A CONVENIENT SYNTHESIS OF NOVEL SPIROISOINDOLONE 
γ-HALOBUTYROLACTONES VIA HALOCYCLIZATION OF 
γ-ETHYLENIC ACIDS

Mohamed M. Rammah, a,d Mohamed Othman, a,* Kabula Ciamala, b Michael Knorr, b Carsten Strohmann, c and Mohamed B. Rammah d

aURCOM, EA 3221, FR CNRS 3038, University of Le Havre, BP 540, F-76058 Le Havre Cedex, France. bInstitut UTINAM UMR CNRS 6213, University of Franche-Comté, F-25030 Besançon Cedex, France. cTechnical University Dortmund, D-44227 Dortmund, Germany. dLCOH, University of Monastir, 5000 Monastir, Tunisia

Abstract – γ-Ethlenic carboxylic acids are cyclized to spiroisoindolone γ-halomethylbutyrolactones, in the presence of NBS or NIS and K₂CO₃. The corresponding haloaspirobutyrolactones were isolated in high yields (57-95%).

INTRODUCTION

In the years since its discovery in the early 1900s, halolactonization has proven to be a versatile reaction in organic synthesis, allowing facile formation of small or medium ring size lactones from γ-unsaturated carboxylic acids, esters or amides. The general method used to halogenate organic substrates has been the use of N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS) or N-iodosuccinimide (NIS).

![Figure 1](image)

In connection with our current research interest in the preparation of nitrogenated and oxygenated compounds containing the isoindolinone moiety with promising pharmaceutical properties, we have...
recently reported a convenient access to various new spiroisoindole-γ-methylene butyrolactones of type II\textsuperscript{5a} and novel spiroisoindole γ-halobutyrolactones of type III\textsuperscript{5c} when γ-acetylenic acids I are reacted with a catalytic amount of Ag\textsubscript{2}CO\textsubscript{3} and NBS/NIS respectively (Figure 1).

Here, we would like to report the synthesis of new spiroisoindolone γ-halobutyrolactones through halolactonization of γ-ethylenic acids 4 with NBX (X: I, Br) as the key step to form the five membered ring. As far as we know, this is the first preparation of γ-(halomethyl)-γ-spirobutyrolactone derivatives containing the isoindole moiety starting from homophthalic acid.

**RESULTS AND DISCUSSION**

The required acids 4 were efficiently obtained, as outlined in Scheme 1, from phthalimides 2.\textsuperscript{5a-c,b,i} After alkylation of 2a-d with allyl bromide (K\textsubscript{2}CO\textsubscript{3}, CH\textsubscript{3}CN, reflux),\textsuperscript{5a-c} the resulting alkylated phthalimides esters 3a-d were converted to the γ-ethylenic carboxylic acids 4a-d in good yields (84-92%) as previously described by our group.\textsuperscript{5a-c}

![Scheme 1](image)

**Scheme 1.** Reagents and conditions: (i) K\textsubscript{2}CO\textsubscript{3}, allyl bromide, MeCN, reflux, 12 h; (ii) a. NaOH, EtOH/H\textsubscript{2}O, rt, 2 h; b. aqueous 1M HCl, 0 °C; (iii) K\textsubscript{2}CO\textsubscript{3}, NBS or NIS, CH\textsubscript{2}Cl\textsubscript{2}, -30 °C

With a large variety of ethylenic carboxylic acids 4a-d in hand, we then investigated the optimal conditions for the halocyclization. Since the diastereoselectivity in halolactonization reactions is significantly affected by the choice of solvent and temperature, the acid 4a chosen as a model was submitted to the halolactonization reaction with iodine (I\textsubscript{2}), N-iodosuccinimide (NIS) and N-bromosuccinimide (NBS) under different conditions (kinetic and thermodynamic controls) and the results are reported in Table 1.
Using standard conditions involving kinetic control, iodine in a mixture of Et₂O and H₂O in the presence of sat. aqueous NaHCO₃ at room temperature (entry 1), a mixture of syn and anti iodo-lactones 5a/b was isolated in 57% chemical yield, but in moderate ratio (70:30) in favor of the syn diastereomer 5a. A similar diastereoselectivity (74:26 entry 2) was observed when the reaction was performed at -30 °C. A prolonged reaction time (entry 3) did not improve the yield. A cleaner reaction occurred with NIS in CH₂Cl₂ (entry 4) at room temperature, to give the diastereomeric mixture of lactones 5a/b in 72% yield and 70:30 ratio. A better diastereoselectivity (82:18, entry 5) was observed when the reaction was performed at -30 °C. Under the same operating conditions and by replacing NIS by NBS (entry 6), acid 4a gave a mixture of bromo-lactones cis-9a and trans-9b in 70% yield, in a ratio of 90:10. A dramatic rate enhancement was observed when the reaction was carried out in the presence equimolar amount of K₂CO₃ (entries 7 and 8). Within 1 h the starting material was consumed to give the iodo-lactones 5a/b (entry 7) in 83% yield with an increase in the ratio cis:trans to 90:10. On bromocyclization, acid 4a gave only one diastereomer 9a (entry 8) in 77% yield. Single-crystal X-ray structure elucidation⁶ on the diastereomer 9a unambiguously established the relative configuration as “cis” and, hence, the relative stereochemistry at C-3, C-5 as 3R⁺, 5S⁺.
The reaction scope was probed by applying these optimal conditions (NXS/CH$_2$Cl$_2$/K$_2$CO$_3$, 2 h, -30 °C) to the other substrates 4b-d, which cyclized smoothly to give the corresponding γ-lactones 5-11 in good yields, with even higher selectivities in favor of the cis-lactones. Silica gel column chromatography was ultimately used to remove the succinimide, and the results are summarized in Table 2.

