

Substituent effects on the $4\pi + 2\pi$ cycloadditions of 4*H*-pyran-4-one derivatives

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Mónika Rudas,^a Imre Fejes,^a Miklós Nyerges,^a Áron Szöllösy,^b László Töke^{a*} and Paul W. Groundwater^c

^a Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest P.O.B. 91, Hungary

^b Institute for General and Analytical Chemistry, Technical University of Budapest, H-1111 Budapest Gellért tér 4, Hungary

^c School of Health Sciences, University of Sunderland, Sunderland, UK SR1 3SD

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The simple γ -pyranones **4**, **5**, and **6** undergo $4\pi + 2\pi$ cycloaddition reactions with Danishefsky's diene **8** and azomethine ylides **12**, **16**, and **25** to give a range of cycloadducts. The position of the electron-withdrawing group is the decisive factor in these reactions, with the 2-substituted derivatives **5** and **6** being less reactive than the 3-substituted γ -pyranone **4**. The esters, **4** and **5**, react *via* addition across the 2,3-C=C bond of the pyranone ring, whilst the aldehyde **6** reacts *via* addition across the C=O of the carbaldehyde group.

In the search for non-cytotoxic antitumour agents, which act *via* the inhibition of protein tyrosine kinases, a variety of flavonoids and their modified or annelated analogues have been synthesised.¹ We have recently prepared a number of pyrano-acridones (e.g. **1**) which exhibited good activity in biological assays for the inhibition of growth factor mediated cell proliferation.² As part of an ongoing investigation in our laboratories into the synthesis of biologically active compounds, we became interested in the reactivity of the 4*H*-pyran-4-ones as 2π components in a variety of $[4\pi + 2\pi]$ cycloaddition reactions.³

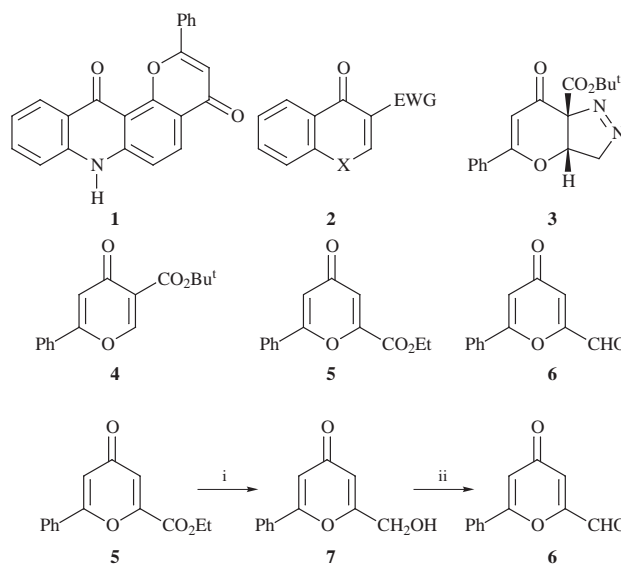
In contrast to the well documented reactivity of 4*H*-benzopyran-4-ones **2a** (X = O, EWG = CN, COOMe) or benzothio-pyranones **2b** (X = S, EWG = CN, COOMe) the cycloadditions of simple γ -pyranones have received rather limited attention. Before the start of our investigations the only previous example was a footnote by McCombie *et al.*,^{6a} who reported that the pyranone ester **4** reacted readily with diazomethane in a 1,3-dipolar cycloaddition to give a single pyrazoline cycloadduct **3**. Since then one further report has emerged on a synthetic entry to the trichothecene skeleton which successfully utilises a simple 4*H*-pyran-4-one as a Diels–Alder component.^{6b}

Results and discussion

We have considered the cycloaddition reactions of three 4*H*-pyran-4-ones, including *tert*-butyl 4-oxo-6-phenyl-4*H*-pyran-3-carboxylate **4** previously studied by McCombie *et al.*^{6a} During our earlier work we observed the non-reactivity of the 2-substituted ester, ethyl 4-oxo-6-phenyl-4*H*-pyran-2-carboxylate **5**, towards different dienes and azomethine ylides. We now describe some cycloadducts using these γ -pyranones as the 2π component. We have also studied the reactivity of 4-oxo-4*H*-pyran-2-carbaldehyde **6** in similar reactions.

Synthesis of the pyranones

The γ -pyranones **4** and **5** were prepared according to literature methods.^{3b,6a,7} The aldehyde **6** has previously been prepared from phenylacetylene derivatives under basic conditions in low yield.⁸ We have developed a new route to aldehyde **6** starting from the readily available ester **5** (Scheme 1). The direct reduction of ester **5** to aldehyde **6** using RedAl, or DIBAL-H at low temperatures was unsuccessful. We have, however, reduced the

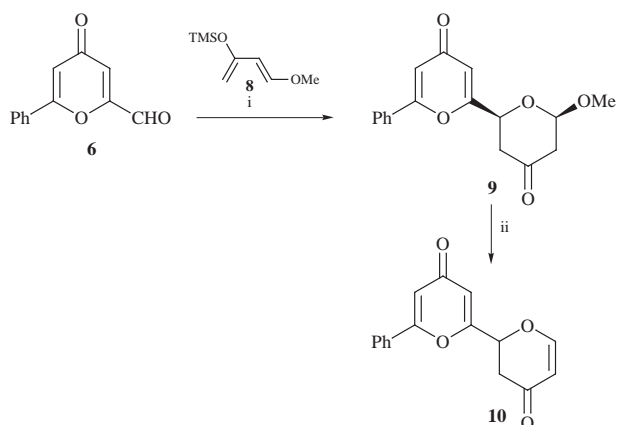


Scheme 1 Reagents and conditions: i, NaBH₄, MeOH; ii, MnO₂.

ester to the corresponding alcohol **7**, which was then readily oxidised to aldehyde **6** by manganese(IV) oxide at room temperature.

