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

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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 $^1$H 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

\[
\text{Diene} + \text{Hydroxylamine} \rightarrow \text{Oxidant} \rightarrow \text{Solvent} \rightarrow \text{Temp. °C} \rightarrow \text{Yield %}
\]

Scheme 2. Reagents: Na\(^{+}\)IO\(_4\)^{−}, or Bu\(^{n+}\)N\(^{+}\)IO\(_4\)^{−}, conditions as Table 1.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>Hydroxylamine</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp. °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3b</td>
<td>4b</td>
<td>NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>0°C</td>
<td>36 5d</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>4b</td>
<td>NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>0°C</td>
<td>47 5b</td>
</tr>
<tr>
<td>3</td>
<td>3c(^a)</td>
<td>4b</td>
<td>NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>0°C</td>
<td>34 5f</td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>4a</td>
<td>NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>0°C</td>
<td>34 5c</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>4a</td>
<td>NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>0°C</td>
<td>51 5a</td>
</tr>
<tr>
<td>6</td>
<td>3c(^a)</td>
<td>4a</td>
<td>NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>0°C</td>
<td>41 5e</td>
</tr>
<tr>
<td>7</td>
<td>3a</td>
<td>4a</td>
<td>NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>-10°C</td>
<td>60 5a</td>
</tr>
<tr>
<td>8</td>
<td>3a</td>
<td>4a</td>
<td>NaIO(_4)</td>
<td>EtOAc:buffer(^b)</td>
<td>0°C</td>
<td>48 5a</td>
</tr>
<tr>
<td>9</td>
<td>3a</td>
<td>4a(^c) Bu(^{n+})N(^{+})IO(_4)^{−}</td>
<td>MeOH</td>
<td>0°C</td>
<td>64 5a</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3a</td>
<td>4a(^c) Bu(^{n+})N(^{+})IO(_4)^{−}</td>
<td>MeOH</td>
<td>0°C</td>
<td>69 5a</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3a</td>
<td>4a(^c) NaIO(_4)</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>0°C</td>
<td>62 5a</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3a</td>
<td>4a(^d) NaIO(_4)^{d}</td>
<td>MeOH: H(_2)O, 1:1</td>
<td>-15°C</td>
<td>85 5a</td>
<td></td>
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<tr>
<td>13</td>
<td>3a</td>
<td>4a</td>
<td>NaIO(_4)</td>
<td>THF: H(_2)O</td>
<td>0°C</td>
<td>64 5a</td>
</tr>
</tbody>
</table>
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 further reduction in yield was observed with both the n-butyl and t-butyl esters (to 26%), using either 4a or 4b. Citric acid buffer at pH6 was used, cf. ref. 17. Inverse addition, viz. hydroxylamine added to mixture of diene and oxidant. 2 eq. of both 4a and NaIO4 used. No water used, addition over 3h. 0.5 eq oxidant, cf. ref. 12, reaction time 2.5h.

Sorbic Alcohol and Derivatives

![Chemical structures of sorbic alcohol and derivatives]

9a R = H
9b R = Ac
9c R = COC₆H₄p-NO₂
9d R = COCMe₃

10a R = H, R' = PhCH₂
10b R = H, R' = Bu'
10c R = Ac, R' = PhCH₂
10d R = Ac, R' = Bu'
10e R = COC₆H₄p-NO₂, R' = Bu'
10f R = COCMe₃, R' = PhCH₂
10g R = COCMe₃, R' = Bu'

11a-g (as 7a-g)