**Table 2. Halocyclization produced via Scheme 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>X$^+$</th>
<th>Product</th>
<th>Yield%</th>
<th>(a/b)dr$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>NIS</td>
<td>5a/5b</td>
<td>83</td>
<td>90/10</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>NIS</td>
<td>6a/6b</td>
<td>95</td>
<td>80/20</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>NIS</td>
<td>7a/7b</td>
<td>71</td>
<td>100/0</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>NIS</td>
<td>8a/8b</td>
<td>67</td>
<td>100/0</td>
</tr>
<tr>
<td>5</td>
<td>4a</td>
<td>NBS</td>
<td>9a/9b</td>
<td>77</td>
<td>100/0</td>
</tr>
<tr>
<td>6</td>
<td>4b</td>
<td>NBS</td>
<td>10a/10b</td>
<td>60</td>
<td>100/0</td>
</tr>
<tr>
<td>7</td>
<td>4c</td>
<td>NBS</td>
<td>11a/11b</td>
<td>73</td>
<td>75/25</td>
</tr>
<tr>
<td>8</td>
<td>4d</td>
<td>NBS</td>
<td>12a/12b</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Diastereomeric ratios were determined on the crude mixture by integration of non-overlapping signals in the $^1$H NMR spectra.

It is noteworthy that, although a variety of bases (NaHCO$_3$, benzyl amine, pyrrolidine), solvent (CH$_2$Cl$_2$, THF, DMF, MeCN, THF/H$_2$O, MeCN/H$_2$O) and NBS ratios were examined, the formation of spirolactones 12a,b from 4d was not accomplished but complete decomposition occurred.

It should be noted that when conducted under Bartlett’s “thermodynamic” conditions (iodine in acetonitrile, entries 9 and 10),$^7$ cis to trans equilibration does not occur. Under these conditions, acid 4a gave a mixture of cis and trans diastereoisomers, the cis diastereoisomer being again the major product. It should also be noted that the iodo lactones 7a and 8a do not interconvert when resubjected to the reaction conditions.

The assignement of all structures reported herein was made on the basis of their X-ray (9a), IR, and NMR spectroscopies ($^1$H, $^{13}$C and DEPT programs). In the case of solids, their elemental analyses were also performed. $^1$H NMR Spectra of 5-11 showed the methylene group of the –N-CH$_2$– moiety as an AB system due to the diastereotopic effect with a coupling constant of $J = 15$-16 Hz characteristic of gem protons. Likewise, the $^{13}$C NMR spectra of the spiro products 5-11 reveled the presence of an additional
secondary (δ ≈ 75 ppm) and primary (δ ≈ 30 ppm for bromine products and δ ≈ 8 ppm for iodide
products) carbons in the aliphatic region as the consequence of the cyclization process.

The formation of two diastereomers of spiropentylactone derivatives could be visualized to proceed
through intermediates A and B (Scheme 3) formed by the addition of iodine (bromine) on either of the
two faces of double bond. Iodonium (bromonium) ion intermediate A would result in the formation of
halolactone product with C-N and CH₂I groups placed syn to each other, while halonium ion intermediate
B would result in formation of product with C-N and CH₂I groups on the opposite faces of furane ring.

**Scheme 3.** Possible mechanisms for the formation of the cis and trans lactones

The present iodine (bromine) mediated intramolecular cyclizations of acids 4 result in formation of the
products with C-N and CH₂I moieties present on same side either exclusively or predominantly and
involve the preferential participation of intermediate A. This preference arises probably due to
stabilization halonium ion intermediate by its electrostatic interactions with free pair of nitrogen in
intermediate A.

**Synthesis of chiral spiropentylactone derivatives**

Having established the facility of acids 4a-d to provide novel interesting spirolactones in good yields, we
extended the halolactonization strategy to the synthesis of chiral spirolahalobutylactones. S-α-Methylbenzylamine was chosen as example for this study.

