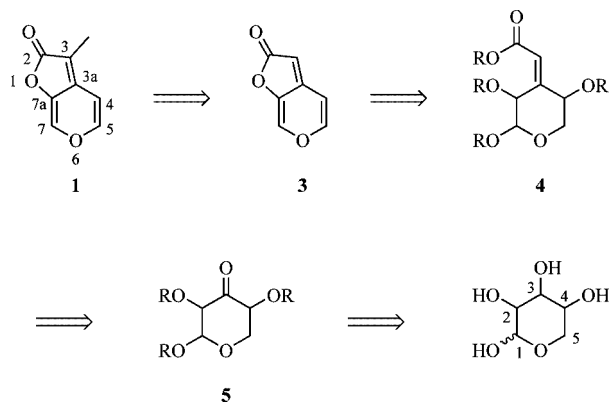


Scheme 1.

Given the intriguing nature of the novel ring system of compound **1**, its potent biological activity and potential industrial applications, we embarked upon developing an improved synthesis of **1** with the added intention of concurrently preparing a number of analogues. With this in mind, our retrosynthetic analysis focussed on the formation of the 2*H*-furo[2,3-*c*]pyran-2-one ring system **3**, with the later functionalisation of this molecule offering a convergent synthesis of **1** (Scheme 2) and analogues. Presumably, **3** could be prepared from a molecule of general structure **4** by way of lactonisation and eliminations across both C4–C5 and C7–C7a. A molecule of structure **4** could, in turn, be obtained through the olefination of a ketone resembling generic compound **5**. Such a ketone is quite clearly the product of a carbohydrate, more specifically a pentose. Further thought reveals that the utilisation of a hexose in such a synthesis would extend the carbon skeleton of **3** at C5, thus providing further scope for synthetic exploration. Given that the germination stimulant's origin within Nature appears to lie in carbohydrates (cellulose)^[7] and in keeping

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with mankind's inclination to mimic Nature, it seemed fitting that our retrosynthetic analysis of **1** had ultimately led us to a carbohydrate starting material (albeit one unrelated to cellulose). Herein, we report the outcomes of our investigations into the use of carbohydrates in the preparation of the potent germination stimulant **1** and analogous compounds.



Scheme 2. Retrosynthetic analysis of **1**.

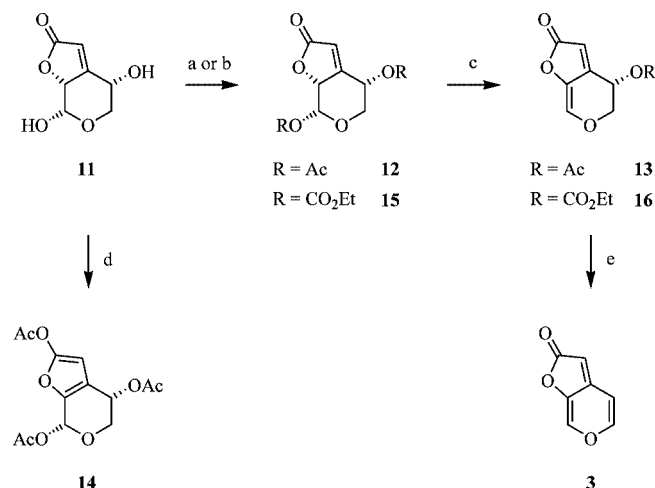
Results and Discussion

Utilisation of a Pentose in the Preparation of **3**

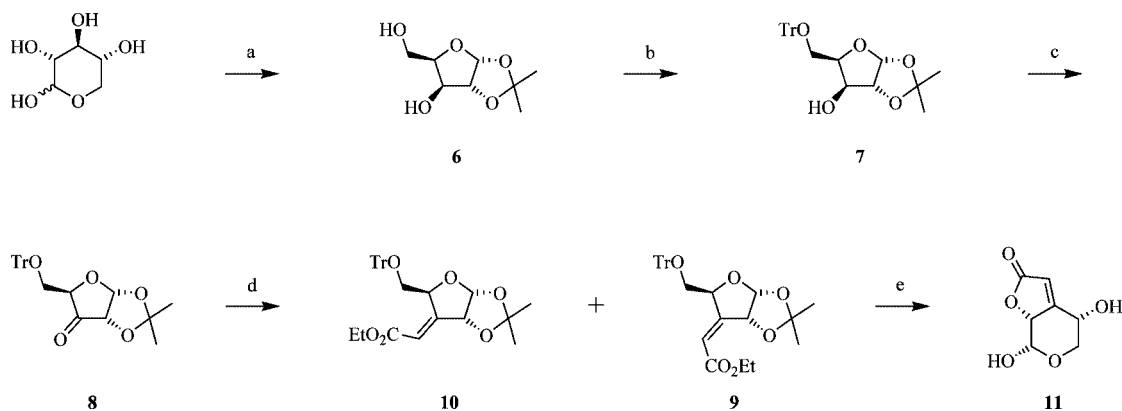
The aforementioned retrosynthetic analysis revealed that a pentose was required for the proposed synthesis, with the obvious choice being abundant and inexpensive D-xylose. Protection of D-xylose was required to enable oxidation and subsequent olefination of C3 (Scheme 2). This requirement was satisfied in an efficacious manner by the regioselective tritylation of 1,2-*O*-isopropylidene-D-xylofuranose (**6**) (an inexpensive, commercially available substrate easily obtained from D-xylose), which gave the alcohol **7** (Scheme 3).^[9] Oxidation of **7**, according to a literature procedure, returned the ketone **8**.^[9] Several attempts at Wittig olefination of **8** went unrewarded; however, adoption of the Horner–Wadsworth–Emmons methodology returned the desired (*Z*)-olefin **9** in high yield and in 19-fold excess of

the undesired (*E*) isomer **10**. Treatment of **9** with aqueous trifluoroacetic acid, in a rapid reaction, resulted in hydrolysis of the trityl ether and acetonide, lactonisation and rearrangement of the resulting hemiacetal (though not necessarily in that order) to give the butenolide **11** in excellent yield.

Hypothetically, compound **3** could be obtained from **11** by way of two eliminations, formally dehydrations, one across C4–C5 and the other across C7–C7a (formerly C1–C2 of D-xylose). Many attempts at the dehydration of **11** directly to **3** were unsuccessful, typically resulting in dark intractable mixtures of products. Treatment of **11** with acetic anhydride in pyridine gave exclusively the α -diacetate **12**, which when treated with triethylamine underwent elimination across C7–C7a to give **13** (Scheme 4). It occurred to us that perhaps **13** could be obtained directly from **11** by performing an acetylation in the presence of a base stronger than pyridine. Curiously, the use of triethylamine in such an acetylation resulted in the exclusive formation of the furan **14**. If nothing else, this result suggested that perhaps the elimination across C7–C7a occurs by way of a stabilised furan oxide intermediate.



Scheme 4. (a) Ac_2O , $\text{C}_5\text{H}_5\text{N}$, 95%; (b) $\text{EtOCOC}_2\text{H}_5$, $\text{C}_5\text{H}_5\text{N}$, 93%; (c) Et_3N , CH_2Cl_2 , 94% or 95%; (d) Ac_2O , Et_3N , $\text{C}_5\text{H}_5\text{N}$, 91%; (e) $(\text{Ph}_3\text{P})_4\text{Pd}$, THF, 84%.



Scheme 3. (a) (i) Me_2CO , H_2SO_4 , (ii) AcOH , H_2O ; (b) TrCl , Et_3N , CH_2Cl_2 ; (c) Ac_2O , Me_2SO ; (d) NaH , $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$, THF (**10**/**9**, 1:19), 5% and 74% from **7**, respectively; (e) $\text{CF}_3\text{CO}_2\text{H}$, H_2O , 83%.

Efforts at conducting the remaining elimination across C4–C5 of **13**, through the use of various bases and acids, went unrewarded. In contrast to the previous case, electronic and stereochemical factors disfavour this elimination. With both product and substrate possessing acid-sensitive (enol-ether) and base-sensitive (lactone) moieties an alternative approach to this elimination was required. Our solution was drawn from the work of Tsuji and Trost,^[10,11] who independently demonstrated that the treatment of allylic acetates, carbonates or halides with palladium(0) catalysts, in the absence of suitable nucleophiles and where possible, resulted in the formation of 1,3-dienes. The mechanism of this reaction has been investigated.^[12] This mild method of elimination appeared ideal as it may be conducted under neutral conditions and the substrate **13**, fortuitously, happened to be an allylic acetate. Indeed, treatment of **13** with tetrakis(triphenylphosphane)palladium(0) in refluxing tetrahydrofuran (THF) returned the desired compound **3**. Our elation was somewhat tempered by the reaction's necessarily high catalyst loading (20 mol-%), long reaction time (2 d) and moderate yield (61%). In general, allylic carbonates have proven to be better substrates than allylic acetates in these Tsuji–Trost eliminations.^[13] With this in mind, we prepared the dicarbonate **15**, which underwent elimination to give **16** in a fashion analogous to the conversion of **12** into **13**. This effort was greatly rewarded when the carbonate **16** was treated with the same palladium(0) catalyst as before in refluxing THF; smooth conversion into **3** was observed in high yield (84%), reasonable time (8 h) and with standard catalyst loadings (4 mol-%). This method has been employed in the preparation of **3** on a multigram scale without incident.

