

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

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Supplementary Information

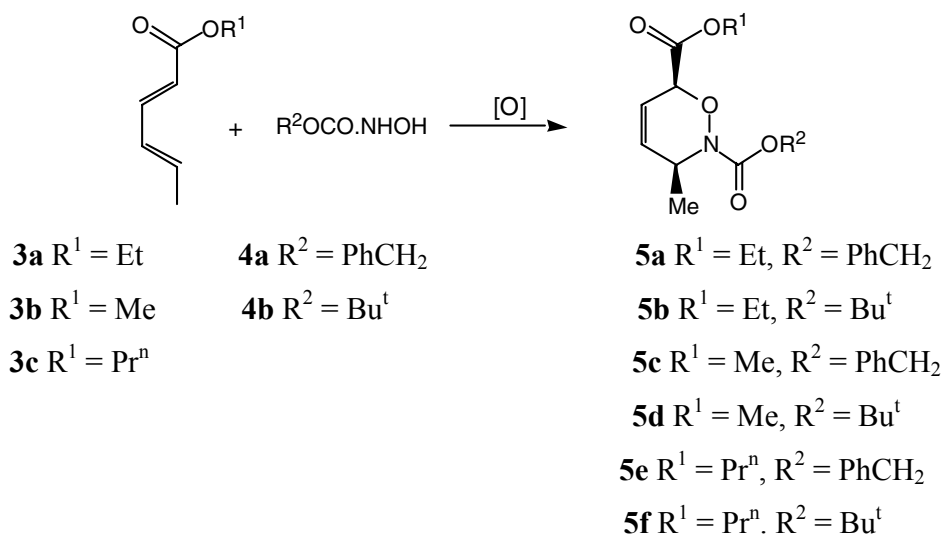
This document contains:

1. Tabulated data on ANDA reactions of sorbate esters and sorbic alcohol and derived esters (Tables 1 and 2).
2. Experimental data and characterisations of compounds not presented in the main paper.
3. Crystal structure data.
4. High resolution ¹H 2D NMR data for compound **10e**.
5. Additional references.

Also NMR photocopy spectra for compounds in both the main paper and this SI document which do not have microanalytical data are included as a separate file.

The numbering schemes follow those of the main paper with a few obvious additions, e. g. sorbate esters other than ethyl become **3b**, **3c**... etc and their derived ANDA adducts become **5c**, **5d**... etc.

Sorbate Esters



Scheme 2. Reagents: Na⁺ IO₄⁻, or Buⁿ₄N⁺ IO₄⁻, conditions as Table 1.

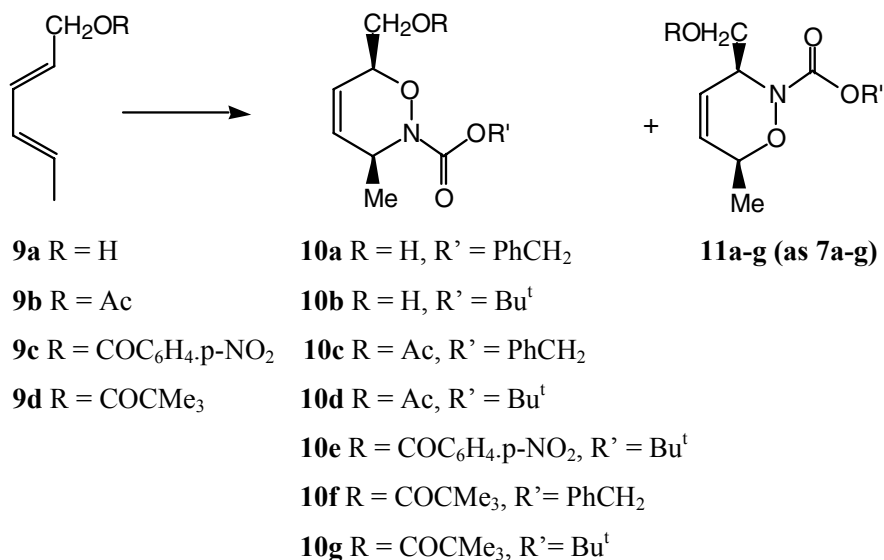
Table 1. The acyl nitroso Diels-Alder reaction of sorbate esters with alkoxy carbonyl nitroso compounds.