**Scheme 4.** Reagents and conditions: (i) S-α-methylbenzylamine; (ii) K₂CO₃, allyl bromide, MeCN,
reflux, 12 h; (iii) a. NaOH, EtOH/H₂O, rt, 2 h; b. aqueous 1M HCl, 0 °C; (iv) K₂CO₃, NBS or NIS, CH₂Cl₂, -30 °C
The required acids 15a,b were efficiently obtained as outlined in Scheme 3, from the bromide 1 in three steps, following our reported procedure.1 Halocyclization of carboxylic acids 15a,b with NBS/NIS in the presence of K2CO3, gave a 4:1 mixture of two diastereomers 16a/16b (X = Br) with NBS and a 3:1 mixture of 17a/17b (X = I) with NIS in yields of 78% and 72%, respectively. It is noteworthy that, even on repeated chromatography and crystallization, it was not possible to isolate pure samples of the minor diastereomers 16b and 17b just the major diastereomers 16a and 17a could be isolated. Importantly, in all cases, the reaction seems to be highly regioselective because during the cyclization process only the exo-dig products were obtained.

CONCLUSION
In conclusion, a highly efficient halocyclization reaction of γ-ethylenic carboxylic acids was developed in the isoindolone series by using X+ (NBS or NIS) and K2CO3. The carboxylic substrates were very easily prepared from simple precursors and the halogen mediated intramolecular cyclization of 4 and 15 selectively afforded the spirobutyrolactones with C-N and CH2-X moieties placed syn to each other as the major or the only product. We now envisage applying this methodology to the synthesis of analogous natural products.

EXPERIMENTAL
General
All melting points were measured on a Boetius micro hotstage and are uncorrected.1H and 13C NMR spectra were recorded respectively at 200 (300) and 50 (75) MHz on a Brucker AC-200 and Brucker AVANCE 300 spectrometers. The infrared spectra were recorded on a Perkin-Elmer FT-IR paragon 1000 spectrometer. Thin-layer chromatography (TLC) was performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230-400 mesh) was used for flash chromatography separations. Some reactions were performed under an inert atmosphere. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt St Aignan, France.

Alkylation with allyl bromide.
Products 3 are prepared according to our previous work.5

1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1H-isooindole-1-carboxylic acid ethyl ester (3a). Yellow liquid; yield: 90%; IR (ν, cm−1 CHCl3) 1688, 1731; 1H NMR (200 MHz, CDCl3, 25 °C) δ 0.84 (t, J = 7.0 Hz, 3H), 2.93 (dd, J = 15.6, J = 6.3 Hz, 1H) 3.09 (dd, J = 15.6, J = 6.3 Hz, 1H), 3.49-3.55 (m, 1H), 3.80-3.87 (m, 1H), 4.57 (d, J = 15.5 Hz, 1H), 4.68-4.90 (m, 4H), 7.15-7.51 (m, 8H), 7.81 (d, J = 8.6 Hz, 1H).
1-Allyl-2-(4-methoxy-benzyl)-3-oxo-2,3-dihydro-1H-isooindole-1-carboxylic acid ethyl ester (3b). Yellow liquid; yield: 68%; IR (ν, cm\(^{-1}\)) CHCl\(_3\) 1690, 1732; \(^1\)H NMR (200 MHz, CDCl\(_3\), 25 °C) δ 0.93 (t, J = 7.0 Hz, 3H), 2.99 (dd, J = 14.8, J = 6.3 Hz, 1H) 3.11 (dd, J = 14.8, J = 6.3 Hz, 1H), 3.62-3.70 (m, 1H), 3.71-3.79 (s, 3H), 3.87 (d, J = 14.8 Hz, 1H), 4.59 (d, J = 14.8 Hz, 1H), 4.70 (d, J = 14.8 Hz, 1H), 4.71-4.96 (m, 3H), 6.81 (d, J = 8.6 Hz, 2H), 7.30-7.39 (m, 3H), 7.43-7.58 (m, 2H), 7.84-7.88 (m, 1H).

1-Allyl-3-oxo-2-thiophen-2-ylmethyl-2,3-dihydro-1H-isooindole-1-carboxylic acid ethyl ester (3c). Yellow liquid; yield: 96%; IR (ν, cm\(^{-1}\)) CHCl\(_3\) 1691, 1732; \(^1\)H NMR (200 MHz, CDCl\(_3\), 25 °C) δ 0.74 (t, J = 7.1 Hz, 3H), 2.79 (dd, J = 14.9, J = 6.2 Hz, 1H), 2.91 (dd, J = 14.9, J = 6.2 Hz, 1H), 3.51-3.61 (m, 1H), 3.70-3.77 (m, 1H), 4.46-4.71 (m, 5H), 6.62-6.66 (m, 1H), 6.78-6.80 (m, 1H), 6.92-6.95 (m, 1H), 7.15-7.25 (m, 2H), 7.27-7.33 (m, 1H), 7.58-7.62 (m, 1H).