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>Hydroxylamine</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Yield %</th>
<th>Prods.</th>
<th>10:11</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>4b</td>
<td>NaIO₄</td>
<td>MeOH: H₂O, 1:1</td>
<td>Nl⁻</td>
<td>10b, 11b</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>9a</td>
<td>4a</td>
<td>Bu₄N⁺IO₄⁻</td>
<td>CH₂Cl₂</td>
<td>87</td>
<td>10a, 11a</td>
<td>3:2</td>
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<tr>
<td>3</td>
<td>9b</td>
<td>4b</td>
<td>Bu₄N⁺IO₄⁻</td>
<td>CH₂Cl₂</td>
<td>89</td>
<td>10d, 11d</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>9b</td>
<td>4a</td>
<td>Bu₄N⁺IO₄⁻</td>
<td>CH₂Cl₂</td>
<td>82</td>
<td>10c, 11c</td>
<td>5:1</td>
</tr>
</tbody>
</table>
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. C₉H₁₄O₂·0.2 H₂O requires C, 68.4; H, 9.1% (hygroscopic); νₓₓₓₓₓ (film) 2966, 2881, 1711, 1645 and 1618 cm⁻¹; δₓₓ (200 MHz): 0.98 (3 H, t, J = 7.2 Hz, CH₃CH₂), 1.58 (2 H, sextet, J = 7.0 Hz, CH₃CH₂CH₂), 1.86 (3 H, d, J = 4.7 Hz, CH₃CH), 4.10 (2 H, t, J = 6.7 Hz, CO₂CH₂CH₂), 5.75 (1 H, dd, J = 15.4 and 0.7 Hz, CHCO₂Me), 6.00-6.30 (2 H, m, CHCH=CHCH) and 7.15-7.30 (1 H, m, CHCH₃); δₓ (100 MHz): 10.8, 19.0, 22.4, 66.2, 119.4, 130.2, 139.5, 145.3 and 167.8; m/z (CI, NH₃)155 (MH⁺, 72%) and 172 (MNH₄⁺, 100%).

3-Methyl-3,6-dihydro-[1,2]oxazine-2,6-dicarboxylic acid 2-benzyl ester 6-methyl ester 5c:
Yield, see Table 1. δₓ (400 MHz): 1.40 (3 H, d, J = 6.9 Hz, CHCH₃), 3.80 (3 H, s, OMe), 4.50 (1 H, m, CHCH₃), 5.15 (1 H, m, CHCO₂Me), 5.20 (2 H, ABq, OCH₂Ph), 5.85 (1 H, m, =CHCHCO₂Me), 5.95 (1 H, m, =CHCHCH₃) and 7.35 (5 H, m, ArH); δₓ (100 MHz): 18.3 (CH₃CH, 1C), 50.9 (CHCH₃, 1C), 53.0 (CO₂Me, 1C), 65.7 (CH₂Ph, 1C), 70.0 (=CHCO₂Me, 1C), 127.4, 128.0, 128.5, 128.7, 129.0 (ArC, 5C), 122.2 (=CHCHCO₂Me, 1C), 131.0 (=CHCHCH₃, 1C), 136.3 (ArC, 1C), 155.2 (NC(O)CH₂Ph, 1C) and 168.1 (CHC(O)OMe, 1C); m/z (CI, NH₃) 309 ([M+NH₄]⁺, 60%), 292 ([M+H]⁺, 15%) and 203 ([M-OCH₂Ph+H]⁺, 12%). Found (CI, NH₃): m/z 309.14475, C₁₅H₂₁N₂O₅ ([M+NH₄]⁺) 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.