Entry	Diene	Hydroxylamine	Oxidant	Solvent	Temp. °C	Yield %
1	3b	4b	NaIO ₄	MeOH: H ₂ O, 1:1	0°C	36 5d
2	3a	4b	NaIO ₄	MeOH: H ₂ O, 1:1	0°C	47 5b
3	3c^a	4b	NaIO ₄	MeOH: H ₂ O, 1:1	0°C	34 5f
4	3b	4a	NaIO ₄	MeOH: H ₂ O, 1:1	0°C	34 5c
5	3a	4a	NaIO ₄	MeOH: H ₂ O, 1:1	0°C	51 5a
6	3c^a	4a	NaIO ₄	MeOH: H ₂ O, 1:1	0°C	41 5e
7	3a	4a	NaIO ₄	MeOH: H ₂ O, 1:1	-10°C	60 5a
8	3a	4a	NaIO ₄	EtOAc:buffer ^b	0°C	48 5a
9	3a	4a^c	Bu ⁿ ₄ N ⁺ IO ₄ ⁻	MeOH	0°C	64 5a
10	3a	4a^c	Bu ⁿ ₄ N ⁺ IO ₄ ⁻	MeOH	0°C	69 5a
11	3a	4a^c	NaIO ₄	MeOH: H ₂ O, 1:1	0°C	62 5a
12	3a	4a^d	NaIO ₄ ^d	MeOH: H ₂ O, 1:1	-15°C	85 5a
13	3a	4a	NaIO ₄	THF: H ₂ O	0°C	64 5a

14	3a	4a	NaIO ₄	MeOH ^c	0°C	55 5a
15	3a	4a	Bu ⁿ ₄ N ⁺ IO ₄ ⁻	CH ₂ Cl ₂	0°C	40 5a

Notes: Unless otherwise stated, diene (1 eq) was reacted with hydroxylamine (1.1 eq) and oxidant (1.1 eq) with the oxidant added last, dropwise, over 10 min. ^a A further reduction in yield was observed with both the n-butyl and t-butyl esters (to 26%), using either **4a** or **4b**. ^b Citric acid buffer at pH6 was used, cf. ref. 17. ^c Inverse addition, viz. hydroxylamine added to mixture of diene and oxidant. ^d 2 eq. of both **4a** and NaIO₄ used. ^e No water used, addition over 3h. ^f 0.5 eq oxidant, cf. ref. 12, reaction time 2.5h.

Sorbic Alcohol and Derivatives



Scheme 4. ANDA Reaction of sorbic alcohol and derived esters. Reagents, as Scheme 2.

Table 2. The acyl nitroso Diels Alder reaction of sorbic alcohol and its esters.

Entry	Diene	Hydroxylamine	Oxidant	Solvent	Yield %	Prods.	10:11
1	9a	4b	NaIO ₄	MeOH: H ₂ O, 1:1	NI ^a	10b, 11b	3:1
2	9a	4a	Bu ⁿ ₄ N ⁺ IO ₄ ⁻	CH ₂ Cl ₂	87	10a, 11a	3:2
3	9b	4b	Bu ⁿ ₄ N ⁺ IO ₄ ⁻	CH ₂ Cl ₂	89	10d, 11d	4:1
4	9b	4a	Bu ⁿ ₄ N ⁺	CH ₂ Cl ₂	82	10c, 11c	5:1

			IO ₄ ⁻					
5	9b	4a	NaIO ₄	MeOH: H ₂ O, 1:1	38	10c, 11c	4:1	
6	9c	4b	Bu ⁿ ₄ N ⁺	CH ₂ Cl ₂	76	10e, 11e	7:1	
			IO ₄ ⁻					
7	9d	4a	Bu ⁿ ₄ N ⁺	CH ₂ Cl ₂	76	10f, 11f	4:1	
			IO ₄ ⁻					
8	9d	4b	Bu ⁿ ₄ N ⁺	CH ₂ Cl ₂	75	10g, 11g	5:1	
			IO ₄ ⁻					

Notes: ^a Not isolated free of unreacted **9a**; yield by NMR, ca. 60%

Experimental

Esterification Reaction General Methods. Method 1: Sorbic acid [(2E,4E)-hexa-2,4-dienoic acid; 1 equiv.] was dissolved in excess alcohol used and conc. H₂SO₄ (2-6 drops) added. The solution was stirred under reflux for 4 h. After the reaction had cooled to ambient temperature, water and ether were added, the layers separated and the aqueous layer washed again with ether. The combined ethereal layers were washed with sat. aq. NaHCO₃ (x 2) then brine. The ethereal layer was dried (MgSO₄), filtered and concentrated *in vacuo* to give pure alkyl sorbate as a yellow oil or liquid.

Method 2 (Me ester): All glassware was dried before use. To sorbic acid [(2E,4E)-hexa-2,4-dienoic acid; 1 equiv.] in dry toluene and dry methanol (3.5:1 v/v) under N₂ was slowly added dropwise TMSCHN₂ (1.1 equiv.). After stirring for 75 min., during which time N₂ gas was evolved, the reaction was concentrated *in vacuo* to give the ester.

(2E,4E)-Hexa-2,4-dienoic acid methyl ester (Methyl sorbate) **3b**:²⁹

Yield 93% (method 2); δ_H (200 MHz): 1.86 (3 H, d, *J* = 5.4 Hz, CH₃CH), 3.74 (3 H, s, CO₂Me), 5.78 (1 H, dd, *J* = 15.4 and 0.7 Hz, CHCO₂Me), 6.00-6.30 (2 H, m, CHCH=CHCH) and 7.19-7.34 (1 H, m, =CHCH₃); δ_C (100 MHz): 18.9 (CH₃CH, 1C), 51.7 (CO₂Me, 1C), 119.0 (CHCH₃, 1C), 130.2 (CHCHCH₃, 1C), 139.7 (CHCHCO₂Me, 1C), 145.5 (CHCO₂Me, 1C) and 168.1 (CO₂Me, 1C).

