Intramolecular 1,3-dipolar cycloaddition reaction of novel 2-azetidinone-tethered alkenyl nitrile oxides

Benito Alcaide,*a Pedro Almendros,b and Elena Sáeza

a Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain. E-mail: alcaideb@quim.ucm.es
b Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain. E-mail: iqoa392@iqog.csic.es

Dedicated to Prof. Enrique Meléndez on the occasion of his 70th birthday
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Abstract
Racemic as well as optically pure fused tricyclic β-lactams are regio and stereoselectively prepared via intramolecular nitrile oxide-alkene cycloaddition reaction of 2-azetidinone-tethered alkenyl oximes or nitro alkanes. The process is more efficient when the nitrile oxide moiety is separated by a methylenic group, rather than being directly linked to the C-4 position of the four-membered ring.

Keywords: Cycloaddition, β-lactam, nitrile oxide, tricycles

Introduction

A 2-azetidinone (β-lactam) skeleton is well established as the key pharmacophore of β-lactam antibiotics, the most widely employed class of antibacterial agents. The importance and structural diversity of biologically active β-lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted 2-azetidinones with attendant control of functional groups and stereochemistry. Tricyclic β-lactam antibiotics, generally referred to as trinems, are a new class of synthetic antibacterial agents featuring good resistance to β-lactamases and dehydropeptidases. Besides, the ever-growing new applications of 2-azetidinones in fields ranging from enzyme inhibition to the use of these products as starting materials to develop new synthetic methodologies, has triggered a renewed interest in the building of new polycyclic β-lactam systems in an attempt to move away from the classical β-lactam antibiotic structures.

The 1,3-dipolar cycloaddition between alkenes and dipoles is one of the most powerful tools for the synthesis of 5-membered heterocycles. Although many investigations have been made in
this field into various types of systems, there is little information available regarding the regio-
and stereochemistry of reactions involving 2-azetidinone-tethered nitrile oxides as chiral building
blocks on the 1,3-dipolar cycloaddition reaction, either inter or intramolecular. Thus, Sandanayaka has recently reported the intermolecular nitrile oxide cycloaddition of a 6-
(nitrileoxidomethyl) penam sulfone with alkenes and alkynes, while Hassner and Padwa
described the intramolecular variant on β-lactams bearing the nitrile oxide tether at N-1. During
the course of our ongoing project directed toward developing efficient routes to prepare chiral
functionalized 2-azetidinones and their synthetic applications, we have used the inter and
intramolecular nitrone-alkene(alkyne) cycloaddition of 2-azetidinone-tethered
alkenyl(alkynyl)nitrones for the preparation of non-conventional β-lactams, as well as
indolizidine and quinolizidine derivatives. In connection with this work, we wish to report here
the intramolecular 1,3-dipolar cycloaddition reaction of 2-azetidinone-tethered alkenyl nitrile
oxides.

Results and Discussion

Starting substrates, 4-oxoazetidine-2-carbaldehydes 1a–e, were prepared both in the racemic
form and in optically pure form using standard methodology. Racemic compound (+)-1e was
obtained as a single cis-diastereoisomer, following our one-pot method from N,N-di-(p-
methoxyphenyl)glyoxal diimine. Enantiopure 2-azetidinones 2a–d were obtained as single cis-
enantiomers from the corresponding imine of (R)-2,3-O-isopropylidenglyceraldehyde, through a
Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et3N. Transesterification of 3-acetoxy-2-azetidinone (+)-2d with sodium methoxide in methanol gave
alcohol (+)-3, which by treatment with allyl bromide under basic conditions gave the 2-
zides for the preparation of non-conventional β-lactams, as well as

\[
\text{Figure 1}
\]
The target molecules in the present study were derived from the intramolecular 1,3-dipolar cycloaddition of the appropriate β-lactam-tethered alkenyl nitrile oxide. This strategy should allow us to get a rapid access to unusual polycyclic β-lactams. Cycloadduct precursors, 2-azetidinone-tethered oximes 5, were smoothly prepared by the condensation of 4-oxoazetidine-2-carbaldehydes 1 with hydroxylamine hydrochloride in benzene at room temperature in the presence of triethylamine (Scheme 1). Oximes 5 were obtained in almost quantitative yields as a mixture of isomers (E/Z) and were used for next step without further purification. Importantly, the β-lactam ring stereochemistry was unaffected by this process.

\[
\begin{align*}
(+)-1a & \quad n = 1, \quad R = \text{Ph} \\
(+)-1c & \quad n = 2, \quad R = \text{Me} \\
(+)-1d & \quad (91\%) \quad E/Z: 55/45 \\
(+)-5a & \quad (100\%) \quad E/Z: 60/40 \\
(+)-5c & \quad (100\%) \quad E/Z: 55/45
\end{align*}
\]

Scheme 1

Nitroalkanes 8 were prepared following the procedure developed by Palomo for related substrates. The reaction of nitromethane with 4-oxoazetidine-2-carbaldehyde (+)-1a in the presence of triethylamine gave a diastereomeric mixture (75:25) of nitro-aldol product (+)-6a (Scheme 2).

\[
\begin{align*}
(+)-1a & \quad \text{PhO} \\
(+)-6a & \quad (92\%) \quad \text{sin/anti: 75/25}
\end{align*}
\]

Scheme 2
The dehydration of nitroaldols 6 was achieved when the hydroxy group was mesylated by methanolsulfonyl chloride in the presence of triethylamine. There was no epimerization of the corresponding β-lactams under the reaction conditions as the 1H NMR of the olefins 7 showed the presence of only a single E-isomer. The nitro olefins were reduced to nitro alkanes 8 by stirring with tributyltinhydride in dichloromethane/methanol (9:1) for 24 hours at room temperature (Table 1).

