Multicomponent diastereoselective synthesis of indolizidines via 1,3-dipolar cycloadditions of azomethine ylides

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Najera, Carmen; University of Alicante, Organic Chemistry
Sansano, Jose; University of Alicante, Organic Chemistry
Keywords: cycloaddition, fused-ring systems, heterocycles, multicomponent reaction, diastereoselectivity
Abstract: The synthesis of polyfunctionalized indolizidines from pipecolinic acid alkyl ester derivatives, aldehydes and a wide range of dipolarophiles by a multicomponent 1,3-dipolar cycloadditions has been developed in a diastereoselective manner. Reactions take place in toluene with short reaction times at 70 °C, giving good yields. The synthesis of these fused heterocycles is also studied starting from the pipecolinic acid, generating the dipole through a decarboxylative route at 120 °C. The relative configuration of the resulting products, as well as the mechanistic pathways are also explained.
SUPPORTING INFORMATION

Multicomponent diastereoselective synthesis of indolizidines via 1,3-dipolar cycloadditions of azomethine ylides

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* cnajera@ua.es

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2. X-Ray diffraction analysis of compound endo-13 ................................................................. S25
1. $^1$H and $^{13}$C NMR spectra

![NMR Spectra Image]
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endo-17

exo-17

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CO₂Me

Ph

CO₂Me

CO₂Me

CO₂Me

CO₂Me

CO₂Me

CO₂Me

CO₂Me
endo'-17 Ph CO_{2}Me

exo'-17 Ph CO_{2}Me

0.65:1
1:0.5

endo-18

exo'-18

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Manuscript Submitted to Synthesis

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany
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C17B 0.182(11) 0.050(5) 0.095(7) -0.001(5) 0.045(7) -0.051(7)
C18 0.0486(16) 0.086(2) 0.0781(19) -0.0125(15) 0.0145(13) -0.0362(15)

_all esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken
into account individually in the estimation of esds in distances, angles
and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell esds is used for estimating esds involving l.s. planes.

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H10A C10 H10B 108.0 . . ?
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H11A C11 H11B 108.0 . . ?
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C1 C14 C4 113.67(17) . . ?
C3 C14 C4 105.92(16) . . ?
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C3 C14 H14 110.8 . . ?
C4 C14 H14 110.8 . . ?
O4 C15 O5 123.5(2) . . ?
O4 C15 C13 124.4(2) . . ?
O5 C15 C13 112.05(17) . . ?
C15 O5 C16A 114.8(6) . . ?
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C17A C16A H16A 110.3 . . ?
O5 C16A H16B 110.3 . . ?
C17A C16A H16B 110.3 . . ?
H16A C16A H16B 108.5 . . ?
C17B C16B O5 112.6(12) . . ?
C17B C16B H16C 109.1 . . ?
O5 C16B H16C 109.1 . . ?
C17B C16B H16D 109.1 . . ?
O5 C16B H16D 109.1 . . ?
H16C C16B H16D 107.8 . . ?
C16B C17B H17D 109.5 . . ?
C16B C17B H17E 109.5 . . ?
H17D C17B H17E 109.5 . . ?
C16B C17B H17F 109.5 . . ?
H17D C17B H17F 109.5 . . ?
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Multicomponent diastereoselective synthesis of indolizidines via 1,3-dipolar cycloadditions of azomethine ylides

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Dedicated to Prof. Dieter Enders

Abstract The synthesis of polyfunctionalized indolizidines from pyroglutamic acid alkyl ester derivatives, aldehydes and a wide range of dipolarophiles by a multicomponent 1,3-dipolar cycloadditions has been developed in a diastereoselective manner. Reactions take place in toluene with short reaction times at 70 °C, giving good yields. The synthesis of these fused heterocycles is also studied starting from the pyroglutamic acid, generating the dipole through a decarboxylative route at 120 °C. The relative configuration of the resulting products, as well as the mechanistic pathways are also explained.

