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Intramolecular Diels–Alder reactions of the furan diene (IMDAF); rapid construction of highly functionalised isoquinoline skeletons

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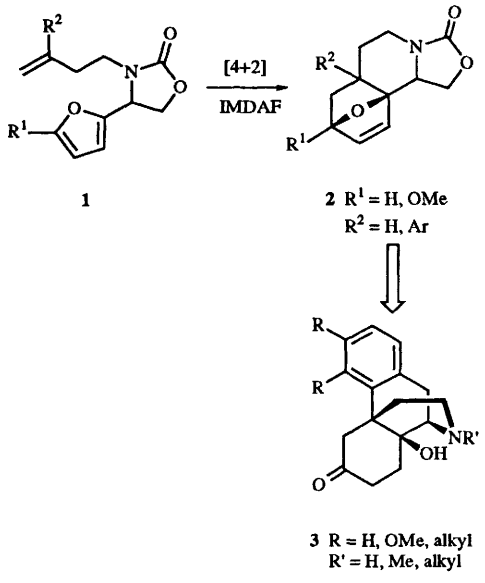
Intramolecular Diels–Alder reaction of substituted furans has been investigated as a prelude to focused application to the synthesis of isoquinoline alkaloids. Several conditions have been investigated for the model compound **6** containing both unactivated dienophile and diene. The best conversion to cycloadduct **8** (84%) was achieved with β-cyclodextrin catalysis. The thermal cyclisation of methoxyfuran precursor **11** gave 55% yield of the cycloadduct **13** and 40% yield of anisole derivative **14**. Finally, the phenyl-substituted precursor **23** was cyclised in a yield of 13% at the expense of undesired elimination of 2-phenylbutadiene. These studies provide preliminary evidence that highly functionalised isoquinolines are accessible by the intramolecular Diels–Alder reaction of furans.

Introduction

Over the years, the intramolecular Diels–Alder reaction (IMDA) has proved a simple but effective step in many natural product syntheses, and the range and variety of triene systems employed is multifarious.[1] Unfortunately, examples employing furan as the dienic component (IMDAF) are less numerous due to a reluctance of the aromatic ring to undergo [4 + 2] cycloaddition. However, in recent years the IMDAF has been studied extensively by several research groups,[2–6] and consequently numerous persuasive methodologies have emerged in order to coerce the participation of the furan ring; these include heat,[4a] β-cyclodextrin catalysis,[3b,4b–d] aqueous conditions,[2a] Lewis acids,[2d,e] high pressure[2b,6a–c,e] and increased side chain substitution.[2c,3a–c,4c,5] In one of several ongoing approaches to morphinan alkaloid systems, such as **3**, we briefly investigated a series of model IMDAF reactions, depicted generally in Scheme 1.

Results and discussion

Our first task was a rapid synthesis of simple trienic models **1**, envisioned *via* alkylation of the known oxazolidinone **4**[7] with suitable electrophiles, Scheme 2. However, attempted reaction with 4-bromobut-1-ene proved exceptionally difficult under standard conditions (NaH, −78 °C, tetrahydrofuran, <2%), probably due to a highly coordinated anion **5**. A move to more polar solvents resulted in enhanced yields,§ the method of choice finally proving to be use of dimethyl sulfoxide at room temperature. The resulting triene **6** when subjected to high temperature under sealed tube conditions furnished a single cycloadduct **8** in 56% yield; unconsumed starting material was easily recovered. Analysis of coupling constants suggested the stereochemistry as shown, and this was supported by positive NOE enhancements. (For example, irradiation of 1-H led to 8.82, 1.24 and 3.47% enhancements of 3-H, 7-H and 13α-H respectively.) This relative stereochemistry was finally proven



Scheme 1

by single crystal X-ray analysis of diol **9** (Fig. 1), obtained *via* catalytic osmylation. Confirmation of stereochemistry allowed us to propose cyclisation of **6** *via* a pseudo-chair transition state **7**, in which the furan diene occupies an *exo* position with respect to the dienophile.

As the yield of adduct **8** was only moderate, we briefly investigated alternative conditions for cyclisation. While Florisil in dichloromethane[2c] and 2.0 mol dm^{-3} $CaCl_2$[2a] showed no reaction, β-cyclodextrin catalysis[8] (1 equiv., H_2O, 65 to 90 °C, 7 d) improved the conversion to 84%. Interestingly, a variety of Lewis acid catalysts¶[2d] failed to give any product, leading us to believe that an unfavourable chelation between the furanyl oxygen and the oxazolidinone moiety must sufficiently deactivate the triene system, either due to electronic or

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‡ To whom correspondence concerning the X-ray crystallographic data should be addressed.
§ All new compounds provided ^{13}C and/or ^{1}H NMR, IR and mass spectral data consistent with their proposed structures.

¶ The Lewis acids employed were $SnCl_4$, BF_3·Et_2O, $Ti(OPr^i)_4$–$TiCl_4$, $EtAlCl_2$, Et_2AlCl and $MeAlCl_2$ at temperatures from −78 °C to room temp., as per ref. 2*d*. Even exposure to the conditions of Martin *et al.* ($EtAlCl_2$ 1.5 equiv., toluene, 120 °C, sealed tube) failed to yield any product.