Diels–Alder reactions

The reactivity of γ -pyranones **4** and **5** towards Danishefsky's diene **8** and 2-trimethylsilyloxybuta-1,4-diene has previously been studied by us.³ The aldehyde **6** did not react, even after long reaction times, with monosubstituted dienes (2-trimethylsilyloxybuta-1,4-diene or 1-methoxybuta-1,4-diene), but from the reaction with Danishefsky's diene **8** we were able to isolate the bis(pyranylketone) **9** (Scheme 2). The stereochemistry of the Diels–Alder adduct was deduced from the 2D-NOESY spectrum. Enhancements of the signals for the H-2' and H-6' protons confirmed that they are on the same face of the molecule, consistent with an *endo*-approach of the dienophile to Danishefsky's diene **8**. The methoxy group was eliminated by the action of trifluoroacetic anhydride, at room temperature, to give the 5',6'-dihydro-2,6'-bipyran **10**. The γ -pyranone aldehyde **6** acts as a heterodienophile in this cycloaddition, with the

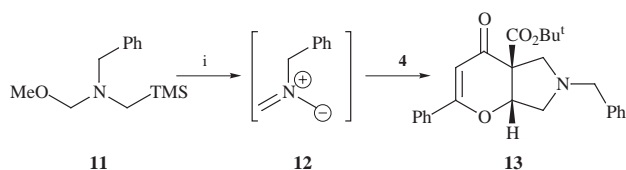


Scheme 2 Reagents and conditions: i, PhCH₃, 70–80 °C, 18 h, 36%; ii, CH₂Cl₂, TFAA, room temp., 48 h, 88%.

C=O double bond being more reactive than the C=C double bond. This is a major difference in comparison with the known reactions of the analogous 4-oxobenzopyran-3-carbaldehydes with electron-rich dienes.^{2a}

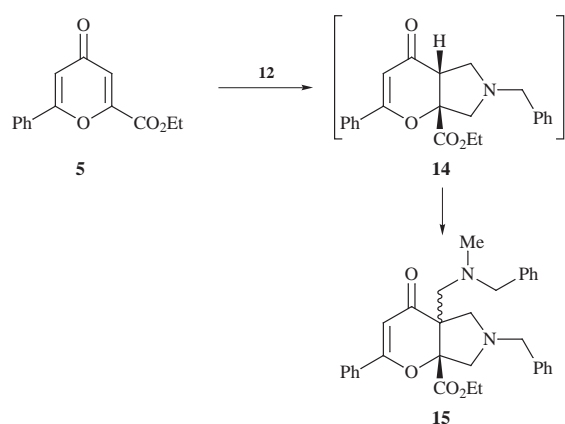
Reactions with non-stabilised azomethine ylides

Both 4H-pyran-4-one derivatives **4** and **5** reacted smoothly with the non-stabilised azomethine ylide **12** [generated by the desilylation method from *N*-benzyl-*N*-(methoxymethyl)(trimethylsilyl)methylamine **11**⁹] at room temperature. The reaction of γ -pyranone **4**, as expected, gave rise to the formation of the hexahydropyrano[2,3-*c*]pyrrole cycloadduct **13** in good yield (Scheme 3).



Scheme 3 Reagents and conditions: i, TFAA, toluene, room temp.

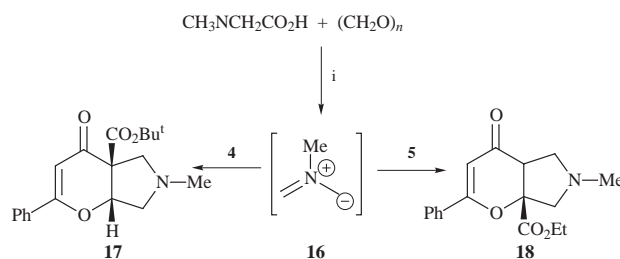
The γ -pyranone **5**, however, reacted slowly, to yield a single product **15**—presumably arising from the reaction of the intermediate cycloadduct **14** with excess of reagent **12**—in moderate yield (Scheme 4).



Scheme 4

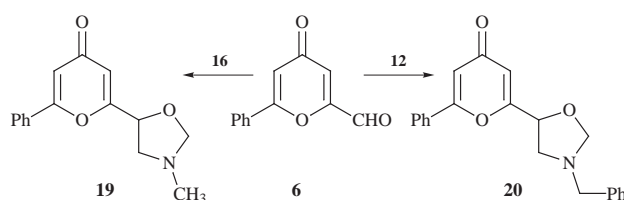
Both 4H-pyran-4-one derivatives **4** and **5** reacted with another non-stabilised azomethine ylide **16**. This dipole was generated by Tsuge's protocol¹⁰ for the decarboxylative condensation of sarcosine with paraformaldehyde. A solution of the γ -pyranone and an excess of sarcosine and paraformaldehyde in toluene was heated under reflux (the water formed was

removed by the aid of a Dean–Stark trap), and this resulted in the formation of the corresponding cycloadducts. The more reactive pyranone **4** gave cycloadduct **17** in a good yield. The less reactive ester **5** reacted also, to give cycloadduct **18**, but the yield was considerably reduced under the same conditions (Scheme 5).



Scheme 5 Reagents and conditions: i, PhCH₃, reflux.

