The acyl nitroso Diels–Alder (ANDA) reaction of sorbate derivatives: an X-ray and ^{15}N NMR study with an application to amino-acid synthesis†

Lee Bollans,[a] John Bacsa,[a] Jonathan A. Iggo,[a] Gareth A. Morris[b] and Andrew V. Stachulski*[a]

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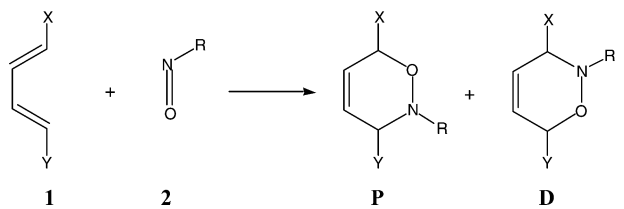
We present a study of the acyl nitroso Diels–Alder (ANDA) reaction of sorbate esters and sorbic alcohol derivatives, using alkoxycarbonyl nitroso dienophiles. An optimisation of the reaction conditions for ethyl sorbate is first presented, and the product is used in an efficient synthesis of 5-methylornithine. Structure–reactivity trends in sorbic alcohol (*E*,*E*-2,4-hexadien-1-ol) and its acylated analogues are then discussed. We present single-crystal X-ray structural proof for key adducts in both series and present in detail a novel HMBC/HSQC (^{1}H–^{15}N) criterion for ready distinction of regioisomers arising from such ANDA reactions.

Introduction

The Diels–Alder reaction of nitroso compounds was first reported by Wichterle[1] in 1947 and has found frequent application in synthesis. Most often the diene substrates have been symmetrical, particularly cycloalka-1,3-dienes:[2,3] with unsymmetrical dienes of type **1** (Scheme 1), the question of preferred regiochemistry of the products from reaction with nitroso compounds **2** arises. A definitive theoretical study by Leach and Houk,[4] with computation of transition states and energetics, showed that the so-called proximal isomer **P** (a term first used by Boger;[5] Scheme 1) was generally favoured over the distal isomer **D** for reactions of 1-substituted 1,3-dienes, whatever the electronic nature of the 1-substituent. The most important frontier molecular interaction is that between HOMO (diene) and LUMO (dienophile): the largest HOMO coefficient of a 1-substituted diene is always at C(4).



Scheme 1 Acyl nitroso Diels–Alder reaction of unsymmetrical dienes. For X > Y, the proximal **P** and distal **D** isomers are defined as shown.

In general terms, the more electron-withdrawing the substituent on the nitroso group, the more efficient is the cycloaddition, by virtue of lowering the LUMO energy. In early work in this area, α-chloro nitroso derivatives were frequently used.[6] Acyl nitroso derivatives, or '*C*-nitrosocarbonyl compounds', were introduced and studied by Kirby *et al.*[7,8] More recently carbamoyl-derived NO dienophiles, especially $PhCH_2OCON{=}O$ and $Bu^tOCON{=}O$, have become popular.[9,10] They are conveniently derived from the corresponding hydroxylamine by *in situ* oxidation. Henceforward we refer to hetero-Diels–Alder reactions of this class as the ANDA (acyl nitroso Diels–Alder) reaction.

Since it introduces 1,4-*N*,*O*-difunctionality in one step with defined relative stereochemistry, the nitroso Diels–Alder reaction continues to attract the synthetic chemist. Recent developments have included the introduction of α-acetoxynitroso derivatives, where the reaction is usefully promoted by Lewis acids in organic media[11a] or by the use of organic–aqueous mixtures.[11b] Also various ANDA products of sorbic alcohol and related derivatives have been transformed into pyrroles.[12] Since absolute stereochemistry can be introduced readily by means of chiral dienophiles,[13,14] the value in synthesis is heightened. In the following we report on our investigations into the ANDA reaction of a number of *unsymmetrical* diene esters and alcohols and show its value with a new synthesis of an alkyl ornithine. We also present structural analysis of the products using both single-crystal X-ray structure determination and a novel ^{1}H–^{15}N HMBC/HSQC NMR method of distinguishing the regioisomers.

Results and discussion

1. Reaction of sorbate esters: an efficient synthesis of 5-methylornithine

Our first investigations were conducted with commercially available ethyl sorbate **3a** and either Z or Boc hydroxylamine **4a,b** using periodate oxidants. According to Houk's prediction[4] this combination is expected to give *entirely* (Scheme 2) the proximal adduct, *viz.* **5a–f**, and indeed this has been observed between sorbate esters and various nitroso dienophiles[15] (a literature correction[16] should also be noted).

We studied in detail and optimised the reaction of ethyl sorbate **3** with $PhCH_2OCON{=}O$ and $Bu^tOCON{=}O$, Scheme 2: full details are in the ESI†. In brief, benzyloxycarbonyl hydroxylamine **4a** gave a higher yield than the *t*-butoxycarbonyl analogue **4b**, and

[a]*Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD, UK. E-mail: stachuls@liv.ac.uk; Fax: 44 (0) 151 794 3588; Tel: 44 (0) 151 794 3542*
[b]*School of Chemistry, University of Manchester, Oxford Rd., Manchester, M13 9PL, UK*

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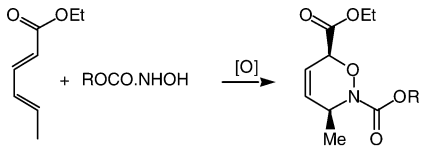


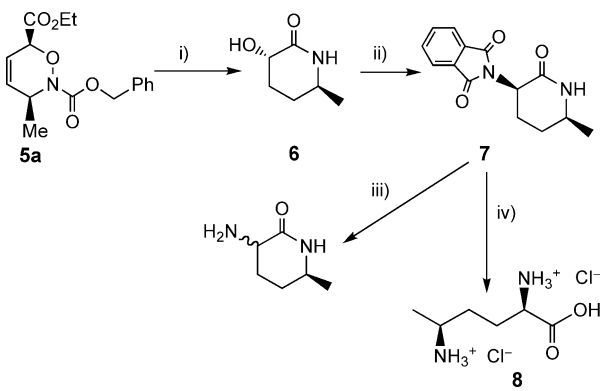
3 **4a** R = $PhCH_2$ **5a** R = $PhCH_2$

4b R = Bu^t **5b** R = Bu^t

Scheme 2 Oxidant: $Na^+ IO_4^-$, or $Bu^n{}_4N^+ IO_4^-$. See ESI† for more details.

