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Stereoselective routes to substituted β-amino carbonyl compounds via heterodiene [4π+2π] cycloadditions of auxiliary-based C_2 symmetric ketene acetals

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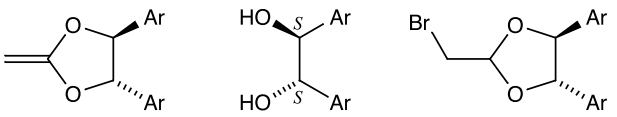
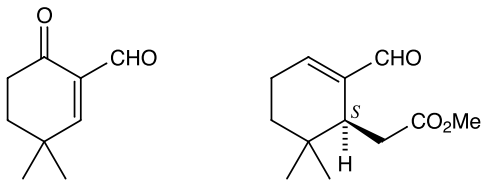
Abstract—Heterodiene [4π+2π] cycloadditions of (*S*,*S*)-4,5-diaryl-2-methylene-1,3-dioxolanes **1** to a series of β-amido-α,β-unsaturated carbonyl compounds are diastereoselective (d.r.≥4:1). The products can be purified by trituration or crystallisation and hydrolysed with acid to generate the corresponding β-amido carbonyl compounds, the overall sequence effecting an auxiliary-based enantioselective conjugate addition of an acetate enolate, leading to β-aminoacid derivatives.

The [4π+2π] cycloaddition of α,β-unsaturated carbonyl compounds (1-oxabutadienes) to alkenes can be an effective route to dihydropyrans and other synthetically useful materials.[1] Our interest in exploiting reactions of this type[2] led us to prepare a series of homochiral C_2-symmetric ketene acetals **1**, starting with the corresponding diols **2** and proceeding via the derived bromoacetals **3**, for use as electron-rich dienophiles, and we established that such systems could serve as recyclable acetate enolate equivalents.[3] In an illustration of our strategy, the aldehyde **4** was transformed into the functionalised α-cyclohomogeranyl system (*S*)-**5** in three steps, the first being a diastereoselective [4π+2π] cycloaddition to the ketene acetal (*S*,*S*)-**1a**.[4] We considered that a similar strategy (Scheme 1) might provide access to homochiral β-amino carbonyl compounds, especially those with synthetic value such as substituted β-aminoacids[5] and piperidines.[6] Related heterodiene cycloadditions have been used before for the preparation of racemic aminosugars[7] and carbapenem precursors,[8] but a variant combining exploitable levels of asymmetric induction and a recyclable auxiliary remained an attractive target.[9] We therefore undertook a study with this objective and herein report our findings in detail.[10]



1 **2** **3**

a Ar = *o*-Tol
b Ar = Ph



4 **5**

In the first part of our study, various cycloadditions were attempted using the ketene acetals **1**,[3] **6**[11] and **7**[12] as 2π components. For use as heterodienes, the ketoesters **10**[8] and **11** were prepared from the respective methoxymethylene compounds **8** and **9**,[13] and on the basis of the evidence presented by Bayles et al.,[8] the isolated product in each case was assigned the (*E*)-geometry. A third heterodiene, the diketone **12**,[14] was accessible from 2,4-pentanedione in a single operation. Various [4π+2π] permutations of these materials provided cycloadducts in the form of dihydropyran-derived ortholactones (Table 1). In an initial experiment, the alkene **6** was treated with a slight excess of the ketoester **10** in THF at room temperature. The resulting cycloaddition took 3 days to reach completion, and a simple isolation procedure gave the ortholactone (±)-**13** in acceptable yield. The ^{1}H NMR spectrum of **13** included signals at δ (ppm) 5.11 (1H, dd, *J*=5.5, 9.5 Hz) and 6.64 (1H, br d, *J*=9.5 Hz), which were assigned to the C-4

Keywords: heterodiene cycloaddition; ketene acetal; chiral auxiliary; β-amino acid; pyrano[4,3-*b*]pyridine.

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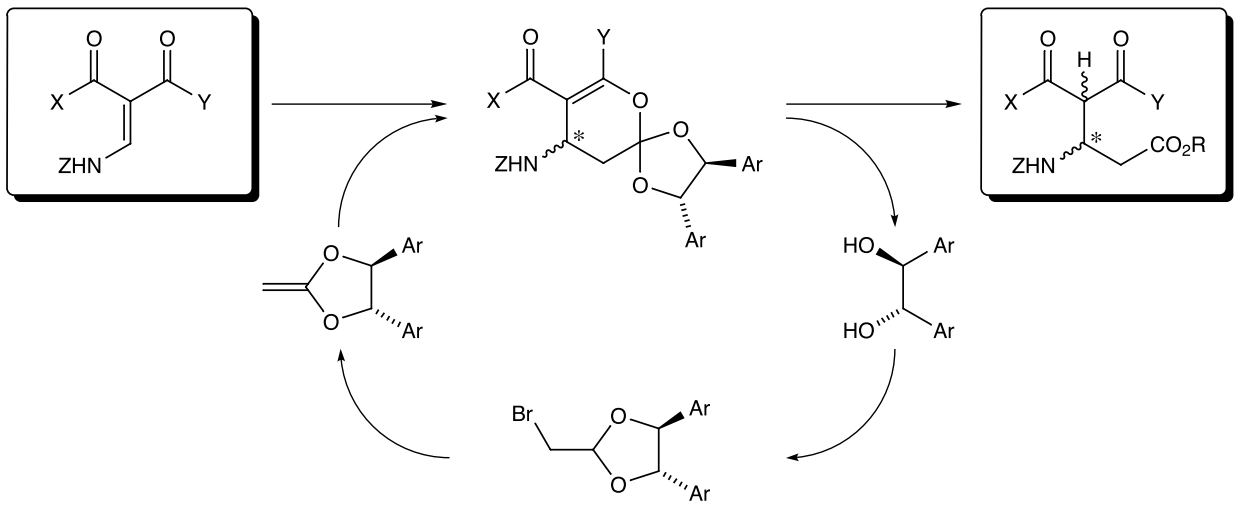


Scheme 1.

methine and amide NH, respectively; signals corresponding to these were characteristic all of the cycloadducts subsequently isolated. The cycloaddition of the ketoester **10** and the cyclic ketene acetal **7** was complete within 2 h, giving the spirocyclic ortholactone (±)-**14**. Although more favourable conditions were employed, it is assumed that the fast reaction of the ketoester **10** with the ketene acetal **7**, compared to that of **6**, is primarily due to steric differences, the reacting π-bond being significantly less encumbered in the cyclic system **7**.

The reaction of equimolar quantities of the ketoester **10** and the ketene acetal (*S*,*S*)-**1a** (THF, −15°C) gave, after 3 days, a crude mixture of the cycloadducts **15** and **16** with a diastereoisomeric ratio (d.r.) of ca. 4:1 as judged by 250 MHz ^{1}H NMR spectroscopy. One crystallisation from isohexane allowed isolation of the major adduct **15** (60%, d.e. >95% by HPLC). An apparent by-product, detected in early samples of the reaction mixture, was identified (by synthesis) as the monoacetate **17**, formed by hydrolysis of unreacted ketene acetal **1a** during isolation or analysis.[15] The cycloaddition between (*S*,*S*)-**1a** and the benzyl ester **11** (entry 4), proceeded more slowly than that of **10** but with similar diastereoselectivity. Detailed analysis of the purified cycloadduct **18** using high field NMR correlation techniques (COSY, HMQC) indicated its constitution and, by comparison, its relationship with the methyl ester **15**. The diketone **12** reacted slowly with the ketene acetal (*S*,*S*)-**1a** (−15°C, 5 days) yielding the mixed cycloadducts **20** and **21** (67%). The major product **20** crystallised from isohexane as colourless needles, mp 112–115°C, and a crystal was analysed by X-ray crystallography. Although this material turned out to be poorly diffracting, the resulting data unequivocally confirmed the gross structure and (4*S*) configuration (Fig. 1).

In previous studies, cycloadditions of the diphenyl ketene acetal **1b** have been less effective than those of the ditolyl compound **1a**, both in terms of the level of diastereoselection observed and the ease with which the resulting cycloadducts could be purified.[3,4] However, in the reactions of **1b** with the ketoester **10** and diketone **12** (entries 6 and 7), the yields of the respective cycloadducts **22** and **24** and their

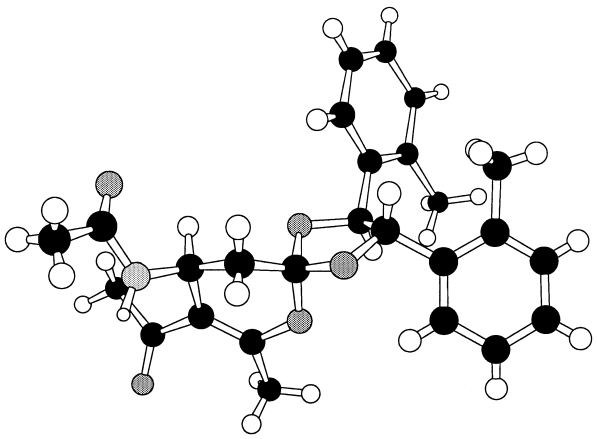


Figure 1. X-Ray structure of the cycloadduct **20**.

purity after crystallisation compared favourably with those derived from **1a**. The structural parallel between the phenyl and tolyl series were readily apparent when their high field NMR spectra were compared, and the (4*S*) configuration of **24** was therefore assigned by comparison with **20**. Similarly, the (4*S*) assignment for **22**, which was verified by a short synthetic sequence as described below, strongly supports the structures assigned to **15** and **18**. Given the ready availability of the auxiliary diol (*S*,*S*)-hydrobenzoin **2b**, the diphenyl ketene acetal **1b** is the most convenient source of this type of cycloadduct.

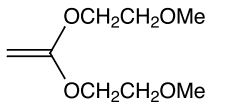
Ortholactones are readily hydrolysed by acid,[16] and the cycloadducts described in Table 1 were converted into esters by treatment with 0.1 M sulfuric acid in THF for a few hours. The ketoester cycloadducts **13** and **14** afforded the respective esters **26** and **27** as ca. 55:45 mixtures of diastereoisomers, as judged by ^{1}H NMR spectroscopy (Scheme 2). The cycloadducts **20**, **22** and **24** derived from the diaryl ketene acetals **1** were similarly transformed into the respective ring-opened derivatives **28**–**30** in fair yields, and it was established that **24** could also be hydrolysed to **30** using citric acid instead of sulfuric acid (Scheme 3). The diastereoisomeric purity of the diketone products **28** and **30** appeared to be the same as that of their precursors. The keto

Table 1. Heterodiene cycloadditions of β-acetamidoenones **10**–**12** with ketene acetals

Entry	Starting material			Solvent	Temperature (°C)	Time (h)	Products	Isolated material	
	Acetal	Diene	Ratio					Ratio	Yield (%)
1	**6**	**10**	0.9:1	THF	+20	72	**13**		64
2	**7**	**10**	10:1	–	+20	2	**14**		63
3	**1a**	**10**	1:1	THF	−15	72	**15**+**16**	≥19:1	60
4	**1a**	**11**	1:1	THF	−15	96	**18**+**19**	4.1:1	62
5	**1a**	**12**	1:1	THF	−15	120	**20**+**21**	≥4:1	67
6	**1b**	**10**	1:1	THF	−20	72	**22**+**23**	≥19:1	61
7	**1b**	**12**	1.1:1	THF	−20	120	**24**+**25**	≥19:1	63

diester **29** was obtained as a 1:1 mixture of C-2 diastereoisomers.