More interestingly, the reactions of 4-oxo-4H-pyran-2-carbaldehyde **6** with these non-stabilised azomethine ylides, **12** and **16**, led to the oxazolidine cycloadducts **19** and **20**. Once again the C=O double bond proved to be more reactive as the dipolarophile in the 1,3-dipolar cycloaddition than the C=C double bond with an electron-withdrawing group (Scheme 6).

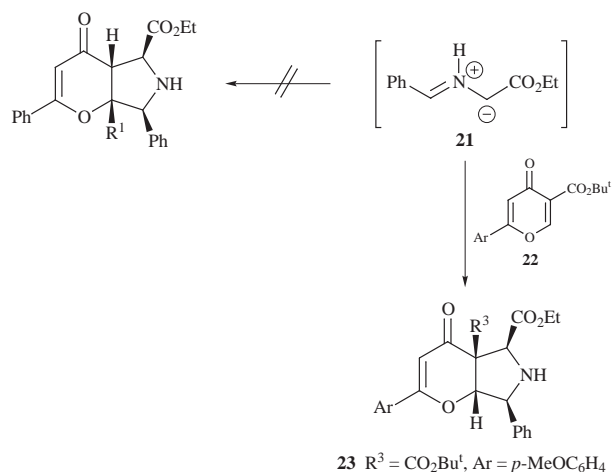


Scheme 6

Reactions with ester-stabilised azomethine ylides

Azomethine ylides stabilised by the presence of one or more electron-withdrawing or conjugating (*e.g.* phenyl) groups are reported to be less reactive in normal electron demand cycloadditions than the corresponding relatively electron-rich unsubstituted analogues. For example, we have previously reported that the azomethine ylide **21** (generated from the imine of glycine esters in the presence of LiBr as a catalyst) acted as a 4 π component in a 1,3-dipolar cycloaddition. Ester **5** was unreactive towards the stabilised azomethine ylide **21** but the reaction with the pyranone **22** gave the cycloadduct **23** in moderate yield (Scheme 7).³ The aldehyde **6** was also unreactive under these conditions.

The 1,3-dipolar cycloadditions of azomethine ylides derived from isoquinolinium salts **24** by deprotonation has previously

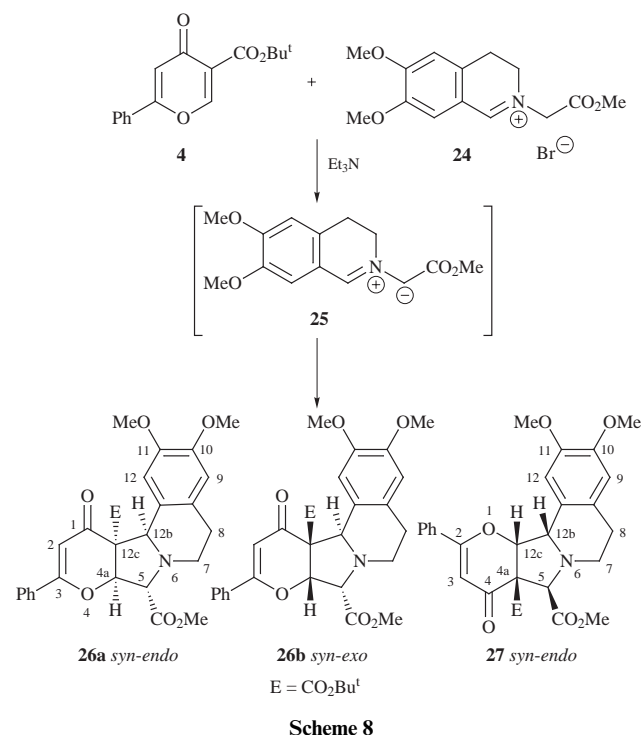


Scheme 7

Table 1 ^1H NMR shifts and coupling constants for cycloadducts **26** and **27**

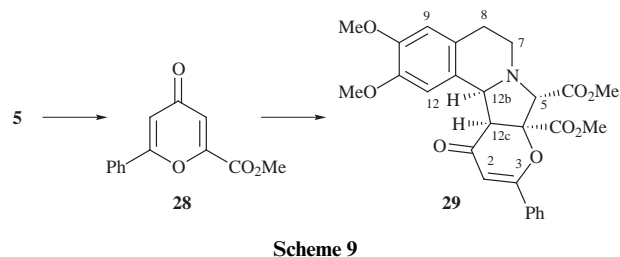
| Entry | $\delta(\text{H-2})$ | $\delta(\text{H-3})$ | $\delta(\text{H-4a})$ | $\delta(\text{H-5})$ | $\delta(\text{H-12b})$ |
|----------------------------|----------------------|----------------------|------------------------|----------------------|------------------------|
| 26a <i>syn-endo</i> | 6.16, s | — | 5.71, d (J 11.5 Hz) | overlapping | 5.25, s |
| 26b <i>syn-exo</i> | 6.22, s | — | 5.87, d (J 5 Hz) | overlapping | 5.30, s |
| 27 <i>syn-endo</i> | — | 6.28, s | — | 4.26, s | 4.37, d (J 6 Hz) |

been reported by us.¹¹ The reaction of the derived ylide **25** with γ -pyranone **4** gave rise to the formation of an inseparable mixture of regio- and stereoisomers of cycloadducts **26** and **27** in good overall yield (Scheme 8). The identifiable signals in the ^1H



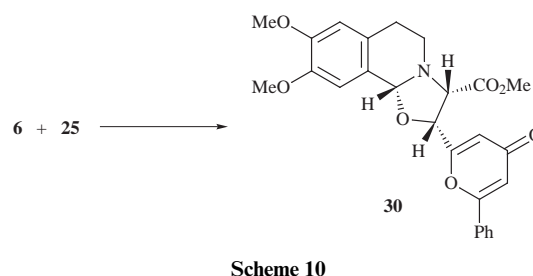
NMR spectrum of the mixture are summarised in Table 1. By comparison of this data with that from our previous work we could deduce the most likely stereochemistry of these cycloadducts.