$NaIO_4$ in aq. MeOH was a fully satisfactory oxidant. In this series organic-soluble periodates (we used mainly $Bu^n{}_4N^+ IO_4^-$) gave *lower* yields, in striking contrast to the sorbic alcohol series (*vide infra*), and indeed $Bu^n{}_4N^+ IO_4^-$ performed better in a more polar solvent, MeOH. A two-phase variant[17] (EtOAc–aq. buffer, pH 5) was less successful here. Interestingly, ethyl ester **3** gave better yields than other simple alkyl esters from Me to Bu^t: we believe this detail has not been noted by others. The reaction was best performed at −10 °C, and using 2 equivalents of oxidant a very good yield of 85% of **5a** was obtained: a similarly improved yield of **5b** was found under these conditions. We suspect that this particular ANDA is close to the reactivity limit, with the additional steric hindrance of BocN=O an additional negative factor. Steric hindrance in the diene (though *without* a conjugating substituent, as here) is known greatly to favour the proximal isomer in a related ANDA, using the dimethyl acetal of sorbic aldehyde.[18]

Adduct **5a** proved to be an ideal α-amino acid precursor. Thus (Scheme 3) exhaustive hydrogenation of **5a** gave the α-hydroxylactam **6** in very good yield, by cyclisation of the intermediate amino-ester: this product was obtained by Belleau *et al.*[6] (where the precursor was accessed using an α-Cl nitroso dienophile). Conversion of OH to NH_2 might be achieved *via* the α-bromide, followed by azide displacement and reduction.[19] We found that, much more conveniently, **6** was an excellent Mitsunobu substrate, and on reaction with phthalimide, Ph_3P and $(Pr^iO_2CN=)_2$ the highly crystalline phthalimide **7** resulted in 66% yield. Single-crystal X-ray analysis of this product (Fig. 1) confirmed both the clean S_N2 inversion in the Mitsunobu step and the regiochemistry of precursor **5a**.



Scheme 3 Synthesis of a single diastereoisomer of 5-Me ornithine. Reagents and conditions: i) Pd, H_2, THF, 65%; ii) phathalimide, Ph_3P, $(Pr^iO_2CN=)_2$, THF, 66%; iii) N_2H_4, $CHCl_3$, 20 °C; iv) aq. HCl, reflux, 100%.

Interestingly, standard hydrazinolysis conditions proved unsatisfactory for deprotection of **7**: in a slow reaction, a mixture of

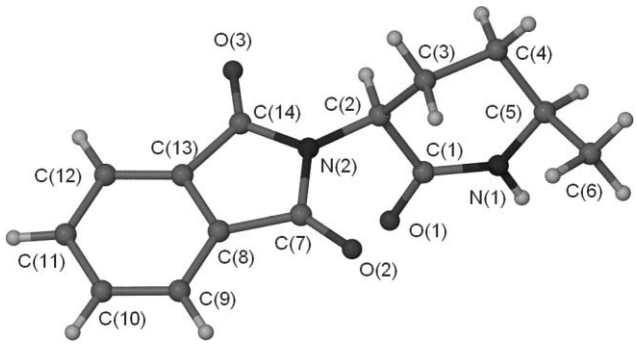


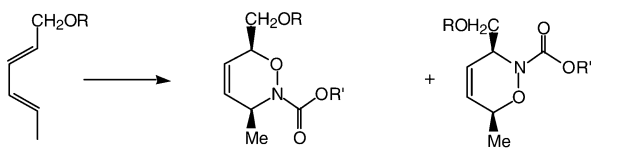
Fig. 1 Single-crystal X-ray structure of phthalimide **7** showing the 2,5-*cis* stereochemistry.

α-NH_2 epimers resulted, reflecting the high acidity of the α-proton. Instead, aqueous acid hydrolysis achieved clean deprotection and ring-opening: the desired amino acid **8** was obtained as a single diastereoisomer in 100% yield. Alkylated analogues of ornithine are of biological interest, *e. g.* 5-fluoromethylornithine is an inhibitor of ornithine aminotransferase.[20]

2. Diene alcohols and derived esters

Sorbic alcohol **9a** is known to give a mixture of proximal and distal adducts on reaction with acylnitroso compounds, as studied by Kouklovsky[12] *et al.* One solution to the regiochemical issue (and obtain exclusively the distal product) is to employ an intramolecular tether, as effectively demonstrated by Sheradsky[15b] and Russell *et al.*[21] We nevertheless probed further the regioselectivity of the *intermolecular* ANDA of sorbic alcohol esters, noting in particular Houk's comment[4] that 'a very sensitive balance between FMO interactions, electrostatics and steric effects' can profoundly affect the outcome. We have also obtained what we believe is the first X-ray structure of an acyl nitroso ANDA product of this type, and evaluated a practical NMR determinant for the regioselectivity of such reactions. Here again we have screened a large number of reactions (see ESI†) and restrict ourselves to the main conclusions here.

Thus (Scheme 4) sorbic alcohol **9a** itself gives a 3:2 proximal: distal (*viz.* **10a** + **11a**) mixture on reaction with ZNHOH and $Bu^n{}_4N^+ IO_4^-$ in CH_2Cl_2, in excellent (87%) yield.[12] In contrast to sorbate esters (*vide supra*) the 'organic' oxidant, viz. $Bu^n{}_4N^+ IO_4^-$ in CH_2Cl_2, was appreciably more effective than $NaIO_4$ in this series. The steric bulk of the nitroso compound has less effect, ZN=O and BocN=O giving similar yields. The relatively high amount of distal product seen with **9a** suggests that in the non-polar solvent (CH_2Cl_2) an H-bonding interaction between the alcohol OH and



9a R = H **10a** R = H, R' = $PhCH_2$ **11a, d, e (as 10a, d, e)**

9b R = Ac **10d** R = Ac, R' = Bu^t

9c R = COC_6H_4.p-NO_2 **10e** R = COC_6H_4.p-NO_2, R' = Bu^t

Scheme 4 Acyl nitroso Diels–Alder reaction of sorbic alcohol and derived esters. Reagents and conditions: as Scheme 2. See ESI† for all analogues studied.

carbonyl O of the dienophile is partly overriding the inherent preference for the proximal isomer. In support of this, use of $NaIO_4$ in aq. MeOH raises the P:D ratio to 3:1 (see ESI†).

Kouklovsky reported that the TBS ether of **9a** strongly favoured the proximal isomer (ratio 7:1).[12] We studied electron-withdrawing substituents, namely the acetate **9b** and 4-nitrobenzoate **9c**. Using BocNHOH and $Bu^n_4N^+IO_4^-$ in CH_2Cl_2, the P:D ratios were between 4:1 and 5:1 for **9b** and 7:1 for **9c**, strongly suggesting an electrostatic effect. In general P and D isomers such as **10d** and **11d** were very close-running in this series, but the proximal adduct **10e** from **9c** was readily purified by crystallisation and gave crystals suitable for a further X-ray structure determination, Fig. 2. Increasing the steric bulk of the ester further, by using the pivalate of **9a**, had little further effect on the P:D ratio: see ESI†.