The Utilisation of a Hexose in the Synthetic Strategy

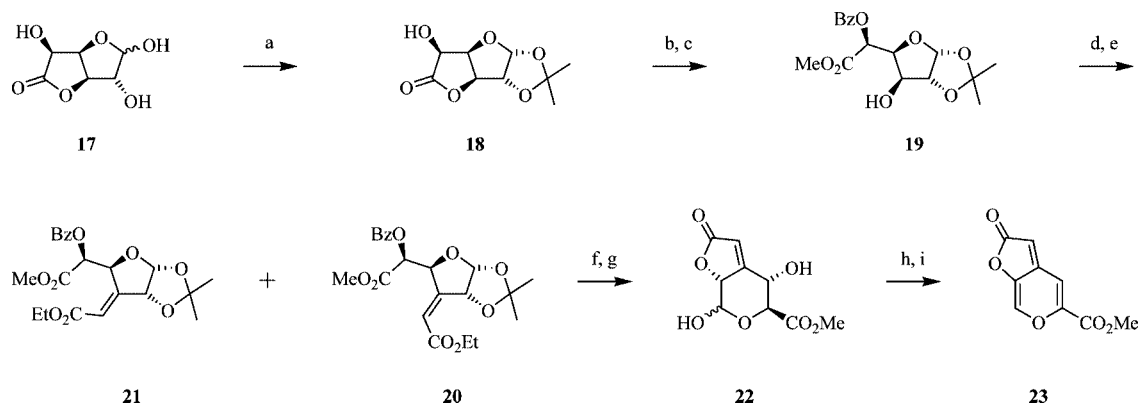
With a good synthetic route to **3** from a pentose established, we elected to extend this strategy further and investigate the utilisation of a hexose in the synthesis of an analogue substituted at C5. With the elimination across C4–C5 proving the more challenging step in the aforementioned

synthesis, we decided to use a hexuronic acid ester substrate, enhancing the acidity of H5 and possibly allowing for the elimination to be performed without the assistance of a palladium(0) catalyst. A convenient substrate for this purpose was inexpensive and commercially available D-glucuronic acid γ -lactone (**17**), as both the acid moiety and O3 are already masked as the lactone (Scheme 5). The acetoneide **18** was prepared from **17** in accordance with the procedure of Fleet and co-workers.^[14] A modified procedure for the benzylation and methanolysis of the lactone **18** gave the alcohol **19**.^[15] Oxidation of **19** with pyridinium dichromate (PDC) presumably gave the ketone, which underwent Wittig olefination to give the desired (*Z*) isomer **20** almost exclusively. Deprotection of the benzoate **20** by the action of alkali resulted in a complex mixture of products. A catalytic, nucleophilic transesterification using sodium cyanide in methanol proved to be more successful in unmasking O5;^[16] however, a mixture of two products was obtained owing to the slow concomitant transesterification of the ethyl ester. This mixture was treated with aqueous trifluoroacetic acid, incurring a transformation analogous to that observed before, to return the butenolides **22** in good yield.

Acetylation of **22** under the usual conditions gave a mixture of three compounds that, by NMR spectroscopy, appeared to be the α - and β -anomers of the diacetate in addition to the product of C7–C7a elimination. This mixture of compounds was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to furnish the furopyranone **23** in excellent yield over the two steps. Several attempts at the direct conversion of **22** into **23** by performing the acetylation in the presence of strong base were unsuccessful, most likely owing to the formation of acyloxyfurans as was observed in the previous synthesis (Scheme 4).

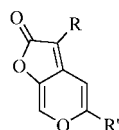
Electrophilic Substitution of **3** and **23** (at C3)

With the construction of the parent heterocycle **3** and a C5 analogue **23** accomplished, elaboration at C3 was now required to prepare the natural product **1** and a suite of its

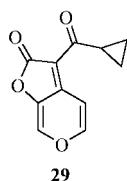


Scheme 5. (a) Me₂CO, H₂SO₄; (b) BzCl, C₅H₅N; (c) Et₃N, MeOH, 79% from **18**; (d) PDC, Ac₂O, CH₂Cl₂; (e) Ph₃PCHCO₂Et, CH₂Cl₂ (**21/20**, 1:99), 0.8% and 88% from **19**, respectively; (f) NaCN, MeOH; (g) CF₃CO₂H, H₂O, 81% from **20**; (h) Ac₂O, C₅H₅N; (i) DBU, CH₂Cl₂, 68% from **22**.

analogues. It was suspected that H3 of the 2*H*-furo[2,3-*c*]pyran-2-one ring system may be susceptible to electrophilic substitution. Formylation at C3 was investigated first as the main target **1** requires the extension of compound **3** by a single carbon atom at this position. Treatment of **3** with the Vilsmeier reagent, followed by base hydrolysis, gave the aldehyde **24** exclusively and in excellent yield (Scheme 6, Table 1). A similar treatment of **23** was equally rewarding, furnishing the aldehyde **25**, though, in contrast to the previous formylation, this reaction required more time at a higher temperature to reach completion. This is most probably a result of the diminished nucleophilicity of C3 given the conjugation of the relevant double bond (C3–C3a) with the electron-withdrawing methyl ester.



- 24:** R = CHO R' = H
25: R = CHO R' = CO₂CH₃
26: R = H R' = CON(CH₃)₂
27: R = COCH₃ R' = H
28: R = COCH₂CH₃ R' = H
30: R = NO₂ R' = H



Scheme 6.

Table 1. Electrophilic substitution of compounds **3** and **23** at C3.

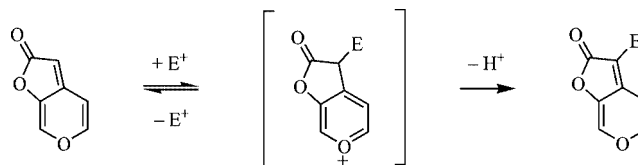
Substrate	Product	Conditions ^[a]	Yield %
3	24	1	92
23	25	1	90
3	27	2	91
3	28	2	89
3	29	2	85
3	30	3	48

[a] (1) (i) POCl₃, DMF, (ii) satd. aq. NaHCO₃; (2) AlCl₃, CH₂Cl₂, RCOCI; (3) NaNO₃, CF₃CO₂H.

Attempts at performing a Vilsmeier acetylation (phosphoryl chloride, dimethylacetamide) were unsuccessful, with **3** offering no reaction and **23** presumably reacting with liberated dimethylamine to give the amide **26**. Friedel–Crafts acylation proved to be more fruitful; the action of a number of acyl chlorides and aluminium(III) chloride on **3** produced the ketones **27–29**, all in excellent yield. These acylations also proved to be regioselective (for C3).

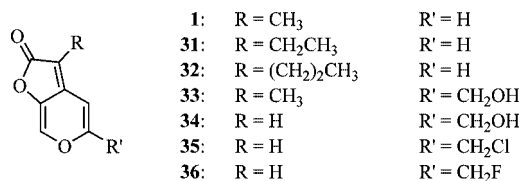
Whilst several nitration protocols were employed on the substrate **3**, only the combination of sodium nitrate and trifluoroacetic acid returned isolable quantities of the nitro compound **30**, albeit in modest yield.^[17] Once again, the substitution occurred exclusively at C3.

The regioselectivity of these substitutions can be rationalised by complementary kinetic and thermodynamic arguments. By inspection, C3 appears to be the more electron-rich and therefore the most nucleophilic carbon atom in compounds **3** and **23**. One would anticipate this to result in favourable kinetics for the formation of the C3-electrophile adduct. Additionally, attack of an electrophile at C3 gives a stable (aromatic) pyrylium ion intermediate, making substitution at this position energetically favoured (Scheme 7).

Scheme 7. Rationalisation for the regioselective electrophilic substitution of **3** (at C3).

Reductions in the Preparation of **1** and Analogues Thereof

To complete the synthesis of **1** we sought a sufficiently mild method for the reductive deoxygenation of the aldehyde **24**. Investigations of numerous methods showed that the *tert*-butylamine–borane/aluminium(III) chloride reagent system of Lau and co-workers was the superior option in this instance;^[18] compound **1** was obtained in high yield from **24** (Scheme 8, Table 2). This completed our synthesis of the natural product **1**, obtained from D-xylose in ten steps and an overall yield of 19%, or 30% in nine steps from 1,2-*O*-isopropylidene-D-xylofuranose (**6**).



Scheme 8.

Table 2. Reductions utilising *t*BuNH₂·BH₃ and AlCl₃.^[a]

Substrate	Product	Yield %
24	1	83
27	31	79
28	32	77
25	33	42
23	34	74
23	35 ^[b]	46

[a] *t*BuNH₂·BH₃ (6 mol-equiv.), AlCl₃ (3 mol-equiv.), CH₂Cl₂ (reflux, 30 min). [b] Extended reaction time of 48 h.

The same borane reagent system was used in the preparation of further analogues; it proved effective in the reduction of the ketones **27** and **28** to **31** and **32**, respectively. An analogous reduction of the aldehyde **25** gave **33**, albeit in modest yield, where the formyl group had been completely reduced but reduction of the ester moiety ceased at the primary alcohol. Given the previous outcome, identical

reaction conditions were employed to produce the alcohol **34** from the ester **23**; prolonged reaction times produced the chloride **35**. The alcohol **34** was also converted into the fluoride **36** by treatment with diethylaminosulfur trifluoride (DAST).