**Table 1. Synthesis of nitroderivatives 7 and 8**

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Nitro alkene</th>
<th>Yield (%)(^a)</th>
<th>Nitro alkane</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-1a</td>
<td>OPh</td>
<td>2-propenyl</td>
<td>(+)-7a</td>
<td>70</td>
<td>(+)-8a</td>
<td>70</td>
</tr>
<tr>
<td>(+)-1b</td>
<td>OPh</td>
<td>3-butenyl</td>
<td>(+)-7b</td>
<td>60</td>
<td>(+)-8b</td>
<td>60</td>
</tr>
<tr>
<td>(±)-1e</td>
<td>2-propenyl</td>
<td>PMP(^b)</td>
<td>(±)-7c</td>
<td>72</td>
<td>(±)-8c</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\) Yield of pure, isolated product with correct analytical and spectral data. \(^b\) PMP = 4-MeOC\(_6\)H\(_4\).

Standard chlorination of oximes 5 with \(N\)-chorosuccinimide or sodium hipochlorite, followed by Et\(_3\)N treatment may generate nitrile oxides intermediates, which should afford the corresponding 1,3-dipolar cycloadducts. Disappointingly, poor yields of tricycles 9 were obtained under a variety of conditions (Table 2).
Table 2. Intramolecular 1,3-dipolar cycloaddition reaction of 2-azetidinone-tethered alkenyl nitrile oxides

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxime</th>
<th>Method&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cycloadduct [Yield (%)]&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Recovered Oxime (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PhO</td>
<td>A, B</td>
<td>(+)-9a</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>PhO</td>
<td>B</td>
<td>(-)-9b</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>PMP</td>
<td>A</td>
<td>(+)-9c</td>
<td>26</td>
</tr>
</tbody>
</table>

<sup>a</sup> Method A: NCS/Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT., 24h. Method B: NaOCl/ Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT., 24h. <sup>b</sup> Yield of pure, isolated product with correct analytical and spectral data. <sup>c</sup> The corresponding cycloadduct was neither detected nor isolated.

The significant recovered amount of the starting oximes, point to difficulties in the nitrile oxide formation step. This fact could explain, at least in part, the low yields for cycloadducts 9. Results above show that the intramolecular 1,3-dipolar cycloaddition nitrile oxide reaction (INOC) of alkenyl 2-azetidinones, bearing nitrile oxide moieties directly linked to the C-4 position of the four-membered ring, is a modest entry to tricyclic 2-azetidinones with a six-membered ring fused to the β-lactam nucleus, but it is not possible to obtain a central five-membered ring.

Our next target was to use the nitroalkanes 8 as INOC reaction precursors to generate the corresponding nitrile oxides via Mukaiyama’s method. Indeed, the treatment of nitro derivatives 8 with phenyl isocyanate under triethylamine catalysis, afforded the corresponding
tricyclic isoxazolines 10 (Scheme 3). The reaction of nitro alkane (+)-8a proceeded in a total stereoselective fashion, achieving the tricyclic 2-azetidinone (+)-10a in good yield (83%) as a single isomer. The INOC reactions of the nitrile oxides derived from nitro compounds (+)-8b and (±)-8c were less stereoselective (Scheme 3). Diastereomers (±)-10c and (±)-10d were separated by column chromatography, while compound 10b was characterized as a mixture of unseparable isomers.

Scheme 3

The reaction of nitro aldol 6a deserves a special mention. On treating compound 6a with acetic anhydride and Et3N, tricycle 11 was obtained in 30% yield as a mixture (65:35) of diastereomers. The process must start through the generation of the dipole (nitrile oxide) with simultaneous protection of the hydroxyl group. Next, the 1,3-dipolar cycloaddition should take place followed by an elimination of acetic acid (Scheme 4).
Scheme 4

The nitrile oxide formation must be prior to the hydroxyl group elimination, because on trying to react the nitro alkane (1)-7a under the above reaction conditions, or under other typical reaction conditions of dipole generation of diene (1)-7a was unaltered (Scheme 5).

Scheme 5

The structure and stereochemistry of all compounds were assigned by NMR studies. The cis-stereochemistry of the four-membered ring was set during the cyclization step to form the 2-azetidinone ring, and it was transferred unaltered during the further synthetic steps. The tricyclic structures (by DEPT, HMQC, HMBC, and COSY) and the stereochemistry (by vicinal proton couplings and qualitative homonuclear NOE difference spectra) of β-lactams 9–11 were established by NMR one- and two-dimensional techniques. Thus, a syn-relative disposition between H4 and H9 was assigned for compound (1)-9b with a long distance coupling constant through four bonds $J_{4,9} = 1.5$ Hz. Furthermore, NOE-irradiation of H4 on compound (1)-9b resulted on enhancements on the signal corresponding to H5 eq (3%), H2ax (2%), H3eq (2%), and H9 (1%), which is in agreement with the proposed stereochemistry. Irradiation of H2 on compound (1)-9c gave a NOE enhancement of 1% on H7, while the long distance coupling constant $J_{2,7} = 0.9$ Hz. Thus, a syn-relative disposition between H2 and H7 was assigned for tricycle (1)-9c (Figure 1).
An anti-relative stereochemistry between the β-lactam hydrogens (H9 and H10) and H3, as well as a trans-diaxial disposition between H2ax and H3 was assigned for compound (+)-10a on the basis of coupling constants (J_{9,10} = 4.1 Hz, J_{2ax,10} = 1.1 Hz, J_{2ax,2eq} = 12.9 Hz, J_{2ax,3} = 10.2 Hz). This stereochemistry was confirmed via NOE enhancement on H8eq (7%) and H3 (1.1%) on irradiating H8ax, and on H2eq (12%), H4ax (3%), and H9 (1.3%) on irradiating H2ax. The stereochemistry for tricycles (±)-10c and (±)-10d was deduced in an analogous way (Figure 2).