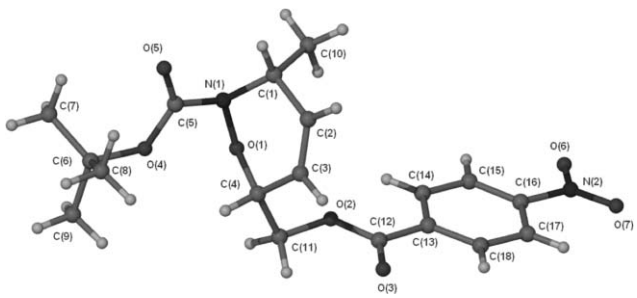
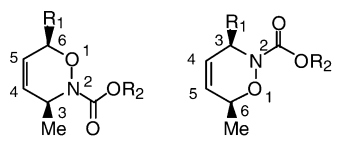


Fig. 2 Single crystal X-ray structure of p-nitrobenzoate **10e**.

The *p*-nitrobenzoate ester **10e** was clearly the proximal isomer and displayed a half-chair structure, Fig. 2. We believe this is the first X-ray structural determination for an *intermolecular* acyl nitroso–diene adduct; a recent report[22] detailed X-ray structures for a regioisomeric pair of *intramolecular* ANDA adducts.

3. NMR Studies: a new criterion for distinguishing proximal and distal adducts

It has been stated[12] that, for a number of ANDA adducts derived from unsymmetrical dienes, the regiochemistry was unambiguously determined using HMBC and HSQC NMR data. Earlier literature[15c,18] relied on correlations of ^{13}C NMR chemical shift data to determine which ring carbon in the dihydrooxazine adducts (see Fig. 3) was attached to N and which to O. In addition, it was postulated that the dihydrooxazines adopted half-chair conformations such that H-6 (proximal isomer) and H-3 (distal isomer) were axially oriented. One important consequence was that a relatively large four-bond coupling, H-6 to H-4, was observed in P adducts (D adducts were not considered). Nevertheless, this still requires a well-defined conformational preference for certainty, *particularly where the relative signs of coupling constants are not determined*, and we sought long-range heteronuclear interactions, which could provide a more general criterion that might encompass a wider range of unsymmetrical ANDA adducts. We now report a new and



P **D** (assuming R_1>Me)

Fig. 3 Numbering system of dihydrooxazines (both regioisomers).

convenient method depending on long-range ^1H–^{15}N interaction, and show its value by assigning unambiguously the P:D mixtures of isomers **10d/11d** and **12/13**. We were initially assisted by a supply of $^{15}NH_2OH{\cdot}HCl$, which was converted into the ^{15}N form of **4b** by the usual procedure.[23]

We first studied **10e** whose structure had been unambiguously determined by X-ray analysis. It was necessary first to assign unambiguously all the protons of **10e**: this was complicated by the large magnitude of the allylic coupling. COSY experiments with a low flip-angle read pulse[24] were used to distinguish between the olefinic protons H-4 and H-5 [see Fig. 3 for numbering] and in particular to determine the signs of the coupling constants, assuming the large vicinal coupling $J_{H\text{-}4,H\text{-}5}$ to be positive. We found that H-4/H-5 were defined as δ 6.02 [1H, ddd, J = +10.5, +4.6 and −2.3 Hz (H-4)] and δ 5.75 [1H, ddd, J = +10.5, −1.8 and +1.5 Hz (H-4)] on the basis of the relative signs of their coupling constants, the vicinal coupling $J_{H\text{-}3,H\text{-}4}$ being positive and the allylic $J_{H\text{-}4,H\text{-}6}$ negative. A complete listing of the ring coupling constants, with signs, is given in the ESI†. A number of attempts were made to find ^{13}C NMR evidence for or against the proximal structure for **10e**. ^{13}C NOE difference experiments showed significant Overhauser effects between the ester carbonyl resonance and a number of ring protons, but none of these effects were diagnostic. ^1H–^{13}C HMBC experiments showed no coupling between the carbonyl and H-3 (δ 4.5); subsequent selective decoupling experiments showed that all the couplings to the ring protons are less than 0.1 Hz, the only significant coupling (*ca.* 1 Hz) being to the methyl protons.

We therefore turned to ^1H–^{15}N HSQC and HMBC measurements. Using the ^{15}N-enriched sample of **4b**, we prepared the ^{15}N version of **5b**, as we were confident this was a single regioisomer.[25] The long-range HSQC spectrum of this product, run with a coherence transfer delay of 31.25 ms, is shown in Fig. 4. The optimum delay for detecting a given coupling J is nominally $1/(4J)$, corresponding here to a J of 8 Hz. In practice the relationship between cross-peak intensity, J, and the delay is complicated by relaxation, homonuclear multiplet structure and field inhomogeneity, and the optimum delay for a given cross-peak is usually significantly less than $1/(4J)$. Fig. 4 shows strong responses for the three-bond ^1H–^{15}N interaction with the terminal

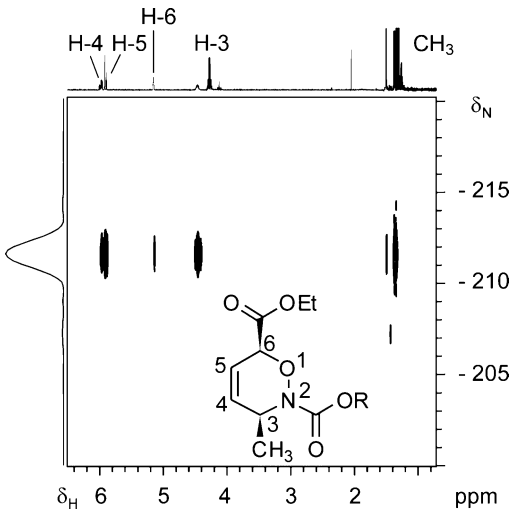


Fig. 4 ^1H–^{15}N long-range HSQC NMR of ^{15}N-enriched **5b** (R = Bu^t), using a coherence transfer delay of 31.25 ms.

methyl group protons and the two-bond interaction with H-3, and somewhat weaker cross-peaks for the three- and four-bond interactions with H4 and H5 respectively. The interaction with H-6 (5-bond through C and 3-bond through O) is extremely weak.