The reaction of ylide **25** with γ -pyranone **5** gave the expected *anti-endo* cycloadduct **29** as a single isomer, but in a very low yield (<5%). The stereochemistry of this adduct has been deduced by comparison to our previous work. Under these reaction conditions the first step was the transesterification of the ethoxycarbonyl function to methoxycarbonyl. Most of the transesterified γ -pyranone **28** was recovered from the reaction mixture (Scheme 9). A larger excess of dipole caused problems



with by-products (which form in the absence of the reactive partner).

Finally, the reaction of ylide **25** with the γ -pyranone aldehyde **6** once again resulted in addition across the $\text{C}=\text{O}$ double bond to give the oxazolidine **30** as a single isomer in a moderate yield (Scheme 10). The stereochemistry of this adduct was confirmed by a 2D-NOESY spectrum.



Experimental

Column chromatography was performed using Merck Kieselgel 60 (70–230 mesh), and TLC on aluminium sheets coated with Kieselgel 60 F₂₅₄. Plates were stained with anisaldehyde solution [glacial acetic acid (100 cm³), sulfuric acid (2 cm³), and anisaldehyde (1 cm³)] and heated at *ca.* 150 °C. IR spectra were obtained on a NICOLET FTIR instrument. Low resolution electron impact mass spectra were obtained on a Fisons VG Platform II or Trio 2000 VG and high resolution spectra on a VG ZAB-E spectrometer (EPSRC Mass Spectrometry Service Centre, Swansea). NMR spectra were obtained on a Bruker AM 500 (500 MHz for ^1H and 125 MHz for ^{13}C) and a Bruker AC 250 instrument at 30 °C. Coupling constants (J) are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. Melting points are uncorrected.

2-Hydroxymethyl-6-phenyl-4H-pyran-4-one 7

Ethyl 4-oxo-6-phenyl-4H-pyran-2-carboxylate **5** (28.4 g, 0.116 mol) was dissolved in methanol (200 cm³) and sodium borohydride (18 g, 0.48 mol) was added in small portions over 30 min. The reaction mixture was refluxed for 3 h, cooled, and treated with 5% aq. HCl (30 cm³). The methanol was removed under vacuum, the residue was dissolved in water (100 cm³) and the aqueous phase extracted with ether (3 × 50 cm³). The organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give the title compound **7** as a white powder (9.76 g, 42%), mp 147–149 °C (Found: C, 71.4; H, 4.9. C₁₂H₁₀O₃ requires C, 71.3; H, 5.0%); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3151 (OH), 1650 (C=O), 1596 (C=C); $\delta_{\text{H}}(500 \text{ MHz}, [^2\text{H}_6]\text{DMSO})$ 4.43 (2H, d, J 7, CH₂), 5.79 (1H, t, J 7, OH), 6.29 (1H, d, J 3, H-5), 6.88 (1H, d, J 3, H-3), 7.61–7.48 (3H, m, H-3',4',5'), 7.98–7.88 (2H, m, H-2',6'); $\delta_{\text{C}}([^2\text{H}_6]\text{DMSO})$ 60.0 (CH₂), 111.1 (CH), 111.9 (CH), 126.4 (2 × CH), 129.5 (2 × CH), 131.3 (quat.), 131.9 (CH), 162.83 (quat.), 169.2 (quat.), 179.3 (C=O); m/z 202 (M⁺, 100%), 174 (43), 157 (74), 129 (24), 115 (34), 105 (74), 102 (88), 77 (65), 69 (52).

4-Oxo-6-phenyl-4H-pyran-2-carbaldehyde 6

2-Hydroxymethyl-6-phenyl-4H-pyran-4-one **7** (0.49 g, 2.4 mmol) was dissolved in dichloromethane (20 cm³) and activated manganese(IV) oxide (1.8 g, 21 mmol) was added. The reaction mixture was stirred efficiently for 48 h at room temperature then the black suspension was filtered through a pad of silica, which was washed with warm ethyl acetate (50 cm³). The resulting solution was evaporated under reduced pressure to give a pale yellow solid. The solid was purified by flash chromatography, eluting with hexane–ethyl acetate (1 : 4) to give the aldehyde **6** as a white powder (0.24 g, 49%), mp 115–116 °C (lit.⁸ 118–119 °C) (Found: C, 71.9; H, 4.1. C₁₂H₈O₃ requires C, 72.0; H, 4.0%); $\nu_{\text{max}}(\text{nujol})/\text{cm}^{-1}$ 1658 (C=O), 1589 (C=C); $\delta_{\text{H}}(250 \text{ MHz}, \text{CDCl}_3)$

6.86 (1H, d, *J* 2.5, H-5), 6.90 (1H, d, *J* 2.5, H-3), 7.63–7.37 (3H, m, H-3',4' and 5'H), 7.93–7.71 (2H, m, H-2' and 6'H), 9.73 (1H, s, CHO); δ_{C} (125 MHz, CDCl₃) 113.0 (CH), 121.5 (CH), 126.2 (2 × CH), 129.2 (2 × CH), 130.2 (quat.), 132.2 (CH), 156.6 (quat.), 163.8 (quat.), 179.3 (quat.), 184.3 (CHO); *m/z* 200 (M⁺, 100%), 172 (95), 157 (20), 115 (25), 105 (15), 102 (33), 77 (41), 69 (40), 51 (18).