1-Allyl-2-furan-2-ylmethyl-3-oxo-2,3-dihydro-1H-isooindole-1-carboxylic acid ethyl ester (3d). Yellow liquid; yield: 82%; IR (ν, cm\(^{-1}\)) CHCl\(_3\) 1694, 1731; \(^1\)H NMR (200 MHz, CDCl\(_3\), 25 °C) δ 1.00 (t, J = 7.0 Hz, 3H), 2.98 (dd, J = 14.8, J = 4.7 Hz, 1H), 3.14 (dd, J = 14.8, J = 4.7 Hz, 1H), 3.73-3.78 (m, 2H), 4.71 (d, J = 15.6 Hz, 2H), 4.73-4.88 (m, 3H), 6.23-6.32 (m, 2H), 7.28-7.29 (m, 1H), 7.37-7.54 (m, 3H), 7.77-7.82 (m, 1H).

Preparation of acids 4 and 15. Products 4 and 15 are prepared according to our previous work.\(^5\)

1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1H-isooindole-1-carboxylic acid (4a). White solid; yield: 92%; mp 123-125 °C; IR (ν, cm\(^{-1}\)) CHCl\(_3\) 1697, 1776; \(^1\)H NMR (200 MHz, CDCl\(_3\), 25 °C) δ 2.88 (dd, J = 14.8, J = 6.2 Hz, 1H) 3.05 (dd, J = 14.8, J = 6.2 Hz, 1H), 4.50 (d, J = 15.6 Hz, 1H), 4.62-4.87 (m, 3H), 4.95 (d, J = 15.6 Hz, 1H), 6.57-6.89 (s, 1H), 7.12-7.58 (m, 8H), 7.83 (d, J = 8.0 Hz, 1H).

1-Allyl-2-(4-methoxy-benzyl)-3-oxo-2,3-dihydro-1H-isooindole-1-carboxylic acid (4b). White solid; yield: 85%; mp 120-122 °C; IR (ν, cm\(^{-1}\)) CHCl\(_3\) 1693, 1714; \(^1\)H NMR (200 MHz, CDCl\(_3\), 25 °C) δ 2.90 (dd, J = 14.8, J = 4.7 Hz, 1H), 3.14 (dd, J = 14.8, J = 4.7 Hz, 1H), 3.71-3.79 (s, 3H), 4.59-4.76 (m, 3H), 4.84 (d, J = 15.6 Hz, 1H), 6.75 (d, J = 8.6 Hz, 2H), 7.25-7.34 (m, 2H), 7.40-7.57 (m, 3H), 7.76-7.82 (m, 1H).

1-Allyl-3-oxo-2-thiophen-2-ylmethyl-2,3-dihydro-1H-isooindole-1-carboxylic acid (4 c). White solid; yield: 85%; mp 120-122 °C; IR (ν, cm\(^{-1}\)) CHCl\(_3\) 1694, 1726; \(^1\)H NMR (300 MHz, CDCl\(_3\), 25 °C) δ 3.03 (dd, J = 14.9, J = 6.2 Hz, 1H) 3.06 (dd, J = 14.9, J = 6.2 Hz, 1H), 3.71 (s, 3H), 4.50 (d, J = 15.6 Hz, 1H), 4.59-4.76 (m, 3H), 4.84 (d, J = 15.6 Hz, 1H), 6.75 (d, J = 8.6 Hz, 2H), 7.25-7.34 (m, 2H), 7.40-7.57 (m, 3H), 7.76-7.82 (m, 1H).

1-Allyl-2-furan-2-ylmethyl-3-oxo-2,3-dihydro-1H-isooindole-1-carboxylic acid (4d). White solid; yield: 74%; mp 136-138 °C; IR (ν, cm\(^{-1}\)) CHCl\(_3\) 1694, 1725; \(^1\)H NMR (200 MHz, CDCl\(_3\), 25 °C) δ 3.03 (dd, J = 14.7, J = 4.7 Hz, 1H), 3.17 (dd, J = 14.7, J = 4.7 Hz, 1H), 4.70 (d, J = 16.4 Hz, 1H), 4.77-4.93
Typical procedure of the spirohalolactonization reaction.

A mixture of ethylenic acid 4 (1 mmole), K$_2$CO$_3$ (1.1 equiv) and NBS or NIS (1.2 equiv) in degassed CH$_2$Cl$_2$ (5 mL) was stirred under argon atmosphere at -30 °C. After the completion of the reaction indicated by TLC analysis, solvent was evaporated under reduced pressure and the crude mixture was purified by silica gel flash chromatography (cyclohexane/EtOAc, 60/40) to give the corresponding lactones 5-11, 16 or 17.