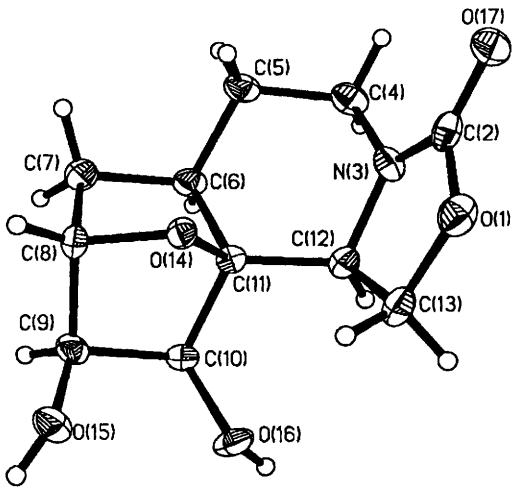
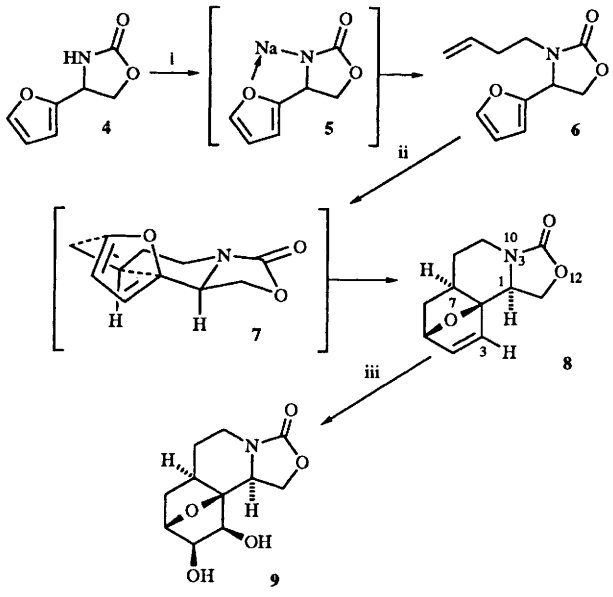


Fig. 1 Thermal ellipsoid plot of compound **9**



Scheme 2 *Reagents and conditions:* i, NaH, 4-bromobut-1-ene, DMSO, room temp., 67%; ii, toluene, sealed tube, 200 °C, 56% *or* β-cyclodextrin, water, 65 to 90 °C, 84%; iii, OsO_4 (cat.), NMNO (excess), Bu^{t}OH–H_2O, 95%

conformational factors in the transition state such as **7** (*i.e.* torquing the diene out of the plane and toward the nitrogen of the oxazolidinone).[10]

We now turned our attention to the corresponding methoxy substituted system **11**, Scheme 3, prepared in disappointingly low yield by adaptation of Ciufolini's method.[7] Unfortunately, aqueous β-cyclodextrin catalysis this time resulted in hydrolysis of the unstable methoxyfuran group. However, thermal cyclisation proceeded well, resulting in the formation of two products, the anisole derivative **13**, isolated in 40% yield, and the hydroxy enone **14**, 55%, the structure of which was once again proved by X-ray (Fig. 2). Although both must arise from the initial bridged adduct **12**, no trace of this compound was evident when the reaction was followed by ^1H NMR in C_6D_6. Therefore, the 'spontaneous' opening of the strained oxygen bridge appears to drive the unfavourable starting material–adduct equilibrium believed to exist in IMDAF reactions,[2d] resulting in a higher overall yield of adducts. Subsequent elimination of water or hydrolysis on work-up/chromatography leads to aromatised **13** and hydroxy enone **14**, respectively.

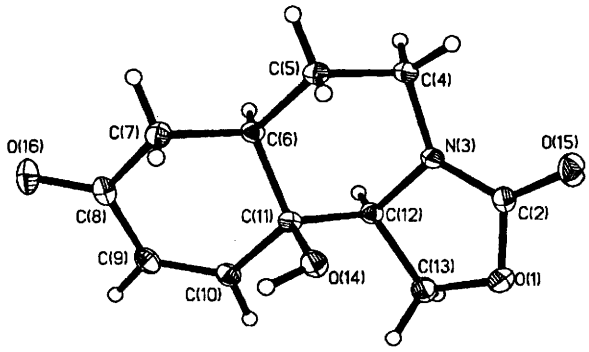
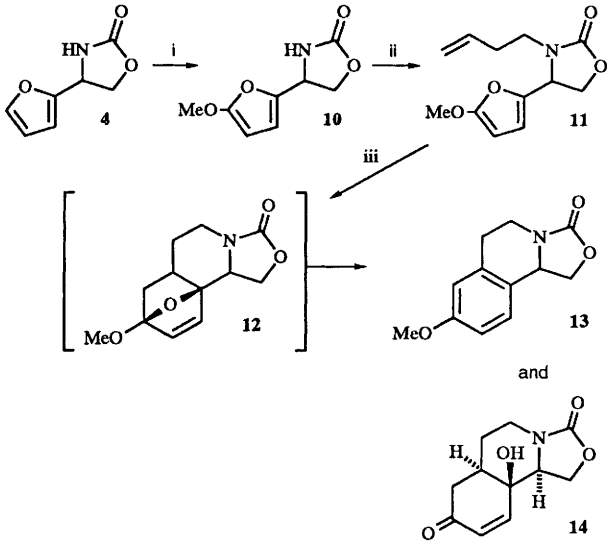