2-tert-Butyl 6-methyl 3-methyl-2H-1,2-oxazine-2,6(3H,6H)-dicarboxylate 5d:
Yield, see Table 1. δₓ (400 MHz): 1.35 (3 H, d, J = 6.7 Hz, CH₂CH), 1.50 (9 H, s, CMe₃), 3.81 (3 H, s, CO₂Me), 4.45 (1 H, m, CHCH₃), 5.15 (1 H, d, J = 1.6 Hz, CHCO₂Me), 5.90 (1 H, m, =CHCHCO₂Et, 1H) and 6.00 (1 H, m, CHCHCH₃); δₓ (100 MHz): 18.3 (CH₂CH, 1C), 28.7 (CMe₃, 3C), 50.8 (CHCH₃, 1C), 53.0 (CO₂Me, 1C), 76.0 (CHCO₂Me, 1C), 82.4 (CMe₃, 1C), 122.3 (=CHCHCO₂Me, 1C), 131.2 (=CHCHCH₃, 1C), 154.5 (NC(O)OC(Me)₃, 1C) and 168.3 (CHC(O)OMe, 1C); m/z (CI, NH₃): 275 ([M+NH₄]⁺, 41%), 258 (MH⁺, 7%), 219 ([M-Bu⁺+NH₄]⁺, 100%), 203 ([M-CO₂Me]⁺, 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. \( \delta_H \) (400 MHz): 0.97 (3 H, t, \( J = 7.4 \) Hz, \( CH_3CH_2 \)), 1.35 (3 H, d, \( J = 6.7 \) Hz, \( CH(CH_3) \)), 1.70 (2 H, sextet, \( J = 7.2 \) Hz, \( CH_2CH(CH_3) \)), 4.15 (2 H, t, \( J = 6.5 \) Hz, \( CO_2CH_2CH_2 \)), 4.45 (1 H, m, \( CHCH_3 \)), 5.25 (3 H, \( CHCO_2nPr \) and \( OCH_2Ph \)), 5.90 (1 H, m, \( =CHCHCH_3 \), 1H) and 7.35 (5 H, m, \( CH_2Ph \)); \( \delta_C \) (100 MHz): 10.7 (\( CH_3CH_2 \), 1C), 18.4 (\( CH_3CH \), 1C), 22.2 (\( CH_2CH_3 \), 1C), 50.7 (\( CHCH_3 \), 1C), 67.7 (\( CO_2CH_2CH_2 \), 1C), 68.1 (\( OCH_2Ph \), 1C), 76.5 (\( CHCH_2OH \), 1C), 122.4 (\( =CHCHCO_2Pr^\oplus \), 1C), 127.4 (\( =CHCHCH_3 \), 1C), 128.0, 128.5, 128.7, 128.9, 129.4 (ArC, 5C), 136.3 (ArC, 1C), 155.2 (\( NC(O)OC(Me)_3 \), 1C) and 167.7 (\( CHC(O)ONPr \), 1C); m/z (CI): 337 ([M+NH4]^+, 100%), 320 ([M+H]^+, 26%), 258 ([M-OnPr+H]^+, 42%). Found (CI, \( NH_3 \)) m/z, 320.15036, \( C_{17}H_{22}NO_5 \) ([M+H]^+) requires 320.14980.