5-(Iodomethyl)-2'-benzyl-4,5-dihydrospiro[furan-1',3-isoinindol-3'-one]-2-one (5a/b). White solid; yield: 83%; mp 187-189 °C; IR (υ, cm$^{-1}$, CHCl$_3$) 1704, 1788; dr: 90/10

Maj (5a): $^1$H NMR (300 MHz, CDCl$_3$, 25 °C) δ 2.30 (dd, $J = 14.0, J = 10.1$ Hz, 1H), 2.45 (dd, $J = 14.0, J = 6.2$ Hz, 1H), 3.25-3.47 (m, 2H), 4.15 (d, $J = 15.6$ Hz, 1H), 4.69-4.83 (m, 1H), 5.41 (d, $J = 15.6$ Hz, 1H), 7.28-7.63 (m, 7H), 7.52-7.63 (m,2H), 7.92-7.96 (m, 1H), $^{13}$C NMR (50 MHz, CDCl$_3$, 25 °C) δ 7.1 (CH$_2$), 37.5 (CH$_2$), 44.5 (CH$_2$), 70.6 (Cq), 75.0 (CH), 120.4 (CH), 124.7 (CH), 127.6 (2 CH), 127.7 (CH), 128.8 (2 CH), 129.9 (CH), 130.4 (Cq), 132.8 (CH), 136.9 (Cq), 143.9 (Cq), 168.7 (CO), 171.6 (CO).

Min (5b): $^1$H NMR (300 MHz, CDCl$_3$, 25 °C) δ 2.51 (d, $J = 6.2$ Hz, 1H), 3.25-3.47 (m, 2H), 4.30 (d, $J = 15.6$ Hz, 1H), 4.69-4.83 (m, 1H), 5.25  (d, $J = 15.6$ Hz, 1H), 7.28 -7.63 (m, 7H), 7.52-7.63 (m,2H), 7.92-7.96 (m, 1H), $^{13}$C NMR (50 MHz, CDCl$_3$, 25 °C) δ 8.4 (CH$_2$), 38.9 (CH$_2$), 44.5 (CH$_2$), 69.5 (Cq), 75.0 (CH), 12 1.7 (CH), 124.2 (CH), 127.5 (2 CH), 128.1 (CH), 128.9 (2 CH), 129.7 (CH), 130.9 (Cq), 132.8 (CH), 136.2 (Cq), 144.6 (Cq), 168.5 (CO), 172.6 (CO). Anal. Calcd for C$_{19}$H$_{16}$INO$_3$ (433.25) : C, 52.67; H, 3.72; N, 3.23. Found: C, 52.72; H, 3.75; N, 3.18.

5-(Iodomethyl)-2'-(4-methoxy-benzyl)-4,5-dihydrospiro[furan-1',3-isoinindol-3'-one]-2-one (6a/b). White solid; yield: 95%; mp 131-133 °C; IR (υ, cm$^{-1}$, CHCl$_3$) 1702, 1789; dr: 80/20

Maj (6a) : $^1$H NMR (300 MHz, CDCl$_3$, 25 °C) δ 2.36 (dd, $J = 13.6, J = 10.1$ Hz, 1H), 2.44 (dd, $J = 13.6, J = 6.4$ Hz, 1H), 3.32 (dd, $J = 10.9, J = 6.4$ Hz, 1H), 3.39 (dd, $J = 10.9, J = 4.1$ Hz, 1H), 3.78 (s, 3H), 4.15 (d, $J = 15.8$ Hz, 1H), 4.73-4.83 (m, 1H), 5.33 (d, $J = 15.8$ Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 2H), 7.23-7.25 (m,2H), 7.38-7.41 (m,1H), 7.53-7.62 (m,2H), 7.92-7.95 (m,1H), $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C) δ 7.0 (CH$_2$), 37.5(CH$_2$), 44.0 (CH$_2$), 55.2 (CH$_3$), 70.6 (Cq), 75.0 (CH), 114.1 (2CH), 120.3 (CH), 124.6 (CH), 129.1 (2CH), 129.9 (CH), 130.5 (Cq), 132.8 (CH), 143.9 (Cq), 159.2 (Cq), 168.6 (CO), 171.6 (CO).