Key words cycloaddition, multicomponent, indolizidine, azomethine ylides, iminium route, decarboxylative route

Introduction

The indolizidine structure can be found in many alkaloid families being the most important moiety in the molecule. These alkaloids, which can be isolated from plant or animal sources, have shown important biological properties and medicinal applications. As representative examples, pharmaceutically interesting tetrahydroxyalkaloids such as castanospermine and 6-epicastanospermine are possible lead compounds in the search for anti-AIDS drugs, and the most simple structure of tashiromine has multiple interesting biological activities (Figure 1).

Many synthetic approaches have been successfully developed to prepare this fused heterocyclic skeleton. Most of them can be classified according to the cyclization order, that means, five-member ring followed by six-membered ring construction (5→6) and vice versa (6→5). The most common used access is the 5→6 pathway, and the reason is the high availability of both natural or synthetic polyfunctionalized pyrrolidines or proline derivatives. In addition, interesting 6→5 sequences have been published.

Such as it has been extensively demonstrated, 1,3-dipolar cycloaddition (1,3-DC) involving azomethine ylides is a potential tool for the construction of complex alkaloid structures. Focusing on 6→5 sequences mediated by these type of cycloadditions generating the intermediate azomethine ylides via decarboxylation route, intramolecular 1,3-DC between δ-chloroaldehydes, glycine and electrophilic alkenes, gave indolizidines in very high yields (Scheme 1a). Another decarboxylations underwent by tetrahydroisoquinoline-3-carboxylic acid and by tetrahydro-β-carboline-3-carboxylic acid also gave polycycles in good yields. In all these examples the chemical yield was almost quantitative (95%) and the mixture of diastereoisomers was notable. In the case of dimethyl fumarate and N-phenylmaleimide (NPM) a 50:50 and a 75:25 mixture of endo:exo adducts was obtained, respectively. The intrinsic thermal isomerization of dimethyl maleate also promoted the generation of a third diastereoisomer (Scheme 1b).

Figure 1. Representative natural indolizidine alkaloids.
Following with the multicomponent 1,3-dipolar cycloaddition strategy designed for the synthesis of pyrrolizidines\(^{17}\) using proline ester hydrochlorides, aldehydes and dipolarophiles, at room temperature, we will survey in this work the general scope of this cycloaddition employing six-membered ring templates for the construction of the fleeting azomethine ylde with aldehydes, and further capture with dipolarophiles. We will study the generation of these intermediates through the iminium route, or through the decarboxylation way. All these reactions will be designed with the idea of increasing the functionality of the resulting polysubstituted indolizidines improving the diastereomeric ratio at the end of the processes. A comparison between both methodologies will be also established.

**Results and discussion**

Following the optimized reaction conditions described by our group in the synthesis of pyrrolizidines\(^{17}\) the first attempt to run 1,3-DC between the iminium salt, generated from methyl pipecolinate hydrochloride (1a) and cinnamaldehyde, and further cyclization with N-substituted maleimides as dipolarophiles was performed at 25 °C in toluene. The reaction did not take place neither using these reaction conditions nor employing the silver catalyzed-process at room temperature.

When increasing the temperature to 70 °C in toluene and in the absence of silver salts the reaction succeeded. Indolizidines (2 and 3) were isolated with high endo-diastereoselectivity (Scheme 2) when methyl pipecolinate and one equivalent of triethylamine were allowed to react with N-methyl maleimide (NMM) or with N-phenyl maleimide (NPM). No differences were observed concerning both of the yield the diastereoselectivity (70:30 dr). Compound (2) was isolated in 81% overall yield (endo-2 59%, and exo-2 22%) and 3 in 75% overall yield (endo-3 55%, and exo-3 20%) (Scheme 2). In contrast, when maleic anhydride was tested higher yield and complete endo-diastereoselectivity was achieved for compound 4 (Figure 2).

