HETEROCYCLES, Vol. 78, No. 11, 2009, pp. 2787 - 2798. © The Japan Institute of Heterocyclic Chemistry
Received, 1st July, 2009, Accepted, 3rd September, 2009, Published online, 7th September, 2009
DOI: 10.3987/COM-09-11787

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

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Abstract – γ-Ethylenic carboxylic acids are cyclized to spiroisoindolone γ-halomethylbutyrolactones, in the presence of NBS or NIS and K_2CO_3. 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 versataile reaction in organic synthesis, allowing facile formation of small or medium ring size lactones[1] from γ-unsaturated carboxylic acids,[2] esters[3] or amides.[4] The general method used to halogenate organic substrates has been the use of *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS) or *N*-iodosuccinimide (NIS).

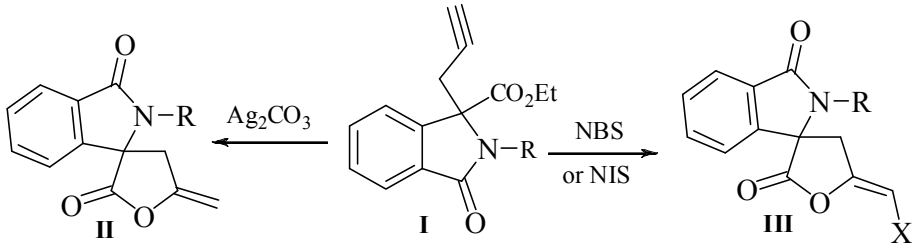


Figure 1

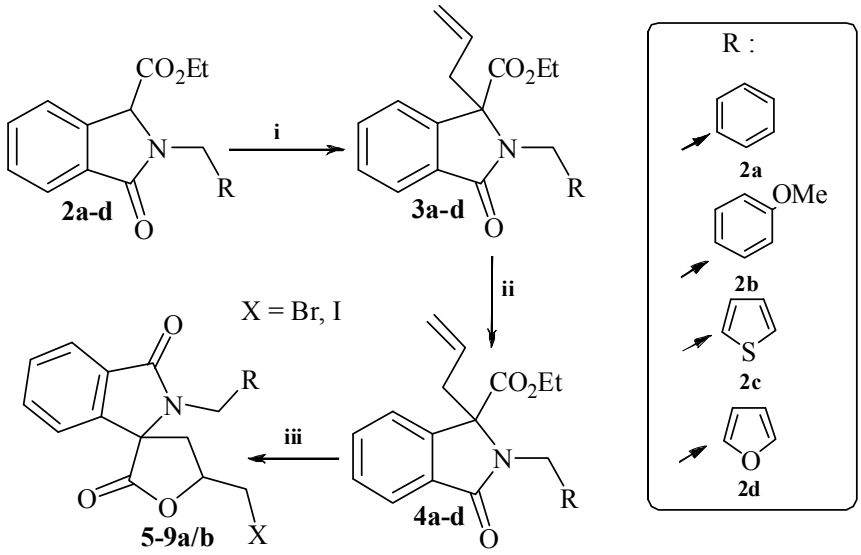
In connection with our current research interest in the preparation of nitrogenated and oxygenated compounds containing the isoindolinone moiety with promising pharmaceutical properties,[5] we have

recently reported a convenient access to various new spiroisoindole-γ-methylene butyrolactones of type **II**[5a] and novel spiroisoindole γ-halobutyrolactones of type **III**[5c] when γ-acetylenic acids **I** are reacted with a catalytic amount of Ag_2CO_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.

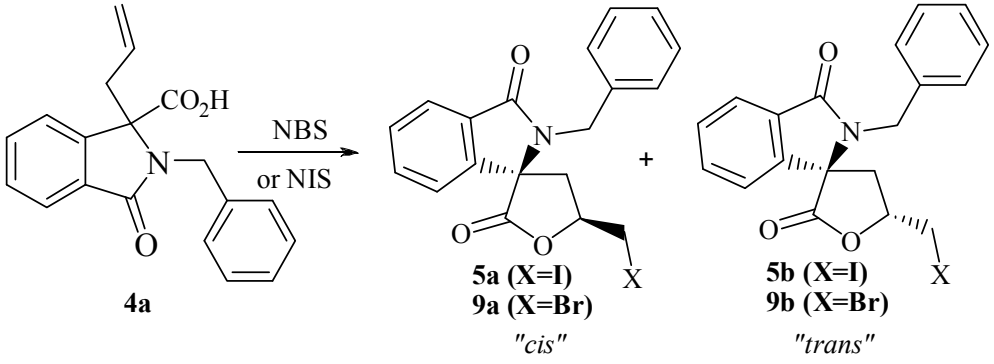
RESULTS AND DISCUSSION

The required acids **4** were efficiently obtained, as outlined in Scheme 1, from phthalimidines **2**.[5a-c,h,i] After alkylation of **2a-d** with allyl bromide (K_2CO_3, CH_3CN, reflux),[5a-c] the resulting alkylated phthalimidines esters **3a-d** were converted to the γ-ethylenic carboxylic acids **4a-d** in good yields (84-92%) as previously described by our group. [5a-c]



Scheme 1. Reagents and conditions: (i) K_2CO_3, allyl bromide, MeCN, reflux, 12 h; (ii) a. NaOH, EtOH/H_2O, rt, 2 h; b. aqueous 1M HCl, 0 °C; (iii) K_2CO_3, NBS or NIS, CH_2Cl_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_2), *N*-iodosuccinimide (NIS) and *N*-bromosuccinimide (NBS) under different conditions (kinetic and thermodynamic controls) and the results are reported in Table 1.

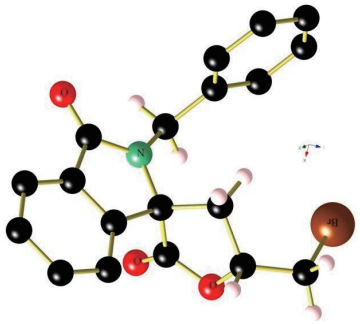


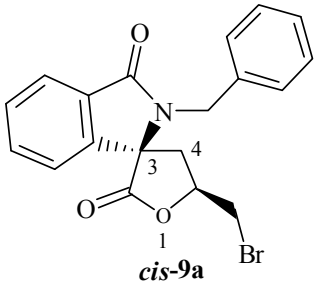
Scheme 2. Reagents and conditions: K_2CO_3, NBS or NIS, CH_2Cl_2, -30 °C

Table 1. Halocyclization of acid **4a**

Entry	Conditions	T°C	Time h	Yield%	**a/b**
1	I_2/Et_2O-aq.$NaHCO_3$	rt	3	57	70:30
2	I_2/Et_2O- aq.$NaHCO_3$	-30	3	64	74:26
3	I_2/Et_2O- aq.$NaHCO_3$	-30	6	60	74:26
4	NIS/CH_2Cl_2	rt	3	72	70/30
5	NIS-CH_2Cl_2	-30	3	76	82/18
6	NBS-CH_2Cl_2	-30	3	70	90/10
7	NIS/CH_2Cl_2/K_2CO_3	-30	1	83	90/10
8	NBS/CH_2Cl_2/K_2CO_3	-30	1	77	100/0
9	I_2/ MeCN	rt	3	60	70/30
10	I_2/ MeCN	-30	3	62	74/26

Using standard conditions involving kinetic control, iodine in a mixture of Et_2O and H_2O in the presence of sat. aqueous $NaHCO_3$ 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 CH_2Cl_2 (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 K_2CO_3 (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 elucidation[6] on the diastereomer **9a** unambiguously established the relative configuration as *"cis"* and, hence, the relative stereochemistry at C-3, C-5 as *3R*, 5S**.





***cis*-9a**

Figure 2. ORTEP drawing of structure **9a**

The reaction scope was probed by applying these optimal conditions (NXS/CH_2Cl_2/K_2CO_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

Entry	Substrate	X^+	Product	Yield%	(**a**/**b**)dr[a]
1	**4a**	NIS	**5a/5b**	83	90/10
2	**4b**	NIS	**6a/6b**	95	80/20
3	**4c**	NIS	**7a/7b**	71	100/0
4	**4d**	NIS	**8a/8b**	67	100/0
5	**4a**	NBS	**9a/9b**	77	100/0
6	**4b**	NBS	**10a/10b**	60	100/0
7	**4c**	NBS	**11a/11b**	73	75/25
8	**4d**	NBS	**12a/12b**	0	-