Min (6b): $^1$H NMR (300 MHz, CDCl$_3$, 25 °C) δ 2.53 (d, $J = 7.6$ Hz, 2H), 3.42 (dd, $J = 10.9, J = 4.1$ Hz, 1H), 3.47 (dd, $J = 10.9, J = 6.4$ Hz, 1H), 3.78 (s, 3H), 4.30 (d, $J = 15.8$ Hz, 1H), 4.73-4.83 (m, 1H), 5.11 (d, $J = 15.8$ Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 2H), 7.23-7.25 (m,2H), 7.38-7.41 (m,1H), 7.53-7.62 (m,2H), 7.92-7.95 (m,1H), $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C) δ 8.4 (CH$_2$), 39.0 (CH$_2$), 44.0 (CH$_2$), 55.2 (CH$_3$),
69.4 (Cq), 75.0 (CH), 114.2 (2CH), 121.7 (CH), 124.2 (CH), 128.9 (2CH), 129.8 (CH), 131.0 (Cq), 132.9 (CH), 144.7 (Cq), 159.4 (Cq), 168.4 (CO), 172.6 (CO). Anal. Calcd for C_{20}H_{18}INO_{4}(463.28): C, 51.85; H, 3.92; N, 3.02. Found: C, 51.82; H, 3.95; N, 3.08.

5-(Iodomethyl)-2'-thiophen-2-ylmethyl-4,5-dihydrospiro[furan-1',3-isointol-3'-one]-2-one (7a).
White solid; yield: 71%; mp 196-198 °C; IR (v, cm⁻¹, CHCl₃) 1700, 1789; ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 2.54 (d, J = 6.8 Hz, 2H), 3.40 (dd, J = 10.2, J = 6.8 Hz, 1H), 3.48 (dd, J = 10.2, J = 3.8 Hz, 1H), 4.47 (d, J = 16.2 Hz, 1H), 4.74-4.86 (m, 1H); 6.95-6.98 (m, 1H), 7.10-7.12 (m, 1H), 7.40-7.42 (m, 1H), 7.54-7.63 (m, 3H), 7.92-7.96 (m, 1H), 13C NMR (75 MHz, CDCl₃, 25 °C) δ 7.2 (CH₂), 37.7 (CH₂), 39.6 (CH₂), 70.5 (Cq), 75.0 (CH), 120.4 (CH), 124.8 (CH), 126.0 (CH), 126.9 (CH), 127.0 (CH), 130.0 (CH), 130.3 (Cq), 132.9 (CH), 139.6 (Cq), 144.0 (Cq), 168.3 (CO), 171.5 (CO). Anal. Calcd for C_{17}H_{14}INO_{3}(439.27): C, 46.48; H, 3.21; N, 3.19. Found: C, 46.42; H, 3.25; N, 3.18.

5-(Iodomethyl)-2'-furan-2-ylmethyl-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (8a).
White solid; yield: 67%; mp 152-154 °C; IR (v, cm⁻¹, CHCl₃) 1705, 1787; ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 2.44 (dd, J = 14.0, J = 10.1 Hz, 1H), 2.63 (dd, J = 14.0, J = 6.0 Hz, 1H), 3.32 (dd, J = 10.1, J = 7.8 Hz, 1H), 3.51 (dd, J = 11.0, J = 3.9 Hz, 1H), 4.42 (d, J = 16.4 Hz, 1H), 4.82-4.96 (m, 1H); 6.35-6.38 (m, 2H), 7.36-7.38 (m, 1H), 7.39-7.41 (m, 1H), 7.53-7.70 (m, 2H), 7.86-7.89 (m, 1H), 13C NMR (75 MHz, CDCl₃, 25 °C) δ 8.2 (CH₂), 39.1 (2CH₂), 70.1 (Cq), 76.4 (CH), 109.6 (CH), 111.0 (CH), 120.3 (CH), 124.6 (CH), 129.8 (CH), 129.9 (Cq), 133.0 (CH), 142.5 (CH), 144.1 (Cq), 149.3 (Cq), 168.2 (CO), 171.5 (CO). Anal. Calcd for C_{19}H_{14}BrNO_{3}(423.21): C, 48.25; H, 3.33; N, 3.31. Found: C, 48.20; H, 3.35; N, 3.38.

5-(Bromomethyl)-2'-benzyl-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (9a).
White solid; yield: 77%; mp 199-201 °C; IR (v, cm⁻¹, CHCl₃) 1705, 1794; ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 2.37 (dd, J = 14.0, J = 6.0 Hz, 1H), 2.51 (dd, J = 14.0, J = 10.1 Hz, 1H), 3.49 (dd, J = 10.1, J = 3.9 Hz, 1H), 3.58 (dd, J = 11.0, J = 4.7 Hz, 1H), 4.12 (d, J = 16.4 Hz, 1H), 4.95-5.08 (m, 1H), 5.34 (d, J = 3.9 Hz, 1H), 7.27-7.43 (m, 6H), 7.52-7.63 (m, 2H), 7.92-7.96 (m, 1H), 13C NMR (75 MHz, CDCl₃, 25 °C) δ 33.5 (CH₂), 35.2 (CH₂), 44.5 (CH₂), 70.2 (Cq), 74.6 (CH), 120.3 (CH), 124.7 (CH), 127.6 (2CH), 127.7 (CH), 128.8 (2CH), 130.0 (CH), 130.5 (Cq), 132.8 (CH), 137.0 (Cq), 143.9 (Cq), 168.7 (CO), 171.4 (CO). Anal. Calcd for C_{19}H_{16}BrNO_{3}(386.25): C, 59.08; H, 4.18; N, 3.63. Found: C, 59.12; H, 4.15; N, 3.68.