Two methods were developed for the removal of the auxiliary moiety, using the ester-amides **29** and **30**. The more economical method takes advantage of the susceptibility to hydrolysis of 2-hydroxyethyl esters, engendered by the catalytic influence of the local hydroxyl function.[17] Transesterification of **29** using methanol and potassium carbonate proceeded at room temperature, giving the methyl ester **31** (65%) and simultaneously making the diol (*S*,*S*)-**2b** available for recycling (Scheme 4). The alternative route from **29** to **31** involved the removal of the auxiliary by catalytic hydrogenation, which cleanly provided the acid **32** and hence, by methylation, the ester **31**. However, this method also sacrificed the original auxiliary, from which only diphenylethane **33** remained. The hydrogenolytic sequence was repeated with the diketoester **30**, providing the ester **35** in 70% yield over two steps.



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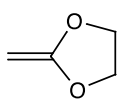

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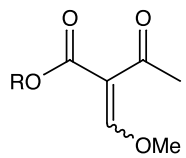
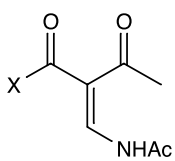
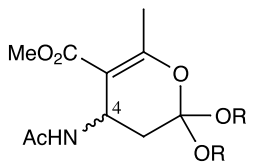


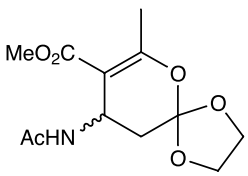
8 R = Me
9 R = Bn



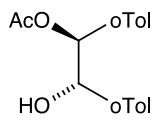
10 X = OMe
11 X = OBn
12 X = Me



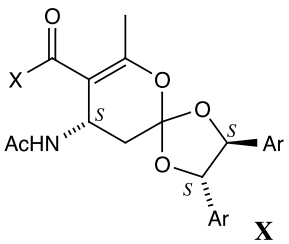
13 R = CH_2CH_2OMe

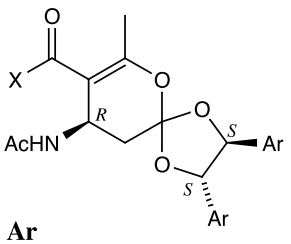


14



17



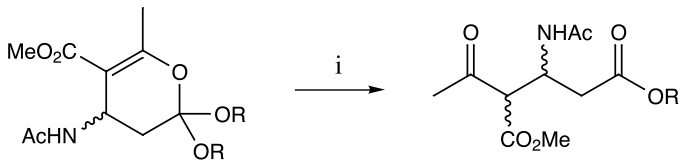


	X	Ar	
15	OMe	*o*-Tol	**16**
18	OBn	*o*-Tol	**19**
20	Me	*o*-Tol	**21**
22	OMe	Ph	**23**
24	Me	Ph	**25**

Confirmation of the absolute stereochemistry of the cycloadduct **22** was obtained by subjecting the derived ester **31** to triethylsilane reduction, as described by Bayles et al.[8] The ^{1}H NMR spectrum of the major product (−)-**36** corresponded to that of racemic material,[8] and its specific rotation confirmed its antipodal relationship with (2*R*,3*S*,4*R*)-**36**, a precursor of the β-lactam antibiotic, thienamycin.[18]

The extension of the above strategy to nitrogen heterocyclic systems was attempted with the uracil derivative **37**,[19] which reacted diastereoselectively with (*S*,*S*)-**1a** to give the spirocyclic pyrano[4,3-*d*]pyrimidines **38** and **39** (50%, d.r. 4.26:1 by HPLC) (Scheme 5). The structures of these cycloadducts were readily assigned by comparison of their distinctive ^{1}H NMR spectra with those of structurally similar analogues derived from chromone-3-carbaldehyde.[3]

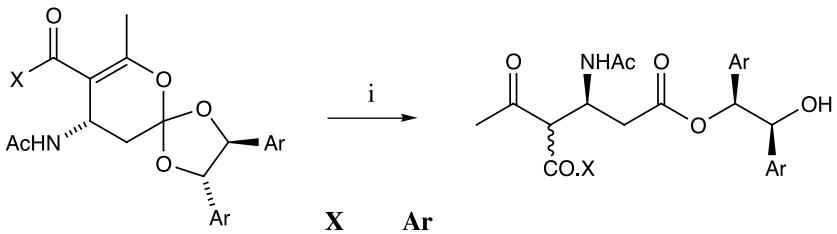
An attempt to transform the piperidine **40**[20] into the potentially useful heterodiene **41** by oxidation with DDQ gave a poor yield; the lability of the product may have been a contributing factor. However, the viability of the proposed heterodiene cycloadditions was established by treating **41** with ethoxyethene, which gave the expected *endo*- and *exo*-cycloadducts **42** and **43** (52%, d.r. 3.4:1), and with 2-methoxypropene, which gave the corresponding adducts **44** and **45** (77%, d.r. 3.6:1) (Scheme 6). These cycloadducts were readily identified by spectroscopy, the ^{1}H NMR signals due to the respective C-5 and C-8 hydrogens being particularly characteristic.[2] A second piperidine heterodiene was prepared from the *N*-tosyl piperidone **46**, this time introducing the unsaturation via the selenium technique.[21] This gave a good yield of the aldehyde **47**, but it too proved unstable. In a trial cycloaddition with ethoxyethene, the aldehyde **47** was converted into the *endo*- and *exo*-cycloadducts **48** and **49** with the expected level of



13 R = CH_2CH_2OMe
14 RR = CH_2CH_2

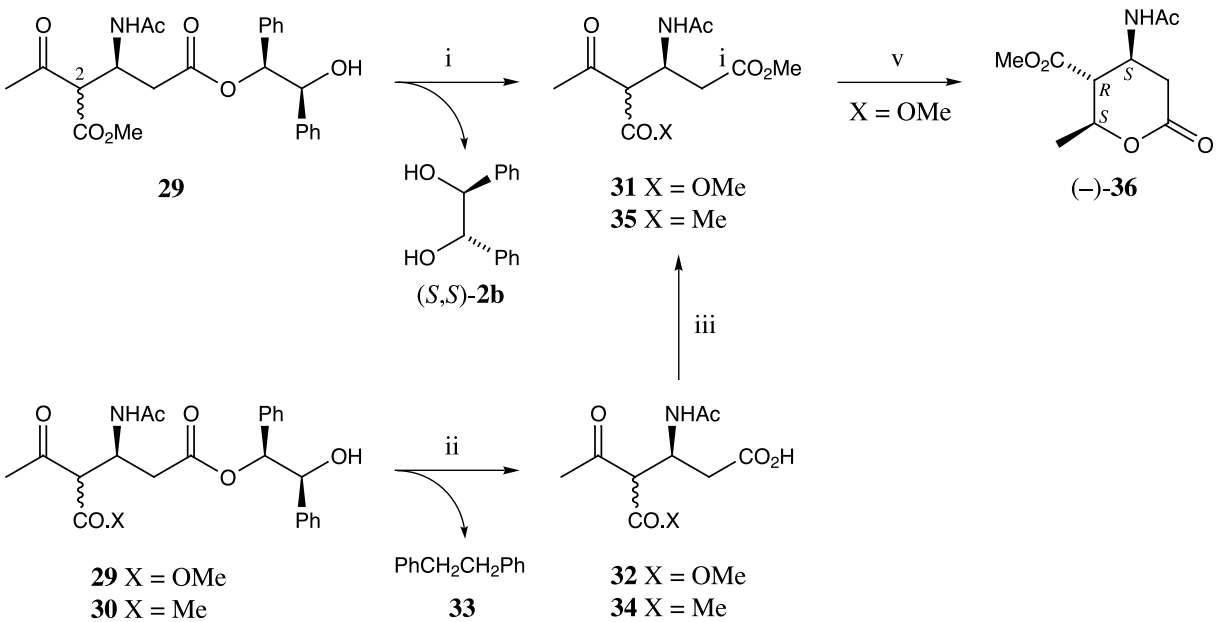
26 R = CH_2CH_2OMe
27 R = CH_2CH_2OH

Scheme 2. *Reagents*: (i) 0.1 M aq. H_2SO_4, THF, 20°C, 14 h (60–75%).



	X	Ar	
20	Me	*o*-Tol	**28**
22	OMe	Ph	**29**
24	Me	Ph	**30**

Scheme 3. *Reagents*; (i) 0.1 M aq. H_2SO_4, THF, 20°C, 1–1.5 h (56–65%).



29

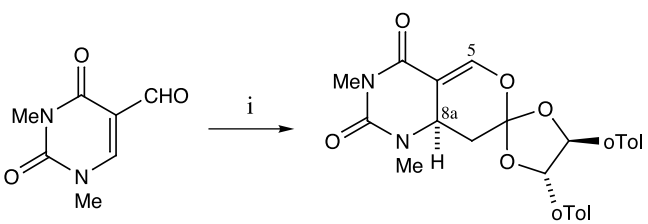
31 X = OMe
35 X = Me

29 X = OMe
30 X = Me

33

32 X = OMe
34 X = Me

Scheme 4. *Reagents*: (i) MeOH, K_2CO_3, 20°C, 16 h (65%); (ii) H_2, Pd–C, MeOH, 3–4 h; (iii) CH_2N_2, Et_2O, EtOH (X=OMe, 61% over two steps; X=Me, 70% over two steps); (iv) Et_3SiH, CF_3CO_2H, CH_2Cl_2, 20°C, 48 h (81%).



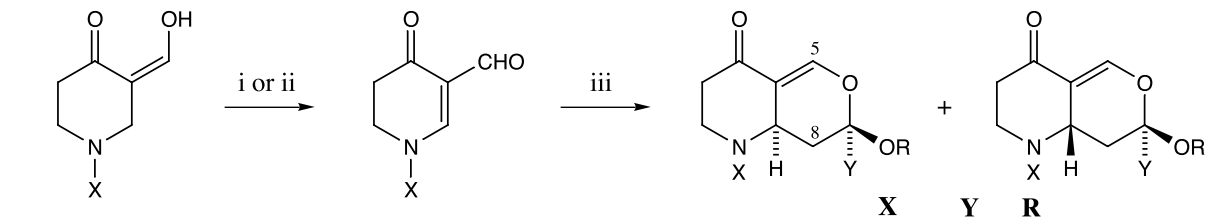
37

38 8a-*R* (shown)
39 8a-*S*

Scheme 5. *Reagents*: (i) 1 equiv. **1a**, THF, −15°C, 72 h (50%; d.r. 81:19).

diastereoselection (3.5:1) but in low total yield (30%). Due to the problems associated with the lability of the aldehydes **41** and **47**, further efforts in this area will focus on the use of alternative heterodienes.