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

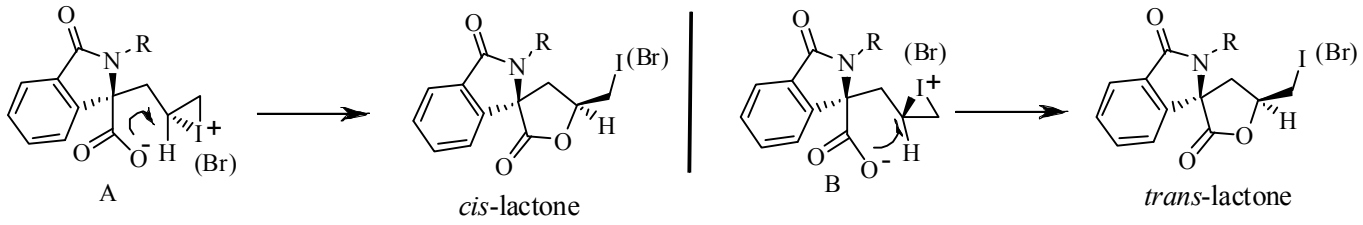
It is noteworthy that, although a variety of bases ($NaHCO_3$, benzyl amine, pyrrolidine), solvent (CH_2Cl_2, THF, DMF, MeCN, THF/H_2O, MeCN/H_2O) and NBS ratios were examined, the formation of spirolactones **12a,b** from **4d** was not accomplished but complete decomposition occurred.

It should be noted that when conducted under Bartlett's "thermodynamic" conditions (iodine in acetonitrile, entries 9 and 10),[8] *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 spirobutyrolactone 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 CH_2I groups placed *syn* to each other, while halonium ion intermediate **B** would result in formation of product with C-N and CH_2I groups on the opposite faces of furane ring.

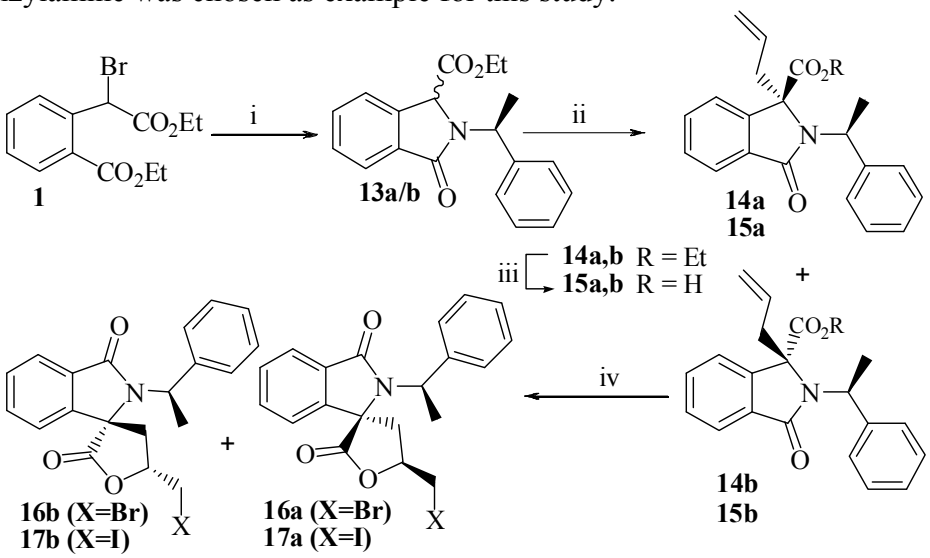


Scheme 3. Possible mechanisms for the formation of the *cis* and *trans* lactones

The present iodine (bromine) mediated intramolecular cyclizations of acids **4** result in formation of the products with C-N and CH_2I 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 spirobutyrolactone 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 spirohalobutyrolactones. *S*-α-Methylbenzylamine was chosen as example for this study.



Scheme 4. Reagents and conditions: (i) *S*-α-methylbenzylamine; (ii) K_2CO_3, allyl bromide, MeCN, reflux, 12 h; (iii) a. NaOH, EtOH/H_2O, rt, 2 h; b. aqueous 1M HCl, 0 °C; (iv) K_2CO_3, NBS or NIS, CH_2Cl_2, -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.[5] Halocyclization of carboxylic acids **15a,b** with NBS/NIS in the presence of K_2CO_3, 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 K_2CO_3. 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 CH_2-X moities 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. ^{1}H and ^{13}C 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 allylyl bromide.