Diels–Alder reactions

2-(2',3',5',6'-Tetrahydro-6'-methoxy-4'-oxo-4'-H-pyran-2'-yl)-6-phenyl-4H-pyran-4-one 9. 4-Oxo-6-phenyl-4H-pyran-2-carbaldehyde **6** (0.15 g, 0.75 mmol) and Danishefsky's diene **8** (0.16 g, 0.93 mmol) were dissolved in dry toluene (8 cm³) and the reaction mixture was stirred at 70–80 °C for 18 h. The reaction mixture was then evaporated under reduced pressure and the residue recrystallised from ether–hexane–ethanol to give the title compound **9** as a light brown powder (80 mg, 36%), mp 122 °C (Found: M⁺, 300.100. Calc. for C₁₇H₁₆O₅: *M*, 300.100); ν_{max} (KBr)/cm⁻¹ 1712 (C=O), 1655 (C=O), 1614 (C=C); δ_{H} (500 MHz, CDCl₃) 2.65 (1H, dd, *J* 15.6 and 7.5, CH₂-5), 2.82 (3H, m, CH₂), 3.56 (3H, s, OMe), 4.73 (1H, dd, *J* 10.9 and 4.0, H-2'), 4.88 (1H, dd, *J* 7.5 and 2.8, H-6'), 6.57 (1H, d, *J* 2, H-3), 6.75 (1H, d, *J* 2, H-5), 7.41 (3H, m, Ph), 7.51 (2H, m, Ph); δ_{C} (125 MHz, CDCl₃) 43.8 (CH₂), 47.1 (CH₂), 56.7 (OCH₃), 69.7 (CH), 101.1 (CH), 111.5 (CH), 112.9 (CH), 125.8 (2 × CH), 129.2 (2 × CH), 130.8 (quat.), 131.7 (quat.), 163.5 (quat.), 164.7 (quat.), 179.7 (C=O), 202.5 (C=O); *m/z* 300 (M⁺, 10%), 199 (60), 186 (28), 170 (100), 105 (11), 102 (21), 58 (19).

2-(2',3'-Dihydro-4'-oxo-4'-H-pyran-2'-yl)-6-phenyl-4H-pyran-4-one 10. 2-(2',3',5',6'-Tetrahydro-6'-methoxy-4'-oxo-4'-H-pyran-2'-yl)-6-phenyl-4H-pyran-4-one **9** (14 mg, 47 μmol) was dissolved in dichloromethane (2 cm³) and trifluoroacetic anhydride (2 drops) was added. The reaction mixture was stirred for 48 hours at room temperature, then saturated aqueous sodium hydrogen carbonate solution (3 cm³) was added. The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure to give **10** as a light yellow solid (11 mg, 88%), mp 131–132 °C (Found: M⁺, 268.0725. Calc. for C₁₆H₁₂O₄: *M*, 268.074); δ_{H} (500 MHz, CDCl₃) 2.91 (1H, dd, *J* 16.5 and 4.5, H-3'), 2.98 (1H, dd, *J* 16.5 and 12.5, H-3'), 5.37 (1H, dd, *J* 12.5 and 4.5, H-2'), 5.61 (1H, d, *J* 6.1, H-5'), 6.53 (1H, s, H-5), 6.77 (1H, s, H-3), 7.47 (1H, d, *J* 6.1, H-6'), 7.53 (3H, m, Ph), 7.73 (2H, d, *J* 7.2, Ph); δ_{C} (125 MHz, CDCl₃) 39.6 (CH₂), 76.5 (CH), 108.4 (CH), 111.9 (CH), 114.0 (CH), 126.0 (2 × CH), 129.4 (2 × CH), 130.8 (quat.), 132.0 (CH), 163.9 (quat.), 162.3 (CH), 161.9 (quat.), 179.5 (C=O), 189.6 (C=O); *m/z* 268 (M⁺, 11%), 239 (22), 212 (13), 170 (100), 115 (13), 102 (33), 77 (18), 69 (18), 55 (11).

1,3-Dipolar cycloadditions of azomethine ylides

Desilylation method—general procedure. The corresponding 4H-pyran-4-one (0.37 mmol) and *N*-benzyl-*N*-(methoxymethyl)(trimethylsilyl)methylamine **11** (0.12 g, 0.55 mmol) were dissolved in dry toluene (5 cm³) and trifluoroacetic acid (1 drop) was added. After stirring for 48 h at room temperature the reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography.

***tert*-Butyl 2-benzyl-1,2,3,3a,7,7a-hexahydro-7-oxo-5-phenylpyrano[2,3-*c*]pyrrole-7a-carboxylate 13.** From *tert*-butyl 4-oxo-6-phenyl-4H-pyran-3-carboxylate **4**, as a pale yellow oil (0.14 g, 91%) (Found: C, 74.2; H, 6.8; N, 3.4. Calc. for C₂₅H₂₇NO₄: C, 74.05; H, 6.7; N, 3.45%); ν_{max} (liquid film)/cm⁻¹ 1728 (ester C=O), 1646 (C=O), 1608 (C=C); δ_{H} (500 MHz, CDCl₃) 1.44 (9H, s, Bu^t), 3.00 (1H, dd, *J* 10.5 and 5, H-3), 3.17 (1H, dd, *J* 10.5 and 7, H-3), 3.28 (1H, d, *J* 10, H-1), 3.34 (1H, d, *J* 10, H-1), 3.63 (1H, d, *J* 13, CH₂Ph), 3.72 (1H, d, *J* 13, CH₂Ph), 5.44 (1H, dd,