Mechanistically, the facial selectivity manifested in the preferential formation of the (4*S*)-cycloadducts **20** and **22** from the respective dienes **10** and **12** is consistent with the concerted cycloaddition models depicted in Figure 2. The most favoured reacting (*s-cis*) conformations available to the heterodienes **10**–**12** are assumed to be the



Scheme 6. *Reagents*; (i) DDQ, CH_2Cl_2, 20°C, 16 h (**41**, 22%); (ii) (a) PhSeCl, CH_2Cl_2, pyridine, 0°C, 20 min, then aq. HCl, then 30% H_2O_2, 0°C (**47**, 63%); (iii) excess RO(Y)C=CH_2, CH_2Cl_2, 20°C, 14–28 days (**42/43**, 52%; **44/45**, 77%; **48/49**, 30%; d.r.≥3:1 in each case).

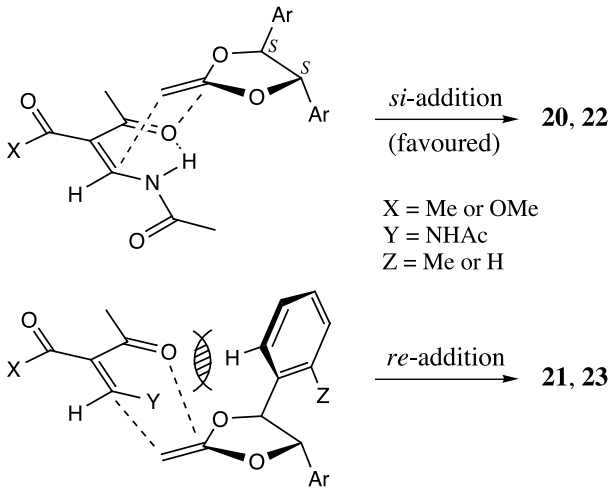


Figure 2. Mechanistic models for the concerted cycloaddition of (*S*,*S*)-**1** to β-acetamidoenones **10** and **12**.

hydrogen-bonded arrangements shown in the Figure. This is supported for the esters **10** and **11** by the ^{13}C NMR studies described by Bayles et al.,[8] which indicated that the preparative routes to these compounds predominantly give rise to the *E*-geometry, and for **12** by the results of calculations.[22] Synthetically, the sequence shown in Scheme 1 has been shown to provide a stereoselective route to a variety of functionalised β-amino carbonyl systems based on a recyclable auxiliary strategy.

1. Experimental

1.1. General

All compounds are racemic unless their names are preceded by stereochemical descriptors. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, IR spectra were of neat thin films on NaCl plates, recorded on a Perkin–Elmer 1710FT spectrometer. NMR spectra were measured on a Bruker AC300 spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz), Bruker DPX250 (^1H at 250 MHz, ^{13}C at 63 MHz) and Bruker Advance 400 (^1H at 400 MHz, ^{13}C at 100 MHz) instruments for solutions in deuteriochloroform with tetramethylsilane as the internal standard; *J* values are quoted to the nearest 0.5 Hz. Assignments for ^{13}C spectra are tentative unless the use of correlation techniques is indicated. Mass spectra were measured on a Finnegan 4500 (low resolution) and Kratos Concept S1 (high resolution) instruments using the ammonia CI method, or on a Micromass Platform II coupled to a Hewlett–Packard HP1100 HPLC system for LC/MS work. Data for most of the peaks of intensity <20% of that of the base peak are omitted. Analytical HPLC and LC/MS were run using the following (generic) conditions on the Hewlett Packard system: Column, Luna 3 micrometer C18(2) 50×2.0 mm; mobile phase, A 1000 mL H_2O+0.5 mL trifluoroacetic acid (TFA), B 1000 mL MeCN+0.5 mL TFA; %B 0 to 95% in 0 to 8 min (linear gradient) then 0% B for 2 min prior to next run; flow rate, 1 mL min^{-1}, temperature, 40°C; injection volume, 1 μL; detection wavelength user selectable, default 220 nm. Optical rotations were measured at 589 nm using an AA-10 polarimeter (Optical Activity Ltd.).

Starting materials and solvents were routinely purified by conventional techniques[23] and most reactions were carried out under nitrogen or argon. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL G/UV_{254} plates. The chromatograms were visualised by the use of UV light or the following developing agents; ethanolic vanillin or potassium permanganate. Unless otherwise indicated, preparative (column) chromatography was carried out using the flash technique[24] on 60H silica gel (Merck 9385), Florisil® (60–100 mesh) or basic alumina. Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, bp 40–60°C, unless otherwise stated. Isohexane (Fisher) is mainly 2-methylpentane. 'Ether' refers to diethyl ether.

1.1.1. (*S*,*S*)-4,5-Bis(2-methylphenyl)-2-methylene-1,3-dioxolane 1a. The following is a modified version of the procedure described previously.[4] To a stirred solution of the (*S*,*S*)-bromoacetal (−)-**2a**[3] (250 mg, 0.72 mmol) in anhydrous THF (15 mL) at −15°C was added solid potassium *t*-butoxide (300 mg, 2.67 mmol) and, a few minutes later, a solution of methyltrioctylammonium chloride (Fluka 69485; 200 mg, 0.49 mmol) in anhydrous THF (2 mL). The reaction mixture was maintained at −15°C for 16–18 h after which time no bromoacetal was detected by HPLC analysis. The reaction mixture was filtered through a short plug of basic alumina, and the filtrate containing the (*S*,*S*) ketene acetal (−)-**1a** (assumed 192 mg, 90%) was used directly. A concentrated sample had δ_H 1.82 (6H, s, 2×ArMe), 3.45 (2H, s, C=CH_2), 5.35 (2H, s, CHAr), 7.05 (2H, dd, *J*=1, 7.5 Hz, 3,3′-ArH), 7.18–7.30 (4H, m,

4,4′,5,5′-ArH), 7.54 (2H, dd, J=1.5, 8 Hz, 6,6′-ArH). HPLC analysis of a THF solution of **1a** showed a single peak, corresponding to the hydrolysis product **17**.

1.1.2. (*S*,*S*)-4,5-Diphenyl-2-methylene-1,3-dioxolane 1b.[3] This was prepared as a solution in THF using the method described for **1a**, starting with the (*S*,*S*)-bromoacetal (−)-**2b**[3] and assuming a yield of 90%.

1.1.3. Benzyl 3-methoxy-2-(1-oxoethyl)prop-2-enoate 9.[13] To a round-bottomed flask fitted with a magnetic stirrer was added anhydrous trimethyl orthoformate (15.9 g, 0.15 mol), benzyl acetoacetate (19.2 g, 0.10 mol) and acetic anhydride (24.5 g, 0.24 mol). The mixture was heated under reflux until complete by TLC (24 h). Concentration of the reaction mixture followed by chromatography gave the title compound **9** (4.25 g, 18%) as an orange solid (*E* and *Z* isomers, ratio ca. 1:1) which was used without further purification; ν_{max} 3543, 1713, 1633, 1588, 1276, 1197, 1138, 1071 cm^{-1}; δ_H (250 MHz) (major isomer) 2.39 (3H, s, Me), 3.97 (3H, s, OMe), 5.21 (2H, s, OCH_2Ph), 7.30–7.40 (5H, m, Ar), 7.58 (1H, s, 1′-H); (minor isomer) 2.31 (3H, s, Me), 4.01 (3H, s, OMe), 5.27 (2H, s, OCH_2Ph), 7.30–7.40 (5H, m, Ar), 7.61 (1H, s, 1′-H); m/z (ES) 235 (M+H$^+$, 100%).

1.1.4. Methyl 3-acetylamino-2-(1-oxoethyl)prop-2-enoate 10.[8] To a solution of methyl 3-methoxy-2-(1-oxoethyl)-prop-2-enoate **8**[13] (700 mg, 4.43 mmol) in THF (10 mL) under argon was added acetamide (260 mg, 4.40 mmol). The reaction mixture was heated at 100°C for 4 h and then concentrated in vacuo. The residue was purified by chromatography, eluting with petroleum–ethyl acetate (4:1), and the major product was crystallised from petroleum ether to obtain the pure title compound **10** (420 mg, 52%) as a light yellow waxy solid which was used without further purification; ν_{max} 3435, 1739, 1718, 1373, 1240, 1025, 764 cm^{-1}; δ_H (300 MHz) 2.23 (3H, s, MeCON), 2.53 (3H, s, 2′-H$_3$), 3.77 (3H, s, CO_2Me), 8.51 (1H, d, J=12 Hz, C=CH), 12.0 (1H, br s, NH); m/z 203 (M+NH$_4^+$, 100%), 186 (M+H$^+$, 60); R_f 0.42 (petroleum–ethyl acetate 2:1).

1.1.5. Benzyl 3-acetylamino-2-(1-oxoethyl)prop-2-enoate (*E*)-11. To a solution of **9** (*E* and *Z* isomers; 1.6 g, 6.8 mmol) in THF (5 mL) under argon was added acetamide (0.60 g, 10.2 mmol). The mixture was heated under reflux for ca. 15 h, allowed to cool and the solvent evaporated. Chromatography of the residue, eluting with ether, gave an orange waxy solid identified as (*E*)-**11** (1.0 g, 56%) (M+H$^+$, 262.1072. $C_{14}H_{16}NO_4$ requires 262.1079); ν_{max} 3261, 1714, 1651, 1574, 1240, 1178, 1068, 995, 783, 753, 699 cm^{-1}; δ_H (250 MHz) (major isomer; signals attributed to the minor isomer are shown in brackets) 2.24 [2.25] (3H, s, MeCON), 2.54 [2.55] (3H, s, 2′-H$_3$), 5.25 [5.30] (2H, s, CH_2O), 7.30–7.40 (5H, m, Ar), 8.57 [8.53] (1H, d, J=12 Hz, 3-H), 12.0 (1H, br s, NH); δ_C (63 MHz) 23.9 (amide Me), 31.6 (C-2′), 66.5 (CH_2O), 108.3 (C-2), 126.9, 128.25, 128.3, 128.5, 128.6, (5×ArCH), 135.9 (ArC-1), 146.6 (C-3), 165.7 (ester CO), 169.2 (amide CO), 201.5 (C-1′); m/z 262 (M+H$^+$, 100%), 186 (64), 107 (84).

1.1.6. *N*-(2-(1-Oxoethyl)-3-oxobut-1-enyl)ethanamide 12.[14] In a round-bottomed flask fitted with a mechanical stirrer was placed anhydrous trimethyl orthoformate (15.9 g, 0.15 mol), 2,4-pentanedione (10.0 g, 0.10 mol) and acetic anhydride (24.8 g, 0.24 mol). The reaction mixture was heated under reflux for 4 h. The residual acetic anhydride was removed by azeotropic distillation with toluene and the residue was filtered through silica using ether. The filtrate was evaporated and taken up in THF (10 mL). To this solution was added acetamide (8.87 g, 0.15 mol) and the reaction mixture heated under reflux for 4 h. Evaporation and chromatography (elution with ether) provided the title compound **12** (5.5 g, 33%) as an orange crystalline solid, mp 64°C [lit.[14] needles, mp 62°C (ethyl acetate)]; ν_{max} 3263, 1728, 1650, 1576, 1167 cm^{-1}; δ_H (250 MHz) 2.28 (3H, s, amide Me), 2.40 (3H, s, ketone Me), 2.52 (3H, s, ketone Me), 8.35 (1H, d, J=11 Hz, 1-H), 12.0 (1H, br s, NH); m/z 170 (M+H$^+$, 100%).