(2E,4E)-Hexa-2,4-dienoic acid n-propyl ester (n-Propyl sorbate) **3c**:^{29,30}

Yield 85% (method 1). Found: C, 68.7; H, 9.3. $C_9H_{14}O_2 \cdot 0.2 H_2O$ requires C, 68.4; H, 9.1% (hygroscopic); ν_{max} (film) 2966, 2881, 1711, 1645 and 1618 cm^{-1} ; δ_H (200 MHz): 0.98 (3 H, t, $J = 7.2$ Hz, CH_3CH_2), 1.58 (2 H, sextet, $J = 7.0$ Hz, $CH_3CH_2CH_2$), 1.86 (3 H, d, $J = 4.7$ Hz, CH_3CH), 4.10 (2 H, t, $J = 6.7$ Hz, $CO_2CH_2CH_2$), 5.75 (1 H, dd, $J = 15.4$ and 0.7 Hz, $CHCO_2Me$), 6.00-6.30 (2 H, m, $CHCH=CHCH$) and 7.15-7.30 (1 H, m, $CHCH_3$); δ_C (100 MHz): 10.8, 19.0, 22.4, 66.2, 119.4, 130.2, 139.5, 145.3 and 167.8; m/z (CI, NH_3) 155 (MH^+ , 72%) and 172 (MNH_4^+ , 100%).

3-Methyl-3,6-dihydro-[1,2]oxazine-2,6-dicarboxylic acid 2-benzyl ester 6-methyl ester 5c:

Yield, see Table 1. δ_H (400 MHz): 1.40 (3 H, d, $J = 6.9$ Hz, $CHCH_3$), 3.80 (3 H, s, OMe), 4.50 (1 H, m, $CHCH_3$), 5.15 (1 H, m, $CHCO_2Me$), 5.20 (2 H, ABq, OCH_2Ph), 5.85 (1 H, m, $=CHCHCO_2Me$), 5.95 (1 H, m, $=CHCHCH_3$) and 7.35 (5 H, m, ArH); δ_C (100 MHz): 18.3 (CH_3CH , 1C), 50.9 ($CHCH_3$, 1C), 53.0 (CO_2Me , 1C), 65.7 (CH_2Ph , 1C), 70.0 ($=CHCO_2Me$, 1C), 127.4, 128.0, 128.5, 128.7, 129.0 (ArC, 5C), 122.2 ($=CHCHCO_2Me$, 1C), 131.0 ($=CHCHCH_3$, 1C), 136.3 (ArC, 1C), 155.2 ($NC(O)CH_2Ph$, 1C) and 168.1 ($CHC(O)OMe$, 1C); m/z (CI, NH_3) 309 ($[M+NH_4]^+$, 60%), 292 ($[M+H]^+$, 15%) and 203 ($[M-OCH_2Ph+H]^+$, 12%). Found (CI, NH_3): m/z 309.14475, $C_{15}H_{21}N_2O_5$ ($[M+NH_4]^+$) requires 309.14505. This compound has not previously been reported in *racemic* form, but has been obtained as a single enantiomer with chirality derived from D-ribose.³¹

2-tert-Butyl 6-methyl 3-methyl-2H-1,2-oxazine-2,6(3H,6H)-dicarboxylate 5d:

Yield, see Table 1. δ_H (400 MHz): 1.35 (3 H, d, $J = 6.7$ Hz, CH_3CH), 1.50 (9 H, s, CMe_3), 3.81 (3 H, s, CO_2Me), 4.45 (1 H, m, $CHCH_3$), 5.15 (1 H, d, $J = 1.6$ Hz, $CHCO_2Me$), 5.90 (1 H, m, $=CHCHCO_2Et$, 1H) and 6.00 (1 H, m, $CHCHCH_3$); δ_C (100 MHz): 18.3 (CH_3CH , 1C), 28.7 (CMe_3 , 3C), 50.8 ($CHCH_3$, 1C), 53.0 (CO_2Me , 1C), 76.0 ($CHCO_2Me$, 1C), 82.4 (CMe_3 , 1C), 122.3 ($=CHCHCO_2Me$, 1C), 131.2 ($=CHCHCH_3$, 1C), 154.5 ($NC(O)OC(Me)_3$, 1C) and 168.3 ($CHC(O)OMe$, 1C); m/z (CI, NH_3): 275 ($[M+NH_4]^+$, 41%), 258 (MH^+ , 7%), 219 ($[M-Bu^t+NH_4]^+$, 100%), 203 ($[M-CO_2Me]^+$, 22%), 201 ($[M-tBu]^+$, 18%), 157 ($[M-Boc+H]^+$, 42%) and 142 ($[M-NBoc]^+$, 39%).