2-\( \text{tert} \)-Butyl 6-n-propyl 3-methyl-2H-1,2-oxazine-2,6(3H,6H)-dicarboxylate 5f:
Yield, see Table 1. \( \delta_H \) (400 MHz): 0.97 (3 H, t, \( J = 7.4 \) Hz, \( CH_3CH_2 \)), 1.35 (3 H, d, \( J = 6.8 \) Hz, \( CH(CH_3) \)), 1.59 (9 H, s, CMe3), 1.70 (3 H, sextet, \( J = 7.0 \) Hz, \( CH_2CH(CH_3) \)), 4.15 (2 H, t, \( J = 6.9 \) Hz, \( CO_2CH_2CH_2 \)), 4.45 (1 H, m, \( CHCH_3 \)), 5.15 (1 H, d, \( J = 1.6 \) Hz, \( CHCO_2Pr^\oplus \)), 5.90 (1 H, m, \( =CHCHCO_2Pr^\oplus \)) and 6.00 (1 H, m, \( =CHCHCH_3 \)); \( \delta_C \) (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 (\( CO_2CH_2CH_2 \), 1C), 75.9 (\( CHCO_2Pr^\oplus \), 1C), 82.3 (\( CMe_3 \), 1C), 122.4 (=\( CHCHCO_2Pr^\oplus \), 1C), 131.2 (=\( CHCHCH_3 \), 1C), 154.6 (\( NC(O)OCMe_3 \), 1C) and 167.9 (\( CHC(O)OPr^\oplus \), 1C); m/z (ES+ve): 609 ([2M+K]^+), 593 ([2M+Na]^+), 324 ([M+K]^+, 42%). Found (ES+ve): 308.1474, \( C_{14}H_{23}NO_5Na \) ([M+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:
Yield, see Table 2. For 10b: Found: m/z, 247.16528. \( C_{11}H_{23}N_2O_4 \) ([M+NH4]^+) requires m/z, 247.16578 ; \( \delta_H \) (200 MHz): 1.32 (3 H, d, \( J = 6.7 \) Hz, \( CH(CH_3) \)), 1.51 (9 H, s, CMe3), 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, \( =CHCHCH_2OH \)) and 5.87 (1 H, ddd, \( J = 10.3, 4.4 \) and 2.2 Hz, \( =CHCHCH_3 \)); \( \delta_C \) (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 (=\( CHCHCH_2OH \), 1C), 130.8 (=\( CHCHCH_3 \), 1C) and 154.9 (\( NC(O)OCMe_3 \), 1C); m/z (CI, \( NH_3 \)): 247 ([M+NH4]^+, 4%), 230 ([M+H]^+,
2\%), 173 ([M-tBu]$^+$, 14\%), 130 ([M-Boc+H]$^+$, 42\%), 100 ([M-ONBoc+H]$^+$, 35\%). The distal isomer 11b was distinguished by $\delta_{H}$ (200 MHz): 1.26 (3 H, d, $J^2 = 6.7$, CH$_3$CH), 1.48 (9 H, s, CMe$_3$) and 5.75-5.85 (2 H, m, CHCH=CHCH); $\delta_{C}$ (100 MHz): 18.5 (CH$_3$CH, 1C), 82.4 (Me$_3$C, 1C), 123.0 (CHCHCH$_3$, 1C), and 131.7 (=CHCHCH$_2$OH, 1C).

**Benzyl 6-(acetoxyethyl)-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. C$_{16}$H$_{19}$NO$_5$ requires C, 62.94; H, 6.3; N, 4.6%; $\delta_{H}$ (400 MHz): 1.35 (3 H, d, $J = 6.7$ Hz, CH$_3$CH), 2.05 (3 H, s, CH$_3$CO), 4.17 (2 H, dd, $J = 12.2$ and 3.5 Hz; $J = 12.2$ and 3.1 Hz, CHCH$_2$OAc), 4.65 (1 H, m, CHCH$_3$), 4.80 (1 H, m, CHCH$_2$OAc), 5.20 (2 H, ABq, OCH$_2$Ph), 5.65 (1 H, m, =CHCHCH$_2$OAc), 5.95 (1 H, m, =CHCHCH$_3$) and 7.35 (5 H, m, ArH); $\delta_{C}$ (100 MHz): 18.5 (CH$_3$CH, 1C), 21.1 (CH$_3$CO, 1C), 50.8 (CHCH$_3$, 1C), 64.4 (CH$_2$OAc, 1C), 68.0 (OCH$_2$Ph, 1C), 74.0 (CHCH$_2$OAc, 1C), 123.4 (=CHCHCH$_2$OAc, 1C), 128.3, 128.4, 128.6, 128.9, 131.2 and 132.5 (=CHCHCH$_3$, 1C), (ArC for proximal and distal), 136.4 (ArC, 1C), 155.2 (NC(O)OCH$_2$Ph, 1C) and 171.2 (CH$_2$OC(O)CH$_3$, 1C); m/z (CI, NH$_3$): 323 ([M+NH$_4$]$^+$, 100\%), 306 ([M+H]$^+$, 35\%), 262 ([M-C(O)CH$_3$]$^+$, 42\%), 108 ([M-C$_9$H$_{12}$NO$_4$]$^+$, 18\%). Found (CI, NH$_3$): m/z 306.13481, C$_{16}$H$_{20}$NO$_5$ ([M+H]$^+$) requires 306.13415. The distal isomer 11c was distinguished by $\delta_{H}$ (400 MHz): 1.28 (3 H, d, $J = 6.7$ Hz, CH$_3$CH), 4.50 (1 H, m, CHCH$_3$), 5.75 (1 H, m, =CHCHCH$_3$) and 6.85 (1 H, m, =CHCHCH$_2$OAc); $\delta_{C}$ (100 MHz): 19.0 (CH$_3$CH, 1C), 63.6 (CH$_2$OAc, 1C), 72.1 (CHCH$_2$OAc, 1C), 122.2 (=CHCHCH$_3$, 1C) and 133.2 (=CHCHCH$_2$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 Et$_2$O (30 mL) and washed with 1 M HCl (3x 30 mL) and brine. After drying (Na$_2$SO$_4$) 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. C$_{11}$H$_{18}$O$_2$ requires C, 72.5; H, 10.0%; C$_{11}$H$_{22}$NO$_2$ ([M+NH$_4$]$^+$) requires
200.16505; $v_{\text{max}}$ (cm$^{-1}$) 2970, 1732 and 1662; $\delta$H (200 MHz, CDCl$^3$): 1.20 (9 H, s, Me$_3$C), 1.77 (3 H, d, $J = 6.7$ Hz, CH$_2$CH), 4.56 (2 H, d, $J = 6.6$ Hz, CH$_2$OPiv), 5.50-5.85 (2 H, m, 2x =CH) and 6.00-6.35 (2 H, m, 2x =CH); $\delta$C (100 MHz, CDCl$^3$): 18.4 (CH$_3$CH), 27.6 (Me$_3$C C=O), 39.1 (CH$_2$OPiv), 65.1 (Me$_3$CC=O), 124.5 (CHCH$_3$), 130.9 (x2) (CHCHCHCH), 134.6 (CHCH$_2$OPiv) and 178.6 (Me$_3$CC=O); m/z (Cl, NH$_3$): 200 ([M+NH$_4^+$]+, 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. C$_{19}$H$_{25}$NO$_5$ requires C, 65.7; H, 7.2; N, 4.0%; C$_{19}$H$_{25}$NO$_5$Na (MNa$^+$) requires m/z, 370.1630; $\delta$H (400 MHz, CDCl$^3$), for 10f: 1.18 (9 H, s, CMe$_3$), 1.34 (3 H, d, $J = 6.7$ Hz, CHCH$_3$), 4.21 (2 H, d, $J = 4.5$ Hz, PivOCH$_2$CH), 4.55 (1 H, m, CHCH$_3$), 4.77 (1 H, m, CHCH$_2$OPiv), 5.16 & 5.24 (2 H, ABq, $J = 12.2$ and 12.3 Hz, OCH$_2$Ph), 5.65 and 5.67 (1 H, dt, $J = 10.3$ and 1.5 Hz, =CHCHCH$_2$OPiv), 5.92 and 5.95 (1 H, ddd, $J = 10.2$, 4.0 and 1.9 Hz, =CHCHCH$_3$) and 7.40 (5 H, m, ArH); $\delta$C (100 MHz): 18.4 (CH$_3$CH, 1C), 27.5 (Me$_3$C, 3C), 50.7 (CH$_3$CH), 64.0 (CH$_2$OCO), 68.0 (ArCH$_2$O), 76.5 (CHCH$_2$OCO), 123.6 (CH=CHCH$_2$OPiv), 127.4-129.1 (ArC$_x$3 + CH=CHCH$_3$), 136.4 (ArC), 155.2 (NC(O)OCH$_2$Ph) and 178.6 (CH$_2$OCOCMe$_3$); m/z (ES+ve mode) 717 [(2M+Na)$^+$], 386 (MK$^+$) and 370 (MNa$^+$); the distal isomer 11f was distinguished by $\delta$H (400 MHz): 1.14 (9 H, s, Me$_3$C), 1.28 (3 H, d, $J = 6.7$ Hz, CH$_2$CH), 4.70 (1 H, m, CHCH$_3$), 5.78 (1 H, m, =CHCHCH$_3$) and 5.85 (1 H, m, =CHCHCH$_2$OPiv); $\delta$C (100 MHz): 19.1 (CH$_3$CH), 63.6 (CH$_2$OCO), 65.8 (CHCH$_3$), 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; C$_{16}$H$_{27}$NO$_5$Na (MNa$^+$) requires m/z, 336.1787; $\delta$H (400 MHz, CDCl$_3$), for 10g: 1.22 (9 H, s, Me$_3$C), 1.32 (3 H, d, $J = 6.7$ Hz, CH$_3$CH), 1.50 (9 H, s, Me$_3$CO), 4.21 (2 H, m, CHCH$_2$OCO), 4.46 (1 H, m, CHCH$_3$), 4.77 (1 H, m, CHCH$_2$OCO), 5.66 (1 H, dt, $J = 10.3$ and 1.5 Hz, CHCHCH$_2$OPiv), and 5.95 (1 H, ddd, $J = 10.3$, 4.7 and 2.3 Hz, CHCHCH$_3$); $\delta$C (100 MHz): 18.3 (CH$_3$CH), 27.6, 28.8 (2xMe$_3$C),
50.5 (CH₂CH), 64.3 (CHCH₂OCO), 75.9 (CHCH₂OCO), 81.9 (2xMe₃C), 123.7 (=CHCH₂OPiv), 131.2 (=CHCH₃), 154.7 (NHCOO) and 178.7 (OCOCMe₂); m/z (ES+ve mode) 649 [2M+Na⁺], 352 (MK⁺) and 336 (MNa⁺); the distal isomer 11g was distinguished by δH (400 MHz): 1.20 (9 H, s, Me₃C), 1.26 (3 H, d, J = 6.7 Hz, CH₃CH), 1.49 (9 H, s, Me₃CO), 4.65 (1 H, m, CHCH₃), 5.79 (1 H, ddd, J = 10.3, 4.1 and 1.8 Hz, CHCHCH₃), and 5.85 (1 H, d, J = 10.4 Hz, CHCH₂OPiv); δC (100 MHz): 19.1 (CH₃CH), 28.0, 28.4 (2xMe₃C) and 63.9 (CH₂OCO).

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; C₁₉H₂₆N₂O₆Na (MNa⁺) requires m/z, 401.1689; δH (400 MHz, CDCl₃): 1.45 (9 H, s, Me₃C), 3.25-3.45 (2 H, m, CHCH₂NHBoc), 3.75 (2 H, m, CH₂OH), 4.55 (1 H, m, CHCH₂OH), 4.65 (1 H, m, CHCH₂NHBoc), 5.05 (1 H, br, NH), 5.21 (2 H, ABq, OCH₂Ph), 5.80-5.95 (2 H, m, CH=CH) and 7.35 (5 H, m, ArH); δC (100 MHz): 28.7 (Me₃C), 43.0 (CH₂NHBoc), 57.2 (CHCH₂OH), 63.5(CH₂OH), 68.4 (CH₂Ph), 76.9 (CHCH₂NHBoc), 80.0 (Me₃C), 125.2 and 128.4 (CH=CH), 129.0, 129.1, 129.2, 136.1 (ArC), 156.2 and 156.4 (2xC=O); m/z (ES+ve mode), 779 ([2M +Na⁺]⁺) and 401 ([M +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; C₁₉H₂₆N₂O₆Na requires m/z, 401.1689; νmax.(film) 3650-3150, 2976, 2900, 2840, 1695 (vs), 1512, 1450 (w) and 733 cm⁻¹; δH (400 MHz, CDCl₃): 1.50 (9H, s, Me₃C), 3.25-3.45 (2 H, m, CHCH₂NHBoc), 3.70-3.90 (2 H, m, CH₂OH), 4.55 (1 H, m, CHCH₂NHBoc), 4.65 (1 H, m, CHCH₂OH), 5.05 (1 H, br, NH), 5.20 (2 H, s, OCH₂Ph), 5.85-5.90 (2 H, m, CH=CH) and 7.35 (5 H, m, ArH); δC (100 MHz): 28.0 (Me₃C), 42.1 (CH₂NHBoc), 54.2 (CHCH₂NHBoc), 62.8 (CH₂OH), 67.5 (CH₂Ph), 77.6 (CHCH₂OH), 79.2 (Me₃C), 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**: C\(_{14}\)H\(_{14}\)N\(_{2}\)O\(_{3}\) \(M = 258.27\); colourless prism, 0.50 × 0.32 × 0.25 mm\(^3\); monoclinic, \(P2_1/c\) (No. 14); \(a = 5.619(1)\ b = 17.695(3)\ c = 12.511(2)\) Å; \(\beta = 102.957(3)\)°; \(V = 1212.2(4)\) Å\(^3\); \(Z = 4\); \(D_c = 1.418\) g/cm\(^3\); \(T = 150(2)\) K. 6404 reflections collected, 2183 unique. \(R_{int} = 0.0316\), final \(Goof = 1.094\). \(R1 = 0.0490\), \(R2 = 0.1015\); 228 parameters, 0 restraints, \(\mu = 0.101\) mm\(^{-1}\).