J 7 and 5, H-3a), 6.09 (1H, s, H-6), 7.28 (5H, m, Ph), 7.43 (2H, t, *J* 7.5, Ph-3' and 5'H), 7.49 (1H, t, *J* 7.5, Ph-4'H), 7.73 (2H, d, *J* 7.5 Hz, Ph-2' and 6'H); δ_{C} (125 MHz, CDCl₃) 26.8 (3 × CH₃), 57.5 (NCH₂), 57.8 (NCH₂), 58.9 (NCH₂), 59.9 (quat.), 81.5 (CH), 81.9 (quat.), 99.1 (CH), 125.5 (2 × CH), 126.1 (CH), 127.3 (2 × CH), 127.5 (2 × CH), 127.7 (2 × CH), 130.7 (CH), 131.8 (quat.), 137.2 (quat.), 166.4 (quat.), 167.2 (C=O), 187.1 (C=O).

Ethyl 2-benzyl-1,2,3,3a,7,7a-hexahydro-7a-[(*N*-methyl-*N*-benzylamino)methyl]-7-oxo-5-phenylpyrano[2,3-*c*]pyrrole-3a-carboxylate 15. From ethyl 4-oxo-6-phenyl-4H-pyran-2-carboxylate **5**, as a pale yellow oil (0.06 g, 29%) (Found: C, 75.5; H, 6.7; N, 5.4. Calc. for C₃₂H₃₄N₂O₄: C, 75.3; H, 6.7; N, 5.5%); ν_{max} (liquid film)/cm⁻¹ 1726 (ester C=O), 1646 (C=O), 1611 (C=C); δ_{H} (500 MHz, CDCl₃) 1.33 (3H, t, *J* 7.2, CH₃CH₂), 2.00 (3H, s, NCH₃), 2.88 (1H, d, *J* 13.5, NCH₂), 3.02 (1H, d, *J* 8.5, NCH₂), 3.05 (1H, d, *J* 13.5, NCH₂), 3.32 (1H, d, *J* 13.5, NCH₂), 3.35 (1H, d, *J* 11.5, NCH₂), 3.41 (1H, d, *J* 11.5, NCH₂), 3.53 (1H, d, *J* 8.5, NCH₂), 3.56 (1H, d, *J* 13.5, NCH₂), 3.67 (1H, d, *J* 13.5, NCH₂), 3.77 (1H, d, *J* 13.5, NCH₂), 4.20 (2H, m, CH₂CH₃), 6.21 (1H, s, H-6), 7.15–7.28 (10H, m, Ph), 7.45 (2H, t, *J* 7.8, H-3',5'), 7.49 (1H, t, *J* 7.8, H-4'), 7.79 (2H, d, *J* 7.8, H-2',6'); δ_{C} (125 MHz, CDCl₃) 14.5 (CH₃CH₂), 43.1 (NCH₃), 59.1 (CH₂), 59.3 (quat.), 59.7 (CH₂), 61.7 (CH₂), 63.1 (CH₂), 64.1 (CH₂), 64.4 (CH₂), 90.2 (quat.), 101.7 (CH), 126.6 (2 × CH), 126.8 (CH), 127.0 (CH), 127.9 (2 × CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.9 (2 × CH), 129.1 (2 × CH), 131.6 (CH), 132.8 (quat.), 138.4 (quat.), 138.9 (quat.), 165.4 (quat.), 170.7 (C=O), 194.5 (C=O).

6-Phenyl-2-(3-benzyl-1,3-oxazolidin-5-yl)-4H-pyran-4-one 20. From 4-oxo-6-phenyl-4H-pyran-2-carbaldehyde **6**, as a white powder (69 mg, 49%), mp 144–145 °C (Found: M⁺, 333.135. C₂₁H₁₉NO₃ requires: *M*, 333.1365); ν_{max} (KBr)/cm⁻¹ 1659 (C=O), 1615 (C=C); δ_{H} (500 MHz, CDCl₃) 3.18 (1H, dd, *J* 11 and 7, H-4'), 3.49 (1H, dd, *J* 11 and 7, H-4'), 3.85 (2H, s, NCH₂), 4.60 (2H, s, H-2'), 4.84 (1H, t, *J* 7, H-5'), 6.51 (1H, d, *J* 1.5, H-5), 6.73 (1H, d, *J* 1.5 Hz, H-3), 7.25–7.35 (6H, m, Ph), 7.48 (2H, m, Ph), 7.72 (2H, m, Ph); δ_{C} (125 MHz, CDCl₃) 57.1 (NCH₂), 58.4 (NCH₂), 72.4 (CH), 88.0 (CH₂), 111.5 (CH), 112.2 (CH), 125.8 (2 × CH), 127.6 (CH), 128.6 (2 × CH), 128.7 (2 × CH), 129.1 (2 × CH), 131.1 (quat.), 131.5 (CH), 138.1 (quat.), 163.5 (quat.), 167.6 (quat.), 179.9 (C=O); *m/z* 333 (M⁺, 5%), 42 (62), 65 (12), 77 (12), 91 (100), 102 (13), 132 (20), 133 (50).

Decarboxylation method—general procedure

The corresponding 4H-pyran-4-one (0.59 mmol), sarcosine (0.20 g, 2.3 mmol) and paraformaldehyde (0.18 g, 5.8 mmol) were suspended in toluene (10 cm³) and the mixture was refluxed for 3 h. The water formed was removed by the aid of a Dean–Stark trap. After completion of the reaction the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography.

***tert*-Butyl 2-methyl-1,2,3,3a,7,7a-hexahydro-7-oxo-5-phenylpyrano[2,3-*c*]pyrrole-7a-carboxylate 17.** From *tert*-butyl 4-oxo-6-phenyl-4H-pyran-3-carboxylate **4** as a white semi-solid (0.14 g, 72%) (Found: C, 69.9; H, 7.2; N, 4.2. Calc. for C₁₉H₂₃NO₄: C, 69.3; H, 7.0; N, 4.3%); ν_{max} (KBr)/cm⁻¹ 1729 (ester C=O), 1648 (C=O), 1609 (C=C); δ_{H} (250 MHz, CDCl₃) 1.44 (9H, s, Bu^t), 2.37 (3H, s, NCH₃), 3.04 (1H, dd, *J* 10.5 and 5, H-3), 3.10 (1H, dd, *J* 10.5 and 6.5, H-3), 3.23 (1H, d, *J* 10.5, H-1), 3.28 (1H, d, *J* 10.5, H-1), 5.42 (1H, dd, *J* 6.5 and 5, H-3a), 6.09 (1H, s, H-6), 7.46 (3H, m, H-3',4',5'), 7.75 (2H, d, *J* 7, H-2',6'); δ_{C} (125 MHz, CDCl₃) 27.8 (3 × CH₃), 42.3 (NCH₃), 58.5 (quat.), 61.2 (CH₂), 61.4 (CH₂), 82.6 (CH), 83.2 (quat.), 100.0 (CH), 126.5 (2 × CH), 128.7 (2 × CH), 131.8 (CH), 132.8 (quat.),

167.6 (quat.), 168.2 (C=O), 188.0 (C=O); m/z 330 (M^+ , 17%), 274 (21), 230 (100).

Ethyl 1,2,3,3a,7,7a-hexahydro-2-methyl-7-oxo-5-phenylpyranol[2,3-*c*]pyrrole-3a-carboxylate 18. From ethyl 4-oxo-6-phenyl-4*H*-pyran-2-carboxylate **5**, as a pale yellow semi-solid (0.067 g, 38%) (Found: M^+ , 301.131. $C_{17}H_{19}NO_4$ requires: M , 301.131); ν_{\max} (KBr)/ cm^{-1} 1726 (C=O), 1648 (C=O), 1603 (C=C); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, t, J 7.2, CH_3CH_2), 2.45 (3H, s, NCH_3), 3.03 (1H, t, J 9.5, H-1), 3.23 (1H, t, J 9.5, H-1), 3.25 (1H, d, J 11, H-3), 3.43 (1H, d, J 11, H-3), 3.50 (1H, t, J 9.4, H-7a), 4.25 (2H, q, J 7.2, OCH_2), 5.99 (1H, s, H-6), 7.44 (2H, t, J 7.5, H-3',5'), 7.51 (1H, t, J 7.5, H-4'), 7.82 (2H, d, J 7.5, H-2',6'); δ_C (125 MHz, $CDCl_3$) 14.2 (CH_3), 42.3 (NCH_3), 51.8 (CH), 59.2 (CH_2), 62.7 (CH_2), 67.3 (OCH_2), 90.2 (quat.), 101.1 (CH), 127.3 (2 \times CH), 128.8 (2 \times CH), 132.1 (CH), 132.9 (quat.), 169.0 (quat.), 170.3 (C=O), 191.0 (C=O); m/z 301 (M^+ , 17%), 255 (30), 202 (28), 154 (12), 150 (31), 105 (56), 82 (79), 77 (30), 69 (15), 57 (100), 42 (22).

6-Phenyl-2-(3-methyl-1,3-oxazolidin-5-yl)-4*H*-pyran-4-one 19. From 4-oxo-6-phenyl-4*H*-pyran-2-carbaldehyde **6**, as a pale yellow oil (71 mg, 47%) (Found: C, 70.2; H, 5.8; N, 5.4. Calcd. for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N, 5.4%). δ_H (250 MHz, $CDCl_3$) 2.53 (3H, s, NCH_3), 3.15 (1H, dd, J 11.8 and 6.5, H-4'), 3.41 (1H, dd, J 11.8 and 6.5, H-4'), 4.52 (1H, d, J 8.2, H-2'), 4.54 (1H, d, J 8.2, H-2'), 4.84 (1H, t, J 6.5, H-5'), 6.49 (1H, d, J 2.3, H-3), 6.72 (1H, d, J 2.3, H-5), 7.51 (3H, m, H-3',4',5'), 7.37 (2H, m, H-2',6'); δ_C (125 MHz, $CDCl_3$) 41.9 (NCH_3), 59.4 (NCH_2), 72.3 (CH), 90.0 (CH_2), 111.5 (CH), 112.1 (CH), 125.8 (2 \times CH), 129.1 (2 \times CH), 131.1 (quat.), 131.5 (CH), 163.5 (quat.), 167.6 (quat.), 179.9 (C=O); m/z 258 (MH^+ , 100%).

Reactions with the dipole generated from 6,7-dimethoxy-2-(methoxycarbonylmethyl)-3,4-dihydroisoquinolinium bromide—general procedure

The appropriate 4*H*-pyran-4-one (1.0 mmol) and 6,7-dimethoxy-(2-methoxycarbonylmethyl)-3,4-dihydroisoquinolin-2-ium bromide **25** (0.29 g, 0.85 mmol) were dissolved in dry methanol (10 cm^3). Triethylamine (0.14 cm^3 , 0.10 g, 1 mmol) was added and the reaction mixture was stirred at room temperature for 10–24 h. The solvent was removed under reduced pressure and the residue was suspended in ether (20 cm^3). The ethereal solution was washed with water (10 cm^3) then brine (5 cm^3), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with hexane–ethyl acetate (1:1).

Mixture of cycloadducts 26 and 27. From *tert*-butyl 4-oxo-6-phenyl-4*H*-pyran-3-carboxylate **4**, as a pale yellow oil (0.47 g, 87%) (Found: MH^+ , 536.2285. $C_{30}H_{34}NO_8$ requires: M , 536.228). Ratio of isomers **26a**:**27** = 29:4:19 (from 1H NMR spectrum). For chemical shifts and coupling constants of identifiable peaks in the 1H NMR spectrum, see Table 1.

Cycloadduct 29. From ethyl 4-oxo-6-phenyl-4*H*-pyran-2-carboxylate **5**, as a pale yellow oil (18 mg, 4%) (Found: C, 66.0; H, 5.5; N, 2.7. Calcd. for $C_{27}H_{27}NO_8$: C, 65.7; H, 5.5; N, 2.8%); δ_H (500 MHz, $CDCl_3$) 2.55 (1H, m, H-8), 2.88 (1H, m, H-8), 3.27 (2H, m, H-7), 3.37 (1H, d, J 7.3, H-12c), 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 3.93 (3H, s, OMe), 4.52 (1H, s, H-5), 4.83 (1H, d, J 7.3, H-12b), 6.06 (1H, s, H-2), 6.60 (1H, s, H-12), 7.10 (1H, s, H-9), 7.50 (3H, m, H-3',4',5'), 7.75 (2H, d, J 7.6, H-2',6'); δ_C (125 MHz, $CDCl_3$) 23.4 (CH_2), 45.3 (CH_2), 52.6 (OMe), 53.6 (OMe), 55.9 (OMe), 56.0 (OMe), 57.9 (CH), 63.8 (CH), 71.1 (CH), 90.2 (quat.), 100.9 (CH), 110.4 (CH), 111.0 (CH), 125.8 (quat.), 126.3 (quat.), 127.1 (2 \times CH), 128.5 (quat.), 128.7 (2 \times CH), 132.1 (CH), 147.7 (quat.), 148.3 (quat.), 168.4 (quat.), 168.8 (quat.), 169.5 (quat.), 189.4 (C=O).

Methyl 4-oxo-6-phenyl-4*H*-pyran-2-carboxylate 28

From ethyl 4-oxo-6-phenyl-4*H*-pyran-2-carboxylate **5**, as a white solid (0.17 g, 74%), mp 125 °C (lit.¹² 127 °C); ν_{\max} (KBr)/ cm^{-1} 1748 (C=O), 1656 (C=O), 1618 (C=C); δ_H (250 MHz, $CDCl_3$) 4.01 (3H, s, OMe), 6.66 (d, 1H, J 2.4, H-5), 7.12 (d, 1H, J 2.4, H-3), 7.53 (3H, m, H-3',4',5'), 7.86 (2H, m, H-2',6'); δ_C (125 MHz, $CDCl_3$) 53.5 (OCH_3) 112.5 (CH), 119.3 (CH), 126.2 (2 \times CH), 129.2 (2 \times CH), 130.5 (quat.), 132.0 (CH), 152.3 (quat.), 160.6 (quat.), 163.9 (quat.), 179.6 (quat.).

8,9-Dimethoxy-3-methoxycarbonyl-2-(4-oxo-6-phenyl-4*H*-pyran-2-yl)-2,3,6,10b-tetrahydro-5*H*-[1,3]oxazolo[2,3-*a*]isoquinoline 30

From 4-oxo-6-phenyl-4*H*-pyran-2-carbaldehyde **6**, as a white solid, recrystallised from ethanol (0.2 g, 44%), mp 133–135 °C (Found: C, 67.4; H, 5.4; N, 3.0. Calcd. for $C_{26}H_{25}NO_7$: C, 67.4; H, 5.4; N, 3.0%) (Found: MH^+ , 464.170. $C_{26}H_{26}NO_7$ requires: M , 464.170); ν_{\max} (KBr)/ cm^{-1} 1747 (C=O), 1665 (C=O); δ_H (500 MHz, $CDCl_3$) 2.66 (1H, m), 2.97–3.13 (3H, m), 3.89 (9H, s, 3 \times OMe), 4.05 (1H, d, J 4.6, H-3), 5.00 (1H, d, J 4.6, H-2), 5.58 (1H, s, H-10b), 6.53 (1H, d, J 1.6, H-5'), 6.65 (1H, s, H-7), 6.71 (1H, d, J 1.6, H-3'), 6.93 (1H, s, H-10), 7.49 (3H, m, Ph), 7.74 (2H, m, Ph); δ_C (125 MHz, $CDCl_3$) 29.4 (Ar- CH_2), 47.8 (CH_2N), 53.0 (OMe), 56.1 (OMe), 56.2 (OMe), 72.6 (CH), 76.7 (CH), 92.6 (CH), 110.7 (CH), 111.4 (CH), 111.7 (CH), 113.0 (CH), 122.3 (quat.), 126.0 (2 \times CH), 127.7 (quat.), 129.3 (2 \times CH), 131.2 (quat.), 131.7 (CH), 148.0 (quat.), 149.8 (quat.), 163.7 (quat.), 165.9 (quat.), 171.5 (C=O), 179.8 (C=O); m/z 465 (24%), 464 (MH^+ , 100).

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