1.1.7. Methyl 4-acetylamino-6,6-bis(2-methoxyethoxy)-5,6-dihydro-2-methyl-4*H*-pyran-3-carboxylate 13. To a solution of 1,1-bis(2-methoxyethoxy)ethene **6**[11] (204 mg, 1.16 mmol) in THF (10 mL) at room temperature was added the diene **10** (250 mg, 1.35 mmol). The reaction was monitored by TLC and appeared to be complete after 72 h. The reaction mixture was concentrated and filtered through an alumina plug to provide the title compound **13** (268 mg, 64%) as an orange solid (M+H$^+$, 362.1821. $C_{16}H_{28}NO_8$ requires 362.1815); ν_{max} 3378, 1712, 1635, 1118, 1062, 1042 cm^{-1}; δ_H (300 MHz) 1.79 (3H, s, MeCON), 2.10–2.25 (2H, obscured m, 5-H$_2$), 2.18 (3H, s, 2-Me), 3.24 (3H, s, OMe), 3.26 (3H, s, OMe), 3.43–3.50 (2H, m, OCH_2C), 3.55–3.70 (6H, m, 3×OCH_2C), 3.58 (3H, s, CO_2Me), 5.11 (1H, dd, J=5.5, 9.5 Hz, 4-H), 6.64 (2H, br d, J=9.5 Hz, NH); m/z 362 (M+H$^+$, 100%), 286 (50), 227 (60).

1.1.8. Methyl 4-acetylamino-5,6-dihydro-2-methylspiro[4*H*-pyran-6,2′-[1,3]dioxolan]-3-carboxylate 14. To *t*-butanol (75 mL) under argon was added potassium metal (2.0 g, 51 mmol) in small portions and the solution heated to 90°C. Once the potassium metal had dissolved to form the *t*-butoxide, 2-bromomethyl-1,3-dioxolane (4.36 g, 26 mmol) was added. After 1 h the resultant ketene acetal **7**[12] was distilled, together with some *t*-butanol, directly into an adjoining flask containing heterodiene **10** (0.50 g, 2.7 mmol). The reaction was stirred at room temperature until no heterodiene was visible by TLC (2 h). The volatiles were removed in vacuo and the residue purified by rapid flash chromatography, eluting with petroleum–ethyl acetate (4:1), to obtain the title compound **14** (460 mg, 63%) as an off-white solid, mp 104–105°C (M+H$^+$, 272.1135. $C_{12}H_{18}NO_6$ requires 272.1134); ν_{max} (Nujol) 3375, 1706, 1632, 1530, 1322, 1266, 1092, 1012, 951, 859 cm^{-1}; δ_H (300 MHz) 1.91 (3H, s, MeCON), 2.05–2.25 (2H, m, 5-H$_2$), 2.21 (3H, s, 2-Me), 3.67 (3H, s, CO_2Me), 4.0–4.3 (4H, m, 4′-H$_2$ and 5′-H$_2$), 5.26 (1H, dd, J=5, 9.5 Hz, 4-H), 5.97 (1H, d, J=9.5 Hz, NH); m/z 272 (M+H$^+$, 100%); R_f 0.55 (petroleum–ethyl acetate 4:1).

1.1.9. Methyl 4-acetylamino-5,6-dihydro-2-methyl-4′*S*,5′*S*-bis(2-methylphenyl)spiro[4*H*-pyran-6,2′-[1,3]dioxolan]-3-carboxylates 15 and 16. To a solution of the ketene acetal (*S*,*S*)-**1a** (168 mg, 0.63 mmol) in THF

(10 mL) at −15°C was added the diene **10** (117 mg, 0.63 mmol). The reaction mixture was maintained at −15°C for 72 h after which no diene was visible by TLC, and the 300 MHz ^{1}H NMR spectrum suggested a d.r. of ca. 4:1. The mixture was concentrated, taken up in DCM (1 mL) and filtered through an alumina plug, eluting with petroleum–ethyl acetate (4:1). Crystallisation from isohexane–ether (1:1) provided the title compound (4*S*,4′*S*,5′*S*)-**15** (164.5 mg, 60%) as a colourless solid (d.r.≥19:1 by 250 MHz NMR) (M+H$^+$, 452.2073. $C_{26}H_{30}NO_6$ requires 452.2073); ν_{max} 3305, 1713, 1633, 1574, 1530, 1324, 1244, 1223, 1130, 1097, 1003, 761 cm^{-1}; δ_H (250 MHz) 1.68 (3H, s, ArMe), 1.78 (3H, s, ArMe), 1.89 (3H, s, MeCON), 2.44 (3H, s, 2-Me), 2.40–2.50 (2H, obscured m, 5-H$_2$), 3.74 (3H, s, CO_2Me), 5.28 (1H, d, *J*=9 Hz, 4′-H or 5′-H), 5.30–5.40 (1H, m, 4-H), 5.54 (1H, d, *J*=9 Hz, 4′-H or 5′-H), 6.00 (1H, d, *J*=9 Hz, NH), 7.06 (2H, d, *J*=7.5 Hz, 3,3′-ArH), 7.20–7.35 (4H, m, 4,4′,5,5′-ArH), 7.57 (2H, d, *J*=8 Hz, 6,6′-ArH); *m/z* 452 (M+H$^+$, 20%), 267 (100), 203 (50), 186 (70); HPLC retention time 5.88 min (purity ≥95%). The following signals were tentatively assigned to the minor diastereoisomer (4*R*,4′*S*,5′*S*)-**16**: δ_H (250 MHz) 1.65 (3H, s, ArMe), 1.74 (3H, s, ArMe).

1.1.10. 1,2-Bis(2-methylphenyl)-ethane-1,2-diol 1-acetate 17. To a solution of ketene acetal (*S*,*S*)-**1a** (50 mg, 0.19 mmol) in THF (5 mL) was added 0.1 M sulfuric acid (2 mL). After stirring for 1 h the reaction mixture was concentrated in vacuo, taken up in DCM, washed with saturated aq. sodium hydrogen carbonate (5 mL), dried and evaporated. Trituration with isohexane provided the title compound **17** (40 mg, 75%) as a colourless solid (M+H$^+$, 285.1486. $C_{12}H_{21}O_3$ requires 285.1491); ν_{max} 3435, 1737, 1645, 1240, 1026, 757 cm^{-1}; δ_H (300 MHz) 1.78 (3H, s, ArMe), 1.86 (3H, s, ArMe), 2.10 (3H, s, COMe), 5.19 (1H, d, *J*=8.5 Hz, H-2), 6.04 (1H, d, *J*=8.5 Hz, H-1), 6.91 (2H, d, *J*=7.5 Hz, 3′,3″-H), 7.07–7.21 (4H, m, 4′,4″,5′,5″-H), 7.44 (1H, dd, *J*=1.5, 7.5 Hz, 6″-H), 7.59 (1H, d, *J*=7.5 Hz, 6′-H); δ_C (75 MHz) 18.9 (*Me*Ar), 23.4 (*Me*Ar), 29.0 (*Me*CO), 72.6 (2-C), 76.2 (1-C), 125.7, 125.9 (5′-C, 5″-C), 127.3, 127.5, 127.9, 128.0 (4′-C, 4″-C, 6′-C, 6″-C), 130.2 (3′-C, 3″-C), 135.3, 135.7, 136.4, 137.1 (1′-C, 1″-C, 2′-C, 2″-C), 170.1 (C=O); *m/z* 302 (M+NH$_4^+$, 30%), 285 (M+H$^+$, 5), 243 (22), 242 (100); HPLC retention time 5.17 min.

1.1.11. Benzyl 4-acetylamino-5,6-dihydro-2-methyl-4′*S*,5′*S*-bis(2-methylphenyl)spiro[4*H*-pyran-6,2′-[1,3]dioxolan]-3-carboxylates 18 and 19. To a solution of the ketene acetal (*S*,*S*)-**1a** (83 mg, 0.31 mmol) in THF (10 mL) at −15°C was added the diene **11** (80 mg, 0.31 mmol). The reaction was maintained at −15°C for 96 h after which no diene was present by HPLC analysis, and the 250 MHz NMR spectrum suggested a d.r. of ca. 4:1. The reaction mixture was concentrated, taken up in DCM (1 mL) and filtered through an alumina plug eluting with ether–isohexane (2:1). Concentration of the filtrate gave the title compound (4*S*,4′*S*,5′*S*)-**18** (101 mg, 62%) as a cream-coloured solid (d.r. 4.1:1 by HPLC)* (M+H$^+$, 528.2394. $C_{32}H_{34}NO_6$ requires 528.2386); ν_{max} 3258, 1715, 1652, 1574, 1275, 1240, 1178, 1077 cm^{-1}; δ_H (400 MHz) 1.69 (3H, s, ArMe), 1.77 (3H, s, MeCON), 1.79 (3H, s, ArMe), 2.39–2.48 (2H, m, 5-H$_2$), 2.45 (3H, s, 2-Me), 5.06 (1H, d, *J*=12 Hz, OCHPh), 5.29 (1H, d, *J*=9 Hz, 5′-H), 5.33 (1H, d, *J*=12 Hz, OCHPh), 5.37–5.45 (1H, m, 4-H), 5.54 (1H, d, *J*=9 Hz, 4′-H), 5.97 (1H, d, *J*=9.5 Hz, NH), 7.02–7.07 (2H, m, 3,3′-ArH), 7.18–7.40 (9H, m, ArH), 7.57 (2H, br d, *J*=8 Hz, 6,6′-ArH); δ_C (100 MHz) 19.2 (ArMe), 20.6 (ArMe), 23.8 (amide Me), 23.9 (2-Me), 35.3 (C-5), 41.4 (C-4), 66.2 (OCH$_2$), 82.2 (C-4′), 84.1 (C-5′), 103.3 (C-3), 119.4 (C-6), 126.7–136.5 (several peaks, Ar), 165.3 (C-2), 167.1 (ester CO), 169.1 (amide CO) [NMR signals were assigned with reference to ^{1}H–^{1}H (COSY) and ^{1}H–^{13}C correlation (HMQC) spectra. Assignments for C-2, C-5 and C-6 are tentative]; *m/z* (FAB) 528 (M+H$^+$, 20%), 481 (20), 368 (100), 156 (25); HPLC retention times 5.87 min (minor isomer, area 11.89), 6.67 min (major isomer, area 48.88). *Trituration with isohexane gave material with d.r. 14:1 [HPLC retention times 5.87 min (minor isomer, area 5.1), 6.67 min (major isomer, area 70.7)]. The minor diastereoisomer (4*R*,4′*S*,5′*S*)-**19** had δ_H (400 MHz) 5.55 (1H, d, *J*=9 Hz, 4′-H) and 6.02 (1H, d, *J*=9.5 Hz, NH).