Following with the study of the general scope several dipolarophiles maintaining the aldehyde structure were tested. The highest endo-diastereoselection was achieved when the less sterically hindered methyl acrylate was employed as dipolarophile (Scheme 3) yielding endo-5 (57%) in a 95:5 dr. When methyl fumarate was used as dipolarophile, the diastereoselectivity observed for compound endo-6 (84:16 dr) was slightly lower than the obtained one for the methyl acrylate but higher than with NMM (Scheme 3). trans-β-Nitrostyrene and chalcone were suitable dipolarophiles for this thermal multicomponent reaction affording indolizidines 7, 8 and 9, respectively. With the conjugated ketone the chemical yield was lower (66% overall yield) than the analogous obtained in the example run with the nitroalkene (72% overall yield). However, apart from the endo-7 cycloadduct (17% yield), the regioisomer exo-8 (55% yield) was also identified in high proportions. In the case of chalcone the unexpected cycloadduct exo-9 was obtained as major product (75:25 dr) (Scheme 3).

Methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10), prepared from phenyl alanine methyl ester\(^{18}\) was also tested in this multicomponent process. Cinnamaldehyde, 10 and NPM were mixed and the reaction was warmed at 70 °C for 17 h. Tetracyclic complex skeleton endo-11 was obtained as major compound in 65% yield, and exo-11 in 11% yield with a 86:14 dr (Scheme 4).
Scheme 3. Multicomponent cycloaddition of piperolic acid methyl ester hydrochloride 1a, cinnamaldehyde and different dipolarophiles.

Scheme 4. Synthesis of indolizidine 11 through the multicomponent cycloaddition of 10 and cinnamaldehyde, with NPM.

Scheme 5. Synthesis of indolizidines endo-12 and endo-13 through multicomponent cycloaddition of piperolic acid alkyl esters 1, with aromatic aldehydes and different dipolarophiles.

A comparison with the thermal 1,3-DC reported in the literature by Joucla and coworkers (Scheme 1b),16 where benzaldehyde was employed, was done. The reaction with N-methylmaleimide did not work under our reaction conditions, and a complex mixture of inseparable products was detected after performing the reaction at 110 °C. However, the reaction involving maleic anhydride, benzaldehyde, and 1a at 70 °C gave a modest isolated chemical yield (27%) of cycloadduct endo-12 as unique diastereoisomer (Scheme 5). Furfural was also tested together with ethyl piperolinate 1b and NMM affording endo-cycloadduct 13 as major compound in 82:18 dr and 48% overall yield (Scheme 5).

Nevertheless, crotonaldehyde, isovaleraldehyde and (2E,4E)-hexa-2,4-dienal showed very poor reactivity. According to our studies, reactions run with all type of alkyles, but specially unsaturated alkyles, were very sensitive to high temperatures (>70 °C) affording decomposition products (detected in crude 1H-NMR spectra).

After careful analysis of 1H-NMR of the reaction crudes, only a mixture of two diastereoisomers was identified. At this point, we can assume that the reaction mechanism proceeds with relative high to excellent diastereocontrol as consequence of the S-type dipole generated by iminium route which attacks preferentially by its α-position to carbon atom of dipolarophile with partial positive charge (Figure 3a). This S-dipole, through the most favorable endo-approach allows the 2,4-trans-2,5-trans arrangement of the five-membered ring (Figure 3b).
A preferential trend was observed in compounds 2, 3, 4, 5, 6, 11, 12 and 13. Only in the example run with the chalcone the exo-diastereoselectivity was preferentially observed presumably due to the high steric interaction between the phenyl group closer to the ketone group and the substituents of the cyclic dipole. In this example a 2,4-cis-2,5-trans arrangement was generated. On the other hand, the cycloadduct resulting from the γ-attack of the S-dipole was preferred in the reaction performed with trans-β-nitrostyrene, which is an excellent Michael acceptor able to trap whatever type of resonance forms. In this case, the new compound 8 was formed by a more feasible exo-attack of the dipolarophile. This identical behavior was described during the multicomponent synthesis of pyrrolizidines because of stereoelectronic effects of the nitroalkene. 