2-Benzyl 6-propyl 3-methyl-2H-1,2-oxazine-2,6(3H,6H)-dicarboxylate 5e:

Yield, see Table 1. δ_{H} (400 MHz): 0.97 (3 H, t, $J = 7.4$ Hz, CH_3CH_2), 1.35 (3 H, d, $J = 6.7$ Hz, CH_3CH), 1.70 (2 H, sextet, $J = 7.2$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.15 (2 H, t, $J = 6.5$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_2$), 4.45 (1 H, m, CHCH_3), 5.25 (3 H, m, CHCO_2nPr and OCH_2Ph), 5.90 (1 H, m, $=\text{CHCHCO}_2\text{Pr}^{\text{n}}$, 1H), 6.00 (1 H, m, $=\text{CHCHCH}_3$, 1H) and 7.35 (5 H, m, CH_2Ph); δ_{C} (100 MHz): 10.7 (CH_3CH_2 , 1C), 18.4 (CH_3CH , 1C), 22.2 (CH_2CH_3 , 1C), 50.9 (CHCH_3 , 1C), 67.7 ($\text{CO}_2\text{CH}_2\text{CH}_2$), 68.1 (OCH_2Ph , 1C), 76.5 (CHCO_2nPr , 1C), 122.4 ($=\text{CHCHCO}_2\text{Pr}^{\text{n}}$), 127.4 ($=\text{CHCHCH}_3$, 1C), 128.0, 128.5, 128.7, 128.9, 129.4 (ArC, 5C), 136.3 (ArC, 1C), 155.2 ($\text{NC}(\text{O})\text{OC}(\text{Me})_3$, 1C) and 167.7 ($\text{CHC}(\text{O})\text{OnPr}$, 1C); m/z (CI): 337 ($[\text{M}+\text{NH}_4]^+$, 100%), 320 ($[\text{M}+\text{H}]^+$, 26%), 258 ($[\text{M}-\text{OnPr}+\text{H}]^+$, 42%). Found (CI, NH_3) m/z, 320.15036, $\text{C}_{17}\text{H}_{22}\text{NO}_5$ ($[\text{M}+\text{H}]^+$) requires 320.14980.

2-tert-Butyl 6-n-propyl 3-methyl-2H-1,2-oxazine-2,6(3H,6H)-dicarboxylate 5f:

Yield, see Table 1. δ_{H} (400 MHz): 0.97 (3 H, t, $J = 7.4$ Hz, CH_3CH_2), 1.35 (3 H, d, $J = 6.8$ Hz, CH_3CH), 1.59 (9 H, s, CMe_3), 1.70 (3 H, sextet, $J = 7.0$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.15 (2 H, t, $J = 6.7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_2$), 4.45 (1 H, m, CHCH_3), 5.15 (1 H, d, $J = 1.6$ Hz, $\text{CHCO}_2\text{Pr}^{\text{n}}$), 5.90 (1 H, m, $=\text{CHCHCO}_2\text{Pr}^{\text{n}}$) and 6.00 (1 H, m, $=\text{CHCHCH}_3$); δ_{C} (100 MHz): 10.6 (CH_3CH_2 , 1C), 18.4 (CH_3CH , 1C), 22.2 (CH_2CH_3 , 1C), 28.4 (CMe_3 , 3C), 50.7 (CHCH_3 , 1C), 67.6 ($\text{CO}_2\text{CH}_2\text{CH}_2$, 1C), 75.9 ($\text{CHCO}_2\text{Pr}^{\text{n}}$, 1C), 82.3 (CMe_3 , 1C), 122.4 ($=\text{CHCHCO}_2\text{Pr}^{\text{n}}$, 1C), 131.2 ($=\text{CHCHCH}_3$, 1C), 154.6 ($\text{NC}(\text{O})\text{OCMe}_3$, 1C) and 167.9 ($\text{CHC}(\text{O})\text{OPr}^{\text{n}}$, 1C); m/z (ES+ve): 609 ($[\text{2M}+\text{K}]^+$), 593 ($[\text{2M}+\text{Na}]^+$), 324 ($[\text{M}+\text{K}]^+$), 308 ($[\text{M}+\text{Na}]^+$). Found (ES+ve): 308.1474, $\text{C}_{14}\text{H}_{23}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) requires 308.1474.

tert-Butyl 6-(hydroxymethyl)-3-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate

(proximal and distal isomers) 10b, 11b:¹² Yield, see Table 2. For **10b**: Found: m/z, 247.16528. $\text{C}_{11}\text{H}_{23}\text{N}_2\text{O}_4$ ($[\text{M}+\text{NH}_4]^+$) requires m/z, 247.16578; δ_{H} (200 MHz): 1.32 (3 H, d, $J = 6.7$ Hz, CH_3CH), 1.51 (9 H, s, CMe_3), 3.60-3.83 (2 H, m, CHCH_2OH), 4.45 (1 H, m, CHCH_3), 4.64 (1 H, m, CHCH_2OH), 5.75 (1 H, ddd, $J = 10.3$, 1.7 and 1.5 Hz, $=\text{CHCHCH}_2\text{OH}$) and 5.87 (1 H, ddd, $J = 10.3$, 4.4 and 2.2 Hz, $=\text{CHCHCH}_3$); δ_{C} (100 MHz): 19.2 (CH_3CH , 1C), 28.7 (CMe_3 , 3C), 51.0 (CH_3CH , 1C), 64.0 (CH_2OH , 1C), 79.0 (CHCH_2OH , 1C), 82.1 (CMe_3 , 1C), 124.3 ($=\text{CHCHCH}_2\text{OH}$, 1C), 130.8 ($=\text{CHCHCH}_3$, 1C) and 154.9 ($\text{NC}(\text{O})\text{OCMe}_3$, 1C); m/z (CI, NH_3): 247 ($[\text{M}+\text{NH}_4]^+$, 4%), 230 ($[\text{M}+\text{H}]^+$,

2%), 173 ([M-tBu]⁺, 14%), 130 ([M-Boc+H]⁺, 42%), 100 ([M-ONBoc+H]⁺, 35%). The distal isomer **11b** was distinguished by δ_{H} (200 MHz): 1.26 (3 H, d, $J^2 = 6.7$, CH_3CH), 1.48 (9 H, s, CMe_3) and 5.75-5.85 (2 H, m, $\text{CHCH}=\text{CHCH}$); δ_{C} (100 MHz): 18.5 (CH_3CH , 1C), 82.4 (Me_3C , 1C), 123.0 (CHCHCH_3 , 1C), and 131.7 ($=\text{CHCHCH}_2\text{OH}$, 1C).

Benzyl 6-(acetoxymethyl)-3-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate

(proximal and distal isomers) 10c, 11c: Yield, see Table 2. For **10c**: Found: C, 63.5; H, 6.4; N, 4.3. $\text{C}_{16}\text{H}_{19}\text{NO}_5$ requires C, 62.94; H, 6.3; N, 4.6%; δ_{H} (400 MHz): 1.35 (3 H, d, $J = 6.7$ Hz, CH_3CH), 2.05 (3 H, s, CH_3CO), 4.17 (2 H, dd, $J = 12.2$ and 3.5 Hz; $J = 12.2$ and 3.1 Hz, CHCH_2OAc), 4.65 (1 H, m, CHCH_3), 4.80 (1 H, m, CHCH_2OAc), 5.20 (2 H, ABq, OCH_2Ph), 5.65 (1 H, m, $=\text{CHCHCH}_2\text{OAc}$), 5.95 (1 H, m, $=\text{CHCHCH}_3$) and 7.35 (5 H, m, ArH); δ_{C} (100 MHz): 18.5 (CH_3CH , 1C), 21.1 (CH_3CO , 1C), 50.8 (CHCH_3 , 1C), 64.4 (CH_2OAc , 1C), 68.0 (OCH_2Ph , 1C), 74.0 (CHCH_2OAc , 1C), 123.4 ($=\text{CHCHCH}_2\text{OAc}$, 1C), 128.3, 128.4, 128.6, 128.9, 131.2 and 132.5 ($=\text{CHCHCH}_3$, 1C), (ArC for proximal and distal), 136.4 (ArC, 1C), 155.2 ($\text{NC(O)OCH}_2\text{Ph}$, 1C) and 171.2 ($\text{CH}_2\text{OC(O)CH}_3$, 1C); m/z (CI, NH_3): 323 ([M+ NH_4]⁺, 100%), 306 ([M+H]⁺, 35%), 262 ([M-C(O)CH₃]⁺, 42%), 108 ([M-C₉H₁₂NO₄]⁺, 18%). Found (CI, NH_3): m/z 306.13481, $\text{C}_{16}\text{H}_{20}\text{NO}_5$ ([M+H]⁺) requires 306.13415. The distal isomer **11c** was distinguished by δ_{H} (400 MHz): 1.28 (3 H, d, $J = 6.7$ Hz, CH_3CH), 4.50 (1 H, m, CHCH_3), 5.75 (1 H, m, $=\text{CHCHCH}_3$) and 6.85 (1 H, m, $=\text{CHCHCH}_2\text{OAc}$); δ_{C} (100 MHz): 19.0 (CH_3CH , 1C), 63.6 (CH_2OAc , 1C), 72.1 (CHCH_2OAc , 1C), 122.2 ($=\text{CHCHCH}_3$, 1C) and 133.2 ($=\text{CHCHCH}_2\text{OAc}$, 1C) with other signals overlapping.