**Crystal structure data for compound 10e**: C\(_{18}\)H\(_{22}\)N\(_{2}\)O\(_{7}\), \(M = 378.38\), colourless plate, 0.50 × 0.40 × 0.15 mm\(^3\), triclinic, space group \(P-1\) (No. 2), \(a = 5.8725(14)\ b = 10.826(3)\), \(c = 14.459(3)\) Å, \(\alpha = 74.694(4)\)°, \(\beta = 88.672(4)\)°, \(\gamma = 85.198(4)\)°, \(V = 883.5(4)\) Å\(^3\), \(Z = 2\); \(D_c = 1.422\) g/cm\(^3\), \(F_{000} = 400\), Bruker D8 diffractometer with APEX detector, MoK\(\alpha\) radiation, \(\lambda = 0.71073\) Å, \(T = 100(2)\) K, \(2\theta_{max} = 54.2\)°, 5215 reflections collected, 3709 unique (\(R_{int} = 0.0156\)). Final \(Goof = 1.096\), \(R1 = 0.0386\), \(wR2 = 0.1029\), \(R\) indices based on 3168 reflections with I >2sigma(I) (refinement on \(F^2\)), 248 parameters, 0 restraints, \(\mu = 0.110\) mm\(^{-1}\).

**Proton 2D NMR data for compound 10e**
A high resolution \(^1\)H COSY spectrum with a 30° read pulse was recorded at 300 MHz and room temperature for 10e. 2048 \(t_1\) increments of 4096 complex points were recorded in a total time of 11 h and processed with one zero-filling in \(F_1\) and a weighting function combining sinebell weighting with a rising exponential of time constant \(2/\pi\) s in both dimensions, with the results shown below.
Coupling constants (Hz) in the table below were determined from resolution-enhanced 1D 500 MHz $^1$H 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.

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**Notes:**
- The coupling constants were determined from resolution-enhanced 1D 500 MHz $^1$H spectra measured with and without homonuclear coupling.
- Signs of coupling constants were deduced by inspection of the layout of passive coupling structure in the low flip angle COSY spectrum.
- The 10.5 Hz vicinal coupling between H4 and H5 was assumed to be positive.
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Additional References