The Versatility of Aldehyde **24** in Preparing Differently Substituted Analogues at C3

Further analogues of **1** were obtained by capitalising on the versatility of the formyl moiety in organic synthesis (Scheme 9). Reductive amination of **24** with dimethylammonium chloride and sodium cyanoborohydride returned the amine **37**. Prolonged treatment of **24** with DAST produced the difluoromethyl analogue **38**. Olefination of the aldehyde **24** yielded the dibromo olefin **39**; all attempts at converting this olefin into an alkyne through treatment with strong lithium bases went unrewarded.^[19] Treatment of aldehyde **24** with *tert*-butylamine–borane returned the alcohol **40**. This alcohol was elaborated further, using methyl iodide in the presence of silver(I) oxide, to give the

methyl ether **41**. Condensation of **24** with hydroxylamine gave but one oxime **42** of (*E*) configuration.^[20] Thionyl chloride was utilised in the dehydration of **42** to the nitrile **43**.

Conclusions

We have established an efficacious route to the novel heterocycles **3** and **23** from a pentose (D-xylose) and hexose (D-glucuronic acid γ -lactone), respectively. In our work compound **3** has served as an intermediate in the preparation of the potent germination stimulant **1**, which has been prepared on a multi-gram scale in nine steps with an overall yield of 30% from 1,2-*O*-isopropylidene-D-xylofuranose **6**; this is a vast improvement on the only method published to date.^[8] Additionally, compounds **3** and **23** have allowed for the preparation of a further 22 analogues of **1** with differing substitutions at both C3 and C5. Several of these analogues have structural features that make them suitable as “mode-of-action” probes in future work.

Experimental Section

General: General experimental procedures have been given previously.^[21]

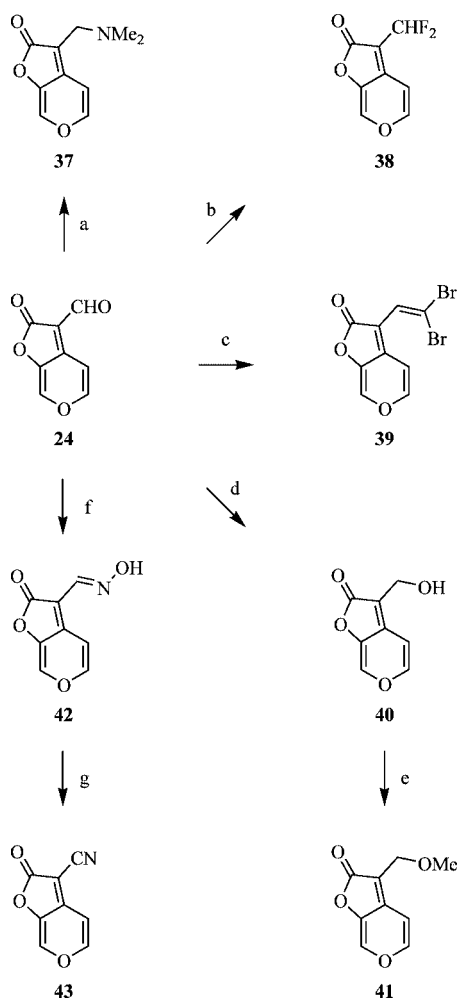
Other General Procedures

Procedure A. Formylation: Phosphoryl chloride (0.70 mL, 7.5 mmol) was added dropwise to the substrate (0.50 mmol) in DMF (3 mL) and the solution stirred at the given temperature for the given period of time. The cooled solution was diluted with CH₂Cl₂ (5 mL), poured into saturated aqueous NaHCO₃ (30 mL) and the mixture stirred (15 min). The mixture was extracted with CH₂Cl₂ (3 $\times$ 10 mL), the combined organic layers were dried (MgSO₄), filtered and concentrated. Flash chromatography gave the aldehyde.

Procedure B. Acylation: Aluminium(III) chloride (0.67 g, 5.0 mmol) was added to the acid chloride (2.5 mmol) and the substrate (0.50 mmol) in CH₂Cl₂ (4 mL) and the mixture stirred at room temperature for the given period of time. The mixture was cooled to 0 °C, and hydrochloric acid (10 mL, 1 M) was added dropwise with stirring. The mixture was extracted with CH₂Cl₂ (3 $\times$ 10 mL), the combined organic layers were dried (MgSO₄), filtered and concentrated. Flash chromatography gave the ketone.

Procedure C. Reduction: Aluminium(III) chloride (0.12 g, 0.90 mmol) was added to *t*BuNH₂·BH₃ (0.16 g, 1.8 mmol) and the substrate (0.30 mmol) in CH₂Cl₂ (6 mL) and the mixture refluxed (20 min). Additional AlCl₃ (40 mg, 0.30 mmol) was added periodically (every 10 min) until the reaction was complete (TLC). The mixture was cooled to 0 °C, and hydrochloric acid (10 mL, 1 M) was added dropwise with stirring. The mixture was extracted with CH₂Cl₂ (3 $\times$ 10 mL), the combined organic layers were dried (MgSO₄), filtered and concentrated. Flash chromatography gave the product.

(*E*)- and (*Z*)-3-Deoxy-3-*C*-[(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-5-*O*-triphenylmethyl- α -D-erythro-pentose (**10** and **9**): Triethyl phosphonoacetate (4.0 mL, 20 mmol) was added dropwise to NaH (0.80 g, 20 mmol, 60% dispersion in mineral oil) in THF (20 mL) at –10 °C, and the mixture stirred (15 min). The crude



Scheme 9. (a) Me₂NH·HCl, NaBH₃CN, MeOH, 62%; (b) DAST, CH₂Cl₂, 79%; (c) CBr₄, Ph₃P, Zn, CH₂Cl₂, 42%; (d) *t*BuNH₂·BH₃, CH₂Cl₂, 86%; (e) MeI, Ag₂O, CH₂Cl₂, 87%; (f) HONH₂·HCl, MeOH, 80%; (g) SOCl₂, Et₃N, CH₂Cl₂, 82%.

ketone **8** [obtained from the alcohol **7**^[9] (4.3 g, 10 mmol)] in THF (20 mL) was added dropwise and the red solution stirred (15 min). Concentration of the mixture and a standard workup (EtOAc) was followed by flash chromatography (EtOAc/petrol, 1:19). The (*E*) isomer **10** was first to elute as a colourless oil (0.25 g, 5%). [α]_D = +186 (CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 1.22 (t, ³J_{H,H} = 7.1 Hz, 3 H, CH₂CH₃), 1.44, 1.50 [2 s, 6 H, C(CH₃)₂], 3.43 [dd, ³J_{H,H} = 2.0, ²J_{H,H} = 9.9 Hz, 1 H, H5], 3.53 [dd, ³J_{H,H} = 2.4, ²J_{H,H} = 9.9 Hz, 1 H, H5], 4.00–4.09 (m, 2 H, CH₂CH₃), 5.31 (ddd, ⁴J_{H,H} = 1.9, 1.9, ³J_{H,H} = 4.6 Hz, 1 H, H2), 5.61 (dddd, ⁴J_{H,H} = 1.9, 1.9, ³J_{H,H} = 2.0, 2.4 Hz, 1 H, H4), 6.09 (dd, ⁴J_{H,H} = 1.9, 1.9 Hz, 1 H, =CH), 6.26 (d, ³J_{H,H} = 4.6 Hz, 1 H, H1), 7.22–7.39 (m, 15 H, Ph) ppm. ¹³C NMR (125.8 MHz, CDCl₃): δ = 14.2 (CH₂CH₃), 27.9, 28.0 [C(CH₃)₂], 60.5 (CH₂CH₃), 66.0 (C5), 81.2, 82.6 (C2,4), 87.3 (CPh₃), 104.7 (C1), 113.5 [C(CH₃)₂], 116.8 (=CH), 127.2–143.8 (Ph), 160.1 (C3), 165.2 (C=O) ppm. HRMS (FAB): *m/z* = 500.2196; [M]⁺ requires 500.2199. Next to elute was the (*Z*) isomer **9** as a colourless oil (3.7 g, 74%). [α]_D = +96.3 (CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 1.32 (t, ³J_{H,H} = 7.1 Hz, 3 H, CH₂CH₃), 1.48, 1.54 [2 s, 6 H, C(CH₃)₂], 3.27 (dd, ³J_{H,H} = 4.0, ²J_{H,H} = 10.0 Hz, 1 H, H5), 3.42 (dd, ³J_{H,H} = 4.1, ²J_{H,H} = 10.0 Hz, 1 H, H5), 4.25 (q, ³J_{H,H} = 7.1 Hz, 2 H, CH₂CH₃), 4.98 (dddd, ³J_{H,H} = 4.0, 4.1, ⁴J_{H,H} = 1.7, 1.7 Hz, 1 H, H4), 5.75–5.78 (m, 2 H, H2, =CH), 6.08 (d, ³J_{H,H} = 4.0 Hz, 1 H, H1), 7.24–7.48 (m, 15 H, Ph) ppm. ¹³C NMR (125.8 MHz, CDCl₃): δ = 14.2 (CH₂CH₃), 27.3, 27.6 [C(CH₃)₂], 60.7 (CH₂CH₃), 65.6 (C5), 78.8, 79.8 (C2,4), 87.1 (CPh₃), 105.5 (C1), 113.0 [C(CH₃)₂], 116.7 (=CH), 127.2–143.6 (Ph), 156.4 (C3), 165.0 (C=O) ppm. HRMS (FAB): *m/z* = 500.2178.

(4S,7S,7aR)-4,7-Dihydroxy-4,5,7,7a-tetrahydro-2H-furo[2,3-c]pyran-2-one (11): Trifluoroacetic acid/H₂O (5 mL, 4:1) was added to the alkene **9** (0.50 g, 1.0 mmol) in CH₂Cl₂ (3 mL) and the yellow solution kept at room temperature (5 min). The solvent was removed, H₂O added and the aqueous solution washed with EtOAc. Concentration of the aqueous layer and recrystallisation of the residue gave the butenolide **11** as colourless needles (0.14 g, 83%); m.p. 184–185.5 °C (MeOH). [α]_D = +168 (H₂O). ¹H NMR [500 MHz, (CD₃)₂SO]: δ = 3.42 (dd, ³J_{H,H} = 10.1, ²J_{H,H} = 10.1 Hz, 1 H, H5), 3.75 (dd, ³J_{H,H} = 7.5, ²J_{H,H} = 10.1 Hz, 1 H, H5), 4.50 (dddd, ⁴J_{H,H} = 1.4, ³J_{H,H} = 5.9, 7.5, 10.1 Hz, 1 H, H4), 4.94 (ddd, ⁴J_{H,H} = 0.8, 1.4, ³J_{H,H} = 4.6 Hz, 1 H, H7a), 5.43 (dd, ³J_{H,H} = 4.6, 4.8 Hz, 1 H, H7), 5.87 (dd, ⁴J_{H,H} = 1.4, 1.4 Hz, 1 H, H3), 5.89 (d, ³J_{H,H} = 5.9 Hz, 1 H, 4-OH), 6.97 (dd, ⁴J_{H,H} = 0.8, ³J_{H,H} = 4.8 Hz, 1 H, 7-OH) ppm. ¹³C NMR [125.8 MHz, (CD₃)₂SO]: δ = 62.6 (C5), 65.5, 78.4 (C4,7a), 90.3 (C7), 111.1 (C3), 170.3 (C3a), 172.8 (C2) ppm. HRMS (FAB): *m/z* = 173.0449; [M + H]⁺ requires 173.0450.

(4S,7S,7aR)-4,7-Diacetoxy-4,5,7,7a-tetrahydro-2H-furo[2,3-c]pyran-2-one (12): Acetic anhydride (0.76 mL, 8.0 mmol) was added to the butenolide **11** (0.34 g, 2.0 mmol) in C₅H₅N (8 mL) and the mixture stirred (2 h). Methanol (1 mL) was added and the solution allowed to stand (10 min). The solvent was removed and a standard workup (EtOAc) followed by flash chromatography (EtOAc/petrol, 1:3) gave the diacetate **12** as a colourless oil (0.49 g, 95%). [α]_D = +188 (CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 2.06, 2.18 (2 s, 6 H, OCOCH₃), 3.54 (dd, ³J_{H,H} = 10.1, ²J_{H,H} = 10.4 Hz, 1 H, H5), 4.16 (dd, ³J_{H,H} = 7.2, ²J_{H,H} = 10.4 Hz, 1 H, H5), 5.02 (dd, ⁴J_{H,H} = 1.4, ³J_{H,H} = 4.6 Hz, 1 H, H7a), 5.69 (ddd, ⁴J_{H,H} = 1.4, ³J_{H,H} = 7.2, 10.1 Hz, 1 H, H4), 6.01 (dd, ⁴J_{H,H} = 1.4, 1.4 Hz, 1 H, H3), 6.52 (d, ³J_{H,H} = 4.6 Hz, 1 H, H7) ppm. ¹³C NMR (125.8 MHz, CDCl₃): δ = 20.6, 20.7 (2 C, OCOCH₃), 62.6 (C5), 66.2, 76.5 (C7a, C4), 88.8 (C7), 114.0 (C3), 161.5 (C3a), 168.5, 169.3, 171.2 (3 C, C2, C=O) ppm. HRMS (FAB): *m/z* = 257.0664; [M + H]⁺ requires 257.0661.

(4S)-4-Acetoxy-4,5-dihydro-2H-furo[2,3-c]pyran-2-one (13): Triethylamine (1 mL) was added to the diacetate **12** (0.26 mg, 1.0 mmol) in CH₂Cl₂ (5 mL) and the solution kept at room temperature (5 min). Concentration of the mixture and flash chromatography (EtOAc/petrol, 1:3) gave the butenolide **13** as a pale yellow oil (0.18 g, 94%). [α]_D = +84.7 (CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 2.13 (s, 3 H, OCOCH₃), 4.19 (dd, ³J_{H,H} = 3.5, ²J_{H,H} = 12.6 Hz, 1 H, H5), 4.33 (dd, ³J_{H,H} = 4.1, ²J_{H,H} = 12.6 Hz, 1 H, H5), 5.84 (ddd, ⁴J_{H,H} = 0.7, ³J_{H,H} = 3.5, 4.1 Hz, 1 H, H4), 5.92 (dd, ⁴J_{H,H} = 0.7, ⁵J_{H,H} = 1.8 Hz, 1 H, H3), 7.07 (d, ⁵J_{H,H} = 1.8 Hz, 1 H, H7) ppm. ¹³C NMR (125.8 MHz, CDCl₃): δ = 20.7 (OCOCH₃), 62.7 (C4), 69.3 (C5), 109.5 (C7), 133.1 (C3), 138.3 (C7a), 145.5 (C3a), 168.8, 169.8 (C2, C=O) ppm. HRMS (FAB): *m/z* = 197.0448; [M + H]⁺ requires 197.0450.

(4S,7R)-2,4,7-Triacetoxy-4,7-dihydro-5H-furo[2,3-c]pyran (14): Triethylamine (0.5 mL) was added to the butenolide **11** (86 mg, 0.50 mmol) and Ac₂O (0.22 mL, 2.0 mmol) in CH₂Cl₂ (2 mL) and the mixture stirred (30 min). Concentration of the mixture and flash chromatography (EtOAc/petrol, 1:3) gave the furan **14** as a pale yellow oil (0.14 g, 91%). [α]_D = +2.7 (CHCl₃). ¹H NMR (600 MHz, CDCl₃): δ = 2.05, 2.13, 2.27 (3 s, 9 H, OCOCH₃), 4.18 (dd, ³J_{H,H} = 6.4, ²J_{H,H} = 12.0 Hz, 1 H, H5), 4.41 (dd, ³J_{H,H} = 3.9, ²J_{H,H} = 12.0 Hz, 1 H, H5), 5.92 (ddd, ⁴J_{H,H} = 1.1, ³J_{H,H} = 3.9, 6.4 Hz, 1 H, H4), 6.14 (dd, ⁴J_{H,H} = 0.6, 1.1 Hz, 1 H, H3), 7.52 (d, ⁴J_{H,H} = 0.6 Hz, 1 H, H7) ppm. ¹³C NMR (150.9 MHz, CDCl₃): δ = 20.5, 20.6, 20.8 (3 C, OCOCH₃), 64.5 (C5), 66.3 (C4), 116.4 (C3), 120.2 (C7), 136.2 (C7a), 153.6 (C2), 166.4, 169.4, 170.5 (3 C, C=O), 166.7 (C3a) ppm. HRMS (FAB): *m/z* = 299.0762; [M + H]⁺ requires 299.0767.

(4S,7R,7aR)-4,7-Bis(ethoxycarbonyloxy)-4,5,7,7a-tetrahydro-2H-furo[2,3-c]pyran-2-one (15): Ethyl chloroformate (3.82 mL, 40.0 mmol) was added dropwise to the butenolide **11** (1.72 g, 10.0 mmol) in C₅H₅N (20 mL) at 0 °C and the mixture stirred (room temp., 1 h). Concentration of the mixture and a standard workup (EtOAc) followed by flash chromatography (EtOAc/petrol, 1:3) gave the carbonate **15** as colourless needles (2.94 g, 93%); m.p. 121–124 °C (EtOAc/petrol). [α]_D = +120 (CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.24–1.35 (m, 6 H, CH₂CH₃), 3.66 (dd, ³J_{H,H} = 10.1, ²J_{H,H} = 10.6 Hz, 1 H, H5), 4.15–4.28 (m, 5 H, CH₂CH₃, H5), 5.01 (ddd, ⁴J_{H,H} = 0.8, 0.8, ³J_{H,H} = 4.6 Hz, 1 H, H7a), 5.56 (dddd, ⁴J_{H,H} = 0.8, 1.9, ³J_{H,H} = 7.1, 10.1 Hz, 1 H, H4), 6.01 (dd, ⁴J_{H,H} = 0.8, 1.9 Hz, 1 H, H3), 6.37 (d, ³J_{H,H} = 4.6 Hz, 1 H, H7) ppm. ¹³C NMR (75.5 MHz, CDCl₃): δ = 14.1, 14.2 (2 C, CH₂CH₃), 62.4 (C5), 65.2, 65.4 (2 C, CH₂CH₃), 69.0, 76.3 (C4,7a), 92.0 (C7), 114.5 (C3), 152.9, 153.7 (2 C, OCO₂), 160.3 (C3a), 171.0 (C2) ppm. HRMS (FAB): *m/z* = 317.0870; [M + H]⁺ requires 317.0873.

(4S)-4,5-Dihydro-4-ethoxycarbonyloxy-2H-furo[2,3-c]pyran-2-one (16): Triethylamine (5 mL) was added to the dicarbonate **15** (2.85 g, 9.00 mmol) in CH₂Cl₂ (30 mL) and the solution kept at room temperature (5 min). Concentration of the mixture and flash chromatography (EtOAc/petrol, 1:3) gave the butenolide **16** as a pale yellow oil (1.93 g, 95%). [α]_D = +84.7 (CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 1.31 (t, ³J_{H,H} = 7.1 Hz, 3 H, CH₂CH₃), 4.20 (dd, ³J_{H,H} = 3.4, ²J_{H,H} = 12.7 Hz, 1 H, H5), 4.24 (q, ³J_{H,H} = 7.1 Hz, 2 H, CH₂CH₃), 4.40 (dd, ³J_{H,H} = 4.0, ²J_{H,H} = 12.7 Hz, 1 H, H5), 5.70 (ddd, ⁴J_{H,H} = 0.8, ³J_{H,H} = 3.4, 4.0 Hz, 1 H, H4), 5.98 (dd, ⁴J_{H,H} = 0.8, ⁵J_{H,H} = 1.8 Hz, 1 H, H3), 7.07 (d, ⁵J_{H,H} = 1.8 Hz, 1 H, H7) ppm. ¹³C NMR (125.8 MHz, CDCl₃): δ = 14.2 (CH₂CH₃), 65.3 (CH₂CH₃), 65.9 (C4), 69.2 (C5), 109.9 (C3), 133.3 (C7), 138.2 (C7a), 144.8 (C3a), 154.1 (OCO₂), 168.9 (C2) ppm. HRMS (FAB): *m/z* = 227.0551; [M + H]⁺ requires 227.0556.

2H-Furo[2,3-*c*]pyran-2-one (3): (a) Tetrakis(triphenylphosphane)-palladium(0) (0.12 g, 0.1 mmol) was added to the acetate **13** (98 mg, 0.50 mmol) in THF (4 mL) and the solution refluxed (48 h). Concentration of the mixture and flash chromatography (EtOAc/petrol, 1:3) gave the butenolide **3** as tan needles (42 mg, 61%); m.p. 109–110 °C (*i*Pr₂O). ¹H NMR [600 MHz, (CD₃)₂CO]: δ = 5.40 (dd, ⁴*J*_{H,H} = 0.5, ⁵*J*_{H,H} = 1.5 Hz, 1 H, H3), 6.91 (dd, ⁴*J*_{H,H} = 0.5, ³*J*_{H,H} = 5.5 Hz, 1 H, H4), 7.72 (d, ³*J*_{H,H} = 5.5 Hz, 1 H, H5), 7.93 (d, ⁵*J*_{H,H} = 1.5 Hz, 1 H, H7) ppm. ¹³C NMR [150.9 MHz, (CD₃)₂CO]: δ = 90.8 (C3), 105.6 (C4), 129.5 (C7), 144.2 (C7a), 146.3 (C3a), 151.2 (C5), 170.6 (C2) ppm. HRMS (EI): *m/z* = 136.0161; [M]⁺ requires 136.0160. (b) Tetrakis(triphenylphosphane)palladium(0) (370 mg, 0.320 mmol) was added to the carbonate **16** (1.81 g, 8.00 mmol) in THF (20 mL) and the solution refluxed (8 h). Concentration of the mixture and flash chromatography (EtOAc/petrol, 1:3) gave the butenolide **3** as tan needles (915 mg, 84%); melting point, ¹H and ¹³C NMR spectra and HRMS data agree with those reported above in (a).

Methyl 5-*O*-Benzoyl-1,2-*O*-isopropylidene- α -D-glucuronate (19): Benzoyl chloride (4.2 mL, 36 mmol) was added dropwise to the lactone **18**^[41] (6.5 g, 30 mmol) in C₅H₅N (24 mL) at 0 °C and the mixture stirred (room temp., 30 min). Water (1.1 mL) was added and the mixture stirred (room temp., 30 min). Concentration of the mixture and a standard workup (EtOAc) gave the crude benzoate as a colourless glass. Triethylamine (1.0 mL) was added to the residue in MeOH (24 mL) at 0 °C and the mixture stirred (1 h). Filtration of the mixture gave the methyl ester **19** as colourless needles (8.4 g, 79%); m.p. 146–148.5 °C (MeOH). [α]_D = +18.9 (CHCl₃). ¹H NMR (600 MHz, CDCl₃): δ = 1.32, 1.51 [2 s, 6 H, C(CH₃)₂], 3.23 (br. d, ³*J*_{H,H} = 5.0 Hz, 1 H, OH), 3.84 (s, 3 H, CO₂CH₃), 4.30–4.34 (m, 1 H, H3), 4.54 (dd, ³*J*_{H,H} = 2.8, 7.2 Hz, 1 H, H4), 4.57 (d, ³*J*_{H,H} = 3.6 Hz, 1 H, H2), 5.55 (d, ³*J*_{H,H} = 7.2 Hz, 1 H, H5), 5.98 (d, ³*J*_{H,H} = 3.6 Hz, 1 H, H1), 7.44–8.08 (m, 5 H, Ph) ppm. ¹³C NMR (150.9 MHz, CDCl₃): δ = 26.4, 27.0 [C(CH₃)₂], 53.2 (CO₂CH₃), 70.6, 74.9, 79.7, 84.9 (C2,3,4,5), 105.3 (C1), 112.4 [C(CH₃)₂], 128.7–134.1 (Ph), 165.9, 169.3 (2 C, C=O) ppm. HRMS (FAB): *m/z* = 353.1231; [M + H]⁺ requires 353.1236.

Methyl (*E*)- and (*Z*)-5-*O*-Benzoyl-3-deoxy-3-*C*-(ethoxycarbonyl)-methylene-1,2-*O*-isopropylidene- α -D-erythro-penturonate (21 and 20): Acetic anhydride (4.7 mL, 50 mmol) was added to PDC (3.8 g, 10 mmol) and the methyl ester **19** (3.5 g, 10 mmol) in CH₂Cl₂ and the mixture refluxed (1 h). The mixture was concentrated, and rapid silica gel filtration (EtOAc/petrol, 4:1) gave the crude ketone as a pale green oil. Ethyl (triphenylphosphoranylidene)acetate (8.7 g, 25 mmol) was added to the crude ketone in CH₂Cl₂ (40 mL) and the mixture stirred (room temp., 2.5 h). The solution was poured into hydrochloric acid (80 mL, 1 M) followed by a standard workup and flash chromatography (EtOAc/petrol, 1:4). The (*E*) isomer **21** was first to elute as a colourless oil (34 mg, 0.8%). [α]_D = +154 (CHCl₃). ¹H NMR (600 MHz, CDCl₃): δ = 1.25 (t, ³*J*_{H,H} = 7.1 Hz, 3 H, CH₂CH₃), 1.38, 1.42 (2 s, 6 H, C(CH₃)₂), 3.71 (s, 3 H, CO₂CH₃), 4.11–4.23 (m, 2 H, CH₂CH₃), 5.30 (ddd, ³*J*_{H,H} = 1.7, ⁴*J*_{H,H} = 2.3, 2.3 Hz, 1 H, H4), 5.80 (d, ³*J*_{H,H} = 1.7 Hz, 1 H, H5), 5.83 (d, ³*J*_{H,H} = 4.7 Hz, 1 H, H1), 5.94 (ddd, ⁴*J*_{H,H} = 2.3, 2.3, ³*J*_{H,H} = 4.7 Hz, 1 H, H2), 6.27 (dd, ⁴*J*_{H,H} = 2.3, 2.3 Hz, 1 H, =CH), 7.42–8.12 (m, 5 H, Ph) ppm. ¹³C NMR (150.9 MHz, CDCl₃): δ = 14.2 (CH₂CH₃), 27.7, 27.8 [C(CH₃)₂], 52.8 (CO₂CH₃), 61.0 (CH₂CH₃), 75.4, 81.3, 82.0 (C2,4,5), 104.8 (C1), 113.4 [C(CH₃)₂], 118.6 (=CH), 128.5–133.6 (Ph), 157.4 (C3), 165.38, 165.44, 168.3 (3 C, C=O) ppm. HRMS (FAB): *m/z* = 421.1518; [M + H]⁺ requires 421.1499. Next to elute was the (*Z*) isomer **20** as colourless needles (3.7 g, 88%); m.p. 95–96 °C (*i*Pr₂O). [α]_D = +158 (CHCl₃). ¹H NMR (600 MHz, CDCl₃): δ = 1.30 (t, ³*J*_{H,H} = 7.1 Hz, 3 H, CH₂CH₃),

1.42, 1.46 [2 s, 6 H, C(CH₃)₂], 3.78 (s, 3 H, CO₂CH₃), 4.24 (q, ³*J*_{H,H} = 7.1 Hz, 2 H, CH₂CH₃), 5.37–5.39 (m, 1 H, H4), 5.60 (d, ³*J*_{H,H} = 2.8 Hz, 1 H, H5), 5.80 (ddd, ⁴*J*_{H,H} = 1.9, 1.9, ³*J*_{H,H} = 4.2 Hz, 1 H, H2), 5.89 (d, ³*J*_{H,H} = 4.2 Hz, 1 H, H1), 5.98 (dd, ⁴*J*_{H,H} = 1.9, 1.9 Hz, 1 H, =CH), 7.43–8.04 (m, 5 H, Ph) ppm. ¹³C NMR (150.9 MHz, CDCl₃): δ = 14.2 (CH₂CH₃), 27.4, 27.6 [C(CH₃)₂], 52.9 (CO₂CH₃), 60.9 (CH₂CH₃), 74.9, 78.9, 80.4 (C2,4,5), 106.1 (C1), 113.4 [C(CH₃)₂], 118.2 (=CH), 128.7–133.8 (Ph), 154.1 (C3), 164.5, 165.4, 167.2 (3 C, C=O) ppm. HRMS (FAB): *m/z* = 421.1510.

(4*S*,5*S*,7*R*/7*S*,7*aR*)-4,7-Dihydroxy-5-methoxycarbonyl-4,5,7,7a-tetrahydro-2H-furo[2,3-*c*]pyran-2-one (22): Sodium cyanide (0.12 g, 2.4 mmol) was added to the alkene **20** (3.4 g, 8.0 mmol) in MeOH (30 mL) and the mixture stirred (5 h). Concentration of the mixture and a standard workup (EtOAc) returned a brown gum. Trifluoroacetic acid/H₂O (10 mL, 4:1) was added to this gum and the solution kept at room temperature (5 min). The solvent was removed, H₂O added and the aqueous solution washed with Et₂O. Concentration of the aqueous layer (room temp.) and flash chromatography (EtOAc/petrol, 7:3) gave the esters **22** as a colourless oil (1.5 g, 81%). ¹H NMR [500 MHz, (CD₃)₂SO]: δ = 3.73 (s, 3 H, β-CO₂CH₃), 3.74 (s, 3 H, α-CO₂CH₃), 3.81 (d, ³*J*_{H,H} = 9.2 Hz, 1 H, α-H5), 4.04 (d, ³*J*_{H,H} = 9.2 Hz, 1 H, β-H5), 4.53 (dd, ³*J*_{H,H} = 6.7, 7.0 Hz, 1 H, α-H7), 4.57–4.64 (m, 2 H, α,β-H4), 4.74 (dd, ⁴*J*_{H,H} = 1.7, ³*J*_{H,H} = 7.0 Hz, 1 H, α-H7a), 5.08 (dd, ⁴*J*_{H,H} = 1.8, ³*J*_{H,H} = 4.5 Hz, 1 H, β-H7a), 5.54 (dd, ³*J*_{H,H} = 4.5, 4.8 Hz, 1 H, β-H7), 5.97 (dd, ⁴*J*_{H,H} = 1.8, 1.8 Hz, 1 H, β-H3), 6.01 (dd, ⁴*J*_{H,H} = 1.7, 1.7 Hz, 1 H, α-H3), 6.31 (d, ³*J*_{H,H} = 6.7 Hz, 1 H, β-4-OH), 6.37 (d, ³*J*_{H,H} = 6.1 Hz, 1 H, α-4-OH), 7.43 (d, ³*J*_{H,H} = 4.8 Hz, 1 H, β-7-OH), 7.43 (d, ³*J*_{H,H} = 6.7 Hz, 1 H, α-7-OH) ppm. ¹³C NMR [125.8 MHz, (CD₃)₂SO]: δ = 52.5 (α,β-CO₂CH₃), 67.5 (β-C5), 68.0 (α-C5), 72.4, 78.1 (β-C4,7a), 77.5, 81.5 (α-C4,7a), 91.0 (β-C7), 98.7 (α-C7), 112.7 (α,β-C3), 168.4–172.5 (6 C, α,β-C2,3a,C=O) ppm. HRMS (FAB): *m/z* = 231.0500; [M + H]⁺ requires 231.0505.

5-Methoxycarbonyl-2H-furo[2,3-*c*]pyran-2-one (23): Acetic anhydride (5.7 mL, 60 mmol) was added to the ester **22** (4.6 g, 20 mmol) in C₅H₅N (30 mL) and the solution allowed to stand (2 h). Methanol (2 mL) was added and the solution again allowed to stand (15 min). The mixture was concentrated, diluted with EtOAc (60 mL) and poured into hydrochloric acid (50 mL, 1 M). A standard workup (omitting the use of saturated aqueous NaHCO₃) gave a dark syrup that, after rapid silica gel filtration (EtOAc/petrol, 1:1), returned a pale yellow gum. 1,8-Diazabicyclo[5.4.0]undec-7-ene (7.5 mL, 50 mmol) was added dropwise to this gum in CH₂Cl₂ (20 mL) and the dark mixture stirred (10 min). The mixture was diluted with CH₂Cl₂ (40 mL) and poured into hydrochloric acid (50 mL, 1 M). The organic layer was washed with H₂O (3 × 50 mL), dried (MgSO₄), filtered and concentrated before flash chromatography (EtOAc/CH₂Cl₂, 3:97) gave the ester **23** as tan needles (2.7 g, 68%); sublimation at 151–154 °C (CH₂Cl₂/petrol). ¹H NMR [600 MHz, (CD₃)₂CO]: δ = 3.95 (s, 3 H, CO₂CH₃), 5.70 (d, ⁵*J*_{H,H} = 1.5 Hz, 1 H, H3), 7.69 (d, ⁵*J*_{H,H} = 0.5 Hz, 1 H, H4), 8.00 (dd, ⁵*J*_{H,H} = 0.5, 1.5 Hz, 1 H, H7) ppm. ¹³C NMR [150.9 MHz, (CD₃)₂CO]: δ = 53.6 (CO₂CH₃), 94.8 (C3), 109.3 (C4), 128.7 (C7), 144.2 (C7a), 145.7, 147.8 (C3a,CO₂CH₃), 160.6 (C5), 170.2 (C2) ppm. HRMS (EI): *m/z* = 194.0216; [M]⁺ requires 194.0215.

3-Formyl-2H-furo[2,3-*c*]pyran-2-one (24): The butenolide **3** (136 mg, 1.00 mmol) was treated according to Procedure A [50 °C, 15 min, flash chromatography (EtOAc/PhMe, 1:2)] to give the aldehyde **24** as tan needles (151 mg, 92%); m.p. 216–217.5 °C (*i*Pr₂O). ¹H NMR [600 MHz, (CD₃)₂CO]: δ = 7.73 (d, ³*J*_{H,H} = 5.1 Hz, 1 H, H5), 8.41

(d, $^3J_{\text{H,H}} = 5.1$ Hz, 1 H, H4), 8.60 (s, 1 H, H7), 9.82 (s, 1 H, CHO) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 100.4$ (C3), 108.1 (C4), 136.0 (C7), 143.7 (C7a), 147.8 (C3a), 156.6 (C5), 168.6 (C2), 185.1 (CHO) ppm. HRMS (FAB): $m/z = 165.0196$; $[\text{M} + \text{H}]^+$ requires 165.0190.

3-Formyl-5-methoxycarbonyl-2H-furo[2,3-c]pyran-2-one (25): The butenolide **23** (97 mg, 0.50 mmol) was treated according to Procedure A [80 °C, 1 h, flash chromatography (EtOAc/petrol, 1:2)] to give the aldehyde **25** as yellow needles (100 mg, 90%); m.p. 158.5–159 °C (Et₂O). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 4.03$ (s, 3 H, CO_2CH_3), 8.27 (s, 1 H, H4), 8.65 (s, 1 H, H7), 9.87 (s, 1 H, CHO) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 54.1$ (CO_2CH_3), 102.7 (C3), 110.2 (C4), 135.3 (C7), 143.9 (C7a), 147.6, 151.9 (C3a, CO_2CH_3), 159.8 (C5), 168.2 (C2), 185.4 (CHO) ppm. HRMS (FAB): $m/z = 223.0250$; $[\text{M} + \text{H}]^+$ requires 223.0243.

5-(Dimethylaminocarbonyl)-2H-furo[2,3-c]pyran-2-one (26): Phosphoryl chloride (0.70 mL, 7.5 mmol) was added dropwise to the ester **23** (97 mg, 0.50 mmol) in dimethylacetamide (5 mL) and the solution stirred (120 °C, 36 h). The cooled solution was diluted with CH_2Cl_2 (5 mL), poured into saturated aqueous NaHCO_3 (30 mL) and stirred (15 min). Standard workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 7:3) gave the amide **26** as colourless needles (76 mg, 73%); m.p. 147–149 °C (EtOAc/petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 3.03$, 3.12 [2 br. s, 6 H, $\text{CON}(\text{CH}_3)_2$], 5.54 (d, $^3J_{\text{H,H}} = 1.5$ Hz, 1 H, H3), 7.14 (d, $^4J_{\text{H,H}} = 0.5$ Hz, 1 H, H4), 7.95 (dd, $^4J_{\text{H,H}} = 0.5$, $^5J_{\text{H,H}} = 1.5$ Hz, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 35.6$, 38.3 [$\text{CON}(\text{CH}_3)_2$], 92.8 (C3), 105.5 (C4), 128.3 (C7), 143.9 (C7a), 146.1 (C3a), 154.2 [$\text{CON}(\text{CH}_3)_2$], 162.3 (C5), 170.4 (C2) ppm. HRMS (FAB): $m/z = 208.0617$; $[\text{M} + \text{H}]^+$ requires 208.0610.

3-Acetyl-2H-furo[2,3-c]pyran-2-one (27): The butenolide **3** (69 mg, 0.50 mmol) was treated according to Procedure B [AcCl , 20 min, flash chromatography (EtOAc/petrol, 2:3)] to give the ketone **27** as colourless needles (81 mg, 91%); m.p. 185–185.5 °C (petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 2.42$ (s, 3 H, CH_3), 7.78 (d, $^3J_{\text{H,H}} = 5.1$ Hz, 1 H, H5), 8.29 (d, $^3J_{\text{H,H}} = 5.1$ Hz, 1 H, H4), 8.49 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 28.9$ (CH_3), 101.1 (C3), 108.5 (C4), 135.0 (C7), 143.4 (C7a), 149.0 (C3a), 155.8 (C5), 168.3 (C2), 193.4 (C=O) ppm. HRMS (EI): $m/z = 178.0265$; $[\text{M}]^+$ requires 178.0266.

3-Propanoyl-2H-furo[2,3-c]pyran-2-one (28): The butenolide **3** (69 mg, 0.50 mmol) was treated according to Procedure B [$\text{CH}_3\text{CH}_2\text{COCl}$, 20 min, flash chromatography (EtOAc/petrol, 1:2)] to give the ketone **28** as colourless plates (86 mg, 89%); m.p. 185–186 °C (petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 1.08$ (t, $^3J_{\text{H,H}} = 7.3$ Hz, 3 H, CH_2CH_3), 2.87 (q, $^3J_{\text{H,H}} = 7.3$ Hz, 2 H, CH_2CH_3), 7.80 (d, $^3J_{\text{H,H}} = 5.1$ Hz, 1 H, H5), 8.29 (d, $^3J_{\text{H,H}} = 5.1$ Hz, 1 H, H4), 8.47 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 8.1$ (CH_2CH_3), 34.8 (CH_2CH_3), 100.7 (C3), 108.5 (C4), 134.8 (C7), 143.5 (C7a), 149.1 (C3a), 155.6 (C5), 168.1 (C2), 196.7 (C=O) ppm. HRMS (EI): $m/z = 192.0423$; $[\text{M}]^+$ requires 192.0423.

3-Cyclopropylcarbonyl-2H-furo[2,3-c]pyran-2-one (29): The butenolide **3** (69 mg, 0.50 mmol) was treated according to Procedure B [cyclopropylcarbonyl chloride, 40 min, flash chromatography (EtOAc/petrol, 1:3)] to give the ketone **29** as colourless plates (87 mg, 85%); m.p. 239–241 °C (petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 0.92$ –1.05 (m, 4 H, CH_2), 3.13–3.18 (m, 1 H, CH), 7.80 (d, $^3J_{\text{H,H}} = 5.1$ Hz, 1 H, H5), 8.29 (d, $^3J_{\text{H,H}} = 5.1$ Hz, 1 H, H4), 8.50 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 11.3$ (CH_2), 18.2 (CH), 101.0 (C3), 108.7 (C4), 135.0 (C7), 143.3 (C7a), 148.8 (C3a), 155.8 (C5), 168.6 (C2), 196.0 (C=O) ppm. HRMS (EI): $m/z = 204.0414$; $[\text{M}]^+$ requires 204.0421.

3-Nitro-2H-furo[2,3-c]pyran-2-one (30): Sodium nitrate (0.21 g, 2.5 mmol) was added to the butenolide **3** (69 mg, 0.50 mmol) in $\text{CF}_3\text{CO}_2\text{H}$ (3 mL) and the mixture stirred (15 min). The dark mixture was diluted with CH_2Cl_2 (5 mL) and poured into saturated aqueous NaHCO_3 (30 mL). Standard workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 1:1) gave the butenolide **30** as yellow plates (44 mg, 48%); m.p. 207–208 °C (Et₂O). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 7.91$ (dd, $^4J_{\text{H,H}} = 0.6$, $^3J_{\text{H,H}} = 5.0$ Hz, 1 H, H5), 8.67 (d, $^3J_{\text{H,H}} = 5.0$ Hz, 1 H, H4), 8.82 (d, $^4J_{\text{H,H}} = 0.6$ Hz, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 107.9$ (C3a), 137.8 (C7), 140.5 (C7a), 144.2 (C3a), 158.2 (C5), 159.3 (C2) ppm. HRMS (EI): $m/z = 181.0018$; $[\text{M}]^+$ requires 181.0012.

3-Methyl-2H-furo[2,3-c]pyran-2-one (1): The aldehyde **24** (49 mg, 0.30 mmol) was treated according to Procedure C [flash chromatography (EtOAc/petrol, 1:3)] to give the butenolide **1** as colourless needles (37 mg, 83%); m.p. 118–120 °C (petrol; ref.^[7] 118–119 °C); the ^1H and ^{13}C NMR spectra and HRMS data agree with those reported.^[8]

3-Ethyl-2H-furo[2,3-c]pyran-2-one (31): The ketone **27** (53 mg, 0.30 mmol) was treated according to Procedure C [flash chromatography (EtOAc/petrol, 1:3)] to give the butenolide **31** as a colourless oil (39 mg, 79%). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 1.13$ (t, $^3J_{\text{H,H}} = 7.6$ Hz, 3 H, CH_2CH_3), 2.37 (q, $^3J_{\text{H,H}} = 7.6$ Hz, 2 H, CH_2CH_3), 6.85 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H5), 7.63 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H4), 7.79 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 13.2$ (CH_2CH_3), 17.1 (CH_2CH_3), 104.2 (C4), 106.0 (C3), 128.4 (C7), 140.2 (C7a), 143.1 (C3a), 150.0 (C5), 170.8 (C2) ppm. HRMS (EI): $m/z = 164.0472$; $[\text{M}]^+$ requires 164.0473.

3-Propyl-2H-furo[2,3-c]pyran-2-one (32): The ketone **28** (58 mg, 0.30 mmol) was treated according to Procedure C [flash chromatography (EtOAc/petrol, 1:4)] to give the butenolide **32** as a colourless oil (41 mg, 77%). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 0.91$ (t, $^3J_{\text{H,H}} = 7.4$ Hz, 3 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.57 (tq, $^3J_{\text{H,H}} = 7.4$, 7.4 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.33 (t, $^3J_{\text{H,H}} = 7.4$ Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 6.84 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H5), 7.63 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H4), 7.78 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 14.1$ ($\text{CH}_2\text{CH}_2\text{CH}_3$), 22.4 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 25.6 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 104.3 (C4), 104.5 (C3), 128.3 (C7), 140.9 (C7a), 143.1 (C3a), 150.1 (C5), 171.0 (C2) ppm. HRMS (EI): $m/z = 170.0628$; $[\text{M}]^+$ requires 170.0630.

5-Hydroxymethyl-3-methyl-2H-furo[2,3-c]pyran-2-one (33): The aldehyde **25** (0.1 g, 0.50 mmol) was treated according to Procedure C [flash chromatography (EtOAc/petrol, 4:1)] to give the alcohol **33** as colourless needles (38 mg, 42%); m.p. 133.5–134.5 °C (*i*-Pr₂O/petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 1.87$ (s, 3 H, CH_3), 4.44 (dd, $^4J_{\text{H,H}} = 0.8$, $^3J_{\text{H,H}} = 6.2$ Hz, 2 H, CH_2), 4.76 (t, $^3J_{\text{H,H}} = 6.2$ Hz, 1 H, OH), 6.78 (d, $^4J_{\text{H,H}} = 0.8$ Hz, 1 H, H4), 7.74 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 7.6$ (CH_3), 61.3 (CH_2), 99.4 (C4), 99.7 (C3), 127.4 (C7), 141.8 (C7a), 142.6 (C3a), 162.5 (C5), 171.4 (C2) ppm. HRMS (FAB): $m/z = 181.0499$; $[\text{M} + \text{H}]^+$ requires 181.0501.

5-Hydroxymethyl-2H-furo[2,3-c]pyran-2-one (34): Aluminium(III) chloride (0.12 g, 0.90 mmol) was added to *t*BuNH₂·BH₃ (0.16 g, 1.8 mmol) and the ester **23** (58 mg, 0.30 mmol) in CH_2Cl_2 (6 mL) and the mixture refluxed (10 min). The mixture was cooled to 0 °C, and hydrochloric acid (10 mL, 1 M) was added dropwise with stirring. Standard workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 4:1) gave the alcohol **34** as colourless needles (37 mg, 74%); m.p. 163–164.5 °C (Et₂O). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: $\delta = 4.47$ (dd, $^4J_{\text{H,H}} = 0.9$, $^3J_{\text{H,H}} = 6.2$ Hz, 2 H, CH_2), 4.82 (t, $^3J_{\text{H,H}} = 6.2$ Hz, 1 H, OH), 5.37 (d, $^5J_{\text{H,H}} = 1.5$ Hz, 1 H, H3), 6.89 (dt, $^5J_{\text{H,H}} = 0.5$, $^4J_{\text{H,H}} = 0.9$ Hz, 1 H, H4), 7.87 (dd, $^5J_{\text{H,H}}$

= 0.5, 1.5 Hz, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 61.2 (CH_2), 90.5 (C3), 100.8 (C4), 128.6 (C7), 143.7 (C7a), 147.4 (C3a), 163.9 (C5), 170.8 (C2) ppm. HRMS (FAB): m/z = 167.0344; $[\text{M} + \text{H}]^+$ requires 167.0344.

5-Chloromethyl-2H-furo[2,3-*c*]pyran-2-one (35): The ester **23** (58 mg, 0.30 mmol) was treated as above for the synthesis of the alcohol **35**, except that the mixture was refluxed for 48 h. Flash chromatography (EtOAc/petrol, 1:4) gave the chloride **35** as pale yellow needles (27 mg, 46%); m.p. 125–125.5 °C (petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 4.64 (s, 2 H, CH_2), 5.49 (d, $^3J_{\text{H,H}} = 1.5$ Hz, 1 H, H3), 7.07 (d, $^5J_{\text{H,H}} = 0.4$ Hz, 1 H, H4), 7.95 (dd, $^5J_{\text{H,H}} = 0.4$, 1.5 Hz, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 42.4 (CH_2), 92.5 (C3), 104.7 (C4), 129.2 (C7), 143.7 (C7a), 146.8 (C3a), 158.0 (C5), 170.6 (C2) ppm. HRMS (EI): m/z = 183.9930; $[\text{M}]^{++}$ requires 183.9927.

5-Fluoromethyl-2H-furo[2,3-*c*]pyran-2-one (36): Diethylaminosulfur trifluoride (80 μL , 0.6 mmol) was added to the alcohol **34** (33 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) and the solution stirred (0 °C, 1 h). The solution was diluted with CH_2Cl_2 (5 mL), poured into saturated aqueous NaHCO_3 (10 mL) and the mixture stirred (15 min). Standard workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 1:4) gave the fluoride **36** as colourless needles (29 mg, 87%); m.p. 99–99.5 °C (petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 5.30 (d, $^2J_{\text{H,F}} = 46.8$ Hz, 2 H, CH_2F), 5.50 (dd, $^5J_{\text{H,H}} = 1.5$, $^6J_{\text{H,F}} = 0.8$ Hz, 1 H, H3), 7.06 (d, $^4J_{\text{H,H}} = 2.2$ Hz, 1 H, H4), 7.96 (d, $^5J_{\text{H,H}} = 1.5$ Hz, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 80.8 (d, $^1J_{\text{C,F}} = 169$ Hz, CH_2F), 92.5 (d, $^5J_{\text{C,F}} = 1.8$ Hz, C3), 104.5 (d, $^3J_{\text{C,F}} = 6.5$ Hz, C4), 129.0 (C7), 143.9 (C7a), 146.6 (C3a), 157.1 (d, $^2J_{\text{C,F}} = 18.2$ Hz, C5), 170.6 (C2) ppm. HRMS (FAB) m/z = 169.0300; $[\text{M} + \text{H}]^+$ requires 169.0301.

3-(Dimethylamino)methyl-2H-furo[2,3-*c*]pyran-2-one (37): Dimethylammonium chloride (0.24 g, 3.0 mmol) was added to the aldehyde **24** (49 mg, 0.30 mmol) in MeOH (5 mL) and the mixture stirred (4 h). Sodium cyanoborohydride (28 mg, 0.45 mmol) was added to the yellow solution and the mixture stirred (16 h). Water (1 mL) was added and the mixture stirred (10 min). Concentration of the mixture and flash chromatography (EtOAc/petrol/ Et_3N , 90:9:1) gave the amine **37** as a pale yellow oil (36 mg, 62%). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 2.39 (s, 6 H, CH_3), 3.46 (s, 2 H, CH_2), 6.98 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H5), 7.71 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H4), 7.89 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 42.7 (CH_3), 53.5 (CH_2), 100.0 (C3), 105.2 (C4), 130.2 (C7), 142.0 (C7a), 143.9 (C3a), 150.7 (C5), 171.2 (C2) ppm. HRMS (EI): m/z = 193.0741; $[\text{M}]^{++}$ requires 193.0739.

3-Difluoromethyl-2H-furo[2,3-*c*]pyran-2-one (38): Diethylaminosulfur trifluoride (0.20 mL, 1.5 mmol) was added to the aldehyde **24** (49 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) and the solution stirred (35 °C, 24 h). The solution was diluted with CH_2Cl_2 (5 mL), poured into saturated aqueous NaHCO_3 (30 mL) and the mixture stirred (15 min). Standard workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 1:4) gave the difluoride **38** as tan needles (44 mg, 79%); m.p. 136–138 °C (decomp.) (petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 6.77 (t, $^2J_{\text{H,F}} = 54.8$ Hz, 1 H, CHF_2), 7.18 (d, $^3J_{\text{H,H}} = 5.4$ Hz, 1 H, H5), 8.07 (d, $^3J_{\text{H,H}} = 5.4$ Hz, 1 H, H4), 8.28 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 96.2 (t, $^2J_{\text{C,F}} = 26.7$ Hz, C3), 105.3 (C4), 112.7 (t, $^1J_{\text{C,F}} = 231.8$ Hz, CHF_2), 133.0 (C7), 142.8 (C7a), 144.7 (t, $^3J_{\text{C,F}} = 2.3$ Hz, C3a), 153.6 (C5), 167.2 (t, $^3J_{\text{C,F}} = 6.9$ Hz, C2) ppm. HRMS (FAB): m/z = 187.0213; $[\text{M} + \text{H}]^+$ requires 187.0207.

3-(2,2-Dibromovinyl)-2H-furo[2,3-*c*]pyran-2-one (39): Carbon tetrabromide (0.73 g, 2.2 mmol) was added to Ph_3P (0.58 g, 2.2 mmol) and Zn (0.14 g, 2.2 mmol) in CH_2Cl_2 (3 mL) and the mixture

stirred (0 °C, 15 min). The aldehyde **24** (0.12 g, 0.75 mmol) was added and the mixture stirred (3 h). The mixture was filtered through Celite and concentrated, before flash chromatography (EtOAc/petrol, 1:9) gave the alkene **39** as yellow needles (0.10 g, 42%); m.p. 130–132 °C (Et_2O /hexane). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 7.10 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H5), 7.32 (s, 1 H, CHCBr_2), 7.98 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H4), 8.17 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 91.5 (CHCBr_2), 100.1 (C3), 107.3 (C4), 129.5 (CHCBr_2), 131.5 (C7), 140.6 (C7a), 143.7 (C3a), 151.8 (C5), 167.9 (C2) ppm. HRMS (FAB): m/z = 318.8600; $[\text{M} + \text{H}]^+$ requires 318.8605.

3-Hydroxymethyl-2H-furo[2,3-*c*]pyran-2-one (40): *tert*-Butylamine–borane complex (78 mg, 0.90 mmol) was added to the aldehyde **24** (49 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) and the solution stirred (1 h). Concentration of the solution and flash chromatography (EtOAc/petrol, 4:1) gave the alcohol **40** as colourless needles (43 mg, 86%); m.p. 144 °C (decomp.) (Et_2O). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 4.04 (t, $^3J_{\text{H,H}} = 5.6$ Hz, 1 H, OH), 4.43 (d, $^3J_{\text{H,H}} = 5.6$ Hz, 2 H, CH_2), 7.01 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H5), 7.70 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H4), 7.89 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 55.2 (CH_2), 104.3 (C3), 105.1 (C4), 129.4 (C7), 142.2, 143.2 (C3a,7a), 150.4 (C5), 169.9 (C2) ppm. HRMS (EI): m/z = 166.0268; $[\text{M}]^{++}$ requires 166.0266.

3-Methoxymethyl-2H-furo[2,3-*c*]pyran-2-one (41): Methyl iodide (0.13 mL, 2.0 mmol) was added to the alcohol **40** (33 mg, 0.20 mmol) and silver(I) oxide (0.12 g, 0.50 mmol) in CH_2Cl_2 (5 mL) and the mixture refluxed (16 h). The mixture was filtered through Celite and concentrated, before flash chromatography (EtOAc/petrol, 1:4) gave the methyl ether **41** as colourless needles (31 mg, 87%); m.p. 63–63.5 °C (petrol). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 3.30 (s, 3 H, CH_3), 4.25 (s, 2 H, CH_2), 6.98 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H5), 7.77 (d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H, H4), 7.95 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 58.2 (CH_3), 64.5 (CH_2), 100.7 (C3), 104.9 (C4), 129.9 (C7), 143.1, 143.5 (C3a,7a), 151.1 (C5), 170.0 (C2) ppm. HRMS (EI): m/z = 180.0420; $[\text{M}]^{++}$ requires 180.0423.

(E)-3-Hydroxyimino-2H-furo[2,3-*c*]pyran-2-one (42): Sodium acetate (49 mg, 0.60 mmol) was added to $\text{NH}_2\text{OH}\cdot\text{HCl}$ (42 mg, 0.60 mmol) and the aldehyde **24** (49 mg, 0.30 mmol) in MeOH and the mixture refluxed (2 h). The mixture was concentrated and a standard workup (CH_2Cl_2) before flash chromatography (EtOAc/petrol, 3:1) gave the oxime **42** as yellow crystals (43 mg, 80%); m.p. 197 °C (decomp.) (Et_2O). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 7.24 (d, $^3J_{\text{H,H}} = 5.3$ Hz, 1 H, H5), 7.93 (s, 1 H, CHNOH), 7.97 (d, $^3J_{\text{H,H}} = 5.3$ Hz, 1 H, H4), 8.16 (s, 1 H, H7), 10.42 (s, 1 H, CHNOH) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 96.7 (C3), 107.2 (C4), 131.7 (C7), 140.7 (C7a), 142.1 (CHNOH), 143.7 (C3a), 153.1 (C5), 168.8 (C2) ppm. HRMS (EI): m/z = 179.0216; $[\text{M}]^{++}$ requires 179.0219.

3-Cyano-2H-furo[2,3-*c*]pyran-2-one (43): Thionyl chloride (70 μL , 1.0 mmol) was added to Et_3N (0.14 mL, 1.0 mmol) and the oxime **42** (36 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) at 0 °C and the mixture stirred (30 min). The solution was diluted with CH_2Cl_2 (5 mL), poured into saturated aqueous NaHCO_3 (30 mL) and stirred (15 min). Standard workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 1:4) gave the nitrile **43** as colourless needles (26 mg, 82%); m.p. 192–193 °C ($i\text{Pr}_2\text{O}$). ^1H NMR [600 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 7.41 (d, $^3J_{\text{H,H}} = 5.2$ Hz, 1 H, H5), 8.38 (d, $^3J_{\text{H,H}} = 5.2$ Hz, 1 H, H4), 8.52 (s, 1 H, H7) ppm. ^{13}C NMR [150.9 MHz, $(\text{CD}_3)_2\text{CO}$]: δ = 75.6 (C3), 106.7 (C4), 113.1 (CN), 134.9 (C7), 143.3 (C7a), 150.8 (C3a), 155.8 (C5), 166.7 (C2) ppm. HRMS (EI): m/z = 161.0115; $[\text{M}]^{++}$ requires 161.0113.

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