Products **3** are prepared according to our previous work.[5]

1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxylic acid ethyl ester (3a). Yellow liquid; yield: 90%; IR (ν, cm^{-1} $CHCl_3$) 1688, 1731; ^{1}H NMR (200 MHz, $CDCl_3$, 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-1*H*-isoindole-1-carboxylic acid ethyl ester (3b). Yellow liquid; yield: 68%; IR (ν, cm^{-1} $CHCl_3$) 1690, 1732; ^1H 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 (m, 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-1*H*-isoindole-1-carboxylic acid ethyl ester (3c). Yellow liquid; yield: 96%; IR (ν, cm^{-1} $CHCl_3$) 1691, 1732; ^1H 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-1*H*-isoindole-1-carboxylic acid ethyl ester (3d). Yellow liquid; yield: 82%; IR (ν, cm^{-1} $CHCl_3$) 1694, 1731; ^1H 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-1*H*-isoindole-1-carboxylic acid (4a). White solid; yield: 92%; mp 123-125 °C; IR (ν, cm^{-1} $CHCl_3$) 1697, 1776; ^1H 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 (sl, 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-1*H*-isoindole-1-carboxylic acid (4b). White solid; yield: 85%; mp 120-122 °C; IR (ν, cm^{-1} $CHCl_3$) 1693, 1714; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.90 (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-3-oxo-2-thiophen-2-ylmethyl-2,3-dihydro-1H-isoindole-1-carboxylic acid (4c). White solid; yield: 85%; mp 120-122 °C; IR (ν, cm^{-1} $CHCl_3$) 1694, 1726; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 3.03 (dd, *J* = 15.3, *J* = 6.0 Hz, 1H), 3.14 (dd, *J* = 15.3, *J* = 6.0 Hz, 1H,), 3.72-4.04 (sl, 1H), 4.68-4.91 (m, 4H), 5.09 (d, *J* = 15.8 Hz, 1H), 6.84-6.87 (m, 1H), 7.05-7.07 (m, 1H), 7.15-7.17 (m, 1H), 7.48-7.60 (m, 3H), 7.84-7.87 (m, 1H).

1-Allyl-2-furan-2-ylmethyl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxylic acid (4d). White solid; yield: 74%; mp 136-138 °C; IR (ν, cm^{-1} $CHCl_3$) 1694, 1725; ^1H 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

(m, 5H), 6.24-6.26 (m, 1H), 6.37-6.39 (m, 1H), 7.49-7.62 (m, 4H), 7.83-7.87 (m, 1H).

Typical procedure of the spirohalolactonization reaction.

A mixture of ethylenic acid **4** (1 mmole), K_2CO_3 (1.1 equiv) and *NBS* or *NIS* (1.2 equiv) in degassed CH_2Cl_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-isoindol-3'-one]-2-one (5a/b). White solid; yield: 83%; mp 187-189 °C; IR (ν, 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), 121.7 (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-isoindol-3'-one]-2-one (6a/b). White solid; yield: 95%; mp 131-133 °C; IR (ν, 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-isoindol-3'-one]-2-one (7a). White solid; yield: 71%; mp 196-198 °C; IR (ν, cm^{-1}, $CHCl_3$) 1700, 1789; ^1H NMR (300 MHz, $CDCl_3$, 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), 5.46 (d, *J* = 16.2 Hz, 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), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 7.2 (CH_2), 37.7 (CH_2), 39.6 (CH_2), 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 $C_{17}H_{14}INO_3S$ (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 (ν, cm^{-1}, $CHCl_3$) 1705, 1787; ^1H NMR (300 MHz, $CDCl_3$, 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* = 10.1, *J* = 3.9 Hz, 1H), 4.42 (d, *J* = 16.4 Hz, 1H), 4.82-4.96 (m, 1H), 5.11 (d, *J* = 16.4 Hz, 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), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 8.2 (CH_2), 39.1 ($2CH_2$), 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 (ν, cm^{-1}, $CHCl_3$) 1705, 1794; ^1H NMR (300 MHz, $CDCl_3$, 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* = 11.0, *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), 5.40 (d, *J* = 16.4 Hz, 1H), 7.27-7.43 (m, 6H), 7.52-7.63 (m, 2H), 7.92-7.96 (m, 1H), ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 33.5 (CH_2), 35.2 (CH_2), 44.5 (CH_2), 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 (ν, cm^{-1}, $CHCl_3$) 1704, 1794; ^1H NMR (300 MHz, $CDCl_3$, 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,