Fig. 2 Thermal ellipsoid plot of compound **14**



Scheme 3 *Reagents and conditions:* i, (a) Br_2, MeOH, 73%; (b) CSA, PhH, heat, < 20%; ii, NaH, but-3-enyl bromide, DMSO, room temp., 66%; iii, benzene, sealed tube, 120 to 165 °C; **13** 40%, **14** 55%

During a brief search for acyclic analogues of oxazolidinone **6**, in order to investigate possible complementary stereochemical consequences, the glycine derivative **15** ‖ was subjected to identical alkylation conditions, Scheme 4. However, to our surprise, only carbamate **17**, the result of C-alkylation, was isolated. We did not expect this system to respond in analogy to the well known C-alkylation of acetamidomalonates. Although this compound failed to cyclise under thermal activation, the β-cyclodextrin catalysed IMDAF afforded a single adduct **19** in 32% yield, the structure of which was once again proven by X-ray crystallography (Fig. 3). An *exo* mode cycloaddition, controlled by intramolecular hydrogen bonding as shown in **18**, may explain the exclusive formation of **19**.

For final advanced model studies we selected the phenyl substituted trienes **21** and **23**, prepared *via* standard alkylation of oxazolidinone **4** with the corresponding methanesulfonate **20**,** Scheme 5. Furanyl derivative **21** proved unreactive under a variety of conditions; steric crowding in the transition state may be retarding the rate of cycloaddition. The poor yield may be attributed to the competing elimination of 2-phenylbutadiene. (This process also accounted for the low yielding

‖ An intermediate in the synthesis of **4**; see ref. 7.

** Prepared by standard mesylation (MsCl 1.2 equiv., NEt_3 1.2 equiv., CH_2Cl_2, 0 °C to room temp.) of the known alcohol.[11]

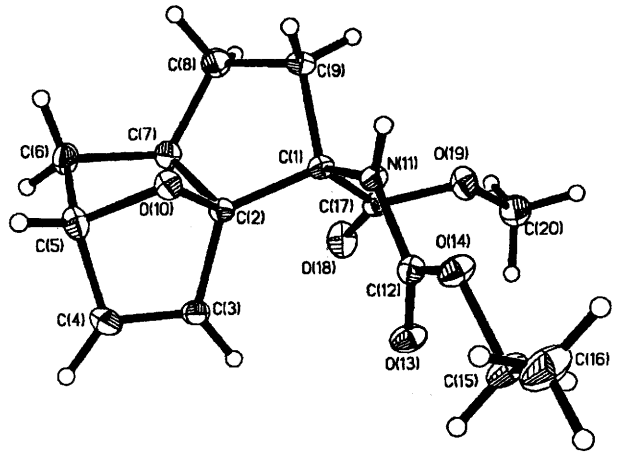
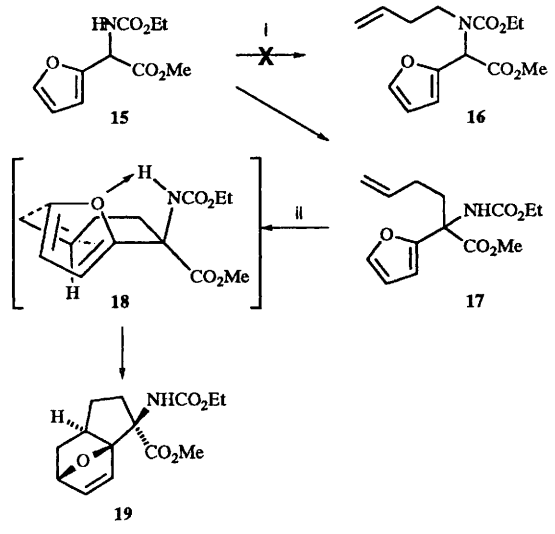
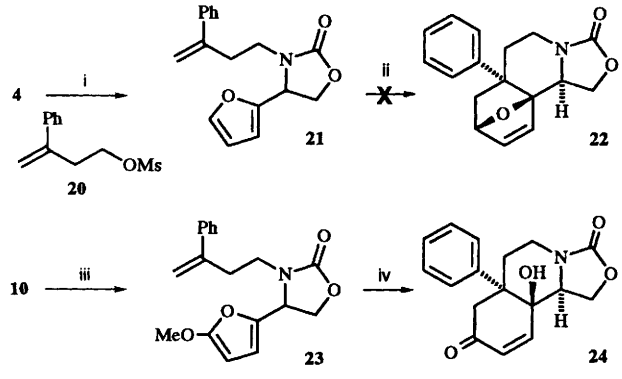


Fig. 3 Thermal ellipsoid plot of compound **19**



Scheme 4 *Reagents and conditions:* i, NaH, but-3-enyl bromide, DMSO, room temp., 58%; ii, β-cyclodextrin, water, 85 °C, 32%



Scheme 5 *Reagents and conditions:* i, NaH, **20**, DMSO, room temp., 40%; ii, toluene, sealed tube, ⩾250 °C, no reaction; iii, as i, 27%; iv, toluene, sealed tube, ⩾250 °C, 13%, plus degradation products

alkylations.) In the case of **23**, any adduct formed would, under the conditions of the reaction, suffer cleavage of the hemiacetal to its enol ether thus driving the reaction ultimately toward **24**, which is obtained during isolation. Stereochemistry was assigned as shown by comparison with previous examples, although we are currently working to obtain suitable crystalline derivatives of this compound.