(2E, 4E)-Hexa-2,4-dienyl-4-pivalate 9d: A solution of (2E, 4E)-hexa-2,4-dienol (1.02g, 10.4 mmol) and pyridine (0.91 mL, 1.1 equiv.) in anhydrous DCM (5 mL) was treated with pivalyl chloride (1.38 mL, 1.1 equiv.) added dropwise at 0°C, then left to stir at 20°C for 6 hours. The white pyridine hydrochloride precipitate was removed by filtration, then the organic layer was diluted with Et₂O (30 mL) and washed with 1 M HCl (3x 30 mL) and brine. After drying (Na_2SO_4) and filtering, the solvent was removed *in vacuo* to give the ester **9d** as a yellow liquid (1.80g, 95%). Found: C, 72.1; H, 9.9; m/z , 200.16519. $\text{C}_{11}\text{H}_{18}\text{O}_2$ requires C, 72.5; H, 10.0%; $\text{C}_{11}\text{H}_{22}\text{NO}_2$ ([M+ NH_4]⁺) requires

200.16505; ν_{\max} (cm⁻¹) 2970, 1732 and 1662; δ_{H} (200 MHz, CDCl₃): 1.20 (9 H, s, Me₃C), 1.77 (3 H, d, J = 6.7 Hz, CH₃CH), 4.56 (2 H, d, J = 6.6 Hz, CH₂OPiv), 5.50-5.85 (2 H, m, 2x =CH) and 6.00-6.35 (2 H, m, 2x =CH); δ_{C} (100 MHz, CDCl₃): 18.4 (CH₃CH), 27.6 (Me₃C C=O), 39.1 (CH₂OPiv), 65.1 (Me₃CC=O), 124.5 (CHCH₃), 130.9 (x2) (CHCHCHCH), 134.6 (CHCH₂OPiv) and 178.6 (Me₃CC=O); m/z (CI, NH₃): 200 ([M+NH₄]⁺, 38%), 182 ([M]⁺, 25%), 98 ([M-Piv]⁺, 100%) and 81 ([M-OPiv]⁺, 73%).

Benzyl 6-[(pivalyloxy)methyl]-3-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (proximal and distal isomers) 10f, 11f: Yield, 76%, yellow oil (Table 2), P:D ratio = 4:1. Found: C, 65.8; H, 7.3; N, 4.0; m/z 370.1617. C₁₉H₂₅NO₅ requires C, 65.7; H, 7.25; N, 4.0%; C₁₉H₂₅NO₅Na (MNa⁺) requires m/z , 370.1630; δ_{H} (400 MHz, CDCl₃), for **10f**: 1.18 (9 H, s, CMe₃), 1.34 (3 H, d, J = 6.7 Hz, CHCH₃), 4.21 (2 H, d, J = 4.5 Hz, PivOCH₂CH), 4.55 (1 H, m, CHCH₃), 4.77 (1 H, m, CHCH₂OPiv), 5.16 & 5.24 (2 H, ABq, J = 12.2 and 12.3 Hz, OCH₂Ph), 5.65 and 5.67 (1 H, dt, J = 10.3 and 1.5 Hz, =CHCHCH₂OPiv), 5.92 and 5.95 (1 H, ddd, J = 10.2, 4.0 and 1.9 Hz, =CHCHCH₃) and 7.40 (5 H, m, ArH); δ_{C} (100 MHz): 18.4 (CH₃CH, 1C), 27.5 (Me₃C, 3C), 50.7 (CH₃CH), 64.0 (CH₂OCO), 68.0 (ArCH₂O), 76.5 (CHCH₂OCO), 123.6 (CH=CHCH₂OPiv), 127.4-129.1 (ArC_{x3} + CH=CHCH₃), 136.4 (ArC), 155.2 (NC(O)OCH₂Ph) and 178.6 (CH₂OCOCMe₃); m/z (ES+ve mode) 717 [(2M+Na)⁺], 386 (MK⁺) and 370 (MNa⁺); the distal isomer **11f** was distinguished by δ_{H} (400 MHz): 1.14 (9 H, s, Me₃C), 1.28 (3 H, d, J = 6.7 Hz, CH₃CH), 4.70 (1 H, m, CHCH₃), 5.78 (1 H, m, =CHCHCH₃) and 5.85 (1 H, m, =CHCHCH₂OPiv); δ_{C} (100 MHz): 19.1 (CH₃CH), 63.6 (CH₂OCO), 65.8 (CHCH₃), with other signals overlapping.

tert-Butyl 6-[(pivalyloxy)methyl]-3-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (proximal and distal isomers) 10g, 11g: Yield, 75%, yellow oil (Table 2), P:D ratio = 4:1. Found: m/z 336.1797; C₁₆H₂₇NO₅Na (MNa⁺) requires m/z , 336.1787; δ_{H} (400 MHz, CDCl₃), for **10g**: 1.22 (9 H, s, Me₃C), 1.32 (3 H, d, J = 6.7 Hz, CH₃CH), 1.50 (9 H, s, Me₃CO), 4.21 (2 H, m, CHCH₂OCO), 4.46 (1 H, m, CHCH₃), 4.77 (1 H, m, CHCH₂OCO), 5.66 (1 H, dt, J = 10.3 and 1.5 Hz, CHCHCH₂OPiv), and 5.95 (1 H, ddd, J = 10.3, 4.7 and 2.3 Hz, CHCHCH₃); δ_{C} (100 MHz): 18.3 (CH₃CH), 27.6, 28.8 (2xMe₃C),