2H), 7.91-7.97 (m, 1H), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 33.6 (CH_2), 35.1 (CH_2), 43.9 (CH_2), 55.2 (CH_3), 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), 168.7 (CO), 171.5 (CO). Anal. Calcd for $C_{20}H_{18}BrNO_4$ (416.27) : C, 57.71; H, 4.36; N, 3.36. Found: C, 57.72; H, 4.35; N, 3.38.

5-(Bromomethyl)-2'-thiophen-2-ylmethyl-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (11a/b). White solid; yield: 73%; mp 181-183 °C; IR (ν, cm^{-1}, $CHCl_3$) 1710, 1795; dr: 75/25

Maj (**11a**): ^{1}H NMR (300 MHz, $CDCl_3$, 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* = 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), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 33.7 (CH_2), 35.3 (CH_2), 39.5 (CH_2), 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).

Min (**11b**): ^{1}H NMR (300 MHz, $CDCl_3$, 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* = 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), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 34.3 (CH_2), 36.5 (CH_2), 39.6 (CH_2), 69.1 (Cq), 75.0 (CH), 121.6 (CH), 124.4 (CH), 126.3 (CH), 127.0 (2CH), 129.9 (CH), 130.4 (Cq), 133.1 (CH), 139.0 (Cq), 144.0 (Cq), 168.3 (CO), 171.4 (CO). Anal. Calcd for $C_{19}H_{14}BrNO_3$ (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-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (16a/b): Yield: 68%; d.r = 80/20

Maj (16a): White solid; mp 156-158°C; IR (ν, cm^{-1} $CHCl_3$) 1705, 1795; ^{1}H NMR (300 MHz, $CDCl_3$, 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), 7.83-7.93 (m, 1H), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 17.5 (CH_3), 30.9 (CH_2), 37.5 (CH_2), 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), 168.7 (CO), 168.9 (CO).

Min (16b): ^{1}H NMR (300 MHz, $CDCl_3$, 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), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 17.1 (CH_3), 29.6 (CH_2), 37.6 (CH_2), 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%; d.r = 75/25

Maj (17a): White solid; mp 138-140 °C; IR (ν, cm^{-1} $CHCl_3$) 1704, 1785; ^1H NMR (300 MHz, $CDCl_3$, 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* = 6.1 Hz, 1H), 1.98 (dd, *J* = 11.4, *J* = 5.7 Hz, 1H) 2.16 (dd, *J* = 11.4, *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), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 7.9 (CH_2), 17.0 (CH_3), 30.9 (CH_2), 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, $CDCl_3$, 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), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 9.3 (CH_2), 14.2 (CH_3), 29.7 (CH_2), 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 $C_{20}H_{18}INO_3$ (447.28): C, 53.71; H, 4.06; N, 3.13. Found: C, 53.82; H, 4.05; N, 3.18.