Conclusions

Our first venture into the area of IMDAF chemistry has produced several examples to add to the growing number in this class of reaction. We are currently adapting this acquired knowledge to the total synthesis of morphinan natural products and will report further results in due course.

Experimental

All non-aqueous reactions were carried out under argon using standard techniques for the exclusion of air and moisture. All solvents used were obtained anhydrous, either by appropriate distillation or by direct purchase. Where necessary, reagents were dried and purified according to the recommended methods. Thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} glass plates. Flash chromatography was performed over Kieselgel 60 silica (EM Reagents, 230–400 mesh). Melting points were determined on an electrothermal apparatus and are uncorrected. Infrared absorption spectra were recorded on a Perkin-Elmer FT-1600 instrument, as thin films or KBr discs. Both ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 400 MHz instrument at 400 and 100 MHz, respectively. *J* Values are given in Hz. ^{13}C Multiplicities were determined by APT experiments. Mass spectra were measured on a VG 7070 EHF instrument, percentile figures refer to relative intensity as a proportion of the base peak.

Preparation of 3-but-3-enyl-4-(furan-2-yl)-1,3-oxazolidin-2-one 6

To a stirred solution of oxazolidinone **4** (153 mg, 1.00 mmol) in dry dimethyl sulfoxide (DMSO) (5 cm^3) was added, in one portion, sodium hydride (29 mg, 1.20 mmol) followed in 30 min by the dropwise addition of 4-bromobut-1-ene (122 mm^3, 1.20 mmol). After 22 h the reaction was quenched with sat. aqueous NH_4Cl (5 cm^3) and then water (20 cm^3) was added and the resultant mixture extracted with Et_2O (5 × 20 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and the volume was reduced under reduced pressure to yield a yellow oil. Purification by flash chromatography (silica ratio 30:1, hexane–EtOAc, 3:1) yielded the title compound **6** as a colourless oil (139 mg, 0.67 mmol, 67%), R_f 0.49 (hexane–EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 2921, 1749 and 1418; δ_H(400 MHz; $CDCl_3$) 7.46 (1 H, dd, *J* 1.7, 0.9), 6.41 (1 H, dd, *J* 3.2, 0.9), 6.40 (1 H, dd, *J* 3.2, 1.7), 5.72 (1 H, m), 5.06 (2 H, m), 4.90 (1 H, dd, *J* 8.9, 6.8), 4.51 (1 H, t, *J* 8.8), 4.36 (1 H, dd, *J* 8.6, 6.8), 3.46 (1 H, ~quintet, *J* ~7.3), 2.96 (1 H, ddd, *J* 14.0, 7.8, 6.1), 2.24 (1 H, m) and 2.15 (1 H, m); δ_C(100 MHz; $CDCl_3$) 157.5 (C), 149.6 (C), 143.6 (CH), 134.7 (CH), 117.2 (CH_2), 110.6 (CH), 109.8 (CH), 66.1 (CH_2), 53.3 (CH), 41.6 (CH_2) and 31.7 (CH_2); *m/z* (CI, 70 eV) 207 ($[M + H]^+$, 100%) and 163 ($[M + H - C_3H_5]^+$, 79) (Found: M, 207.0882. $C_{11}H_{13}NO_3$ requires *M*, 207.0895).

Diels–Alder cycloaddition of triene 6

Method A. Thermal reaction. A solution of triene **6** (202 mg, 0.975 mmol) in dry toluene (11 cm^3) was placed in a heavy walled, Teflon capped, resealable tube and rigorously degassed under a stream of argon. The tube was sealed and heated to ~200 °C in a sand bath for 130 h. After cooling and opening of the tube the solvent was removed under reduced pressure to yield a pale brown solid. Purification by flash chromatography (silica ratio 70:1, hexane–EtOAc, gradient elution 1:1 to $1:2^{\cdot 7}$) yielded (1*SR*,2*SR*,5*SR*,7*RS*)-2,5-epoxy-12-oxa-10-azatricyclo-[8.3.0.$0^{2,7}$]tridec-3-en-11-one **8** as a colourless solid (113 mg, 0.557 mmol, 56%).

Method B. β-Cyclodextrin catalysed reaction. A suspension of triene **6** (17.5 mg, 0.084 mmol) in H_2O (2 cm^3) was sonicated for 15 min, to give an emulsion. β-Cyclodextrin (96 mg, 0.08 mmol) was added and the mixture heated to 55 °C. After 30 h, the temperature was raised to 75 °C, and again after 60 h to 90 °C. After 7 days total, water (15 cm^3) was added and the mixture extracted with CH_2Cl_2 (5 × 10 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and the volume was reduced under reduced pressure to yield a colourless solid. Purification by flash chromatography (silica ratio 60:1, hexane–EtOAc, 2:1) yielded cycloadduct **8** as a colourless solid (14.6 mg, 0.070 mmol, 84%), R_f 0.12 (hexane–EtOAc, 1:1); mp 115–117 °C (from benzene); ν_{max}(KBr)/cm^{-1} 2920, 1733 and 1240; δ_H(400 MHz; [$^2H_6$]DMSO) 6.51 (1 H, dd, *J* 5.7, 1.8), 6.06 (1 H, d, *J* 5.7), 4.97 (1 H, dt, *J* 4.7, 0.7, 0.7), 4.52 (1 H, ddd, *J* 8.9, 4.6, 0.6), 4.36 (1 H, dd, *J* 8.7, 8.2), 4.09 (1 H, dd, *J* 8.2, 4.7), 3.56 (1 H, ddd, *J* 13.3, 4.6, 2.1), 2.98 (1 H, td, *J* 13.3, 13.3, 2.6), 1.82 (1 H, ddt, *J* 13.3, 5.8, 2.7, 2.7), 1.71 (1 H, m, *J* 2.4), 1.47 (1 H, dd, *J* 11.3, 7.5), 1.34 (1 H, ddd, *J* 11.2, 4.7, 2.6) and 1.19 (1 H, dtd, *J* 13.1, 13.1, 11.4, 4.6); δ_C(100 MHz; $CDCl_3$) 156.9 (C), 139.8 (CH), 133.0 (CH), 84.0 (C), 79.1 (CH), 63.3 (CH_2), 54.9 (CH), 40.2 (CH_2), 34.5 (CH_2), 33.8 (CH) and 29.9 (CH_2); *m/z* (CI, 70 eV) 207 ([M + H]$^+$, 100%) (Found: M, 207.090 408. $C_{11}H_{13}NO_3$ requires *M*, 207.089 543 4).

Preparation of (1*SR*,2*SR*,3*SR*,4*RS*,5*SR*,7*RS*)-2,5-epoxy-12-oxa-10-azatricyclo[8.3.0.0^{2,7}]tridecane-3,4-diol 9

To a stirred suspension of adduct **8** (41.4 mg, 0.20 mmol) and *N*-methylmorpholine *N*-oxide (NMNO) (25.8 mg, 0.22 mmol) in 3:2 *tert*-butyl alcohol–water (3 cm^3), was added a catalytic quantity of osmium tetroxide (10 drops of a 2% solution in *tert*-butyl alcohol) and stirring continued. As TLC analysis showed the reaction to be proceeding sluggishly, additional NMNO was added, after 9 h (13.0 mg, 0.11 mmol) and again after 24 h (25.8 mg, 0.22 mmol), accompanied as well with further osmium tetroxide solution (20 drops) and tetrahydrofuran (1 cm^3). After 48 h, 2% $NaHSO_3$ (10 cm^3) and 1 mol dm^{-3} HCl (10 cm^3) were added and the resulting mixture extracted with 2:1 chloroform–isopropyl alcohol (6 × 15 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield a green solid. Purification by recrystallization (hexanes–methanol) yielded the title compound **9** as pale gold crystals (45.8 mg, 0.19 mmol, 95%), R_f 0.18 (EtOAc–MeOH, 19:1); mp 240–242 °C (decomp.) (from isopropyl alcohol–H_2O); ν_{max}(KBr)/cm^{-1} 3349, 1730 and 1021; δ_H(400 MHz, [$^2H_6$]DMSO) 4.93 (1 H, d, *J* 5.6, OH), 4.60 (1 H, d, *J* 6.1, OH), 4.35 (1 H, dd, *J* 8.6, 6.3), 4.30 (1 H, t, *J* 8.8), 4.15 (2 H, m), 3.65 (1 H, t, *J* 5.4), 3.60 (1 H, t, *J* 5.8) and 3.50 (1 H, ddd, *J* 13.4, 4.6, 1.8); δ_C(100 MHz; [$^2H_6$]DMSO) 156.8 (C), 83.8 (C), 81.2 (CH), 75.1 (CH), 73.9 (CH), 65.0 (CH_2), 53.3 (CH), 35.7 (CH), 33.5 (CH_2) and 30.3 (CH_2), N–CH_2 obscured by DMSO; *m/z* (CI, 70 eV) 242 ([M + H]$^+$, 100%) (Found: M, 241.0953. $C_{11}H_{15}NO_5$ requires *M*, 241.0950). A crystal suitable for X-ray analysis was obtained by slow evaporation from an aqueous solution.

Preparation of 4-(5-methoxyfuran-2-yl)-3-but-3-enyl-1,3-oxazolidin-2-one 11

To a stirred solution of oxazolidinone **10** (230 mg, 1.255 mmol) in dry DMSO (5 cm^3) was added, in one portion, sodium hydride (36 mg, 1.51 mmol) and stirring continued. After 15 min, 4-bromobut-1-ene (153 mm^3, 1.51 mmol) was added dropwise and stirring continued for 1 h at room temperature. The reaction was quenched with sat. aqueous NH_4Cl (15 cm^3), and then water (5 cm^3) was added and the resultant mixture extracted with Et_2O (5 × 20 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield a yellow oil. Further purification by flash chromatography (silica ratio 30:1, hexane–EtOAc, gradient elution, 4:1 to 2:1) yielded the title compound **11** as a colourless oil (196 mg, 0.83 mmol, 66%), R_f 0.64 (hexane–EtOAc, 1:2); ν_{max}(neat)/cm^{-1} 2937, 1747 and 1583; δ_H(400 MHz; $CDCl_3$) 6.26 (1 H, d, *J* 3.2), 5.70 (1 H, m), 5.10 (1 H, dd, *J* 3.3, 0.6), 5.02 (2 H, m), 4.71 (1 H, dd, *J* 8.8, 7.5), 4.43 (1 H, t, *J* 8.8), 4.30 (1 H, ~t, *J* ~7.5), 3.82 (3 H, s), 3.41 (1 H, ~quintet, *J* ~7.3), 2.97 (1 H, ddd, *J* 14.0, 7.8, 6.1) and 2.18 (2 H, m); δ_C(100 MHz; $CDCl_3$) 162.2 (C), 157.5 (C), 138.6 (C), 134.8 (CH), 117.1 (CH_2), 111.9 (CH), 80.3 (CH), 65.8 (CH_2), 57.8 (CH_3), 53.6 (CH), 41.4 (CH_2) and 31.7 (CH_2); *m/z* (EI, 70 eV) 237 ([M]$^+$, 5%) (Found: M, 238.1056. $C_{12}H_{15}NO_4$ requires *M*, 238.1079).

Diels–Alder cycloaddition of triene 11

A solution of triene **11** (28.3 mg, 0.119 mmol) in C_6D_6 (~1 cm^3) was placed in a heavy walled, resealable NMR tube and rigorously degassed under a stream of argon. The tube was sealed and heated to 125 °C in a sand bath. After 48 h, the temperature was raised to 165 °C for a further 72 h. After cooling and opening of the tube the solvent was removed under reduced pressure to yield a brown solid. Purification by flash chromatography (silica ratio 100:1, hexane–EtOAc, gradient elution 2:1 to EtOAc) yielded two main products, along with traces of starting material and its hydrolysis product. First, the less polar 5-methoxy-12-oxa-10-azatricyclo[8.3.0.0^{2,7}]trideca-2^7,3,5-trien-11-one **13** eluted and crystallized as a pale yellow solid (10.7 mg, 0.047 mmol, 40%), R_f 0.33 (hexane–EtOAc, 1:1); mp 131–132 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 1750, 1506 and 1242; δ_H(400 MHz; $CDCl_3$) 6.90 (1 H, dd, *J* 8.5, 0.3), 6.80 (1 H, dd, *J* 8.4, 2.6), 6.66 (1 H, d, *J* 2.4), 4.95 (1 H, tm, *J* 7.5), 4.76 (1 H, t, *J* 8.4), 4.14 (1 H, dd, *J* 8.2, 6.4), 4.06 (1 H, ddd, *J* 13.2, 6.3, 1.8), 3.77 (3 H, s), 3.19 (1 H, ddd, *J* 13.1, 11.8, 4.3), 3.02 (1 H, ddd, *J* 16.2, 11.8, 6.4) and 2.68 (1 H, ddm, *J* 16.3, 3.7); δ_C(100 MHz; $CDCl_3$) 158.8 (C), 157.5 (C), 135.1 (C), 126.7 (C), 125.9 (CH), 114.0 (CH), 113.5 (CH), 69.5 (CH_2), 55.3 (CH_3), 53.9 (CH), 38.6 (CH_2) and 27.8 (CH_2); *m/z* (CI, 70 eV) 220 ([M + H]$^+$, 100%) (Found: M, 219.0906. $C_{12}H_{13}NO_3$ requires *M*, 219.0895). Secondly, the more polar (1*RS*,2*RS*,7*RS*)-2-hydroxy-12-oxa-10-azatricyclo[8.3.0.0^{2,7}]tridec-3-ene-5,11-dione **14** was obtained as colourless crystals (14.6 mg, 0.065 mmol, 55%), R_f 0.33 (EtOAc–methanol, 19:1); mp 198–200 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3371, 1700 and 1250; δ_H(400 MHz; [$^2H_6$]acetone) 6.86 (1 H, d, *J* 9.9), 5.96 (1 H, d, *J* 10.0), 4.72 (1 H, d, *J* 0.8), 4.51 (1 H, dd, *J* 8.7, 4.4), 4.38 (1 H, t, *J* 8.8), 3.81 (2 H, m), 3.00 (1 H, ddd, *J* 13.3, 12.6, 3.8), 2.59 (1 H, dd, *J* 17.5, 14.0), 2.26 (2 H, m), 1.83 (1 H, qd, *J* 3 × 12.6, 5.2) and 1.42 (1 H, dm, *J* 12.4); δ_C(100 MHz; [$^2H_6$]acetone) 198.2 (C), 149.0 (C), 147.2 (CH), 139.1 (CH), 67.0 (C), 62.7 (CH_2), 60.7 (CH), 41.0 (CH_2), 40.9 (CH), 40.1 (CH_2) and 25.7 (CH_2); *m/z* (CI, 70 eV) 224 ([M + H]$^+$, 100%) (Found: M, 223.0835. $C_{11}H_{13}NO_4$ require *M*, 223.0845). A crystal suitable for X-ray analysis was obtained by slow evaporation from a hexane–EtOAc solution.

Attempted preparation of methyl 2-[but-3-enyl(ethoxycarbonyl)-amino]-2-(furan-2-yl)acetate 16

To a stirred solution of carbamate **15** (630 mg, 2.77 mmol) in dry DMSO (10 cm^3) was added, in one portion, sodium hydride (80 mg, 3.33 mmol) followed in 30 min by 4-bromobut-1-ene (338 mm^3, 3.33 mmol). After 20 h the reaction was quenched with sat. aqueous NH_4Cl (5 cm^3), water (20 cm^3) was added and the resultant mixture extracted with Et_2O (5 × 20 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield a yellow oil. Further purification by flash chromatography (silica ratio 100:1, hexane–EtOAc, gradient elution, 9:1 to 6:1) yielded 2-(ethoxycarbonylamino)-2-(2-furyl)hex-5-enoate **17** as a pale

yellow oil (455 mg, 1.62 mmol, 58%), R_f 0.32 (hexane–EtOAc, 4:1); ν_{max}(neat)/cm^{-1} 3421, 1728 and 1262; δ_H(400 MHz; $CDCl_3$) 7.34 (1 H, dd, *J* 1.7, 0.9), 6.36 (2 H, m), 6.09 (1 H, br s, NH), 5.79 (1 H, m), 5.04 (1 H, ddd, *J* 17.2, 3.4, 1.7), 4.98 (1 H, ddd, *J* 10.2, 2.9, 1.3), 4.06 (2 H, m), 3.74 (3 H, s), 2.77 (1 H, br s), 2.42 (1 H, ddd, *J* 13.7, 10.8, 5.6), 2.12 (1 H, m), 1.89 (1 H, m), 1.22 (3 H, br m), spectrum broadened in parts due to rotamers; δ_C(100 MHz; $CDCl_3$) 171.1 (C), 152.0 (C), 142.0 (CH), 137.1 (CH), 115.3 (CH_2), 110.6 (CH), 107.5 (CH), 65.0 (C), 60.8 (CH_2), 53.3 (CH_3), 32.8 (CH_2), 28.0 (CH_2) and 14.4 (CH_3), furan 4° carbon obscured, some parts of spectrum doubled due to rotamers; *m/z* (CI, 70 eV) 282 ([M + H]$^+$, 8%) and 193 ([M − $NHCO_2Et$]$^+$, 100) (Found: M, 281.1263. $C_{14}H_{19}NO_5$ requires *M*, 281.1263).

Diels–Alder cycloaddition of triene 17

A suspension of triene **17** (397 mg, 1.41 mmol) and β-cyclodextrin (1.60 g, 1.41 mmol) in H_2O was sonicated for 45 min, and the resulting mixture stirred at 85 °C for 7 days. Water (100 cm^3) was added, and the mixture shaken with EtOAc (50 cm^3). The resulting emulsion was filtered through Celite, the layers were separated and extracted with further EtOAc (2 × 75 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and reduced under reduced pressure to yield a brown oil. Purification by flash chromatography (silica ratio 150:1, hexane–EtOAc, gradient elution, 9:1 to 5:1) yielded methyl (1*RS*,5*RS*,8*RS*)-9-(ethoxycarbonylamino)-1,4-epoxybicyclo-[4.3.0]non-2-ene-9-carboxylate **19** as colourless crystals (125 mg, 0.45 mmol, 32%), R_f 0.42 (hexane–EtOAc 2:1); mp 124–126 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3341, 1733 and 1249; δ_H(400 MHz; $CDCl_3$) 6.25 (1 H, dd, *J* 5.9, 1.6), 6.16 (1 H, d, *J* 5.8), 5.52 (1 H, br s, NH), 4.98 (1 H, dd, *J* 4.5, 1.6), 4.02 (2 H, q, *J* 7.1), 3.74 (3 H, s), 2.79 (1 H, m), 2.05 (3 H, m), 1.69 (1 H, ddd, *J* 11.4, 4.5, 3.0), 1.51 (1 H, dd, *J* 11.4, 7.6), 1.47 (1 H, m) and 1.15 (3 H, t, *J* 7.1); δ_C(100 MHz; $CDCl_3$) 172.6 (C), 155.8 (C), 136.5 (CH), 133.9 (CH), 99.3 (CH_2), 79.5 (CH_3), 64.5 (C), 60.9 (C), 52.6 (CH), 42.2 (CH), 38.0 (CH_2), 35.0 (CH_2) and 29.0 (CH_2); *m/z* (CI, 70 eV) 282 ([M + H]$^+$, 100%) (Found: M, 282.1346. $C_{14}H_{20}NO_5$ requires *M*, 282.1341). A crystal suitable for X-ray analysis was obtained by crystallization from hexane–EtOAc solution.

Preparation and Diels–Alder cycloaddition of 4-(5-methoxyfuran-2-yl)-3-(3-phenylbut-3-enyl)-1,3-oxazolidin-2-one 23

To a stirred solution of oxazolidinone **10** (117 mg, 0.635 mmol) in dry DMSO (2 cm^3) was added, in one portion, sodium hydride (15.2 mg, 0.635 mmol) and stirring continued. After 10 min, a solution of methanesulfonate **20** (0.529 mmol) (freshly prepared from the corresponding known alcohol)** in dry DMSO (2 cm^3) was added dropwise and stirring continued for 4 h. Additional sodium hydride (6.4 mg, 0.265 mmol) was added and stirring continued for a further 12 h. The reaction was quenched with sat. aqueous NH_4Cl (10 cm^3). Water (10 cm^3) was added and the resultant mixture extracted with Et_2O (5 × 20 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent reduced under reduced pressure to yield a yellow oil. Further purification by flash chromatography (silica ratio 100:1, hexane–EtOAc, gradient elution, 4:1 to 2:1) yielded the title compound **23** as an unstable colourless oil (44.0 mg, 0.140 mmol, 26.5%). A solution of this triene (22.5 mg, 0.072 mmol) in [$^2H_8$]toluene (~1 cm^3) was immediately placed in a heavy walled, resealable NMR tube and rigorously degassed under a stream of argon. The tube was sealed and heated to 250 °C in a sand bath. After 90 h, the tube was cooled and opened. The solvent was removed under reduced pressure to yield a yellow paste. Purification by preparative TLC (hexane–EtOAc, 1:3) yielded (2*SR*,7*RS*,1*RS*)-2-hydroxy-7-phenyl-12-oxa-10-azatricyclo[8.3.0.0^{2,7}]tridec-3-ene-5,11-dione **24** as a colourless solid (2.7 mg, 0.009 mmol, 12.5%), R_f 0.31 (hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3392, 1701 and 1457; δ_H(400 MHz; $CDCl_3$) 7.2 (5 H, m), 6.96 (1 H, d, *J* 10.0), 6.08 (1 H, d, *J* 10.0), 4.58 (1 H, m), 4.43 (1 H, m), 4.39 (1 H, t, *J* 8.8), 3.71 (1 H, m), 3.12 (1 H, d, *J* 16.8), 2.62 (1 H, m), 2.55 (1 H, d, *J* 16.8), 2.48 (1 H, m), 2.22 (1 H, br s, OH) and 2.01 (1 H, dm, *J* 13.6); *m/z* (CI, 70 eV) 300 ([M + H]$^+$, 32%) (Found: M, 300.1212. $C_{17}H_{17}NO_4$ requires *M*, 300.1236. (Other compounds isolated were decomposition products, arising from furan hydrolysis, or elimination of oxazolidinone to 2-phenylbutadiene.)

Crystal structure determinations

Crystals were mounted using epoxy resin at the end of thin quartz fibres.

Crystal data. 9, $C_{11}H_{15}NO_5$, *M* = 241.2, orthorhombic, *a* = 10.769(8), *b* = 12.712(10), *c* = 7.916(6) Å, *V* = 1084(1) Å^3 (by least-squares refinement on diffractometer angles for 50 automatically centred reflections, λ = 0.710 73 Å), space group $Pna2_1$, *Z* = 4, *D* = 1.479 g cm^{-3}, crystal dimensions 0.3 × 0.4 × 0.6 mm.

Data collection and processing.—Siemens R3m/v diffractometer, 2θ–θ scan mode with ω scan width 0.60° plus Kα separation, ω scan speed 3.00–14.65° min^{-1}, graphite monochromated Mo-Kα radiation; 1029 reflections measured ($3.5 \leqslant \theta \leqslant 50°$, $+h$, $+k$, $+l$), 1029 discrete reflections, giving 895 with $F > 2.0\sigma(F)$. No detectable crystal decay.

Structure analysis and refinement.—Direct methods solution. Full-matrix least-squares refinement using SHELXTL Plus software (PC Version). All non-hydrogen atoms were refined anisotropically while all hydrogen atoms places at calculated positions. Weighting scheme: $w^{-1} = \sigma^2(F) + 0.0009F^2$. Final *R* and R_w values are 0.0491 and 0.0450.

Crystal data. 14, $C_{11}H_{13}NO_4$, *M* = 223.2, orthorhombic, *a* = 14.785(3), *b* = 5.721(1), *c* = 12.180(2) Å, *V* = 1030.2(4) Å^3 (by least-squares refinement on diffractometer angles for 50 automatically centred reflections, λ = 0.710 73 Å), space group $Pca2_1$, *Z* = 4, *D* = 1.439 g cm^{-3}, crystal dimensions 0.5 × 0.5 × 0.5 mm.

Data collection and processing.—Siemens R3m/v diffractometer, ω scan mode with ω scan width 1.00°, ω scan speed 7.32–29.30° min^{-1}, graphite monochromated Mo-Kα radiation; 804 reflections measured ($3.5 \leqslant \theta \leqslant 50°$, $+h$, $+k$, $+l$), 804 discrete reflections, giving 746 with $F > 2.0\sigma(F)$. No detectable crystal decay.

Structure analysis and refinement.—Direct methods solution. Full-matrix least-squares refinement using SHELXTL Plus software (PC Version). All non-hydrogen atoms were refined anisotropically while all hydrogen atoms places at calculated positions. Weighting scheme: $w^{-1} = \sigma^2(F) + 0.0010F^2$. Final *R* and R_w values are 0.0388 and 0.0456.

Crystal data. 19, $C_{14}H_{19}NO_5$, *M* = 281.3, orthorhombic, *a* = 116.035(3), *b* = 8.226(3), *c* = 20.920(4) Å, *V* = 2759(1) Å^3 (by least-squares refinement on diffractometer angles for 50 automatically centred reflections, λ = 0.710 73 Å), space group *Pbca*, *Z* = 8, *D* = 1.354 g cm^{-3}, crystal dimensions 0.4 × 0.5 × 0.6 mm.

Data collection and processing.—Siemens R3m/v diffractometer, ω scan mode with ω scan width 1.00°, ω scan speed 7.32–39.30° min^{-1}, graphite monochromated Mo-Kα radiation; 3160 reflections measured ($3.5 \leqslant \theta \leqslant 50°$, $+h$, $+k$, $+l$), 3160 discrete reflections, giving 1679 with $F > 3.0\sigma(F)$. No detectable crystal decay.

Structure analysis and refinement.—Direct methods solution. Full-matrix least-squares refinement using SHELXTL Plus software (PC Version). All non-hydrogen atoms were refined anisotropically while all hydrogen atoms places at calculated

positions. Weighting scheme: $w^{-1} = \sigma^2(F) + 0.0001F^2$. Final R and R_w values are 0.0555 and 0.0594.

Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **9**, **14** and **19** have been deposited at the Cambridge Crystallographic Data Centre.††

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†† For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1.

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