The relative configuration of the major endo-cycloadducts 2-6 and 11-13 was proposed according to unambiguous nOe experiments. A representative example of these analyses is shown in Figure 4. The most stable conformations of endo-5 and endo-6 have been represented with the corresponding nOe effects detected. It is noteworthy to indicate that a small, but definitive, increment of electronic population in the signal of effects detected. It is noteworthy to indicate that a small, but definitive, increment of electronic population in the signal of the C3 position was irradiated. In addition, this configuration was identical to the obtained by Joucla et al. after X-ray diffraction analysis. and also with the same structural arrangement of pyrrolizidines obtained after multicomponent 1,3-DC involving prolinates. At the end of the experimental work an X-ray diffraction analysis of crystalline major diastereoisomer endo-13 could be performed confirming all these stereoechemical results obtained by NMR experiments (Scheme 5).

Next, we study the availability of performing the corresponding 1,3-DC starting from pipicolic acid 14, aldehydes and dipolarophiles. In this reaction, the necessary decarboxylation of the iminium salt generated in situ occurred at higher temperatures (refluxing toluene) (Scheme 6). To the best of our knowledge, this type of cycloaddition of 14 has not been reported yet. Thus, compound 14, cinnamaldehyde, and NMM were diluted in toluene and the mixture was heated in a sealed tube at 120 °C (bath temperature) obtaining a mixture of four different stereoisomers 15 in 89% overall yield (Table 1, entry 1). In all cases the diastereomeric ratio observed in the crude 1H-NMR spectra was identical to the analogous one determined after separation of each isomers by column chromatography.

With NPM chemical yield of 16 was lower (78%) but the endo-diastereoselection was the highest of all this series of decarboxylative reactions using cinnamaldehyde (Table 1, entry 2). Dimethyl and diisobutyl fumarates gave both identical chemical yields (75%) and mixtures of diastereoisomers of products 17 and 18 (Table 1, entries 3 and 4). Non-symmetrical dipolarophiles such as tert-butyl acrylate and trans-β-nitrostyrene were next evaluated. Compounds 19 and 20 were isolated in 52 and 40% overall yields, respectively (Table 1, entries 5 and 6). Finally, benzaldehyde was tested with 14 and NPM affording a very high yield (95%) of compound 21 as mixture of four stereoisomers (Table 1, entry 7). However, the reaction with NMM or tert-butyl acrylate only afforded decomposition products at the end of the reaction. Other aldehydes such as crotonaldehyde, isovaleraldehyde and furfural also failed as starting materials in the multicomponent reaction employing NMM.

After careful analyses of selective nOe experiments of each isolated product/mixture, and by comparison of the analogous chemical shifts and coupling constants we could identify each structure. 1,3-DC starting from phenylglyoxal 22, aldehydes and nitrostyrene were next evaluated. Compounds 24, 25, 26 and 27, for the α-position. S-Shape dipoles underwent thermal stereomutation in the iminium salt affording unstable U-shape dipole, which is the responsible of the generation of
endog- and exog-diastereoisomers. Besides, the regioselectivity of this cycloaddition was very high because we could not detect any stereoisomer due to the attack of the dipole by its γ-position (Figure 6).

Table 1. Multicomponent 1,3-DC by mixing amino acid 14, aldehydes, and dipolarophiles at 120 °C.

<table>
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<th>Entry</th>
<th>R1</th>
<th>Dipolarophile</th>
<th>Product</th>
<th>Yield (%)a</th>
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<tr>
<td>1</td>
<td>(E)-PhCH=CH-</td>
<td>NMM</td>
<td>15</td>
<td>89</td>
<td>35:22:20:23</td>
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<tr>
<td>2</td>
<td>(E)-PhCH=CH-</td>
<td>NPM</td>
<td>16</td>
<td>78</td>
<td>45:17:18:20</td>
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<tr>
<td>3</td>
<td>(E)-PhCH=CH-</td>
<td>Dimethyl fumarate</td>
<td>17</td>
<td>75</td>
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</tr>
<tr>
<td>4</td>
<td>(E)-PhCH=CH-</td>
<td>Diisobutyl fumarate</td>
<td>18</td>
<td>75</td>
<td>35:30:19:17</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(E)-PhCH=CH-</td>
<td>tert-Butyl acrylate</td>
<td>19</td>
<td>52</td>
<td>39:28:17:16</td>
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</tr>
<tr>
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<td>trans-β-Nitrostyrene</td>
<td>20</td>
<td>40</td>
<td>43:25:11:21</td>
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<td>Ph</td>
<td>NPM</td>
<td>21</td>
<td>95</td>
<td>57:25:13:5</td>
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</table>

aOverall chemical yield isolated after flash chromatography.

bMixture of diastereoisomers detected by 1H-NMR of the crude mixture and after the separation of all of the corresponding diastereoisomers.

As conclusion, we have prepared indolizidines from methyl pipercolinate and methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate in a multicomponent 1,3-DC using functionalized conjugate aldehydes as cinnamaldehyde and different dipolarophiles at 70 °C. The major isomers resulted from the attack of the reactive S-shape dipole, prepared via the iminium route, by its α-position affording all cis-endo diastereoisomers. Under these reaction conditions, the diastereoselection was notably higher than the analogous ones reported in the literature at 110 °C. In other side, the appearance of the U-shape dipole at 120 °C allowed to obtain two more diastereoisomers (endo' and exo') when the multicomponent sequence dealt with a dipole generated by a decarboxylative route. Here, endo-cycloadduct was the major isomer, especially when a bulky substituent in the dipolarophile was bonded (Ph, Bu1, Bu2) but with very significant amounts of the corresponding exo-adduct. In all these examples, the diastereomeric ratio was very low. No regioisomeric adducts controlled by a γ-attack were obtained in any case.
Experimental part

Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra, recorded on a Nicolet 510 P-FT, are listed. For solid samples ATR device was employed. 1H-NMR (300 MHz) and 13C-NMR (75 MHz) spectra were obtained on a Bruker AC-500 using CDCl3 as solvent and TMS as internal standard.

Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 and high-resolution mass spectra were obtained on a Finnigan MAT 95XL. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized under UV light (λ = 254 nm). Flash chromatography was done using Merck silica gel 60 (0.040–0.063 mm).

General procedure for the synthesis of indolines 3-9

To a solution of the pipelic acid methyl ester hydrochloride 1 (40 mg, 0.22 mmol) in toluene (1 mL), Et3N (1 equiv, 3.05 μL, 0.22 mmol), the corresponding aldehyde (1 equiv, 0.22 mmol) and the dipolarophile (1 equiv, 0.22 mmol) were added. The resulting mixture was stirred at 70 °C for 17 h. EtOAc (5 mL) and H2O (5 mL) were added and the organic phase was separated, dried (MgSO4), and evaporated to obtain the crude product.

Methyl (3aS,4S,9αR,9βR*)-1,3-dioxo-2-phenyl-4-[(E)-2-styryl]dehydro-9αF-pyrrolo[3,4-α]indolizine-9a-carboxylate (endo-2)

Yield: 36 mg (59%), colorless prisms, mp 134–135 °C (EtO).

IR (neat): 1734, 1698, 1213 cm⁻¹.

1H-NMR: δ = 1.17–1.23 (m, 1H, NCH), 1.21–1.38 (m, 2H, NCH), 1.74–1.80 (m, 1H, NCH), 1.78 (dt, J = 13.1, 3.2 Hz, 1H, CH2), 2.10–2.16 (m, 1H, CH2), 2.34–2.37 (m, 1H, CH2), 2.81–2.84 (2dd, J = 2.7 Hz, 2H, NCH2), 3.03 (s, 3H, NCH3), 3.25 (dd, J = 8.0, 7.9 Hz, 1H, NCH2), 3.35 (s, 3H, CH3), 3.76 (s, 3H, OCH3), 4.18 (dd, J = 9.2, 8.0 Hz, 1H, NCO), 5.88 (dd, J = 15.6, 9.2 Hz, 1H, PhCH2), 6.68 (d, J = 15.6 Hz, 1H, PhCH2), 7.22–7.35 (3m, 3H, ArH), 7.36–7.45 (m, 2H, ArH).