REFERENCES AND NOTES

1. (a) A. N. French, S. Bissmire, and T. Wirth, *Chem. Soc. Rev.,* 2004, **33**, 354; (b) V. Blot, V. Reboul, and P. Metzner, *J. Org. Chem.,* 2004, **69**, 1196; (c) G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321; (d) P. A. Bartlett, In *Asymmetric Synthesis*; ed. by J. D. Morrison, Academic Press: Orlando, 1984; Vol. 3, p. 411; (e) M. D. Dowle and D. I. Davies, *Chem. Soc. Rev*., 1979, **8**, 171; (f) H. O. House, *Modern Synthetic Reactions*; W. A. Benjamin, Inc.: New York, 1972; p. 441; (g) J. Bougault, *Ann. Chim. Phys.,* 1908, **14**, 145; (h) J. Bougault, *Ann. Chim. Phys.,* 1908, **15**, 296.
2. (a) J. M. Garnier, S. Robin, and G. Rousseau, *Eur. J. Org. Chem.,* 2007*,* 3281; (b) M.-X. Wang and S.-M. Zhao, *Tetrahedron: Asymmetry,* 2002, **13**, 1695; (c) I. G. Collado, J. G. Maders, G. M. Massanet, and F. R. Luis, *Tetrahedron Lett.,* 1990, **31**, 563; (d) R. C. Cambie, P. S. Rutledge, R. F. Somerville, and P. D. Woodgate, *Synthesis,* 1988, 1009; (e) D. Evans, J. W. Magee, and J. H. Schauble, *Synthesis,* 1988, 862; (f) A. Toshimitsu, K. Teras, and S. Uemura, *Tetrahedron Lett.,* 1984, **25**, 5917; (g) P. A. Bartlett, D. P. Richardson, and J. Meyerson, *Tetrahedron,* 1984, **40**, 2317; (h) C. Cook, Y. Cho, S. Jew, Y. Suh, and E. Kang, *Arch. Pharm. Res.,* 1983, **6**, 45; (i) S. Jew, *Arch. Pharm. Res.,* 1982, **5**, 97; (j) S. Terashima and S. Jew, *Tetrahedron Lett*., 1977, **11**, 1005.

3. For a example see: (a) M. Pattarozzi, C. Zonta, Q. B. Broxterman, B. Kaptein, R. De Zorzi, L. Randaccio, P. Scrimin, and G. Licini, *Org. Lett.,* 2007, **9**, 2365; (b) K. Maeda, R. A. Miller, R. H. Szumigala, Jr., A. Shafiee, S. Karady, and J. D. Armstrong, *Tetrahedron Lett.,* 2005, **46**, 1545; (c) J. A. Macritchie, T. M. Peakman, A. Silcock, and C. L. Willis, *Tetrahedron Lett.,* 1998, **39**, 7415.
4. For example see: (a) A. V. Lozanova, T. M. Ugurchieva, M. V. Zlokazov, A. V. Stepanov, and V. Veselovsky, *Mendeleev Commun.,* 2006, **16**, 15; (b) E. Rozner and Y. Liu, *Org. Lett.,* 2003, **5**, 181. (c) S. Robin, and G. Rousseau, *Tetrahedron,* 1998, **54**, 13681; (d) M. Fujita, O. Kitagawa, T. Suzuki, and T. Taguchi, *J. Org. Chem.*, 1997, **62**, 7330.
5. (a) M. M. Rammah, M. Othman, K. Ciamala, C. Strohmann, and M. B. Rammah, *Tetrahedron,* 2008, **64***,* 3505; (b) R. Ben Othman, S. Coste, and B. Decroix, *Tetrahedron,* 2008, **64**, 559; (c) M. M. Rammah, M. Othman, M. Msaddek, and M. B. Rammah, *Heterocycles,* 2008, **75***,* 1971; (d) M. J. Tranchant, C. Moine, R. Ben Othman, T. Bousquet, M. Othman, and V. Dalla, *Tetrahedron Lett.,* 2006, **47***,* 4477; (e) R. Ben Othman, A. Fousse, T. Bousquet, M. Othman, and V. Dalla, *Org. Lett.*, 2005, **7**, 2825; (f) R. Ben Othman, T. Bousquet, M. Othman, and V. Dalla, *Org. Lett.,* 2005, **7**, 5335; (g) R. Akué-Gédu, S. Al Akoum Ebrik, A. Witczak-Legrand, D. Fasseur, S. El Ghammarti, D. Couturier, B. Decroix, M. Othman, M. Debacker, and B. Rigo, *Tetrahedron,* 2002, **58**, 9239; (h) M. Othman, P. Pigeon, and B. Decroix, *Tetrahedron,* 1998, **54**, 8737; (i) M. Othman and B. Decroix, *Synth. Commun.,*1996, **26**, 2803.
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
7. (a) P. A. Bartlet and J. Myerson, *J. Am. Chem., Soc.,* 1978*,* **100***,* 3950; (b) P. A. Bartlett and J. Myerson, *J. Org. Chem.,* 1979, **44**, 1625; (c) P. A. Bartlett and F. B. Gonzãlez, *Org. Synth.,* 1985, **64**, 175.