**Conclusions**

The intramolecular 1,3-dipolar cycloaddition nitrile oxide reaction (INOC) of alkenyl 2-azetidinones, bearing nitrile oxide moieties directly linked to the C-4 position of the four-membered ring, is a modest entry to tricyclic 2-azetidinones with a six-membered ring fused to the β-lactam nucleus. However, the INOC reaction of related alkenyl 2-azetidinones bearing nitrile oxide moieties separated by a methylenic group to the C-4 position is a fair entry to this kind of β-lactams.
Experimental Section

General Procedures. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in CDCl$_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS ($^1$H, 0.0 ppm), or CDCl$_3$ ($^{13}$C, 76.9 ppm). Low and high resolution mass spectra were taken on a HP5989A spectrometer using the chemical ionization modes (CI) unless otherwise stated. Specific rotation $\left[\alpha\right]_D$ is given in deg per dm at 20 °C, and the concentration ($c$) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General procedure for the synthesis of 2-azetidinone-tethered oximes 5

Hydroxylamine hydrochloride (2.0 mmol) and triethylamine (2.0 mmol) were sequentially added at room temperature to a well stirred solution of the corresponding 4-oxoazetidine-2-carbaldehyde (1.0 mmol) in benzene (10 mL). After the resulting suspension was stirred at room temperature overnight, the solvent was removed under reduced pressure. Then, the mixture was diluted with dichloromethane and washed with saturated aqueous NaHCO$_3$ and water. The organic extract was dried (MgSO$_4$) and concentrated under reduced pressure to give analytically pure compounds 5.

Oxime (++)-5b. From 229 mg (1.41 mmol) of aldehyde (+)-1g, 247 mg (100%) of compound 77b, as a E/Z mixture (60/40) of isomers, was obtained as a white solid. NMR data: $\delta^H$ (CDCl$_3$) 9.50 (brs, 1H, OH), 7.39 (d, 0.6 H, HC=N, $J_3$ = 8.1 Hz), 6.86 (d, 0.4 H, H-4, $J_3$ = 6.8 Hz, $J = 6.8$ Hz), 4.63 (d, 0.4 H, H-3, $J_3$ = 4.6 Hz), 4.60 (d, 0.6 H, H-3, $J_3$ = 4.5 Hz), 4.31 (dd, 0.6 H, H-4, $J_3$ = 8.1 Hz, $J = 4.5$ Hz), 3.43 (s, 3H, O-CH$_3$), 3.39 (m, 1H, N-CH$_2$), 3.15 (m, 1H, N-CH$_2$), 2.27 (m, 2H, CH$_2$). $\delta^C$ (CDCl$_3$) 167.1 (C=O, Z), 166.9 (C=O, M), 147.0 (C=N, M), 146.8 (C=N, M), 134.3 (HC=CH$_2$, M + m), 117.4 (HC=CH$_2$, M + m), 84.7 (C-3, M + m), 58.9, 58.7, 57.6 (O-CH$_2$, M + m), 51.6, 40.4 (N-CH$_2$, m), 39.9 (N-CH$_2$, M), 31.7 (CH$_2$, M), 31.6 (CH$_2$, m). IR (KBr, cm$^{-1}$): v 3315, 1751.

Oxime (++)-5c. From 100 mg (0.38 mmol) of aldehyde (+)-3, 106 mg (100%) of compound 78, as a E/Z mixture (55/45) of isomers was obtained as a brown solid. NMR data: $\delta^H$ (CDCl$_3$) 8.75 (brs, 1H, OH), 7.54 (d, 0.55H, J = 8.1 Hz, HC=N), 7.36 (m, 2H, Ar), 6.97 (d, 0.45H, J = 7.3 Hz, HC=N), 6.86 (m, 2H, Ar), 5.91 (m, 1H, 2xC=CH$_2$), 5.35 (m, 5H, 4xCH=C$_2$, E, Z, H4 Z), 4.96 (d, 0.45H, H-3, $J_3$ = 4.8 Hz), 4.92 (d, 0.55H, H-3, $J_3$ = 4.8 Hz, $J = 4.8$ Hz), 4.76 (dd, 0.55H, H-4, $J = 8.1$, 4.8 Hz), 4.23 (d, 0.90H, J = 18.7 Hz, OCHH), 4.18 (d, 1.10H, J = 18.4 Hz, OCHH), 3.78 (s, 1.35H, O-CH$_3$), 3.77 (s, 1.65H, O-CH$_3$). $\delta^C$ (CDCl$_3$) 163.4 (NC=O, M), 163.3 (NC=O, M), 156.7 (C=N, M), 156.6 (C=N, M), 147.7 (C), 133.1 (HC=CH$_2$, M, m), 130.7 (C), 130.4 (C), 118.8 (HC=CH$_2$, m), 118.7 (HC=CH$_2$, M), 118.5 (CH, M), 118.1 (CH, m), 114.5 (CH, m), 114.4 (CH, M), 82.3 (C-3, m), 82.2 (C-3, M), 72.4 (C-4, m), 72.3 (C-4, M), 56.9 (O-CH$_2$, M + m), 55.5 (O-CH$_3$, M + m). IR (KBr, cm$^{-1}$): v 3284, 1733, 1514.
Procedure for the synthesis of nitroaldol (+)-6a. To a solution of the aldehyde (+)-1a (150 mg, 0.65 mmol) in nitromethane (1.5 mL) cooled to –20 °C, was added triethylamine (1.5 mmol). The resulting mixture was stirred at room temperature for 3h. The crude of reaction was poured into water. The organic layer was washed with HCl 5%, NaHCO3 (saturated solution) and brine, was dried (MgSO4) and concentrated under reduced pressure. After chromatography of the residue eluting with hexanes/ethyl acetate (5:1), compound (+)-6a was obtained (92%) as a mixture (75/25) of isomers, as a colourless oil.

NMR data: \( \delta \) (CDCl3) 7.29 (m, 4H, Ar, \( M_m \)), 6.95 (m, 6H, Ar, \( M_m \)), 5.66 (m, 2H, \( HC=CH_2 \), \( M_m \)), 5.18 (m, 6H, H3, HC=CH\( M_m \)), 4.50 (m, 6H, H4, CH\( M_m \)), 3.85 (m, 6H, \( NC\)H\( HNO_2 \), \( M_m \)), 3.16 (s broad, 2H, OH, \( M_m \)).

IR (CHCl3, cm\(^{-1}\)):
\( \nu \) 3346, 1745.

General procedure for the synthesis of nitroalkenes 7
To a solution of the corresponding \( \beta \)-lactam (1.0 mmol) in nitromethane (1.5 mL) was added triethylamine (1.5 mmol), and the resulting mixture was stirred at room temperature until completion (typically 3 h). Evaporation of the solvent under reduced pressure gave a residue, which was dissolved in dried dichloromethane (4.5 mL) and dropwise added at –78 °C to a mixture of triethylamine (0.41 mL, 3.0 mmol) and methanesulfonyl chloride (3.0 mmol). After stirring for 30 min at –78 °C, triethylamine (3.0 mmol) was added to the solution at –50 °C. The resulting mixture was gradually warmed up to room temperature during 7 h, poured into water, and extracted with dichloromethane. The organic layer was washed with 0.1 N HCl (3 x 4.0 mL) and then with aqueous NaHCO3 (4.0 mL, saturated solution). The organic layer was separated and dried (MgSO4). Evaporation of the solvent at reduced pressure gave the nitroalkenes 7, which were purified by chromatography on silica gel.

Nitroalkene (+)-7a. From 266 mg (1.15 mmol) of aldehyde (+)-1a, 220 mg (70%) of compound (+)-7a was obtained as a yellow solid after purification by flash chromatography (hexanes/ethyl acetate 1:1). Mp: 99-100 °C (hexanes/ethyl acetate). \([\alpha]_D = + 9.7 \) (c 0.6, CHCl3). NMR data: \( \delta \) (CDCl3) 7.26 (m, 7H, Ar and \( C\)H\( C=C\)H\( NO_2 \)), 5.70 (m, \( HC=CH_2 \)), 5.46 (d, H-3, \( ^3J = 4.6 \) Hz), 5.29 (m, 2H, \( HC=CHH \)), 4.60 (ddd, H-4, \( ^3J = 7.1 \) Hz, \( ^3J = 4.6 \) Hz, \( ^3J = 0.5 \) Hz), 4.13 (ddt, \( ^2J = 15.4 \) Hz, \( ^2J = 5.6 \) Hz, \( ^2J = 1.3 \) Hz, \( N-CH_2 \)), 3.71 (ddd, \( ^2J = 15.4 \) Hz, \( ^2J = 6.9 \) Hz, \( ^2J = 1.1 \) Hz, \( NCHH \)). \( \delta \) (CDCl3) 164.3 (NC=O), 156.6 (C), 142.9 (CH=CH\( NO_2 \)), 135.0 (CH=CHNO2), 130.3 (CH=CH2), 129.7 (CH), 122.9 (CH), 120.3 (CH=CH2), 115.4 (CH), 82.3 (C-3), 55.3 (C-4), 43.7 (N-CH2). IR (KBr, cm\(^{-1}\)): v 1751, 1647. MS (EI), \( m/z \) : 274 (M\(^+\)), 89, 228 (92), 181 (50).

Nitroalkene (+)-7b. From 210 mg (0.86 mmol) of aldehyde (+)-1b, 169 mg (60%) of compound (+)-7b was obtained as an orange oil after purification by flash chromatography (hexanes/ethyl acetate 2:1). \([\alpha]_D = + 33.8 \) (c 1.0, CHCl3). NMR data: \( \delta \) (CDCl3) 7.18 (m, 4H, 2Ar+\( HC=CHNO_2 \)), 6.95 (m, 3H, Ar), 5.68 (m, 1H, \( HC=CH_2 \)), 5.36 (dd, H-3, \( ^3J = 4.63 \) Hz, \( ^3J = 0.5 \) Hz).
1.7 Hz), 5.24 (m, 2H, HC=CHH), 4.53 (dd, H-4, J = 6.6 Hz, J3,4 = 4.6 Hz), 3.55 (m, NCHH), 3.21 (m, NCHH), 2.37 (m, 2H, CHH). δC (CDCl3) 165.0 (N=O), 157.0 (C), 142.8 (CH=CHNO2), 135.3 (CH=CH), 134.2 (CH=CH), 129.8 (CH), 122.9 (CH), 118.1 (CH=CH2), 115.5 (CH), 82.4 (C-3), 55.9 (C-4), 40.3 (N-CH2), 32.0 (CH2). IR (CHCl3, cm-1): ν1768, 1598.