13C-NMR: δ = 21.7 (NCH3), 24.7 (NCH2), 25.1 (NCH), 32.0 (CCH2), 43.8 (CCH2), 47.9 (NCHCO), 51.8 (OCH3), 65.2 (NCH), 66.9 (COO), 126.7, 128.6, 128.7, 134.5, 136.8 (Ar, C=C), 173.6, 175.3 (2xNCO), 175.9 (C=O, Me).

MS (EI): m/z = 368 (M+, 3%), 310 (20), 309 (100), 224 (12).

HRMS (DIP) calc'd for C24H19N3O3: 368.1746; found 368.1750.

Methyl (3aS,4S,9αR,9βR*)-1,3-dioxo-2-phenyl-4-[(E)-2-styryl]dehydro-9αF-pyrrolo[3,4-α]indolizine-9a-carboxylate (endo-3)

Yield: 52 mg (55%), pale yellow oil.

IR (neat): 2933, 1710, 1498, 1448, 1375, 1179, 1309, 1192 cm⁻¹.

1H-NMR: δ = 1.17–1.23 (m, 1H, NCH2), 1.28–1.35 (m, 1H, NCH2), 1.38–1.48 (m, 1H, NCH2), 1.62–1.68 (m, 1H, NCH2), 1.78 (dt, J = 13.1, 3.2 Hz, 1H, CH2), 2.53 (dd, J = 13.1, 1.5 Hz, CH2), 2.82–2.93 (m, 2H, NCH2), 3.41 (q, J = 8.0 Hz, 1H, NCH2), 3.51 (dd, J = 8.0 Hz, 1H, NCH2), 3.79 (s, 3H, OCH3), 4.29 (dd, J = 8.9, 8.0 Hz, 1H, NCO), 6.01 (dd, J = 15.7, 8.9 Hz, 1H, PhCH2), 6.72 (d, J = 15.7 Hz, 1H, PhCH2), 7.16–7.35 (5m, 5H, ArH), 7.37–7.50 (m, 5H, ArH).

13C-NMR: δ = 21.8 (NCH3), 24.9 (NCH2), 32.1 (CCH2), 440 (NCH2), 48.0 (NCHCO), 51.4 (CCH2), 51.9 (OCH3), 65.5 (NCH), 70.4 (COO), 126.7, 126.9, 127.7, 127.9, 128.6, 128.8, 129.3, 132.0, 134.4, 136.8 (Ar, C=C), 173.6 (CO), 174.2 (CO), 175.0 (C=O).

MS (EI): m/z = 430 (M+, 3%), 372 (26), 371 (100), 224 (6).

HRMS (DIP) calc'd for C24H19N3O3: 430.1893; found 430.1911.
To a solution of the amine \( \text{R}* \) (40 mg, 0.22 mmol) in toluene (1 mL), the corresponding aldehyde (1 equiv, 0.22 mmol) and the dipolarophile (1 equiv, 0.22 mmol) were added. The resulting mixture was stirred at 70 °C for 17 h. EtOAc (5mL) and H\( _2 \)O (5 mL) were added and the organic phase was separated, dried (MgSO\(_4\)), and evaporated to obtain the crude product which was purified by flash chromatography (silica-gel) in good chemical yields (see text).

\[ \begin{align*}
\text{Yield:} &\ 20\% \ (\text{mp} \ 121-124 \ ^\circ C \text{ (EtO)}).
\end{align*} \]

\( \text{IR (neat):} 1718, 1682, 1470, 1207 \ \text{cm}^{-1} \).
Yield: 2 mg (5%) yellow sticky oil.

IR (neat): 2938, 1697, 1433, 1382, 1219, 1239, 1138, 1039, 965, 749 cm⁻¹.

¹H-NMR δ (TMS) 1.11–1.28 (m, 5H, CH₂), 1.34–1.45 (m, 4H, NCH₂CH₂), 1.50–1.66 (m, 4H, NCH₂CH₂), 1.69–1.90 (m, 1H, NCH₂CH₂), 2.18–2.36 (m, 1H, NCH₂CH₂), 2.79–2.93 (m, 1H, NCH₂CH₂), 3.08–3.09 (m, 1H, NCH₂CH₂), 3.16–3.32 (m, 1H, NCH₂CH₂), 4.13 (m, 1H, H₂O), 7.46–7.47 (m, 1H, CH₂).

MS (EI): m/z = 372 (M⁺; 23%), 371 (13), 282 (19), 281 (100), 199 (1), 167 (10).
**Synthesis**

Disobutyl (15S,2S,3S,4R,8aR*-3-[(6S)-1,3-dimethyl-2,6-dioxopiperidin-2-yl]octahydropyridine-1,2-dicarboxylate (endo-18) and disobutyl (1R,2R,3S,4R,8aR*-3-[(6S)-1,3-dimethyl-2,6-dioxopiperidin-2-yl]octahydropyridine-1,2-dicarboxylate (exo-18)

Yield: 4.9 mg (37%), yellow oil.

IR (neat): 2930, 2855, 1717, 1549, 1496, 1449, 1362, 1264, 1144, 967, 736, 694 cm⁻¹.

HRMS (DIP) calcd. for C₁₁₂H₁₇O₂₆ 262 (M⁺), 244 (15), 226 (22), 198 (100), 174 (32), 152 (14), 224 (99), 190 (80), 164 (13), 151 (12), 137 (15).

HRMS (DIP) calcd. for C₁₁₂H₁₇O₂₆: 262.3272, found: 262.3271.

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IR (neat): 2938, 2855, 1717, 1549, 1496, 1449, 1362, 1264, 1144, 967, 736, 694 cm⁻¹.

HRMS (DIP) calcd. for C₁₁₂H₁₇O₂₆: 262.3272, found: 262.3271.

(3aS,4R,9aR,9bR*)-2,4-Diphenyl-1,2,3-tetrahydro-1H-pyrrrolo[3,4-a]acridin-1,2(2H)-dione (endo-21)

Yield: 26 mg (42%), yellow oil.

IR (neat): 2934, 2854, 1712, 1496, 1376, 1173, 743, 698 cm⁻¹.

HRMS (DIP) calcd. for C₁₁₂H₁₇O₂₆: 262.3272, found: 262.3271.

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The Spanish Ministerio de Economía e Innovación (MCIINN) (projects CTQ2010-20387 and Consolider Ingenio 2010, CSD2007-00006), the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51923-REDI), FEDER, the Generalitat Valenciana (PROMETEO 2009/039 and PROMETEOII/2014/017), and the University of Alicante. L. M. thanks Spanish Government for a fellowship.

**Supporting Information**

YES (this text will be updated with links prior to publication)

**References**

(15S,2S,3S,4R,8aR*)-1-Nitro-2-phenyl-3-[(6S)-1,3-dimethyl-2,6-dioxopiperidin-2-yl]octahydropyridine-1,2-dicarboxylate (endo-20)

Yield: 19 mg (18%), brown sticky oil.

IR (neat): 2938, 2855, 1717, 1549, 1496, 1449, 1362, 1264, 1144, 967, 736, 694 cm⁻¹.

HRMS (DIP) calcd. for C₁₁₂H₁₇O₂₆: 262.3272, found: 262.3271.
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3. Procedures employing an intramolecular cyclization affording simultaneously 5 and 6 membered rings have seldom been reported. See, for example: Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. Tetrahedron 2014, 70, 204-211.


20 Available structure deposited in CCDC with number 1496416.