50.5 (CH_3CH), 64.3 (CHCH_2OCO), 75.9 (CHCH_2OCO), 81.9 ($2\times\text{Me}_3\text{C}$), 123.7 ($=\text{CHCHCH}_2\text{OPiv}$), 131.2 ($=\text{CHCHCH}_3$), 154.7 (NHCOO) and 178.7 (OCOCMe_3); m/z (ES+ve mode) 649 [$(2\text{M}+\text{Na})^+$], 352 (MK^+) and 336 (MNa^+); the distal isomer **11g** was distinguished by δ_{H} (400 MHz): 1.20 (9 H, s, Me_3C), 1.26 (3 H, d, $J = 6.7$ Hz, CH_3CH), 1.49 (9 H, s, Me_3CO), 4.65 (1 H, m, CHCH_3), 5.79 (1 H, ddd, $J = 10.3, 4.1$ and 1.8 Hz, CHCHCH_3), and 5.85 (1 H, d, $J = 10.4$ Hz, $\text{CHCHCH}_2\text{OPiv}$); δ_{C} (100 MHz): 19.1 (CH_3CH), 28.0, 28.4 ($2\times\text{Me}_3\text{C}$) and 63.9 (CH_2OCO).

Compounds **12** and **13** were prepared from the appropriate diene (whose synthesis will be described in detail elsewhere) by the ANDA reaction, Method B (see main MS) with ZNHOH on a 2 mmolar scale in 79% overall yield. They were fully separated by chromatography:

Benzyl 6-[(t-butoxycarbonylamino)methyl]-3-(hydroxymethyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate 12. Yield, 37%. Found: m/z , 401.1699; $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_6\text{Na}$ (MNa^+) requires m/z , 401.1689; δ_{H} (400 MHz, CDCl_3): 1.45 (9 H, s, Me_3C), 3.25-3.45 (2 H, m, $\text{CHCH}_2\text{NHBoc}$), 3.75 (2 H, m, CH_2OH), 4.55 (1 H, m, CHCH_2OH), 4.65 (1 H, m, $\text{CHCH}_2\text{NHBoc}$), 5.05 (1 H, br, NH), 5.21 (2 H, ABq, OCH_2Ph), 5.80-5.95 (2 H, m, $\text{CH}=\text{CH}$) and 7.35 (5 H, m, ArH); δ_{C} (100 MHz): 28.7 (Me_3C), 43.0 (CH_2NHBoc), 57.2 (CHCH_2OH), 63.5 (CH_2OH), 68.4 (CH_2Ph), 76.9 ($\text{CHCH}_2\text{NHBoc}$), 80.0 (Me_3C), 125.2 and 128.4 ($\text{CH}=\text{CH}$), 129.0, 129.1, 129.2, 136.1 (ArC), 156.2 and 156.4 ($2\times\text{C}=\text{O}$); m/z (ES+ve mode), 779 ($[2\text{M}+\text{Na}]^+$) and 401 ($[\text{M}+\text{Na}]^+$).

Benzyl 3-[(t-butoxycarbonylamino)methyl]-6-(hydroxymethyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate 13. Yield, 42%. Found: m/z , 401.1684; $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_6\text{Na}$ requires m/z , 401.1689; ν_{max} (film) 3650-3150, 2976, 2900, 2840, 1695 (vs), 1512, 1450 (w) and 733 cm^{-1} ; δ_{H} (400 MHz, CDCl_3): 1.50 (9H, s, Me_3C), 3.25-3.45 (2 H, m, $\text{CHCH}_2\text{NHBoc}$), 3.70-3.90 (2 H, m, CH_2OH), 4.55 (1 H, m, $\text{CHCH}_2\text{NHBoc}$), 4.65 (1 H, m, CHCH_2OH), 5.05 (1 H, br, NH), 5.20 (2 H, s, OCH_2Ph), 5.85-5.90 (2 H, m, $\text{CH}=\text{CH}$) and 7.35 (5 H, m, ArH); δ_{C} (100 MHz): 28.0 (Me_3C), 42.1 (CH_2NHBoc), 54.2 ($\text{CHCH}_2\text{NHBoc}$), 62.8 (CH_2OH), 67.5 (CH_2Ph), 77.6 (CHCH_2OH), 79.2 (Me_3C), 125.4,