Armed with this information, we re-examined **10e** using *natural abundance* ^{1}H–^{15}N HSQC and were pleased to find clear-cut results using experiments with a total data acquisition time of about 20 h and setting a range of coherence transfer delays (83.3, 31.25 and 20.8 ms) corresponding to ^{1}H–^{15}N couplings of $J = 3$, 8 and 12 Hz (Fig. 5; the spectrum shown was run at a delay of 31.25 ms, nominally $J = 8$ Hz). There was a clear splitting of the Me doublet into a double doublet and further interactions with the olefinic protons. There was some variation in response for cross-peaks with the olefinic Hs: at 83.3 ms the strongest response was from H-5 whereas at 31.25 ms (as shown) the stronger response was from H-4 and a large coupling to methine proton H-3 was observed. At 20.8 ms a cross-peak for the N coupling to H-4 was seen but none for H-3. Nevertheless, a consistent coupling to the Me protons was seen in all three experiments, with *no* evidence of coupling to H-6 or the CH_2 group. We obtained a clearer result

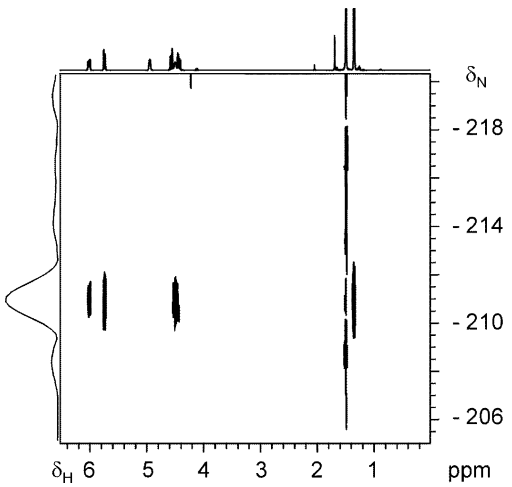
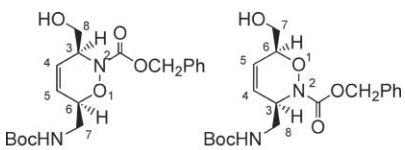


Fig. 5 ^{1}H–^{15}N long-range HSQC NMR of natural ^{15}N abundance **10e** (aryl hydrogens excluded) using a coherence transfer delay of 31.25 ms, equivalent to 8 Hz.

in a gradient HMBC (gHMBC) experiment, which allowed the NH coupling constants to be determined. Using a delay of 125 ms (corresponding to a 4 Hz coupling) the only significant interactions seen were with the Me protons and the H-4 olefinic H. A cross-section of this experiment at the ^{15}N frequency is shown (Fig. 6). There is a clear splitting of the Me doublet into a double doublet and a further doublet splitting of the olefinic proton multiplet: both heteronuclear coupling constants J_{NH} were approximately 3 Hz.

We applied these methods to a more stringent test, namely the assignment of the proximal/distal mixture of **10d** and **11d**. Here, as **11d** comprises just 20% of the total product (*vide supra*), long acquisition was essential but after 60 h using a coherence transfer delay of 20.8 ms the minor isomer peaks were sufficiently strong and the ^{1}H–^{15}N HSQC spectrum showed a firm distinction between the major and minor isomer peaks (Fig. 7). The clearest indication is given by the strong interaction between ^{15}N and the Me protons in the proximal isomer **10d** (this corresponds to the situation in **4b** and **10e**), whereas the distal isomer **11d** showed *no* interaction between ^{15}N and the Me protons but a strong interaction, again presumably 3-bond, between ^{15}N and the non-equivalent CH_2 protons. We had already confidently assigned the CH_2 signal of the minor isomer **11d** to the region δ 4.10–4.30, overlapping with the major isomer CH_2. It is also clear that the coupling from N to *both* olefinic Hs is significant here for each regioisomer, with the minor/major pairs being correctly distinguished (*e. g.* δ 5.80, 5.90 for the minor isomer olefinic Hs).

In the preceding example, the HSQC interaction differentiated between nearby CH_2 and CH_3 groups. We now demonstrate that, in a case where a near-symmetrical diene is used and the two ANDA adducts are formed in almost equal amounts, two CH_2 groups can be clearly distinguished. Thus the distal/proximal pair **12** (37% of mixture) and **13** (42%) were prepared and separated.[26]



12 **13**

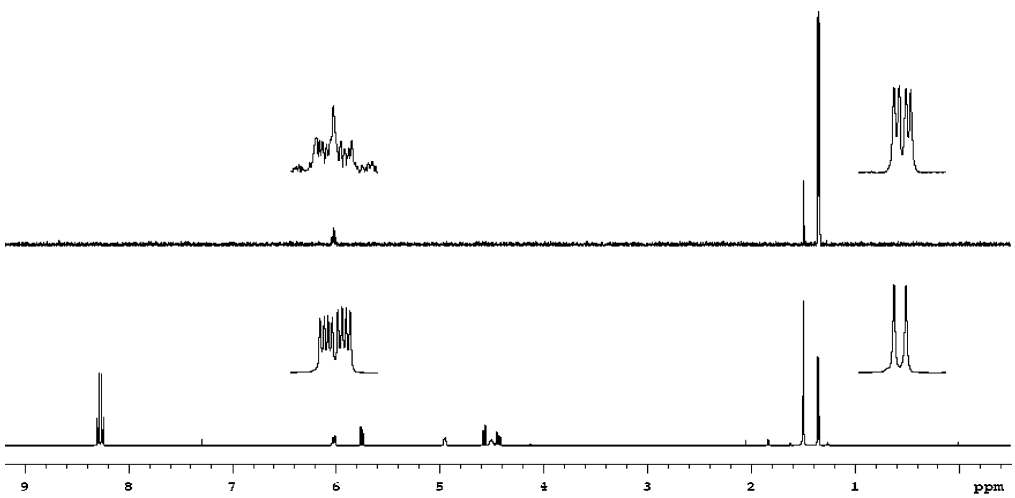


Fig. 6 (Top) F_2 cross-section through the 500 MHz gHMBC spectrum of **10e** at the ^{15}N chemical shift; (bottom) full proton spectrum of **10e**.

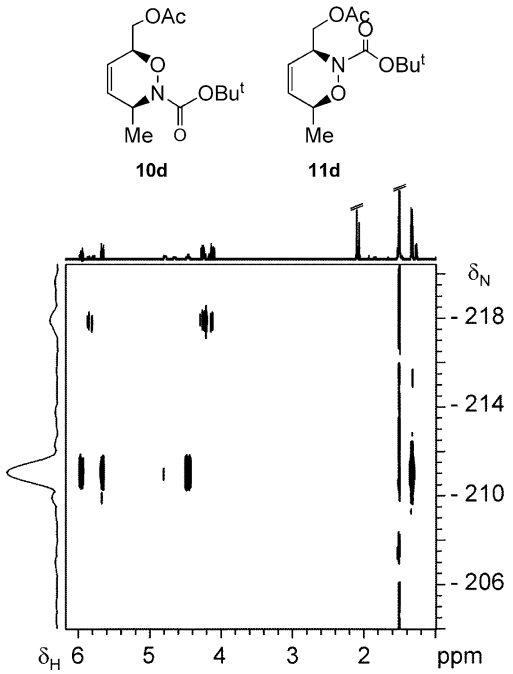


Fig. 7 The ^{1}H–^{15}N long-range HSQC spectrum of a mixture of **10d** and **11d** (4:1) acquired over 60 h with a coherence transfer delay of 42 ms, equivalent to 12 Hz.