**Nitroalkene (+)-7c.** From 160 mg (0.65 mmol) of aldehyde (+)-1e, 136 mg (72%) of compound (+)-7c was obtained as an orange solid after purification by flash chromatography (hexanes/ethyl acetate 1:1). Mp: 119-121 °C (hexanes/ethyl acetate). NMR data: δH (CDCl3) 7.25 (dd, J = 13.5, 5.9 Hz, H=CHNO2), 7.18 (d, 2H, J = 8.9 Hz, Ar), 6.97 (d, J = 13.5 Hz, H=CHNO2), 6.80 (d, 2H, J = 8.9 Hz, Ar), 5.72 (m, H=CH2), 5.10 (m, 2H, CH=CHH), 4.76 (t, H-4, J = 5.9 Hz,), 3.73 (m, H-3 and O-CH3,), 2.60 (m, CHH), 2.25 (m, CHH). δC (CDCl3) 165.8 (N=O), 157.6 (C), 144.7, 136.4, 134.9, 129.8, 118.2 (CH), 117.0, 114.7 (CH), 64.5, 55.7 (O-CH3), 53.4, 29.5. IR (KBr, cm-1): ν1751. MS (EI), m/z: 292 (M+ +1, 32), 149 (100).

**General procedure for the synthesis of nitroalkanes 8**

To a solution of the corresponding nitroalkene (1.0 mmol) in dichloromethane (4.0 mL) and methanol (0.4 mL) was added tributyl tin hydride (0.31 mg, 1.2 mmol), and the mixture was stirred at room temperature for 24 h. Evaporation of the solvent under reduced pressure gave an oil, which was triturated with ethanol and filtered off to give the corresponding nitroalkane, which were purified by chromatography on silica gel.

**Nitroalkane (+)-8a.** From 180 mg (0.66 mmol) of nitroalkene (+)-7a, 127 mg (70%) of compound (+)-8a was obtained as a yellow oil after purification by flash chromatography (hexanes/ethyl acetate 2:1). [α]D = + 135.1 (c 0.8, CHCl3). NMR data: δH (CDCl3) 7.30 (m, 2H, Ar), 7.05 (m, 3H, Ar), 5.80 (m, H=CH2), 5.33 (m, 2H, CH=CHH), 5.30 (d, H-3, J = 4.9 Hz), 4.52 (td, 2H, J = 6.8 Hz, J = 2.4 Hz, CHHNO2), 4.04 (ddt, J = 15.6 Hz, J = 5.8 Hz, J = 1.2 Hz, NCHH), 4.07 (m, H-4), 3.78 (dtt, J = 15.6 Hz, J = 6.6 Hz, J = 1.2 Hz, NCHH), 2.50 (m, 2H, CHH). δC (CDCl3) 165.5 (N=O), 157.3 (C), 131.1 (CH=CH2), 129.9 (CH), 122.9 (CH=CH2), 119.9 (CH), 115.8 (CH), 80.9 (C-3), 72.0 (CH2NO2), 55.1 (C-4), 43.7 (N-CH2), 26.4 (CH2). IR (CHCl3, cm-1): ν1760, 1598. MS (EI), m/z: 277 (M+ +1, 100), 249 (28).

**Nitroalkane (+)-8b.** From 120 mg (0.42 mmol) of nitroalkene (+)-7b, 73 mg (60%) of compound (+)-8b was obtained as a yellow oil after purification by flash chromatography (hexanes/ethyl acetate 1:1). [α]D = + 87.6 (c 2.0, CHCl3). NMR data: δH (CDCl3) 7.24 (m, 2H, Ar), 6.98 (m, 3H, Ar), 5.72 (m, H=CH2), 5.22 (d, H-3, J = 4.9 Hz), 5.11 (m, 2H, CH=CHH), 4.44 (m, 2H, CHHNO2), 4.04 (dt, H-4, J = 8.1 Hz, J = 4.9 Hz, 3), 3.58 (m, NCHH), 3.14 (m, NCHH), 2.36 (m, 4H, CH2). δC (CDCl3) 165.6 (N=O), 157.1 (C), 134.3 (CH=CH2), 129.7 (CH), 122.7 (CH), 117.8 (CH=CH2), 115.6 (CH), 80.4 (C3), 71.8 (CH2NO2), 54.8 (C4), 39.8 (CH2), 32.0 (CH2), 28.1 (CH2). IR (CHCl3, cm-1) ν1757. MS (EI), m/z: 291 (M+ +1, 100), 263 (17).

**Nitroalkane (+)-8c.** From 60 mg (0.21 mmol) of nitroalkene (+)-7c, 49 mg (81%) of compound (+)-8c was obtained as a orange solid after purification by flash chromatography (hexanes/ethyl acetate 1:1). [α]D = - 160.3 (c 0.8, CHCl3). NMR data: δH (CDCl3) 7.26 (m, 2H, Ar), 7.05 (m, 3H, Ar), 5.72 (m, H=CH2), 5.22 (d, H-3, J = 4.9 Hz), 5.11 (m, 2H, CH=CHH), 4.44 (m, 2H, CHHNO2), 4.04 (dt, H-4, J = 8.1 Hz, J = 4.9 Hz, 3), 3.58 (m, NCHH), 3.14 (m, NCHH), 2.36 (m, 4H, CH2). δC (CDCl3) 165.6 (N=O), 157.1 (C), 134.3 (CH=CH2), 129.7 (CH), 122.7 (CH), 117.8 (CH=CH2), 115.6 (CH), 80.4 (C3), 71.8 (CH2NO2), 54.8 (C4), 39.8 (CH2), 32.0 (CH2), 28.1 (CH2). IR (CHCl3, cm-1) ν1757. MS (EI), m/z: 291 (M+ +1, 100), 263 (17).
acetate 2:1, 1% Et$_3$N). Mp: 91-93 °C (hexanes/ethyl acetate). NMR data: $\delta_H$ (CDCl$_3$) 7.23 (m, 2H, Ar), 6.77 (m, 2H, Ar), 5.85 (m, CH=CH$_2$), 5.12 (m, 2H, CH=CHH), 4.37 (td, 2H, $J$ = 6.2 Hz, $J$ = 1.8 Hz, CHHNO$_2$), 4.20 (ddd, H-3, $J$ = 9.7 Hz, $^3J$ = 5.4 Hz, $J$ = 4.4 Hz), 3.08 (s, 3H, O-CH$_3$), 3.48 (dt, H-4, $J$ = 9.4 Hz, $^3J$ = 5.4 Hz), 2.62 (m, 2H, CHH), 2.29 (m, 2H, CHH). $\delta_C$ (CDCl$_3$) 165.8 (NC=O), 156.5, 134.8, 129.8, 119.5, 117.1, 114.6, 72.2, 55.4, 51.9, 50.8, 28.5, 25.6. IR (KBr, cm$^{-1}$): $\nu$ 1735 MS (EI), $m/z$: 290 (M+, 45), 291 (7), 149 (100), 134 (59).

**Procedure for the synthesis of tricycle (–)-9b.** 13% Aqueous sodium hypochlorite (0.6 mmol) was added, drop by drop, at 0°C, to a well stirred solution of oxime (+)-5b (50 mg, 0.25 mmol) and triethylamine (0.5%) in anhydrous dichloromethane (1.5 mL). The mixture was allowed to heat to room temperature and then was stirred during 26 h. The mixture was diluted with H$_2$O and was extract with dichloromethane. The extract organic was dried (MgSO$_4$) and concentrated under reduced pressure. Flash column chromatography of this mixture eluting with hexanes/ethyl acetate (1:2) gave 12 mg (25%) of compound (–)9b as a white solid. Mp: 127-128 °C (hexanes/ethyl acetate). NMR data: $\delta_H$ (CDCl$_3$) 4.84 (dd, H-10, $^3J$ = 4.1 Hz, $^5J$ = 0.9 Hz), 4.66 (dd, H-5', $^3J$ = 10.5 Hz, $^2J$ = 8.0 Hz) 4.42 (dd, H-5, $^3J$ = 10.5 Hz, $^2J$ = 8.0 Hz), 2.05 (m, H-3'), 1.59 (qd, H-3, $^1J$ = 12.6 Hz, $^3J$ = 4.9 Hz). $\delta_C$ (CDCl$_3$) 167.1 (C-11), 150.6 (C-8), 86.5 (C-10), 72.5 (C-5), 59.6 (O-CH$_3$), 52.5 (C-9), 46.7 (C-4), 37.0 (C-2), 29.6 (C-3). $[\alpha]_D$ = – 8.7 (c 1.1, CHCl$_3$). IR (KBr, cm$^{-1}$): v 1749. MS (EI), $m/z$: 197 (M++1, 15), 196 (M+, 100), 140 (29), 125 (67), 82 (71). Anal. Calcd. for C$_{14}$H$_{14}$N$_2$O$_3$ (258.27): C, 65.11; H, 5.46; N, 10.85. Found: C, 65.21; H, 5.40; N, 10.80.

**Procedure for the synthesis of tricycles (+)-9c and (+)-9d.** To a solution of N-chlorosuccinimide (0.36 mmol) in anhydrous dichloromethane (2 mL), under argon atmosphere, at 0°C was added dropwise a solution of oxime (+)-5c (100 mg, 0.36 mmol) in anhydrous dichloromethane (4 mL). The mixture was stirred for 5 h until reached room temperature. Then, triethylamine was added (1 mmol) and the mixture was stirred for 12 h. The organic mixture was washed with water, dried (MgSO$_4$) and concentrated under reduced pressure. Chromatography of this mixture eluting with hexanes/ether (1:1.5) allowed to obtain 23 mg (25%) of compound (+)9c as a white solid, mp: 166-167 °C (hexanes/ethyl acetate), $[\alpha]_D$= + 243.0 (c 1.0, CHCl$_3$), as well as 9 mg (10%) of compound (+)-9d as a white solid, mp 127-129 °C (hexanes/ethyl acetate), $[\alpha]_D$= + 3.3 (c 0.9, CHCl$_3$). NMR data of tricycle (+)-9c: $\delta_H$ (CDCl$_3$) 7.56 (d, 2H, J = 8.9 Hz, Ar), 7.17 (d, 2H, J = 8.9 Hz, Ar) 5.23 (d, H-10, $^3J$ = 5.5 Hz), 4.94 (dd, H-2, $^3J$ = 5.5 Hz, $^4J$ = 0.6 Hz), 4.56 (dd, H-2, J = 8.1 Hz, OCHH), 4.24 (dd, J = 10.9 Hz, J = 5.1 Hz, OCHH), 3.72 (s, O-CH$_3$), 3.69 (m, 2H, OCHH, OCHH), 3.42 (m, H-7). $\delta_C$ (CDCl$_3$) 162.7 (C-11), 156.9 (C), 154.1 (C-3), 129.9 (C), 119.3 (CH), 114.3 (CH), 77.8 (C-10), 69.7 (O-CH$_2$), 65.4 (O-CH$_2$), 55.5 (O-CH$_3$), 48.2 (C-2), 44.9 (C-7). IR (KBr, cm$^{-1}$): v 1755, 1508. Anal. Calcd. for C$_{14}$H$_{14}$N$_2$O$_4$ (274.27): C, 61.31; H, 5.14; N, 10.21. Found : C, 61.23; H, 5.18; N, 10.17.
NMR data of tricycle (+)-9d: δ_H (CDCl_3) 7.44 (d, 2H, J = 8.9 Hz, Ar), 6.89 (d, 2H, J = 8.9 Hz, Ar), 5.32 (d, H-10, J = 5.4 Hz), 5.05 (d, H-2, J = 5.4 Hz), 4.82 (dd, J = 10.7 Hz, J = 8.3 Hz, OCHH), 4.36 (dd, J = 12.7 Hz, J = 7.3 Hz, OCHH), 4.06 (dd, J = 13.7 Hz, J = 8.3 Hz, OCHH), 3.93 (dd, J = 12.7 Hz, J = 1.9 Hz, OCHH), 3.80 (s, 3H, O-CH_3), 3.50 (m, H-7).

δ_C (CDCl_3) 161.9 (C-11), 157.1 (C), 155.2 (C-3), 130.6 (C), 118.2 (CH), 114.7 (CH), 82.7 (C-10), 75.8 (O-CH_2), 65.8 (O-CH_2), 55.5 (O-CH_3), 50.4 (C-2), 42.0 (C-7). Anal. Calcd. for C_{14}H_{14}N_2O_4 (274.27): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.40; H, 5.10; N, 10.16.

General procedure for the synthesis of cycloadducts 10
To a solution of the corresponding nitroalkane 8 (1.0 mmol) in dry chloroform (30 mL), at room temperature, was added phenyl isocyanate (2.3 mmol), followed by triethylamine (0.3 mmol). The mixture was stirred for 10 h, during which time diphenylurea precipitated, and was separated as a solid by filtration. The filtrate was washed with water and dried (MgSO_4). The solvent was removed under reduced pressure to leave a semisolid, which was purified by chromatography on silica gel.

Cycloadduct (+)-10a. From 50 mg (0.18 mmol) of nitroalkane (+)-8a, 38 mg (83%) of compound (+)-10a was obtained as a white solid after purification by flash chromatography (chloroform/ethyl acetate 5:1). Mp: 181-182 °C (chloroform/ethyl acetate). [a]_D = + 41.7 (c 0.9, CHCl_3). NMR data: δ_H (CDCl_3) 7.25 (m, 2H, Ar), 6.90 (m, 3H, Ar), 5.37 (dd, H-10, J = 4.1 Hz, J = 1.2 Hz), 4.51 (dd, H-4', J = 10.7 Hz, J = 8.5 Hz), 4.37 (dd, H-2', J = 13.1, J = 8.5 Hz), 3.97 (m, H-9), 3.92 (t, H-4, J = 9.3 Hz) 3.42 (m, H-3), 2.81 (dd, H-8', J = 14.1 Hz, J = 5.4 Hz), 2.78 (m, H-2), 2.61 (ddd, H-8, J = 14.1 Hz, J = 10.2 Hz, J = 1.5 Hz).

δ_C (CDCl_3) 164.3 (C11), 156.7 (C), 154.6 (C-7), 129.7 (CH), 122.6 (CH), 115.0 (CH), 81.1 (C-10), 71.2 (C-4), 53.9 (C-9), 46.3 (C-3), 43.4 (C-2), 23.8 (C-8). IR (KBr, cm⁻¹): ν = 1751. MS (EI), m/z: 258 (M⁺, 4), 165 (100), 77 (31). Anal. Calcd. for C_{14}H_{14}N_2O_3 (258.27): C, 65.11; H, 5.46; N, 10.85. Found: C, 65.02; H, 5.40; N, 10.90.

Cycloadduct 10b. From 45 mg (0.15 mmol) of nitroalkane (+)-8b, 21 mg (50%) of compound 10b, as a mixture (63/37) of isomers, was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate 9:1). NMR data: δ_H (CDCl_3) 1.90 (m, 2H, H-3, H-3'), 2.54 (ddd, J = 0.63H, J = 14.2 Hz, J = 11.7 Hz, J = 1.1 Hz), 2.95 (m, 2H), 3.33 (m, 2H), 3.73 (ddd, J = 0.63H, J = 11.4 Hz, J = 4.2 Hz, J = 2.6 Hz), 3.84 (dd, J = 0.37H, H-5, J = 12.4 Hz, J = 8.3 Hz), 4.02 (t, J = 0.63H, H-5, J = 8.4 Hz), 4.11 (m, J = 1.37H), 4.50 (dd, J = 0.63H, H-5', J = 10.5 Hz, J = 8.5 Hz), 4.54 (dd, J = 0.37H, H-5', J = 8.3 Hz, J = 7.3 Hz), 5.22 (dd, J = 0.63H, H-11, J = 4.2 Hz, J = 1.1 Hz), 5.26 (dd, J = 0.37H, H-11.1, J = 4.6 Hz, J = 1.1 Hz), 6.94 (m, 3H, Ar), 7.25 (m, 2H, Ar). δ_C (CDCl_3) 164.8 (C-12, M), 164.5 (C-12, m), 158.9 (C-8, M), 158.2 (C-8, m), 157.0 (C, M + m), 129.7 (CH, M + m), 122.5 (CH, M + m), 115.3 (CH, M), 115.2 (CH, M), 80.8 (C-11, m), 79.4 (C-11, M), 74.7 (C-5, M), 74.0 (C-5, m), 56.3 (M), 56.1 (m), 50.8 (m), 50.3 (M), 40.9 (m), 40.0 (M), 28.9, 28.8, 28.7, 27.9. IR (CHCl_3, cm⁻¹): ν = 1750. MS (EI), m/z : 272 (M⁺, 88), 271 (1), 149 (100), 123 (59).

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Cycloadducts (±)-10c and (±)-10d. From 100 mg (0.35 mmol) of nitroalkane (±)-8c, and after flash chromatography eluting with ethyl acetate, 49 mg (51%) of the compound (±)-10c, mp 143-144°C (white solid), and 11 mg (11%) of compound (±)-10d, mp 148-149°C (white solid), were obtained. NMR data of (±)-10c:

δH (CDCl3) 7.20 (2H, J = 9.0 Hz, Ar), 6.80 (2H, J = 9.0 Hz, Ar), 4.49 (dd, H-7, 3J = 9.9 Hz, 2J = 8.1 Hz), 4.42 (td, H2, J = 5.4 Hz, 3J = 1.1 Hz), 3.76 (dd, H-7, 3J = 11.1 Hz, 2J = 8.1 Hz), 3.70 (s, O-CH3), 3.58 (td, H-10, 3J = 5.4 Hz, 3J = 1.1 Hz), 3.44 (m, H-8), 3.22 (dd, H-3, 2J = 19.5 Hz, 3J = 1.1 Hz), 2.83 (ddd, H-3, 2J = 19.5, 3J = 5.7 Hz, 4J = 1.9 Hz), 2.45 (ddd, H-9, 3J = 13.5 Hz, 3J = 4.8 Hz, 3J = 2.0 Hz), 1.65 (td, H-9, J = 13.5 Hz, 3J = 5.7 Hz).

δC (CDCl3) 165.1 (C-11), 156.8 (C4), 156.6 (C), 129.5 (CH), 118.6 (CH), 114.7 (CH), 72.7 (C-7), 55.5 (O-CH3), 48.7 (C-2), 48.2 (C-10), 43.8 (C-8), 25.4 (C-9), 22.0 (C-3). IR (KBr, cm−1): ν 1747, 1515. MS (EI), m/z: 272 (M+ + 88), 273 (18), 271 (5), 149 (100), 123 (59). IR (KBr, cm-1): ν 1747, 1515. Anal. Calcd. for C15H16N2O3 (272.30): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.26; H, 5.89; N, 10.25. NMR data of (±)-10d:

δH (CDCl3) 7.20 (m, 2H, Ar), 6.80 (m, 2H, Ar), 4.56 (dd, H-7, 3J = 10.2 Hz, 2J = 8.2 Hz), 4.48 (ddd, H-2, 3J = 5.3 Hz, 3J = 4.5 Hz, 3J = 2.2 Hz), 3.85 (dd, H-7, 3J = 14.1 Hz, 2J = 8.2 Hz), 3.70 (s, O-CH3), 3.50 (ddd, H-10, 3J = 6.8 Hz, 3J = 5.3 Hz, 3J = 3.6 Hz), 3.36 (m, H-8), 3.18 (dd, H-3, 3J = 15.0 Hz, 3J = 2.2 Hz), 2.64 (ddd, H-3, 3J = 15.0, 3J = 4.5 Hz, 4J = 1.5 Hz), 2.20 (ddd, H-9, 3J = 15.5 Hz, 3J = 8.8 Hz, 3J = 6.8 Hz), 2.10 (dt, H-9, 3J = 15.5 Hz, 3J = 3.6 Hz). δC (CDCl3) 165.1 (C-11), 156.8 (C4), 156.6 (C), 129.5 (CH), 114.6 (CH), 74.8 (C-7), 55.5 (O-CH3), 51.9 (C-2), 48.2 (C-10), 43.5 (C-8), 24.7 (C-9), 21.2 (C-3). IR (KBr, cm−1): ν 1735, 1514. Anal. Calcd. for C15H16N2O3 (272.30): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.08; H, 5.88; N, 10.33.

Procedure for the synthesis of tricycle 11. To a solution of nitroaldol 6a (200 mg, 0.68 mmol) and a catalytic amount of DMAP in dichloromethane at 0 °C under argon was slowly added triethylamine (2.4 mmol) and acetic anhydride (1.2 mmol). The mixture was stirred at room temperature for 17 h, and then water was added. The solution was extract with ethyl acetate, the organic layer was dried (MgSO4), and concentrated at reduced pressure. After chromatography on silica gel eluting with (hexanes/ethyl acetate 1:1) gave 53 mg of compound 11 (30%) as a mixture of isomers (65/35). NMR data: δH (CDCl3) 7.31 (m, 4H, Ar, m), 7.01 (m 6H, Ar, M, m), 5.95 (s, H-8, m), 5.92 (s, H-8, M), 5.73 (s, H-10, m), 5.66 (s, H-10, M), 4.66 (m, H-4’M, H-4’m), 4.29 (m, H-2’M, H-2’m), 3.85 (m, H-3M, H-3m, H-4M, H-4m), 3.44 (m, H-2, m), 3.32 (m, H-2, M). δC (CDCl3) 163.1 (C-11, M), 162.9 (C-11, m), 156.6 (C, M, m), 152.4 (C-7, M), 152.1 (C-7, m), 146.7 (C-9, M), 146.4 (C-9, m), 129.7 (CH, M, m), 123.1 (C, M, m), 115.8 (CH, M), 115.6 (CH, m), 89.1 (C-8, M), 88.9 (C-8, m), 82.5 (C-10, M), 82.0 (C-10, m), 71.7 (C-4, M, m), 44.6 (C-3, M, m), 42.3 (C-2, m), 41.7 (C-2, M). IR (CHCl3, cm−1): ν 1750. Anal. Calcd. for C14H12N2O3 (256.26): C, 65.62; H, 4.72; N, 10.39. Found: C, 65.73; H, 4.69; N, 10.44.
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