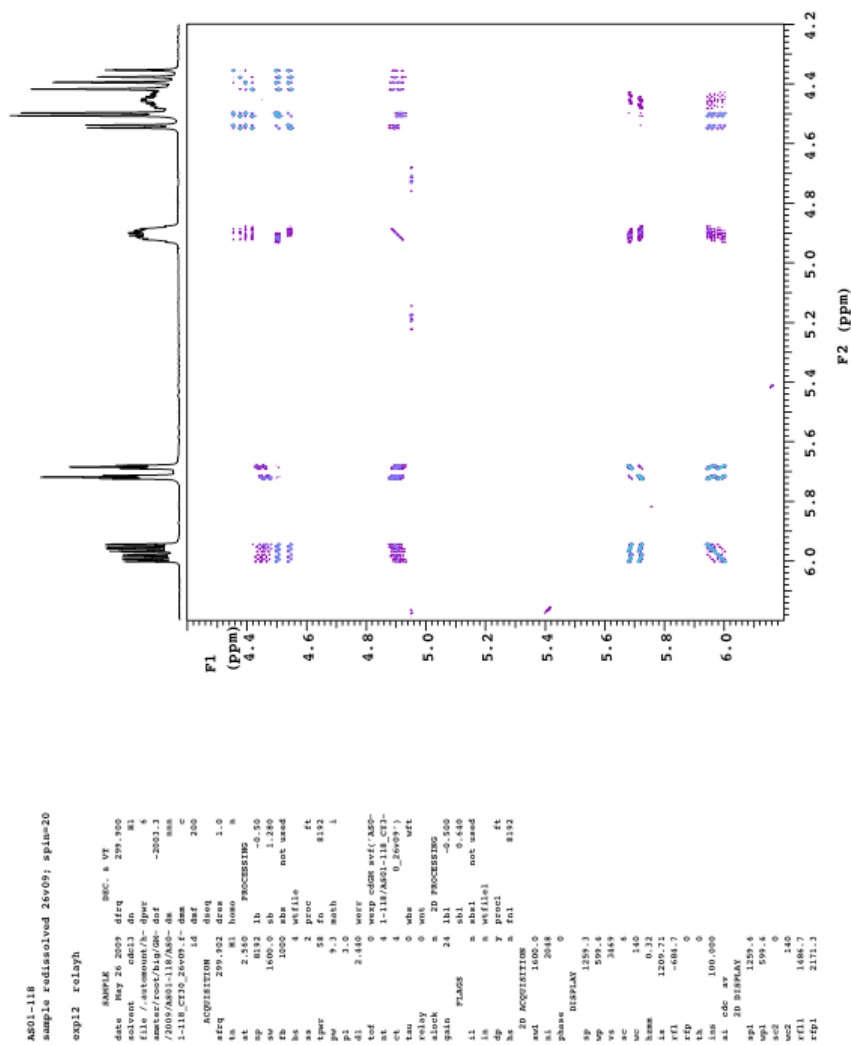
126.1 (CH=CH), 127.6, 127.9, 128.2, 135.4 (ArC), 155.0 and 155.6 (2xC=O); m/z 401 (MNa⁺, 100%) and 417 (MK⁺, 23%).

Crystal structure data for compound 7: C₁₄H₁₄N₂O₃ *M* = 258.27; colourless prism, 0.50 × 0.32 × 0.25 mm³; monoclinic, *P*2₁/*c* (No. 14); *a* = 5.619(1) *b* = 17.695(3) *c* = 12.511(2) Å; β = 102.957(3)°; *V* = 1212.2(4) Å³; *Z* = 4; *D*_c = 1.418 g/cm³; *T* = 150(2)K. 6404 reflections collected, 2183 unique. *R*_{int} = 0.0316, final *Goof* = 1.094. *RI* = 0.0490, *R2* = 0.1015; 228 parameters, 0 restraints, μ = 0.101 mm⁻¹

Crystal structure data for compound 10e: C₁₈H₂₂N₂O₇, *M* = 378.38, colourless plate, 0.50 × 0.40 × 0.15 mm³, triclinic, space group *P*-1 (No. 2), *a* = 5.8725(14), *b* = 10.826(3), *c* = 14.459(3) Å, α = 74.694(4), β = 88.672(4), γ = 85.198(4)°, *V* = 883.5(4) Å³, *Z* = 2, *D*_c = 1.422 g/cm³, *F*₀₀₀ = 400, Bruker D8 diffractometer with APEX detector, MoKα radiation, λ = 0.71073 Å, *T* = 100(2)K, 2θ_{max} = 54.2°, 5215 reflections collected, 3709 unique (*R*_{int} = 0.0156). Final *Goof* = 1.096, *RI* = 0.0386, *wR2* = 0.1029, *R* indices based on 3168 reflections with *I* > 2σ(*I*) (refinement on *F*²), 248 parameters, 0 restraints, μ = 0.110 mm⁻¹.

Proton 2D NMR data for compound 10e

A high resolution ¹H COSY spectrum with a 30° read pulse was recorded at 300 MHz and room temperature for **10e**. 2048 t₁ increments of 4096 complex points were recorded in a total time of 11 h and processed with one zero-filling in F₁ and a weighting function combining sinebell weighting with a rising exponential of time constant 2/π s in both dimensions, with the results shown below.



Coupling constants (Hz) in the table below were determined from resolution-enhanced 1D 500 MHz ^1H spectra measured with and without homonuclear coupling, and signs of coupling constants were deduced by inspection of the layout of passive coupling structure in the low flip angle COSY spectrum assuming the 10.5 Hz vicinal coupling between H4 and H5 to be positive.

Proton	3	4	5	6
3	-	+4.6	-1.8	+2.6
4	+4.6	-	+10.5	-2.3
5	-1.8	+10.5	-	+1.5
6	+2.6	-2.3	+1.5	-

Additional References

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