5-(Bromomethyl)-2'-4-methoxy-benzyl-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (10a).
White solid; yield: 60%; mp 118-120 °C; IR (v, cm⁻¹, CHCl₃) 1704, 1794; ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 2.38 (dd, J = 14.2, J = 6.2 Hz, 1H), 2.58 (dd, J = 14.2, J = 10.2 Hz, 1H), 3.53 (dd, J = 11.0, J = 3.9 Hz, 1H), 3.62 (dd, J = 11.0, J = 5.5 Hz, 1H), 3.79 (s, 3H), 4.12 (d, J = 15.7 Hz, 1H), 4.98-5.11 (m, 1H), 5.34 (d, J = 15.7 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.27-7.31 (m, 2H), 7.36-7.45 (m, 1H), 7.53-7.64 (m,
5-(Bromomethyl)-2'-thiophen-2-ylmethyl-4,5-dihydropyrano[1',3'-isoindol-3'-one]-2-one (11a/b). White solid; yield: 73%; mp 181-183°C; IR (ν, cm⁻¹, CHCl₃) 1710, 1795; dr: 75/25

**Maj (11a):** ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 2.49 (dd, J = 13.7, J = 6.4 Hz, 1H), 2.74 (dd, J = 13.7, J = 9.8 Hz, 1H), 3.61 (dd, J = 11.3, J = 3.9 Hz, 1H), 3.69 (dd, J = 11.3, J = 5.1 Hz, 1H), 4.44 (d, J = 16.2 Hz, 1H), 5.03-5.12 (m, 1H), 5.45 (d, J = 16.2 Hz, 1H), 6.94-6.97 (m, 1H), 7.08-7.10 (m, 1H), 7.40-7.42 (m, 1H), 7.55 -7.61 (m, 3H), 7.92 -7.95 (m, 1H), ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ 33.6 (CH₂), 35.1 (CH₂), 43.9 (CH₂), 55.2 (CH₃), 70.2 (Cq), 74.6 (CH), 114.1 (2CH), 120.3 (CH), 124.6 (CH), 128.1 (Cq), 129.0 (2CH), 129.9 (CH), 130.5 (Cq), 132.8 (CH), 143.9 (Cq), 159.1 (Cq), 167.8 (CO), 171.5 (CO). Anal. Calcd for C₂₀H₁₈BrNO₄ (416.27): C, 57.71; H, 4.36; N, 3.36. Found: C, 57.72; H, 4.35; N, 3.38.

Min (11b): ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 2.39 (dd, J = 14.2, J = 10.2 Hz, 1H), 2.66 (dd, J = 14.2, J = 5.1 Hz, 1H), 3.79 (dd, J = 11.3, J = 4.9 Hz, 1H), 3.87 (dd, J = 11.3, J = 3.7 Hz, 1H), 4.54 (d, J = 15.4 Hz, 1H), 4.73-4.81 (m, 1H), 5.33 (d, J = 15.4 Hz, 1H), 6.94-6.97 (m, 1H), 7.08-7.10 (m, 1H), 7.40-7.42 (m, 1H), 7.55-7.61 (m, 3H), 7.92-7.95 (m, 1H), ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ 33.7 (CH₂), 35.3 (CH₂), 39.5 (CH₂), 70.0 (Cq), 74.7 (CH), 120.3 (CH), 124.8 (CH), 126.0 (CH), 126.9 (2CH), 130.0 (CH), 130.3 (Cq), 132.9 (CH), 140.0 (Cq), 144.0 (Cq), 168.3 (CO), 171.4 (CO). Anal. Calcd for C₁₉H₁₄BrNO₃ (392.27): C, 52.05; H, 3.60; N, 3.57. Found: C, 52.12; H, 3.65; N, 3.68.

5-(Bromomethyl)-2'-((S)-1-phenylethyl)-4,5-dihydropyrano[1',3'-isoindol-3'-one]-2-one (16a/b): Yield: 68%; dr = 80/20

**Maj (16a):** White solid; mp 156-158°C; IR (ν, cm⁻¹, CHCl₃) 1705, 1795; ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 1.25 (d, J = 7.2 Hz, 3H), 1.55 (dd, J = 14.7, J = 5.9 Hz, 1H) 1.58 (dd, J = 14.7, J = 10.1 Hz, 1H), 1.91 (dd, J = 11.0, J = 3.9 Hz, 1H) 2.00 (dd, J = 11.0, J = 5.3 Hz, 1H), 5.52-5.60 (m, 1H), 5.96 (q, J = 7.3, 1H), 7.16-7.25 (m, 1H), 7.27-7.34 (m, 2H), 7.47-7.54 (m, 2H), 7.55-7.51 (m, 1H), 7.65-7.72 (m, 1H), 7.78-7.82 (m, 1H), 8.73-7.93 (m, 1H), ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ 17.5 (CH₃), 30.9 (CH₂), 37.5 (CH₂), 57.7 (CH), 75.4 (Cq), 78.4 (CH), 123.4 (CH), 127.7 (CH), 128.1 (2CH), 128.4 (2CH), 130.3 (CH), 131.4 (CH), 132.7 (CH), 140.5 (Cq), 143.0 (Cq), 148.8 (Cq), 168.3 (CO), 171.4 (CO).