1.1.12. 4-Acetylamino-3,4-dihydro-6-methyl-4′*S*,5′*S*-bis(2-methylphenyl)-5-(1-oxoethyl)spiro[2*H*-pyran-2,2′-[1,3]dioxolans] 20 and 21. To a solution of ketene acetal (*S*,*S*)-**1a** (168 mg, 0.63 mmol) in THF (10 mL) at −15°C was added the diene **12** (110 mg, 0.63 mmol). After 5 days at −15°C analysis by HPLC revealed the absence of any starting material, and the 250 MHz NMR spectrum indicated a d.r. of ≥4:1. The reaction mixture was concentrated and the residue was taken up in DCM (1 mL) and filtered through a plug of basic alumina, eluting with more DCM. Evaporation of the solvent gave the title compound (4*S*,4′*S*,5′*S*)-**20** (184 mg, 67%) as a solid (d.r. ≥4:1 by 250 MHz NMR). Crystallisation from isohexane gave **20** as colourless needles, mp 112–115°C (d.r. ≥19:1 by 400 MHz NMR) (M+H$^+$, 436.2119. $C_{26}H_{30}NO_5$ requires 436.2124); ν_{max} (Nujol) 3308, 1677, 1585, 1320, 1257, 1242, 1224, 1129, 1098, 1002, 935, 880, 762, 728 cm^{-1}; δ_H (400 MHz) 1.70 (3H, s, ArMe), 1.79 (3H, s, ArMe), 1.93 (3H, s, MeCON), 2.28 (3H, s, MeCOC), 2.37 (3H, s, 6-Me), 2.45 (1H, dd, *J*=2, 14 Hz, 3-H), 2.50 (1H, dd, *J*=6, 14 Hz, 3-H), 5.27 (1H, d, *J*=9 Hz, 4′ or 5′-H), 5.38–5.44 (1H, m, 4-H), 5.55 (1H, d, *J*=9 Hz, 4′ or 5′-H), 6.17 (1H, d, *J*=10 Hz, NH), 7.04–7.08 (2H, m, 3,3′-ArH), 7.20–7.35 (4H, m, 4,4′,5,5′-ArH), 7.57 (2H, dd, *J*=2, 8 Hz, 6,6′-ArH); δ_C (100 MHz) 19.2 (two peaks, MeAr), 21.0 (6-Me), 23.9 (amide Me), 29.7 (*Me*CO.C), 35.4 (C-3), 42.2 (C-4), 81.8 (C-4′ or C-5′), 83.8 (C-4′ or C-5′), 111.1 (C-5), 118.6 (C-2), 126.3–136.1 (several peaks, ArC), 163.3 (C-6), 169.0 (amide CO), 199.5 (ketone CO) [NMR signals were assigned with reference to a ^{1}H–^{13}C correlation (HMQC) spectrum; assignments for C-2, C-5 and C-6 are tentative]; *m/z* 436 (M+H$^+$, 10%), 242 (30), 76 (100). The following signals were tentatively assigned to the minor diastereoisomer (4*R*,4′*S*,5′*S*)-**21**: δ_H (400 MHz) 1.67 (3H, s, ArMe), 1.76 (3H, s, ArMe), 1.94 (3H, s, MeCON), 5.34 (1H, d, *J*=9 Hz, 4′ or 5′-H), 7.88 (2H, dd, *J*=2, 8 Hz, 6,6′-ArH). The identity of the cycloadduct hydrolysis product **28** (analytical HPLC retention time 4.89 min), **17** (5.17 min) and **20** (5.79 min) were confirmed by the following LC-MS data [retention times (min), M+H, assignment]: 5.94, 436, **20**; 5.56, 256, **17**; 5.07, 454, **28**.

1.1.13. Crystal data for 20.[25] Monoclinic; *C*2; *a*=21.201(4) Å, *b*=9.944(2) Å, *c*=13.660(2) Å,

V=2708.6(8) Å ^{3}; Z=4; goodness-of-fit on F^2 1.170; final R indices [$I>2\sigma(I)$] R_1=0.1274, wR_2=0.3262; R indices (all data) R_1=0.1897, wR_2=0.3972. The crystal quality was very poor and due to a paucity of observed data all carbon atoms were refined isotropically.

1.1.14. Methyl 4-acetylamino-5,6-dihydro-2-methyl-4′*S*,5′*S*-diphenylspiro[4*H*-pyran-6,2′-[1,3]dioxolan]-3-carboxylates 22 and 23. To a solution of the ketene acetal (*S*,*S*)-**1b** (236 mg, 1.0 mmol) in THF (5 mL) at −20°C was added a solution of heterodiene **10** (185 mg, 1.0 mmol) in THF (10 mL). The reaction mixture was maintained at −20°C until the reaction was complete by ^{1}H NMR spectroscopy (72 h). The reaction mixture was concentrated in vacuo, dissolved in DCM (5 mL) and filtered through alumina, eluting with more DCM. Concentration and trituration with isohexane provided an orange solid, which was suspended in hot isohexane (2 mL) and treated dropwise with DCM until the solution clarified. The solution was then allowed to cool in a refrigerator, which gave the title compound (4*S*,4′*S*,5′*S*)-**22** as a white solid (260 mg, 61%), d.r. ≥19:1 by 300 MHz ^{1}H NMR spectroscopy (M+H$^+$, 424.1771. $C_{24}H_{26}NO_6$ requires 424.1760); ν_{max} 3302, 1713, 1632, 1515, 1324, 1245, 1127, 1100, 1005, 868, 760, 701 cm^{-1}; δ_H (300 MHz) 1.88 (3H, s, MeCON) [minor product 1.89], 2.38 (3H, s, 6-Me), 2.36–2.41 (2H, obscured m, 3-H$_2$), 3.70 (3H, s, CO_2Me), 4.95 (1H, d, J=8.5 Hz, 4′-H or 5′-H) [minor product 4.87], 5.29 (1H, d, J=9 Hz, 4′-H or 5′-H) [minor product 5.08], 5.30–5.40 (1H, m, 4-H), 5.98 (1H, d, J=9.5 Hz, NH), 7.16–7.28 (4H, m, ArH), 7.32–7.37 (6H, m, ArH); δ_C (75 MHz) 20.2 (2-Me), 23.7 (amide Me), 34.7 (C-5), 41.0 (C-4), 51.8 (OMe), 85.1 (C-4′ or C-5′), 87.3 (C-4′ or C-5′), 103.3 (C-3), 119.3 (C-6), 126.6, 126.7, 128.8, 129.0, 135.4, 137.1 (Ar), 164.5 (C-2), 167.6 (ester CO), 169.0 (amide CO) (assignments based on comparison with benzyl analogue); *m*/*z* 424 (M+H$^+$, 22%), 239 (85), 186 (100). The mother liquor from the crystallisation of **22** provided a sample enriched in the minor product (4*R*,4′*S*,5′*S*)-**23**, enabling its characteristic ^{1}H NMR signals to be assigned as indicated above.

1.1.15. 4-Acetylamino-3,4-dihydro-6-methyl-4′*S*,5′*S*-diphenyl-5-(1-oxoethyl)spiro[2*H*-pyran-2,2′-[1,3]dioxolan] 24 and 25. To a solution of the ketene acetal (*S*,*S*)-**1b** (95.2 mg, 0.40 mmol) in THF (10 mL) at −20°C was added a solution of heterodiene **12** (72 mg, 0.43 mmol) in THF (2 mL). The mixture was maintained at −20°C until the reaction was complete by ^{1}H NMR spectroscopy (120 h). The reaction mixture was concentrated in vacuo, dissolved in DCM (5 mL) and filtered through alumina, eluting with more DCM. Concentration and trituration with isohexane provided an orange solid, which was suspended in hot isohexane and treated dropwise with DCM until the solution clarified. The solution was then allowed to cool in a refrigerator, which gave the title compound (4*S*,4′*S*,5′*S*)-**24** as the major product (102 mg, 63%), d.r. ≥19:1 by 300 MHz ^{1}H NMR spectroscopy (M+H$^+$, 408.1802. $C_{24}H_{26}NO_5$ requires 408.1811); ν_{max} 3305, 1733, 1651, 1580, 1279, 1243, 1179, 1000, 937, 869, 761, 700 cm^{-1}; δ_H (300 MHz) 1.91 (3H, s, MeCON), 2.25 (3H, s, MeCOC), 2.30 (3H, s, 6-Me), 2.39 (1H, dd, J=2, 14 Hz, 3-H), 2.47 (1H, dd, J=6, 14 Hz, 3-H), 4.95 (1H, d, J=9 Hz, 4′ or 5′-H), 5.29 (1H, d, J=9 Hz, 4′ or 5′-H), 5.35–5.42 (1H, m, 4-H), 6.17 (1H, d, J=10 Hz, NH), 7.18–7.28 (4H, m, ArH), 7.33–7.38 (6H, m, ArH); δ_C (75 MHz) 20.5 (6-Me), 23.4 (amide Me), 29.2 (*Me*CO.C), 34.9 (C-3), 41.9 (C-4), 85.1 (C-4′ or C-5′), 87.4 (C-4′ or C-5′), 111.3 (C-5), 118.9 (C-2), 126.7, 126.8, 128.8, 129.1, 135.4, 136.9 (Ar), 163.3 (C-6), 169.0 (amide CO), 199.5 (ketone CO) (assignments based on comparison with the tolyl analogue **20**); *m*/*z* 409 (25%), 408 (M+H$^+$, 100), 239 (71), 170 (53).

1.1.16. 2-Acetyl-3-acetylaminopentanedioic acid 1-methyl ester 5-(2-methoxyethyl) ester 26. To a solution of the cycloadduct **13** (20 mg, 0.06 mmol) in THF (5 mL), was added 0.1 M sulfuric acid (1 mL). The reaction mixture was stirred at room temperature. After overnight stirring (ca. 14 h) TLC indicated that the reaction was complete, and the mixture was concentrated, taken up in DCM (5 mL), washed with saturated aq. sodium hydrogen carbonate (5 mL), dried and evaporated to provide the title compound **26** (10 mg, 60%) as a colourless solid (d.r. ca. 1.2:1 by 300 MHz ^{1}H NMR spectroscopy) (M+H$^+$, 304.1389. $C_{13}H_{22}NO_7$ requires 304.1396); ν_{max} 3387, 1730, 1260 cm^{-1}; δ_H (300 MHz) (major isomer; distinguishable values for minor isomer are shown in brackets) 1.89 (3H, s, MeCON), 2.27 [2.23] (3H, s, 2′-H$_3$), 2.56–2.66 (1H, m, 4-H), 2.70–2.80 (1H, m, 4-H), 3.34 (3H, s, CH_2O*Me*), 3.52–3.59 (2H, m, 2″-H$_2$), 3.72 [3.70] (3H, s, CO_2Me), 4.02 (1H, d, J=4 Hz, 2-H), 4.18–4.25 (2H, m, 1″-H$_2$), 4.97–5.07 [4.82–4.92] (1H, m, 3-H), 6.65 [6.50] (1H, br d, J=8 Hz, NH); *m*/*z* 321 (M+NH$_4^+$, 30%), 304 (40), 242 (90).

1.1.17. 2-Acetyl-3-acetylaminopentandioic acid 1-methyl ester 5-(2-hydroxyethyl) ester 27. To a solution of the cycloadduct **14** (100 mg, 0.37 mmol) in THF (5 mL) under argon was added 0.1 M sulfuric acid (3.7 mL). On addition of the acid the colour of the reaction mixture changed from orange to pale yellow, and after 0.5 h TLC indicated that the reaction was complete. The reaction mixture was concentrated, extracted with ethyl acetate (2×5 mL), washed with saturated aqueous sodium hydrogen carbonate (5 mL), dried and evaporated. The residue was chromatographed (elution with ethyl acetate) to obtain the title compound **27** (80 mg, 75%) as an off-white solid (d.r. ca. 1.2:1 by 300 MHz ^{1}H NMR spectroscopy) (M+H$^+$, 290.1252. $C_{12}H_{20}NO_7$ requires 290.1240); ν_{max} 3418, 1733, 1652, 1551, 1262, 1207, 1084, 1023 cm^{-1}; δ_H (300 MHz) (major isomer; distinguishable values for minor isomer in brackets) 1.93 (3H, s, MeCON), 2.29 [2.26] (3H, s, 2′-H$_3$), 2.55–2.75 (2H, m, 4-H$_2$), 3.76 [3.73] (3H, s, CO_2Me), 3.7–3.9 (2H, m, 2″-H$_2$), 4.05–4.35 (3H, m, 2-H and 1″-H$_2$), 5.1–5.2 [4.95–5.05] (1H, m, 3-H), 6.81 (1H, t, J=9 Hz, NH) [6.69 (1H, br d, J=9 Hz, NH)]; *m*/*z* 290 (M+H$^+$, 100%), 272 (25), 164 (45).

1.1.18. 4-Acetyl-3-acetylamino-5-oxohexanoic acid 1,2-bis(2-methylphenyl)-2-hydroxyethyl ester 28. To a solution of the cycloadduct **20** (23 mg, 0.05 mmol) in THF (2 mL) was added 0.1 M sulfuric acid (0.5 mL). The reaction mixture was stirred at room temperature for 1 h, at which point HPLC analysis indicated that the reaction was complete. The reaction mixture was concentrated, taken up in DCM (5 mL), washed with saturated aq. sodium hydrogen carbonate (2×5 mL), dried and evaporated to provide the title compound **28** (13 mg, 56%) as a white solid

(M+H$^+$, 454.2219. $C_{26}H_{32}NO_6$ requires 454.2229); ν_{max} 3424, 1737, 1651, 1241, 1179 cm^{-1}; δ_H (300 MHz) 1.80 (3H, s, ArMe), 1.87 (3H, s, ArMe), 1.92 (3H, s, MeCON), 2.15 (3H, s, 2′-Me), 2.24 (3H, s, 6-Me), 2.60 (1H, dd, *J*=7, 15 Hz, 2-H), 2.70 (1H, dd, *J*=7, 15 Hz, 2-H), 4.07 (1H, d, *J*=6 Hz, 4-H), 5.10–5.20 (1H, m, 3-H), 5.24 (1H, d, *J*=9 Hz, 2″-H), 6.11 (1H, d, *J*=9 Hz, 1″-H), 6.74 (1H, d, *J*=10 Hz, NH), 6.90–7.00 (2H, m, 3,3′-ArH), 7.07–7.23 (4H, m, 4,4′,5,5′-ArH), 7.46 (1H, br d, *J*=8 Hz, 6-ArH), 7.60 (1H, br d, *J*=8 Hz, 6′-ArH); *m/z* 454 (M+H$^+$, 10%), 436 (15), 230 (100), 212 (25); analytical HPLC retention time 4.88 min.

1.1.19. 2-Acetyl-3-acetylaminopentanedioic acid 5-(2-hydroxy-1,2-diphenyl)ethyl ester 1-methyl ester 29. To a solution of the cycloadduct (4*S*,4′*S*,5′*S*)-**22** (100 mg, 0.24 mmol) in THF (5 mL) was added 0.1 M sulfuric acid (2.5 mL, 0.25 mmol). The reaction mixture was stirred at room temperature for 1.5 h at which point ^{1}H NMR analysis indicated that the reaction was complete. The mixture was concentrated, taken up in DCM (5 mL), washed with saturated aq. sodium hydrogen carbonate (3 mL), dried and evaporated to obtain the title compound **29** (68 mg, 65%) as a white solid mixture of (2*R*,3*S*,1″*S*,2″*S*) and (2*S*,3*S*,1″*S*,2″*S*) diastereoisomers (ratio ca. 1:1 by NMR) (M+H$^+$, 442.1858. $C_{24}H_{28}NO_4$ requires 442.1866); ν_{max} 3418, 1737, 1718, 1669, 909, 734 cm^{-1}; δ_H (300 MHz) 1.88 and 1.89 (total 3H, 2×s, MeCON), 2.21 and 2.24 (total 3H, 2×s, 2′-Me), 2.58–2.78 (2H, m, 4-H$_2$), 3.69 and 3.73 (total 3H, 2×s, CO_2Me), 3.85–3.89 (total 1H, m, 2-H), 4.90 and 4.91 (total 1H, 2×d, *J*=8 Hz, 2″-H), 5.0–5.1 and 5.1–5.2 (total 1H, 2×m, 3-H), 5.79 and 5.80 (total 1H, 2×d, *J*=8 Hz, 1″-H), 6.62 and 6.73 (total 1H, 2×d, *J*=9.5 Hz, NH), 7.03–7.10 (4H, m, ArH), 7.12–7.18 (6H, m, ArH); *m/z* 442 (M+H$^+$, 2%), 228 (29), 214 (45), 186 (77), 169 (24), 160 (22), 134 (49), 77 (100).

1.1.20. 4-Acetyl-3-acetylamino-5-oxohexanoic acid 1,2-diphenyl-2-hydroxyethyl ester 30. *Method* 1. To a solution of the cycloadduct (4*S*,4′*S*,5′*S*)-**24** (102 mg, 0.25 mmol) in THF (5 mL) was added 0.1 M sulfuric acid (2.5 mL). The reaction mixture was stirred at room temperature for 1.5 h at which point ^{1}H NMR analysis indicated that the reaction was complete. The mixture was concentrated, taken up in DCM (5 mL), washed with saturated aq. sodium hydrogen carbonate (3 mL), dried and evaporated to obtain the title compound (3*S*,1″*S*,2″*S*)-**30** (60 mg, 56%) as an off-white solid, d.r. ≥19:1 by 300 MHz ^{1}H NMR spectroscopy (M+H$^+$, 426.1916. $C_{24}H_{28}NO_6$ requires 426.1917); ν_{max} 3367, 1729, 1702, 1659, 1261, 1177, 758, 700 cm^{-1}; δ_H (300 MHz) 1.88 (3H, s, MeCON), 2.12 (3H, s, 2′-Me), 2.21 (3H, s, 6-Me), 2.60 (1H, dd, *J*=9, 15 Hz, 2-H), 2.65 (1H, dd, *J*=8.5, 15 Hz, 2-H), 4.04 (1H, d, *J*=5 Hz, 4-H), 4.90 (1H, d, *J*=8 Hz, 2″-H), 5.05–5.15 (1H, m, 3-H), 5.83 (1H, d, *J*=8 Hz, 1″-H), 6.71 (1H, d, *J*=9.5 Hz, NH), 7.05–7.12 (4H, m, ArH), 7.15–7.20 (6H, m, ArH); *m/z* 426 (M+H$^+$, 10%), 232 (45), 214 (85), 212 (100), 170 (58), 119 (49); R_f 0.38 (hexane–ethyl acetate 1:9).

Method 2. The procedure described in method 1 was repeated with **24** (11.5 mg) using 1 equiv. 0.1 M aq. citric acid instead of sulfuric acid. After 48 h the reaction was complete, and isolation as before gave a sample of **30** (6 mg, 50%) which was identical by NMR spectroscopy to the product obtained by method 1.

1.1.21. Dimethyl 2-acetyl-3-acetylaminopentanedioate 31. *Method* 1. To a solution of **29** (50 mg, 0.11 mmol) in anhydrous methanol (5 mL) was added potassium carbonate (103 mg, 0.73 mmol). The mixture was stirred overnight and then concentrated, diluted with DCM (5 mL), washed with 0.1 M hydrochloric acid (5 mL), dried and evaporated. Chromatography, eluting with ethyl acetate, provided the diol (*S*,*S*)-**2b** (16 mg, 66%) and a sample of the diester **31** (19 mg, 65%) which was identical (TLC, NMR) to the material produced by method 2 (see below). The recovered diol **2b** was identical (TLC, NMR) to an authentic sample, and had an enantiomeric purity of >80% when estimated by 300 MHz ^{1}H NMR spectroscopy in the presence of 4 equiv. of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol, as described.[3]

Method 2. To a solution of **29** (50 mg, 0.11 mmol) in anhydrous methanol (5 mL) was added 5% Pd/C catalyst (1 mg) and the reaction mixture was stirred under an atmosphere of hydrogen at room temperature until no starting material could be detected by TLC (3–4 h). The solution was filtered through Celite® and evaporated. Washing the resultant solid with isohexane removed the by-product (1,2-diphenylethane **33**) and provided 2-acetyl-3-acetylaminopentanedioic acid 1-methyl ester **32** (18 mg) as a white solid which ^{1}H NMR spectroscopy indicated was a mixture (ca. 1:1) of diastereoisomers [δ_H (d$_6$-acetone) 1.84, 1.86 (each 3H, s, MeCON), 2.23, 2.26 (each 3H, s, 2′-H$_3$), 3.70, 3.71 (each 3H, s, OMe)]. The sample of **32** was dissolved in ethanol (10 mL) and treated dropwise with a slight excess of diazomethane in ether (Caution—Hazardous; prepared[26] from Diazald®). After 5 min the reaction was quenched by the dropwise addition of 4 M acetic acid until the yellow colour of the reaction mixture faded. The solution was concentrated, diluted with ethyl acetate (8 mL), washed with saturated aq. sodium hydrogen hydrogen carbonate, and dried. Evaporation gave the title compound **31** (18 mg, 61%) as a white solid [1:1 mixture of (2*R*,3*S*) and (2*S*,3*S*) diastereoisomers] (M+H$^+$, 260.1134. $C_{11}H_{18}NO_6$ requires 260.1134); ν_{max} 3407, 1734, 1660 cm^{-1}; δ_H (300 MHz) 1.92 (3H, s, MeCON), 2.25, 2.28 (total 3H, 2×s, 2′-H$_3$), 2.5–2.8 (2H, m, 4-H$_2$), 3.66, 3.68, 3.72, 3.74 (total 6H, 4×s, OMe), 4.01–4.07 (total 1H, m, 2-H), 4.80–4.90, 4.95–5.05 (total 1H, 2×m, 3-H), 6.47, 6.63 (total 1H, 2×d, *J*=9.5 Hz, NH); *m/z* 260 (M+H$^+$, 100).

1.1.22. Methyl 4-acetyl-3-acetylamino-5-oxohexanoate 35. To a solution of the ester **30** (40 mg, 0.094 mmol) in anhydrous methanol (5 mL) was added 5% Pd/C catalyst (1 mg) and the reaction mixture was stirred under an atmosphere of hydrogen at room temperature until no starting material could be detected by TLC (3–4 h). The solution was filtered through Celite® and evaporated. Washing the resultant solid with isohexane removed the by-product (1,2-diphenylethane **33**) and provided (3*S*)-4-acetyl-3-acetylamino-5-oxohexanoic acid **34** as a white solid (15 mg) [ν_{max} 3377, 1721, 1620, 1257 cm^{-1}; δ_H (300 MHz) 1.85 (3H, s, MeCON), 2.16 (3H, s, 2′-Me), 2.26 (3H, s, 6-Me)], which was dissolved in ethanol (10 mL) and treated dropwise with a slight excess of diazomethane in

ether (Caution—Hazardous; prepared[26] from Diazald®). After 5 min the reaction was quenched by the dropwise addition of 4 M acetic acid until the yellow colour of the reaction mixture faded. The solution was concentrated, diluted with ethyl acetate (8 mL), washed with saturated aq. sodium hydrogen hydrogen carbonate, and dried. Evaporation gave the title compound (3*S*)-**35** (16 mg, 70%) as a white solid (M+H$^+$, 244.1184. $C_{11}H_{18}NO_5$ requires 244.1185); ν_{max} 3278, 1735, 1715, 1655 cm^{-1}; δ_H (300 MHz) 1.91 (3H, s, MeCON), 2.16 (3H, s, 2′-H$_3$), 2.28 (3H, s, 6-H$_3$), 2.55 (1H, dd, *J*=8, 16.5 Hz, 2-H), 2.67 (1H, dd, *J*=5.5, 16.5 Hz, 2-H), 3.67 (3H, s, OMe), 4.25 (1H, d, *J*=5 Hz, 4-H), 4.93–5.03 (1H, m, 3-H), 6.53 (1H, d, *J*=9.5 Hz, NH); *m*/*z* 244 (M+H$^+$, 100); R_f 0.33 (ethyl acetate). The isolated sample of **33** was identical (TLC, NMR) to commercial material (Lancaster Synthesis, 4977).

1.1.23. Methyl 4-acetylamino-2-methyl-6-oxotetrahydropyran-3-carboxylate 36. To a solution of diester **31** (14 mg, 0.054 mmol) in anhydrous DCM (0.5 mL) under argon at room temperature was added trifluoroacetic acid (0.5 mL) and triethylsilane (29 mg, 0.25 mmol). The mixture was stirred for 48 h, after which the reaction appeared to be complete by TLC. Evaporation followed by chromatography provided the title compound (2*S*,3*R*,4*S*)-**36** (10 mg, 81%) as a yellow oil (M+H$^+$, 230.1024. $C_{10}H_{16}NO_5$ requires 230.1028); $[\alpha]_D^{22}=-12\pm1.5$ (*c* 2.0, $CHCl_3$) {lit.[18] for (2*R*,3*S*,4*R*)-**36**, $[\alpha]_D^{20}=+22.4$ (*c* 1.35, $CHCl_3$)}; ν_{max} 3416, 1727, 1662, 1646, 1217, 768, 750 cm^{-1}; δ_H (300 MHz) 1.39 (3H, d, *J*=6 Hz, 2-Me), 1.96 (3H, s, MeCON), 2.56 (1H, dd, *J*=6.5, 17 Hz, 5-H), 2.58 (1H, dd, *J*=8, 10.5 Hz, 3-H), 3.00 (1H, dd, *J*=7, 17 Hz, 5-H), 3.75 (3H, s, OMe), 4.49 (1H, dd, *J*=6, 10.5 Hz, 2-H), 4.54–4.64 (1H, m, 4-H), 5.75 (1H, br s, NH);[27] *m*/*z* (CI) 247 (M+NH$_4^+$, 96%), 230 (M+H$^+$, 100); *m*/*z* (EI) 230 (M+1, 100), 186 (22), 171 (27), 170 (100), 156 (20), 128 (70); R_f 0.20 (ethyl acetate).

1.1.24. 1,3-Dimethyl-2,4-dioxopyrimidine-5-carbaldehyde 37.[19] To a solution of phosphorus oxychloride (1.64 g, 10.7 mmol) in dry DMF (6 mL) at 0°C was added 1,3-dimethyluracil (1.0 g, 7.1 mmol). The reaction mixture was then heated at 90°C for 1 h. The solvent was removed in vacuo and the residue dissolved in cold water. The resulting precipitate was collected on a filter and crystallised from petroleum (bp 60–80°C) to obtain the title compound **37** (0.657 g, 55%) as a crystalline solid; ν_{max} 1633, 1486 cm^{-1}; δ_H (300 MHz) 3.37 (3H, s, NMe), 3.51 (3H, s, NMe), 8.05 (1H, s, 6-H), 10.02 (1H, s, CHO); *m*/*z* 169 (M+H$^+$, 100%).

1.1.25. 1,3-Dimethyl-1,7,8,8a-tetrahydro-4′*S*,5′*S*-bis(2-methylphenyl)spiro[pyrano[4,3-*d*]pyrimidine-7,2′-[1,3]dioxolan]-2,4-diones 38 and 39. To a solution of the ketene acetal (*S*,*S*)-**1a** (85 mg, 0.32 mmol) in THF (5 mL) at −15°C was added the aldehyde **37**[19] (58 mg, 0.32 mmol). The reaction mixture was maintained at −15°C and monitored by TLC. After 72 h the reaction appeared to be complete. Concentration of the reaction mixture provided a yellow solid which was crystallised from isohexane to obtain the title compound (8a*R*,4′*S*,5′*S*)-**38** (69.5 mg, 50%) as a white solid (d.r. 4.26:1 by HPLC; ≥4:1 by 300 MHz ^{1}H NMR) (M+H$^+$, 435.1919. $C_{25}H_{27}N_2O_5$ requires 435.1920); ν_{max} 1702, 1666, 1632, 1334, 1215, 1134, 1004, 902, 885, 762 cm^{-1}; δ_H (300 MHz) (distinguishable values for **39** are shown in brackets) 1.66 (3H, s, ArMe), 1.77 (3H, s, ArMe), 2.27 (1H, t, *J*=12 Hz, 8-H$_{ax}$), 2.75 (1H, dd, *J*=5, 12 Hz, 8-H$_{eq}$), 3.07 [3.08] (3H, s, NMe), 3.23 [3.21] (3H, s, NMe), 4.40 (1H, ddd, *J*=2, 5, 12 Hz, 8a-H), 5.31 (1H, d, *J*=9 Hz, 4′-H), 5.58 [5.43] (1H, d, *J*=9 Hz, 5′-H), 6.95–7.10 (2H, m, 3,3′-ArH), 7.15–7.30 (4H, m, 4,4′,5,5′-ArH), 7.50–7.60 (2H, m, 6,6′-ArH), 7.70 [7.62] (1H, d, *J*=2 Hz, 5-H); *m*/*z* (FAB) 435 (M+H$^+$, <1%), 368 (32), 256 (100), 254 (46), 156 (82); HPLC retention times 5.32 min (minor isomer, area 6.62), 6.10 min (major isomer, area 28.17).

1.1.26. 1-Carbethoxy-3-hydroxymethylene-4-piperidone 40.[20] In a 3-necked flask equipped with a calcium chloride guard tube, argon inlet, dropping funnel and magnetic stirrer were placed sodium hydride (60% dispersion in mineral oil; 4.8 g, 0.12 mol), dry ether (100 mL) and ethanol (10 mL). The reaction vessel was cooled with an ice bath and treated dropwise with a mixture of 1-carbethoxy-4-piperidone (10.26 g, 0.06 mol) and ethyl formate (8.90 g, 0.12 mol) in dry ether (150 mL). The mixture turned lemon in colour and was stirred at room temperature overnight (16 h). TLC analysis of the orange mixture indicated the presence of starting material, so ethanol (10 mL) was added and the reaction was stirred for a further 2 days. The mixture was then poured into a separating funnel and the solid residue was extracted with water (150 mL). The ethereal layer was extracted once more with water (150 mL) and the aqueous extracts were combined and acidified with 6 M hydrochloric acid (140 mL). The aqueous mixture was then extracted with ether (2×200 mL) and the ethereal extracts were washed with brine (150 mL), dried and evaporated to give a viscous orange viscous oil. Purification by vacuum distillation gave **40** (2.86 g, 24%) as a yellow oil, bp 130°C (0.6 mm Hg); lit.[20] bp 130–131°C (2 mm Hg) (M+NH$_4^+$, 299.1059. $C_{13}H_{19}N_2O_4S$ requires 299.1065); ν_{max} 3400 br, 1719 cm^{-1}; δ_H (300 MHz) 1.25 (3H, t, *J*=7 Hz, Me), 2.47 (2H, t, *J*=6 Hz, 5-H$_2$), 3.62 (2H, t, *J*=6 Hz, 6-H$_2$), 4.15 (2H, q, *J*=7 Hz, OC*H*$_2$Me), 4.23 (2H, s, 2-H$_2$), 8.50 (1H, br s, C*H*OH), 14.1 (1H, br s, OH); *m*/*z* (peaks ≥10%) 217 (M+NH$_4^+$, 100%), 200 (12).

1.1.27. 1-Carbethoxy-3-formyl-5,6-dihydro-4-pyridone 41. A solution of the hydroxymethylene compound **40** (2.76 g, 13.9 mmol) in DCM (50 mL) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.5 g). The mixture was stirred overnight (16 h) and a second portion of DDQ (0.5 g) was added. The reaction was then diluted with pentane (60 mL) and filtered. The resulting solution was evaporated and the residue chromatographed, eluting with petroleum–ethyl acetate (1:1). The resulting solid was washed with a 1% solution of sodium bicarbonate, to give the title compound **41** (387 mg, 22%) as buff-coloured crystals, mp 74–77°C (M+H$^+$, 198.0766. $C_9H_{12}NO_4$ requires 198.0766); ν_{max} (Nujol) 1741, 1667, 1574 cm^{-1}; δ_H (300 MHz) 1.37 (3H, t, *J*=7 Hz, Me), 2.63 (2H, t, *J*=7.5 Hz, 5-H$_2$), 4.07 (2H, t, *J*=7.5 Hz, 6-H$_2$), 4.37 (2H, q, *J*=7 Hz, OC*H*$_2$Me), 8.66 (1H, s, 2-H), 9.93 (1H, s, CHO); *m*/*z* (peaks ≥10%) 215 (M+NH$_4^+$, 100%), 198 (50), 187 (17), 170 (19).

1.1.28. 7-Ethoxy-4-oxo-3,4,8,8a-tetrahydro-2*H*,7*H*-pyrano[4,3-*b*]pyridine-1-carboxylic acid ethyl esters 42 and 43. To a solution of the pyridone **41** (0.175 g,

0.89 mmol) in DCM (20 mL) was added ethoxyethene (1.28 g, 20 equiv.) and the mixture was stirred at room temperature. TLC after 2 weeks indicated that the reaction was incomplete. Ethoxyethene (2 mL) was added and after a further 2 weeks of stirring at room temperature, TLC showed that the reaction had gone to completion. The NMR spectrum of the crude reaction mixture indicated that the ratio of **42/43** was 77:23. The mixture was evaporated and the residue purified by flash chromatography over Florisil (15 g), eluting with petroleum–ethyl acetate (3:1), to give the mixed cycloadducts **42** and **43** (124 mg, 52%) as a colourless oil ($M+H^+$, 270.1342. $C_{13}H_{20}NO_5$ requires 270.1341); ν_{max} 1735 br, 1374, 1238 br, 1046 cm^{-1}; (**42**) δ_H (300 MHz) 1.2–1.3 (6H, m, CO_2CH_2Me, OCH_2Me), 1.74 (1H, apparent q, J=ca. 12 Hz, 7β-H_{ax}), 2.35–2.45 (2H, m, 3-H_2), 2.5–2.6 (1H, m, 8α-H_{eq}), 3.06 (1H, ddd, J=5, 10.5, 13.5 Hz, 2-H_{ax}), 3.62 (1H, qd, J=7, 9.5 Hz, OC*H*Me), 3.97 (1H, qd, J=7, 9.5 Hz, OC*H*Me), 4.16 (2H, q, J=7 Hz, CO_2CH_2Me), 4.2–4.3 (1H, m, 2-H_{eq}), 4.77 (1H, ddd, J=2, 5, 11.5 Hz, 8a-H), 5.26 (1H, dd, J=2.5, 10 Hz, 7-H), 7.36 (1H, d, J=2 Hz, 5-H). Flash chromatography of the mixed (3:1) cycloadducts over alumina, eluting with petroleum–ethyl acetate (1:1), gave the title compound **43** ($M+H^+$, 270.1346. $C_{13}H_{20}NO_5$ requires 270.1341); δ_H (300 MHz) 1.18 (3H, t, J=7 Hz, OCH_2Me), 1.27 (3H, t, J=7 Hz, CO_2CH_2Me), 1.74 (1H, dt, J=ca. 3, 12 Hz, 7β-H_{ax}), 2.35–2.55 (3H, m, 3-H_2, 7α-H_{eq}), 3.05–3.15 (1H, m, 2-H_{ax}), 3.59 (1H, dq, J=9.5, 7 Hz, OC*H*Me), 3.82 (1H, dq, J=9.5, 7 Hz, OC*H*Me), 4.15–4.25 (2H, m, CO_2CH_2Me), 4.25–4.35 (1H, m, 2-H_{eq}), 4.80–4.90 (1H, narrow m, 8a-H), 5.23 (1H, br s, 7-H), 7.32 (1H, d, J=2 Hz, 5-H); *m/z* 270 ($M+H^+$, 100%), 215 (35), 207 (20), 198 (21), 187 (22), 170 (28).

1.1.29. 7-Methoxy-7-methyl-4-oxo-3,4,8,8a-tetrahydro-2*H*,7*H*-pyrano[4,3-*b*]pyridine-1-carboxylic acid ethyl ester 44 and 45. To a solution of the pyridone **41** (0.1 g, 0.51 mmol) in DCM (20 mL) was added 2-methoxypropene (0.735 g, 10 mmol, 20 equiv.) and the mixture was stirred at room temperature. TLC after 2 weeks indicated that the reaction was incomplete. 2-Methoxypropene (3 mL) was added and after a further 2 weeks of stirring at room temperature, TLC showed that the reaction had gone to completion. Chromatography over silica gel (50 g), eluting with petroleum–ethyl acetate (4:1), gave the mixed cycloadducts **44** and **45** (105 mg, 77%; ratio 3.6:1 by NMR) as a pale yellow oil. Further chromatography, eluting with cyclohexane–ether–DCM (2:4:1), afforded the title compounds **44** (19 mg) and **45** (11 mg) as colourless oils; (**44**) ($M+H^+$, 270.1332. $C_{13}H_{20}NO_5$ requires 270.1341); δ_H (300 MHz) 1.27 (3H, t, J=7 Hz, CO_2CH_2Me), 1.47 (3H, s, Me), 1.86 (1H, apparent t, J=12 Hz, 7β-H_{ax}), 2.30–2.50 (3H, m, 7α-H_{eq}, 3-H_2), 3.05–3.20 (1H, m, 2-H), 3.36 (3H, s, OMe), 4.09–4.22 (2H, m, CO_2CH_2Me), 4.25–4.35 (1H, m, 2-H), 4.72 (1H, ddd, J=2, 5, 11 Hz, 8a-H), 7.38 (1H, d, J=2 Hz, 5-H); *m/z* 270 ($M+H^+$, 73%), 273 (46), 256 (20), 215 (100), 198 (21); (**45**) ($M+H^+$, 270.1345. $C_{13}H_{20}NO_5$ requires 270.1341); δ_H (300 MHz) 1.27 (3H, t, J=7 Hz, CO_2CH_2Me), 1.49 (3H, s, Me), 2.30–2.60 (4H, m, 3-H_2, 7-H_2), 2.95–3.15 (1H, m, 2-H), 3.29 (3H, s, OMe), 4.1–4.25 (2H, m, CO_2CH_2Me), 4.25–4.35 (1H, m, 2-H), 4.83 (1H, ddd, J=2, 5, 11.5 Hz, 8a-H), 7.29 (1H, d, J=2 Hz, 5-H); *m/z* 270 ($M+H^+$, 52%), 242 (100), 215 (86), 198 (33), 160 (94), 73 (27).

1.1.30. 3-Hydroxymethylene-1-*p*-toluenesulfonyl-4-piperidone 46. A suspension of sodium hydride (60% dispersion in mineral oil; 158 mg, 3.96 mmol) in ether (30 mL) was treated with a few drops of dry ethanol. The reaction vessel was cooled with an ice bath and treated dropwise with a mixture of *N*-tosyl-4-piperidone[28] (500 mg, 1.98 mmol) and ethyl formate (2.93 g, 39.5 mmol) in ether (20 mL). The mixture became yellow in colour and was stirred at room temperature for 64 h. Ethanol (10 mL) was then added and the mixture stirred for a further 2 h. Water (30 mL) was added, the aqueous phase was separated and the organic phase was extracted again with water (30 mL). The combined aqueous extract was acidified to pH 3 using 6 M hydrochloric acid and then extracted with DCM (3×50 mL). The organic phase was washed with brine (50 mL), dried and reduced in volume. The solution of **46** thus obtained was stored in the freezer until required ($M+NH_4^+$, 299.1059. $C_{13}H_{19}N_2O_4S$ requires 299.1065); ν_{max} 3400 br, 1719 cm^{-1}; δ_H (300 MHz) 2.41 (3H, s, Me), 2.53 (2H, t, J=6 Hz, 5-H_2), 3.25 (2H, t, J=6 Hz, 6-H_2), 3.84 (2H, s, 2-H_2), 7.32 (2H, d, J=8 Hz, 3′-H, 5′-H), 7.66 (2H, d, J=8 Hz, 2′-H, 6′-H), 8.53 (1H, s, C*H*OH), 14.0 (1H, br s, OH); *m/z* 299 ($M+NH_4^+$, 30%), 189 (29), 143 (100), 128 (32), 126 (55), 118 (61).

1.1.31. 3-Formyl-5,6-dihydro-1-*p*-toluenesulfonyl-4-pyridone 47. To a stirred solution of phenylselenenyl chloride (398 mg, 2.08 mmol) in DCM (40 mL) at 0°C was added pyridine (172 mg, 2.17 mmol). The solution, which turned from red to orange in colour, was stirred at 0°C for 20 min and then treated with a solution the hydroxymethylene compound **46** (556 mg, 1.98 mmol) in DCM (4 mL). This was stirred at 0°C for 20 min. before being washed with 10% hydrochloric acid (2×30 mL). The solution was then cooled back to 0°C and treated with 30% hydrogen peroxide (0.67 mL). Four more portions of 30% hydrogen peroxide (each 0.67 mL) were added at intervals of 10, 20, 30 and 30 min, and the mixture was finally stirred for a further 30 min. Water (20 mL) was then added and the organic layer was washed with saturated sodium bicarbonate solution (3×20 mL), dried and evaporated to give the crude title compound **47** (346 mg, 63%) as an orange oil. Purification by chromatography over silica gel (20 g), eluting with petroleum–ethyl acetate (1:1), resulted in loss of material and gave a sample of the aldehyde **47** (25 mg, 4.5%) as a pale yellow oil; δ_H (300 MHz) 2.45 (3H, s, Me), 2.59 (2H, t, J=7.5 Hz, 5-H_2), 3.81 (2H, t, J=7.5 Hz, 6-H_2), 7.39 (2H, d, J=8.5 Hz, 3′-H, 5′-H), 7.74 (2H, d, J=8.5 Hz, 2′-H, 6′-H), 8.57 (1H, s, 2-H), 9.89 (1H, s, CHO); *m/z* 297 ($M+NH_4^+$, 30%), 280 ($M+H^+$, 17), 174 (35), 143 (100), 126 (50).

1.1.32. 7-Ethoxy-1-(toluene-4-sulfonyl)-1,2,3,7,8,8a-hexahydropyrano[4,3-*b*]pyridin-4-ones 48 and 49. A solution of the aldehyde **47** (24 mg, 0.09 mmol) in DCM (5 mL) was treated with a large excess of ethoxyethene and the mixture stirred at room temperature for 2 weeks. Evaporation to dryness gave a yellow oil (36 mg) which was passed down a plug of silica gel to give a pale yellow oil (9 mg, 30%). By ^1H NMR spectroscopy the ratio of *endo*/*exo* cycloadducts was ca. 3.5:1. The following signals are those due to the major diastereoisomer **48**; the few distinguishable peaks due to the minor diastereoisomer **49** are marked thus (*)

($M+H^+$, 352.1225. $C_{17}H_{22}NO_5S$ requires 352.1219); δ_H (300 MHz) 1.23 (3H, t, J=7 Hz, OCH_2Me *), 1.25 (3H, t, J=7 Hz, OCH_2Me), 1.90–2.05 (2H, m, 7β-H_{ax}, 3-H_{ax}), 2.16 (1H, td, J=2.5, 17.5 Hz, 3-H_{eq}), 2.41 (3H, s, ArMe), 2.67 (1H, ddd, J=2.5, 5, 13 Hz, 7α-H_{eq}), 3.34 (1H, ddd, J=2.5, 12.5, 15 Hz, 2-H_{ax}), 3.43 (1H, ddd, J=2.5, 12.5, 15 Hz, 2-H^*_{ax}), 3.63 (1H, dq, J=9.5, 7 Hz, OC*H*Me), 3.86 (1H, ddd, J=2.5, 5, 15 Hz, 2-H_{eq}), 3.97 (1H, dq, J=9.5, 7 Hz, OC*H*Me), 4.57 (1H, ddd, J=2, 5, 11.5 Hz, 8a-H *), 4.64 (1H, ddd, J=2, 5, 11.5 Hz, 8a-H), 5.26 (1H, dd, J=2.5, 10 Hz, 7-H), 7.30 (2H, d, J=8 Hz, 3′-H, 5′-H), 7.36 (1H, d, J=2 Hz, 5-H), 7.71 (2H, d, J=8 Hz, 2′-H, 6′-H); m/z 369 ($M+NH_4^+$, 68%), 352 (65), 297 (65), 280 (100), 198 (36), 196 (42), 174 (60), 143 (38), 126 (48).

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