Here a ^{1}H–^{15}N HSQC experiment essentially the same as that used for **10d/11d** (Fig. 7), but with an acquisition time of 16 h, showed a clear three-bond interaction between the ring nitrogen N-2 and the C-8 methylene protons (*viz.* CH_2OH), but no interaction to the C-7 methylene protons (CH_2NHBoc) in compound **12**. (See ESI†; note that N-2 is easily distinguished from the other nitrogen by its chemical shift of –220 ppm). This is consistent with Fig. 7 where only the distal isomer **11d** showed such a 3-bond interaction; no interaction between N-2 and CH_2OH is expected in compound **13**, *cf.* **10d**. This result has also been independently confirmed by X-ray analysis of the bis-Boc analogue of **12**. In the 1D proton spectrum of **12**, the olefinic protons are overlapping (H-3 and H-6 are also partially overlapping) and we do not believe a confident assignment could be made by the older criterion,[18] *viz.* lower-field olefinic H diametrically opposite ring oxygen.

Conclusions

We have conducted a study of the acyl nitroso Diels–Alder reaction between a series of unsymmetrical diene esters and alcohols and alkoxycarbonyl nitroso compounds. High yields were obtained straightforwardly using appropriate periodate oxidants, though careful attention to detail was needed, with $NaIO_4$/aq. MeOH giving significantly better yields on sorbate esters whereas $Bu^n{}_4N^+IO_4^-$ in CH_2Cl_2 was the reagent of choice for sorbic alcohol and its acyl derivatives. Sorbate esters gave essentially complete preference for the proximal regioisomeric product, but sorbic alcohol and its acyl derivatives gave significant variation, though the proximal adduct was always favoured. We have additionally obtained a single-crystal X-ray structure for a proximal adduct (**10e**). For definitive assignment of regioisomers, especially in cases where a significant mixture results, we have found that natural abundance ^{1}H–^{15}N HMBC/HSQC is an excellent method: differing 3-bond connectivities in the regioisomers are clearly distinguished. Finally, we have demonstrated the synthetic value of the sorbate ester adduct **5a** by conversion to a single diastereoisomer of an alkylated ornithine analogue **8** in three steps: a highly efficient Mitsunobu reaction of phthalimide with an α-hydroxylactam is a notable feature of this sequence.

Experimental

^{1}H NMR spectra were recorded for $CDCl_3$ solutions (unless otherwise stated) on a Bruker 500 Avance II+ (500 MHz), a Bruker 400 Avance (400 MHz), a Bruker AMX 200 (200 MHz) or a Bruker AMX 250 (250 MHz) spectrometer; ^{13}C NMR spectra were recorded on a Bruker 400 Avance (at 100 MHz) and a Bruker Avance 500 MHz instrument was used for some of the ^{1}H–^{15}N correlations, notably Fig. 6. Chemical shifts are recorded (δ_H, δ_C) in ppm and coupling constants (J) are recorded in hertz (Hz). Chemical shifts were referenced to residual non-deuterated solvent present in the sample, *e.g.* $CHCl_3$ in $CDCl_3$, or to a calibration reference of tetramethylsilane (TMS) incorporated in the sample. Proton (^{1}H) spectra were assigned using COSY data (where necessary) while carbon (^{13}C) spectra were assigned using HMQC data. Proximal and distal regioisomers of ANDA reaction products were assigned using a combination of various NMR techniques, including ^{1}H–^{15}N HMBC, and X-ray crystallography; *vide supra*. Elemental analyses were performed in the University of Liverpool microanalysis laboratory by Mr. S. Apter. Mass spectra were recorded on a VG analytical 7070E machine or a Fison TRIO spectrometer using electron ionisation (EI) or chemical ionisation (CI). Infrared spectra were recorded on a JASCO 4100 type A FT/IR spectrometer in the range of 4000–600 cm^{-1}. Samples were either a liquid film or solid sample. All absorptions are reported as wave numbers, ν (cm^{-1}). Melting points were measured using a Stuart melting point apparatus (SMP3 model) and are uncorrected. Thin layer chromatography was carried out on Merck 5 × 2 cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 $F_{254}$with visualisation by $KMnO_4$ stain, ninhydrin or anisaldehyde. Preparative column chromatography was carried out using ICN (230–400 mesh) silica gel under bellows pressure.

General procedure for synthesis of *N*-alkoxycarbonyl hydroxylamines

A suspension of hydroxylamine hydrochloride (1.5*N* mmol) and potassium carbonate (0.75*N* mmol, 1.5 equiv.) in a 1:1 ether–water mixture was stirred for approx. 1 h with the evolution of CO_2. Benzyl chloroformate (1.0*N* mmol) or di-*tert*-butyl dicarbonate (1.0*N* mmol) was added portionwise at 0 °C and the suspension was stirred at r.t. for 5–16 h. The solids were filtered from the organic layer and the aqueous layer washed with ether. The combined organic layers were then dried ($MgSO_4$), filtered and the organic layer evaporated to give a colourless liquid that crystallised overnight. If necessary, recrystallisation (cyclohexane–toluene) gave a pure product.

***N*-Benzyloxycarbonylhydroxylamine 4a.** Yield, 91% on a scale of 129 mmol hydroxylamine hydrochloride, mp (from toluene–cyclohexane) 68–70 °C (lit.[27] mp 62–64 °C from ether–hexane); δ_H (200 MHz): 5.19 (2H, s, CH_2Ph), 5.30 (1H, s, OH), 6.82 (1H,

bs, NH) and 7.20–7.40 (5H, m, ArH). (Lit.[27] δ_H 5.19 (2 H, s, CH_2Ph), 5.89 (1H, s), 7.21 (1H, s) and 7.36 (5 H, s).

***N*-*tert*-Butoxycarbonyl hydroxylamine 4b.** Yield, 84% on a scale of 136 mmol hydroxylamine hydrochloride, mp 52–54 °C (from ether) (lit.[23] mp 58–59 °C, pet. ether); δ_H (200 MHz): 1.50 (9 H, s, CMe_3), 6.35 (1H, s, OH) and 7.00 (1H, s, NH). (Lit.[16] δ_H 1.48 (9 H, s, CMe_3) and 6.55, 7.01 (2 H, 2bs, NHOH).

^{15}*N*-*tert*-Butoxycarbonyl hydroxylamine ^{15}N-4b. This was obtained on a 5 mmol scale by the above procedure but using 1.25 eq of both hydroxylamine and base as a colourless liquid that crystallised overnight. Recrystallisation gave pure product as a clear solid (0.56 g, 73%), mp 57–58 °C (from cyclohexane–toluene); δ_H (400 MHz): 1.50 (9 H, s, CMe_3), 6.80 (1H, s, OH) and 7.00 (1H, s, NH). [Lit.[16] δ_H ($CDCl_3$): 1.48 (9 H, s, CMe_3,), 6.55, 7.01 (2 H, 2 br s, NHOH)]; δ_C (100 MHz): 28.6 (CMe_3, 3C), 82.6 (*C*Me$_3$, 1C), 159.2 and 160.0 (d, $J = 8$ Hz, C=O); *m*/*z* (CI, NH_3): 152 ([M + NH_4]$^+$, 6%), 134 ([M]$^+$, 100%), 117 ([M – OH]$^+$, 98%), 74 ([M – C(O)NHOH + H]$^+$, 31%), 58 ([M – OC(O)NHOH]$^+$, 10%). Found (CI, NH_3): *m*/*z*, 152.10578; $C_5H_{15}{}^{15}NNO_3$ ([M + NH_4]$^+$) requires 152.10530.

General methods for the acyl nitroso Diels–Alder reactions

Method 1. To a mixture of the diene (1 equiv.) and hydroxylamine (1 equiv.) in 1:1 MeOH–H_2O was slowly added dropwise, with stirring, a solution of $NaIO_4$ (1 equiv.) in H_2O at 0 °C. After addition the reaction was left to stir for 30 min at the same temperature during which time a heavy precipitate of $NaIO_3$ appeared. The reaction was allowed to warm to 20 °C and stirred for a further 40 min. Water and ether were then added and the layers separated. The aqueous layer was washed again with ether and the combined ethereal layers were washed with satd. aq. $NaHCO_3$ (× 3) then brine. After drying ($MgSO_4$), filtering and concentration *in vacuo*, the product was purified by flash chromatography (ethyl acetate–hexane) to give pure product. For additional variants, see notes with Tables 1 and 2 in the ESI†.

Method 2. To a solution of the diene (1 equiv.) and hydroxylamine (1 equiv.) in CH_2Cl_2 at 0 °C was slowly added dropwise, with stirring, $Bu^n{}_4N^+IO_4^-$ (0.5 equiv.) in CH_2Cl_2. After addition, the reaction was purged with N_2 and left to stir for 2.5 h at 20 °C under N_2 during which time a yellow-orange colour appeared. Ethyl acetate and water were added and the layers separated. The aqueous layer was washed again with ethyl acetate and the combined organic layers washed with satd. aq. $Na_2S_2O_3$, satd. aq. $NaHCO_3$ (× 2) then brine. After drying over $MgSO_4$, filtering and concentration *in vacuo*, the product was purified by flash chromatography (ethyl acetate–hexane) to give pure product. For additional variants, see notes with Tables 1 and 2 in the ESI†.

2-Benzyl 6-ethyl 3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2,6-dicarboxylate 5a

Yield, 85% (method 1, 2 eq. of ZNHOH). δ_H (200 MHz): 1.31 (3H, t, $J = 7.2$, CH_3CH_2), 1.38 (3H, d, $J = 6.9$, CH_3CH), 4.27 (2 H, q, $J = 7.2$, CH_2CH_3), 4.54 (1H, m, $CHCH_3$), 5.15 (1H, m, $CHCO_2Et$), 5.20 (2 H, ABq, OCH_2Ph), 5.90 (1H, m, =CHCHCO$_2$Et), 6.00 (1H, m, =CHCHCH$_3$), 7.40 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.5 (CH_3CH_2, 1C), 18.4 (CH_3CH, 1C), 50.9 ($CHCH_3$, 1C), 62.2 (CH_2CH_3, 1C), 68.1 (CH_2Ph, 1C), 76.4 ($CHCO_2Et$, 1C), 122.4 ($CHCHCO_2Et$, 1C), 127.4 ($CHCHCH_3$, 1C), 128.0 (*Ph*, 1C), 128.5, 128.7 (×2), 129.0 (*Ph*, 4C), 136.3 (*Ph*, 1C), 155.1 (N*C*(*O*)OCH$_2$Ph, 1C) and 167.6 (*C*(*O*)OEt, 1C); $\nu_{max.}$(film) 3033, 2979, 1731, 1706, and 698 cm^{-1}; *m*/*z* (CI, NH_3): 323 ([M + NH_4]$^+$, 13%), 288 (100%), 172 ([M – PhCH$_2$OC(O) + H]$^+$, 44%), 169 (34%), 108 (29%). Found (CI, NH_3) *m*/*z* 323.16040, $C_{16}H_{23}N_2O_5$ ([M + NH_4]$^+$) requires 323.16071.

2-*tert*-Butyl 6-ethyl 3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2,6-dicarboxylate 5b

Yield, 47% (method 1). Found: C, 57.20; H, 7.86; N, 5.09. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N 5.16; δ_H (200 MHz,): 1.30 (3H, t, $J = 7.1$ Hz, CH_3CH_2), 1.37 (3H, d, $J = 6.0$ Hz, CH_3CH,), 1.50 (9 H, s, CMe_3), 4.26 (2 H, q, $J = 7.1$ Hz, CH_2CH_3), 4.45 (1H, m, $CHCH_3$), 5.15 (1H, d, $J = 1.6$ Hz, $CHCO_2Et$,), 5.90 (1H, m, =CHCHCO$_2$Et) and 5.98 (1H, m, =CHCHCH$_3$); δ_C (100 MHz): 14.5 (CH_3CH_2, 1C), 18.3 (CH_3CH, 1C), 28.7 (CMe_3, 3C), 50.8 ($CHCH_3$, 1C), 62.1 (CH_2CH_3, 1C), 75.9 ($CHCO_2Et$, 1C), 82.3 (*C*Me$_3$, 1C), 122.1 (=CHCHCO$_2$Et, 1C), 131.1 (=CHCHCH$_3$, 1C), 154.5 (N*C*(O)OC(Me)$_3$, 1C) and 167.8 (CH*C*(O)OEt, 1C). Found (CI, NH_3): *m*/*z*, 289.17633; $C_{13}H_{25}N_2O_5$ ([M + NH_4]$^+$) requires *m*/*z*, 289.17635.

2-*tert*-Butyl 6-ethyl 3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2,6-dicarboxylate ^{15}N-5b

Yield, 27% (method 1). Found: C, 57.20; H, 7.86; N, 5.09; *m*/*z* 290.17271. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N, 5.16%; $C_{13}H_{25}{}^{15}NO_5N$ ([M + NH_4]$^+$) requires 290.17228; δ_H (200 MHz): 1.30 (3H, t, $J = 7.1$ Hz, CH_3CH_2), 1.37 (3H, dd, $J = 6.0$ and 1 Hz, $CH_3CH^{15}N$), 1.50 (9 H, s, CMe_3), 4.26 (2 H, q, $J = 7.1$ Hz, CH_2CH_3), 4.45 (1H, m, $CHCH_3$), 5.15 (1H, d, $J = 1.6$ Hz, $CHCO_2Et$), 5.90 (1H, m, =CHCHCO$_2$Et) and 5.98 (1H, m, =CHCHCH$_3$); δ_C (100 MHz): 14.5 (CH_3CH_2, 1C), 18.3 (CH_3CH, 1C), 28.7 (CMe_3, 3C), 50.7 and 50.8 ($CHCH_3$, 1C, $J = 7$), 61.6 (CH_2CH_3, 1C), 76.0 ($CHCO_2Et$, 1C), 82.3 (*C*Me$_3$, 1C), 122.4, 122.5 (=CHCHCO$_2$Et, 1C) and 131.1 (=CHCHCH$_3$, $J = 2$, 1C), 154.4 and 154.7 (N*C*(*O*)OC(Me)$_3$, $J = 21$, 1C) and 167.9 (CH*C*(O)OEt, 1C); *m*/*z* (CI, NH_3): 290 ([M + NH_4]$^+$, 66%), 273 ([M + H]$^+$, 15%), 216 ([M – Bu^t + H]$^+$, 18%), 199 ([M – CO_2Et]$^+$, 12%), 172 ([M – Boc + H]$^+$, 36%) and 157 ([M – O^{15}NBoc + NH_3]$^+$, 36%).

(3*R*,6*R*)/(3*S*,6*S*)-3-Hydroxy-6-methylpiperidin-2-one 6[6]

10% Pd/C (2 g) was added to a solution of dihydrooxazine **5a** (5.72 g, 18.7 mmol) in anhydrous THF (20 mL) and the mixture was hydrogenated under H_2 (30 atm). The catalyst was filtered and washed with THF and Pr^{i}OH, then the combined filtrate and washings were evaporated and the residue recrystallised from THF to afford the product **6** as a solid (1.57 g, 65%), mp 151–153 °C. Found: C, 55.7; H, 8.6; N, 10.9; *m*/*z* 130.08660; $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.8%; $C_6H_{12}NO_2$ (MH$^+$) requires *m*/*z*, 130.08681; $\nu_{max.}$(cm^{-1}) 3315, 3178, 2929 and 1650; δ_H (CD_3OD, 400 MHz): 1.15 (3H, d, $J = 6.5$ Hz, CH_3CH), 1.35, 1.60, 1.90 and 2.05 (4H, 4 m, CH_2CH_2), 3.40 (1H, m, CH_3CHN) and 3.90 (1H,

m, CH_2CHO); δ_C (CD_3OD, 100 MHz): 23.2, 30.7 (×2), 51.0, 69.1 and 175.9; *m/z* (CI, NH_3) 147 (MNH_4^+, 100%), 130 (MH^+, 93%) and 114 (29%).

2-[(3*R*,6*S*)/(3*S*,6*R*)-6-Methyl-2-oxopiperidin-3-yl]isoindoline-1,3-dione 7

($Pr^iO_2CN{=}$)$_2$ (1.07 g, 5.30 mmol) in THF (5 mL) was added to a solution of lactam **6** (0.65 g, 5.03 mmol), phthalimide (0.82 g, 5.60 mmol) and Ph_3P (1.45 g, 5.53 mmol) in THF (10 mL) with stirring under N_2 at 20 °C. After 5 days the solid was filtered off, then the mother liquors were concentrated to yield a further crop; recrystallisation of the combined solids from THF afforded pure product **7** (0.85 g, 66%), mp 55–56 °C. Found: C, 64.9; H, 5.4; N, 10.8; *m/z*, 259.10737; $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5; N, 10.9%; $C_{14}H_{15}N_2O_3$ (MH^+) requires *m/z*, 259.10827; $\nu_{max.}$(cm^{-1}) 3182, 2962, 1709, 1666 and 1387; δ_H (400 MHz): 1.40 (3H, d, J = 6.6 Hz, CH_3CH), 1.85, 2.00, 2.10 and 2.55 (4H, 4 m, CH_2CH_2), 3.75 (1H, m, CH_3CHN), 4.75 (1H, m, $CH_2CHNPhth$), 5.90 (1H, br, NH), 7.70 and 7.85 (4H, 2 m, ArH); δ_C (100 MHz): 22.2, 22.4, 27.8, 47.8, 48.8, 123.5, 132.1, 134.1, 167.7 and 167.8; *m/z* (CI, NH_3) 259 (MH^+, 100%), 276 (MNH_4^+, 51%) and 518 [2(MH^+), 25%].

(2*S*,5*R*)/(2*R*,5*S*)-2,5-Diaminohexanoic acid dihydrochloride 8 (5-methylornithine dihydrochloride)

Phthalimide **7** (0.102 g, 0.395 mmol) was heated at reflux in 6 M HCl (10 mL) for 5 h. The solution was cooled, washed with ether (2 × 5 mL) and EtOAc (1 × 5 mL) and the aqueous layer was concentrated to dryness, affording the dihydrochloride **8** as a yellow powder (0.086 g, quant.). Found: *m/z*, 293.2202; $C_{12}H_{29}N_4O_4$ [(2M + H)$^+$] requires *m/z*, 293.2189; $\nu_{max.}$(cm^{-1}) 3398, 2897, 1720, 1589, 1384 and 1223; δ_H (CD_3OD, 400 MHz): 1.35 (3H, d, J = 6.6 Hz, CH_3CH), 1.85, 2.05 (4H, 2 m, CH_2CH_2), 3.40 (1H, m, $CHCH_3$) and 4.05 (1H, t, J = 6.1 Hz, CH_2CHN); δ_C (CD_3OD, 100 MHz): 18.9, 28.0, 31.7, 49.0, 53.9 and 171.7; *m/z* (ES +ve mode) 147 (MH^+) and 293 [(2M + H)$^+$].

(2*E*,4*E*)-Hexa-2,4-dienyl-4-nitrobenzoate 9c

4-Nitrobenzoyl chloride (2.04 g, 11 mmol) was added in one portion to a solution of (2*E*,4*E*)-hexa-2,4-dienol (0.98 g, 10 mmol) and pyridine (1.2 mL) in CH_2Cl_2 (15 mL), which was stirred under N_2 at 0 °C and protected from light. After 1 h the mixture was diluted with EtOAc (70 mL) and washed sequentially with 3 M HCl (3×), water, satd. aq. $NaHCO_3$ soln. and brine. After drying over $MgSO_4$ the solution was evaporated to give crude product as a solid (2.50 g, approx. quant.), which was sufficiently pure for further use; an analytical sample was obtained by chromatography, eluting with 30% EtOAc–hexane, giving **9c** as a rather light-sensitive white solid (1.29 g, 52%), mp 57–59 °C. Found: C, 63.1; H, 5.35; N, 5.6; *m/z*, 270.0741. $C_{13}H_{13}NO_4$ requires C, 63.2; H, 5.3; N, 5.7%; $C_{13}H_{13}NO_4Na$ requires *m/z*, 270.0742; δ_H (200 MHz): 1.78 (3H, d, J = 6.4 Hz, CH_3CH), 4.85 (2H, d, J = 6.7 Hz, CH_2CH), 5.80 (2H, m, 2-H + 5-H), 6.10 (1H, m, 4-H), 6.36 (1H, dd, J = 15.1 and 10.2 Hz, 3-H) and 8.25 (4H, dd, ArH); *m/z* (ES +ve mode) 270 (MNa+, 100%), 517 (2M + Na^+, 72%).

Benzyl 6-(hydroxymethyl)-3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (proximal and distal isomers) 10a, 11a[28]

Yield, 87% (method 2). For **10a**: Found: C, 64.0; H, 6.55; N, 5.3. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%; δ_H (400 MHz): 1.35 (3H, d, J = 6.7 Hz, $CHCH_3$), 3.65 and 3.77 (2H, dd, J = 12.4 and 3.0 Hz, J = 12.4 and 6.5 Hz, CH_2OH), 4.52 (1H, m, $CHCH_3$), 4.70 (1H, m, $CHCH_2OH$), 5.20 (2H, ABq, CH_2Ph), 5.70 (1H, dt, J = 10.3 and 1.6 Hz, $=CHCHCH_2OH$), 5.91 (1H, ddd, J = 10.3, 4.5 and 2.3 Hz, $=CHCHCH_3$) and 7.35 (5H, m, Ph); δ_C (100 MHz): 18.7 ($CHCH_3$, 1C), 51.0 ($CHCH_3$, 1C), 64.0 (CH_2OH, 1C), 68.0 (CH_2Ph, 1C), 79.4 ($CHCH_2OH$, 1C), 124.2 ($=CHCHCH_2OH$, 1C), 127.4, 128.0, 128.4, 128.7, 128.9, 129.0 and 131.7 (ArC and $CH=CHCH$, 7C; both proximal and distal), 130.6 ($=CHCHCH_3$, 1C), 136.4 (ArC, 1C) and 155.3 ($NC(O)OCH_2Ph$, 1C); MS (*m/z*, CI): 281 ([M + NH_4]$^+$, 40%), 264 ([M + H]$^+$, 13%), 173 ([M – CH_2Ph + H]$^+$, 8%), 114 ([M – $NC(O)CH_2Ph$]$^+$, 27%), 98 ([M – $ONC(O)CH_2Ph$]$^+$, 66%). Found (CI, NH_3): *m/z*, 281.14958; $C_{14}H_{21}N_2O_4$ ([M + NH_4]$^+$) requires 281.15013. The distal isomer **11a** was distinguished by δ_H (400 MHz): 1.25 (3H, d, J = 6.7 Hz, CH_3CH) and 5.75–5.85 (2H, m, $CH=CHCH$); δ_C (100 MHz): 19.2 (CH_3CH, 1C), 63.7 ($HOCH_2CH$, 1C) and 68.2 (CH_2Ph, 1C); as noted above, the olefinic carbons of the distal isomer cannot be distinguished with certainty from the Ar carbons.

tert-Butyl 6-(acetoxymethyl)-3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (proximal and distal isomers) 10d, 11d

Yield, 89% (method 2). For **10d**, found: δ_H (400 MHz): 1.33 (3H, d, CH_3CH, J = 6.7 Hz), 1.50 (9 H, s, CMe_3), 2.10 (3H, s, CH_3CO), 4.13 and 4.25 (2H, m, CH_2OAc), 4.46 (1H, m, $CHCH_3$), 4.79 (1H, m, $CHCH_2OAc$), 5.66 (1H, dt, J = 10.3 and 1.6 Hz, $=CHCHCH_2OAc$), 5.95 (1H, ddd, J = 10.3, 4.6 and 2.3 Hz, $=CHCHCH_3$); δ_C (100 MHz): 18.4 (CH_3CH, 1C), 21.2 (CH_3CO, 1C), 28.7 (Me_3C), 50.6 ($CHCH_3$, 1C), 64.7 (CH_2OAc), 75.6 ($CHCH_2OAc$, 1C), 81.9 (CMe_3, 1C), 123.3 ($=CHCHCH_2OAc$, 1C), 131.5 ($=CHCHCH_3$, 1C), 154.6 ($NC(O)OCH_2Ph$, 1C) and 171.3 ($CH_2OC(O)CH_3$, 1C); *m/z* (CI, NH_3): 289 ([M + NH_4]$^+$, 3%), 272 ([M + H]$^+$, 1%), 172 ([M – Boc + H]$^+$, 11%), 156 ([M – OAc – Bu^t]$^+$, 26%), 140 ([M – OAc – OBu^t]$^+$, 15%), 112 ([M – OAc – Boc]$^+$, 7%). Found (CI+) 289.17578, $C_{13}H_{25}N_2O_5$ ([M + NH_4]$^+$) requires 289.17635. The distal isomer **11d** was distinguished by δ_H (400 MHz): 1.27 (3H, d, CH_3CH, J = 6.7 Hz), 2.05 (3H, s, CH_3CO), 4.65 (1H, m, $CHCH_3$), 5.78 (1H, ddd, J = 10.4, 4.3 and 2.1 Hz, $=CHCHCH_3$), and 5.86 (1H, dt, J = 10.3 and 1.6 Hz, $=CHCHCH_2OAc$); δ_C (100 MHz, $CDCl_3$): 19.1 (CH_3CH, 1C), 63.9 (CH_2OAc, 1C) and 73.4 ($CHCH_2OAc$, 1C) with other signals overlapping.

tert-Butyl 6-[(4-nitrobenzoyloxy)methyl]-3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (proximal and distal isomers) 10e, 11e

Yield, 76% (method 2). The major (proximal) isomer was isolated by crystallization from EtOAc–hexane: **10e**, mp 118–119 °C. Found: C, 57.05; H, 5.85; N, 7.4. $C_{18}H_{22}N_2O_7$ requires C, 57.1; H, 5.8; N, 7.4%; δ_H (400 MHz): 1.35 (3H, d, J = 6.7 Hz, CH_3CH), 1.50 (9 H, s, Me_3C), 4.43 and 4.57 (2H, 2dd, J = 12.2 and 6.9 Hz; 12.2 and 2.7 Hz; $CHCH_2OCOAr$), 4.50

(1H, m, CHCH$_3$), 4.95 (1H, m, CHCH$_2$OCOAr), 5.75 (1H, dt, J = 10.5 and 1.5 Hz, =CHCHCH$_2$OCOAr), 6.02 (1H, ddd, J = 10.5, 4.6 and 2.3 Hz, =CHCHCH$_3$) and 8.03 (4H, dd, ArH); δ_C (100 MHz): 18.4 (CH_3CH, 1C), 28.7 (CMe_3, 3C), 50.7 (CH$_3$$CH$, 1C), 65.8 ($CH_2$OAc, 1C), 75.6 ($CHCH_2$OAc, 1C), 82.1 ($CMe_3$), 123.0 (=$CH$CHCH$_2$OCOR), 123.9, 131.3 (ArC, each 2C), 131.9 (=CHCHCH$_3$), 135.5, 151.0 (ArC), 154.5 (NC(O)OCH$_2$Ph, 1C) and 164.8 (CH$_2$OC(O)Ar, 1C); m/z (CI, NH$_3$) 396 (MNH$_4^+$, 100%). The distal isomer **11e** was distinguished by δ_H (400 MHz): 1.26 (3H, d, J = 6.7 Hz, CH_3CH), 5.80–5.95 (2H, m, 2 × =CH) and 8.30 (4H, dd, ArH, partially overlapping); no ^{13}C NMR was determined for this isomer in view of the very small amount.

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