Min (16b): ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 1.25 (d, J = 7.2 Hz, 3H), 1.44 (dd, J = 14.9, J = 10.3 Hz, 1H) 1.49 (dd, J = 14.9, J = 6.2 Hz, 1H), 1.91 (dd, J = 11.0, J = 5.5 Hz, 1H) 2.00 (dd, J = 11.0, J = 3.9 Hz, 1H), 5.52-5.60 (m, 1H), 5.86 (q, J = 7.3, 1H), 7.16-7.25 (m, 1H), 7.27-7.34 (m, 2H), 7.47-7.54 (m, 2H), 7.55-7.51 (m, 1H), 7.65-7.72 (m, 1H), 7.78-7.82 (m, 1H), 7.83-7.93 (m, 1H), ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ 17.1 (CH₃), 29.6 (CH₂), 37.6 (CH₂), 54.1 (CH), 75.3 (Cq), 79.6 (CH), 123.6 (CH), 127.6 (CH), 128.0 (2CH), 128.3 (2CH), 129.4 (CH), 131.9 (CH), 133.2 (CH), 140.7 (Cq), 142.8 (Cq), 148.9.
(Cq), 168.2 (CO), 169.8 (CO). Anal. Calcd for C_{20}H_{18}BrNO_{3} (400.28): C, 60.01; H, 4.53; N, 3.50. Found: C, 60.02; H, 4.55; N, 3.38.

5-(Iodomethyl)-2′-((S)-1-phenylethyl)-4,5-dihydrospiro[furan-1’,3'-isoindol-3’-one]-2-one (17a/b): Yield: 57%; dr = 75/25

**Maj (17a):** White solid; mp 138-140 °C; IR (ν, cm⁻¹ CHCl₃) 1704, 1785; ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 1.23 (d, J = 7.2 Hz, 3H), 1.41 (dd, J = 14.8, J = 10.0 Hz, 1H) 1.56 (dd, J = 14.8, J = 4.3 Hz, 1H), 4.00-4.19 (m, 1H), 5.85 (q, J = 7.3, 1H), 7.37-7.53 (m, 4H), 7.54 -7.70 (m, 2H), 7.72 -7.90 (m, 2H), 7.91 -7.96 (m, 1H), 13C NMR (75 MHz, CDCl₃, 25 °C) δ 7.9 (CH₂), 17.0 (CH₃), 30.9 (CH₂), 60.4 (CH), 74.0 (Cq), 76.2 (CH), 123.5 (CH), 124.7 (CH), 127.4 (2CH), 128.2 (2CH), 128.8 (CH), 130.2 (Cq), 131.8 (CH), 133.9 (CH), 140.5 (Cq), 147.2 (Cq), 167.2 (CO), 176.5 (CO).

**Min (17b):** ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 1.20 (d, J = 7.2 Hz, 3H), 1.39 (dd, J = 14.8, J = 6.1 Hz, 1H), 1.53 (dd, J = 14.8, J = 10.1 Hz, 1H), 1.95 (dd, J = 11.4, J = 3.9 Hz, 1H) 2.11 (dd, J = 11.4, J = 5.7 Hz, 1H), 3.59-3.84 (m, 1H), 4.64 (q, J = 7.3, 1H), 7.37-7.53 (m, 4H), 7.54-7.70 (m, 2H), 7.72-7.90 (m, 2H), 7.91-7.96 (m, 1H), 13C NMR (75 MHz, CDCl₃, 25 °C) δ 9.3 (CH₂), 14.2 (CH₃), 29.7 (CH₂), 57.9 (CH), 74.5 (Cq), 76.1 (CH), 123.1 (CH), 126.1 (CH), 127.9 (2CH), 128.4 (CH), 128.7 (2CH), 129.7 (Cq), 132.5 (CH), 133.6 (CH), 136.1 (Cq), 150.8 (Cq), 167.7 (CO), 177.0 (CO). Anal. Calcd for C_{20}H_{18}INO₃ (447.28): C, 53.71; H, 4.06; N, 3.13. Found: C, 53.82; H, 4.05; N, 3.18.

REFERENCES AND NOTES


6. Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 716551 for product 9a. Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk.