Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 3505–3516
Tetrahedron
www.elsevier.com/locate/tet

Silver-catalyzed spirolactonization: first synthesis of spiroisoindole-γ-methylene-γ-butyrolactones

Mohamed M. Rammah [a,d], Mohamed Othman [a,*], Kabula Ciamala [b], Carsten Strohmann [c], Mohamed B. Rammah [d]

[a] URCOM, Université du Havre, BP 540, 25 rue Philippe Lebon, 76058 Le Havre Cedex, France
[b] Institut UTINAM UMR CNRS 6213, Université de Franche-Comté, F-25030 Besançon Cedex, France
[c] Institut für Anorganische, Chemie, Universität Würzburg, D-97074, Germany
[d] LCOH, Université de Monastir, 5000 Monastir, Tunisia

Received 12 December 2007; received in revised form 30 January 2008; accepted 31 January 2008
Available online 6 February 2008

Abstract

γ-Acetylenic carboxylic acids are cyclized to spirolactones under mild conditions, in the presence of Ag_2CO_3 catalyst. The corresponding spiro-5-alkylidene-γ-butyrolactones were isolated in high yields, and this process constitutes an easy and efficient route to analogous structures of natural products of biological interest.
© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Exocyclic enol lactones (Fig. 1) are useful intermediates for the synthesis of a variety of natural products, which display a wide range of biological activities.[1,4b,5d,7b] Compounds containing this moiety are reported to have cytotoxic, insecticidal, and antibiotic properties. As a consequence, much attention has been paid to the synthesis of γ-methylene-γ-butyrolactone derivatives. Of the existing strategies for their syntheses, those based on transition metal-catalyzed cyclization of alkynoic acids by Au, Ag, Hg, Rh or Pd[2–7] are arguably the most effective.

On the other hand, the dihydroisoindolin-1-one ring system is present in numerous synthetic and natural compounds, which exhibit interesting biological properties. For example, 3-substituted dihydroisoindolin-1-ones such as pazinaclone **I**[8] and zoplicone **II**[9] possess a pharmaceutical profile similar to benzodiazepines (sedatives, hypnotics)[10] and have been commercialized as anxiolytics (Fig. 2).

In recent years, increasing attention has been focused on spirocyclic compound synthesis due to their interesting conformational features and their structural implications in biological and environmental systems.[11–13] For example, spirocyclic isoindolin-1-one **III**[14] was described as an aldose reductase inhibitor and antihyperglycemic agent.

In this context and in connection with our current research interest in the preparation of biologically relevant nitrogenated and oxygenated compounds,[15,16] we wish to describe in this paper a convenient silver salt catalyzed procedure as a novel and

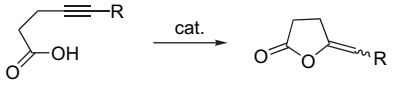


Figure 1.

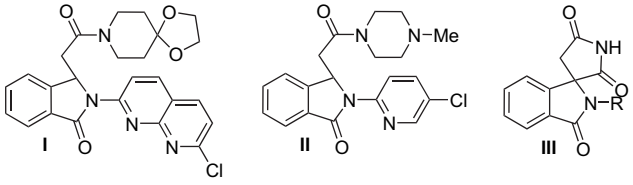
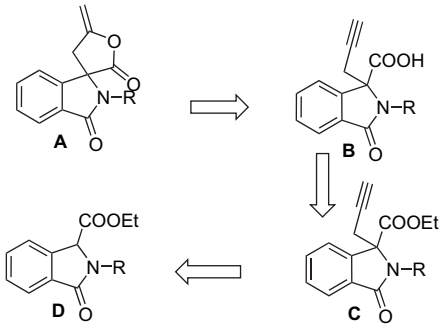


Figure 2.

* Corresponding author. Tel.: +33 02 32 74 44 01; fax: +33 02 32 74 43 91.
E-mail address: mohamed.othman@univ-lehavre.fr (M. Othman).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.01.137



Scheme 1. Retrosynthetic approach.

expedient entry to diverse spirocyclic compounds containing the γ-methylene-γ-butyrolactone and the dihydroisoindolin-1-one moieties from commercially available homophthalic acid.

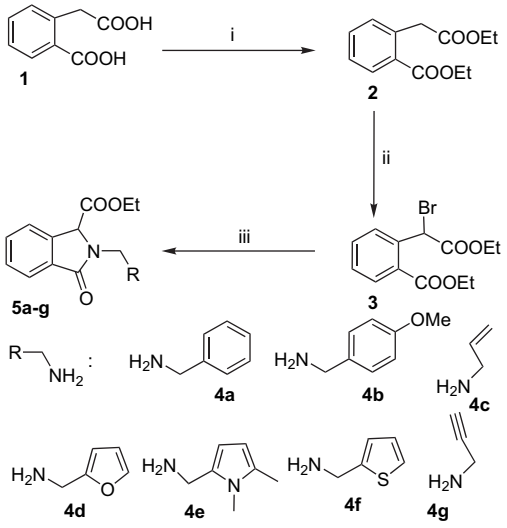
Our retrosynthetic strategy is outlined in Scheme 1. Spirolactone **A** can be readily obtained by catalytic silver cyclization of acid **B**, which in turn can be obtained by propargylation and saponification of phthalimidine **D**.

2. Results and discussion

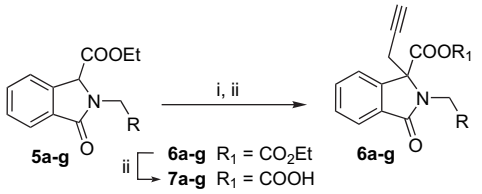
2.1. Synthesis of achiral spirobutyrolactone derivatives

We started our synthesis from diethylhomophthalate **2** readily available in quantitative yield, through the esterification of commercially available homophthalic acid **1**, as previously described by our group.[16] The conversion of **2** into the corresponding diethyl α-bromohomophthalate **3** was accomplished under standard conditions by treatment with *N*-bromosuccinimide and a catalytic amount of AIBN. Condensation of bromine **3** with 2 equiv of the required primary amines **4a**–**g** in acetonitrile at room temperature for 8 h[16] afforded the desired bicyclic lactams **5a**–**g** in high yields ranging from 84 to 92% (Scheme 2).

It should be noted that phthalimidines **5** could be efficiently prepared by lithiation with LDA of isoindolinones derivatives.[17]



Scheme 2. Reagents and conditions: (i) HCl, EtOH, 0 °C, 4 h then reflux, 4 h; (ii) NBS, AIBN, CCl_4, reflux, 12 h; (iii) amines **4a**–**g**, CH_3CN, rt, 8 h.



Scheme 3. Reagents and conditions: (i) K_2CO_3, propargyl bromide, CH_3CN, reflux, 12 h, 80–97%; (ii) (a) NaOH, EtOH/H_2O, rt, 2 h; (b) aqueous 1 M HCl, 0 °C, 72–98%.

Treatment of lactams **5** with K_2CO_3 to effect enolate formation followed by alkylation with propargyl bromide, afforded alkylated phthalimidines esters **6a**–**g** in good yields (80–97%) (Scheme 3).

Esters **6a**–**g** were then treated with a molar excess of 1 M aqueous NaOH solution and ethanol at room temperature for 2 h, followed by acidification with diluted HCl at 0 °C to give the corresponding carboxylic acids **7a**–**g** in 72–98% yield.

With a large variety of acetylenic carboxylic acids **7a**–**g** in hand, we then investigated the optimal conditions for the spirolactone formation.

In their pioneering work on silver-catalyzed heterolactonization, Pale and co-workers[4c] established that acetylenic acids could be efficiently cyclized by a catalytic amount of silver carbonate (10 mol %). The cyclization proved to be highly regioselective and the exocyclic α-methylene heterocycles resulting from an *exo*-dig ring closure were always exclusively isolated.

Using the same protocol on the compound **7a** chosen as model, we found that the use of just 5 mol % of Ag_2CO_3 in toluene at 80 °C cleanly afforded in a short reaction time (15 min) the corresponding spiro-5-alkylidene-γ-butyrolactone **8a** in quantitative yield (Table 1, entry 1). IR, ^1H and ^{13}C NMR spectroscopies unambiguously confirmed the expected cyclic structure for this compound. Particularly characteristic were the exocyclic enol lactone data, with the methylene protons at 4.52 and 4.98 ppm, the lactone carbon at 170.5 ppm, and the methylene carbons at 151.3 and 91.6 ppm. The reaction has been scaled up to 5 g with no loss in yield (Scheme 4).

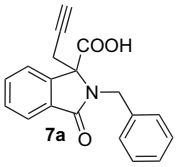
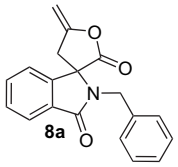
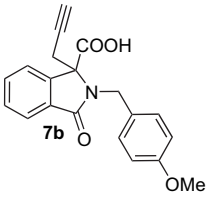
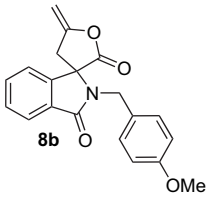
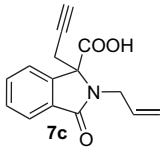
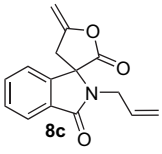
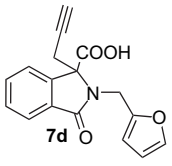
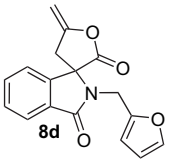
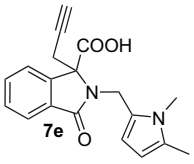
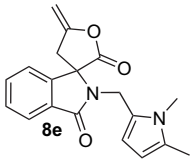
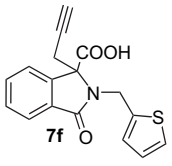
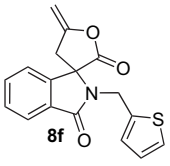
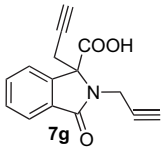
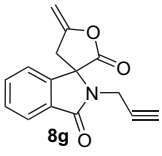
The reaction scope was probed by applying these optimal conditions to the other substrates **7b**–**g**, which cyclized smoothly to offer the spiro compounds **8b**–**g** in good yields (Table 1). As far as we know, this is the first preparation of γ-spirobutyrolactone derivatives containing the isoindole moiety starting from homophthalic acid.

Importantly, in all cases, the reaction seems to be highly regioselective because during the cyclization process only the *exo*-dig products were obtained.

It is worth noticing that the use of dichloromethane or tetrahydrofuran led to the formation of the desired spirolactone in lower isolated yields (Table 1, entry 1). It should also be noted that the presence of an allylic or propargylic side chains in acids **7c** and **7g** was compatible with the reaction conditions and no other competitive addition was observed.

In order to study the generality of this silver-catalyzed spirolactonization, the unsubstituted acid **11** and the methyl

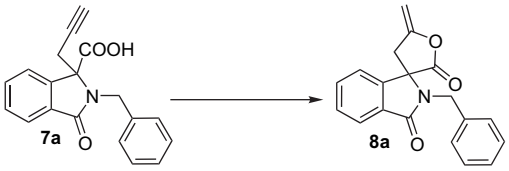
Table 1
Spirocyclization produced via Scheme 3

Entry[a,b]	Substrate	Product	Yield %
1			100 74[c] 78[d]
2			89
3			80
4			78
5			100
6			98
7			74

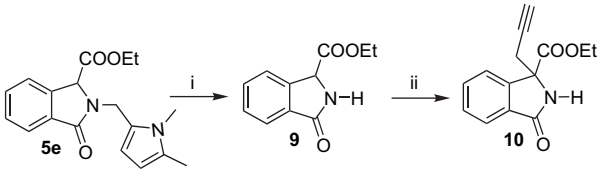
[a] All the reactions were conducted under Argon.
[b] All the reactions were carried out using 5 mol % of Ag_2CO_3.
[c] The reaction was carried out using CH_2Cl_2 at reflux.
[d] The reaction was carried out using THF at reflux.

substituted acid **15** were synthesized and then submitted to the above conditions.

Our initial efforts on the synthesis of acid **11** started from the phthalimidine-3-carboxylate derivative **5e**, which upon treatment with 4 equiv of trifluoroacetic acid (TFA less toxic than BBr_3)[18] in dichloromethane at room temperature for 12 h afforded the desired phthalimidine **9** in 84% yield (Scheme 5).



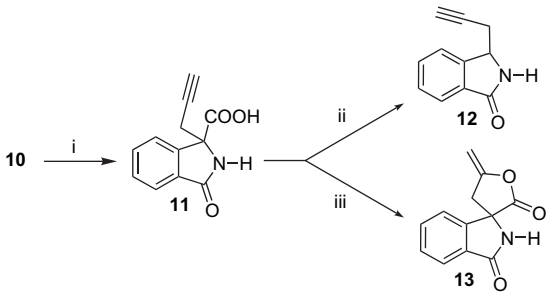
Scheme 4. Reagents and conditions: (i) Ag_2CO_3, toluene, 80 °C, 100%.



Scheme 5. Reagents and conditions: (i) TFA, CH_2Cl_2, rt, 12 h, 84%; (ii) K_2CO_3, propargyl bromide, CH_3CN, reflux, 12 h, 80%.

Alkylation of **9** with propargyl bromide under standard conditions followed by basic saponification of the ester function of the resulting phthalimidine **10**, gave the acid **11** in 52% yield after the two steps.

Acid **11** was next treated with Ag_2CO_3 (5 mol %) according to the protocol given above. The examination of the TLC of the reaction mixture indicated the presence of only one product (less polar), which, after a classical workup, was identified as compound **12**, resulting from the thermal decarboxylation of the acid function (Scheme 6).



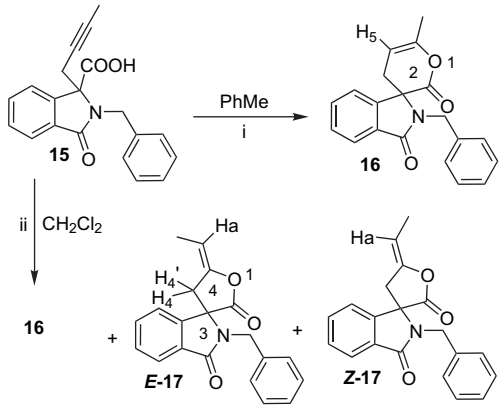
Scheme 6. Reagents and conditions: (i) (a) NaOH, EtOH/H_2O, rt, 2 h; (b) aqueous 1 M HCl, 0 °C, 65%; (ii) Ag_2CO_3, toluene, 80 °C, 15 min, 100%; (iii) Ag_2CO_3, CH_2Cl_2, reflux, 48 h, 40%.

It is noteworthy that, although a variety of reaction temperatures and Ag_2CO_3 ratios were explored, the formation of spirolactone **13** was not accomplished. This is probably due to the facile decarboxylation of acid **11** as well as its low solubility in the solvent of the reaction.

On the other hand, when the reaction was tested in various solvents such as THF, DMF, dichloromethane, and H_2O with 10 mol % of Ag_2CO_3 at room temperature and at reflux, only in refluxing dichloromethane, trace amounts of the spirolactone **13** were obtained. The acetylenic acid **11** gave only **12** in refluxing THF, DMF, or H_2O, and remained unchanged at room temperature. After optimization of the reaction conditions,

we found that the best result was obtained with 20 mol % Ag_2CO_3 in refluxing dichloromethane. This gave the desired compound **13** in a moderate yield of 40%.

Using the same operating methods previously used to obtain acid **7a**, we then prepared the methyl substituted acid **15** to look at the stereoselectivity of this spirolactonization (Scheme 7).



Scheme 7. Reagents and conditions: (i) Ag_2CO_3, toluene, 80 °C, 1 h, 34%; (ii) Ag_2CO_3, CH_2Cl_2, reflux, 4 h, 38%.

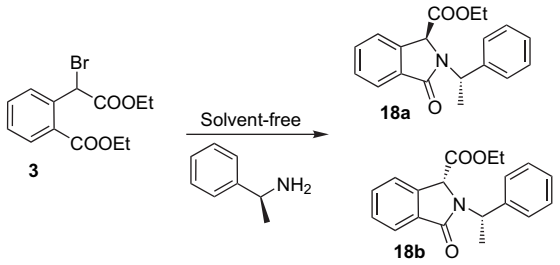
Cyclization of acid **15** using the above optimized conditions proceeded more slowly (1 h) than the corresponding terminal acetylenic acid **7a** (15 min) and resulted in the exclusive formation of the six membered ring spirolactone **16** in 34% yield. The structure of this product was unambiguously determined by usual spectrometric methods (^{1}H, 2D, and ^{13}C NMR). For example, in the ^{1}H NMR spectrum, the proton H_5 resonates at 4.40 ppm as a multiplet (J_{H5-H4}=2.0 Hz, $J_{H5-H(CH3)}$=2.3 Hz, $J_{H5-H4'}$=7.0 Hz). The protons of the methyl group appear as a multiplet ($J_{H(CH3)-H4}$=2.0 Hz, $J_{H(CH3)-H4'}$=2.0 Hz, $J_{H(CH3)-H5}$=2.3 Hz) at 1.68 ppm due to the coupling with the two protons H_4 and H_5. Additional support was provided by ^{13}C NMR spectroscopy, which detected a carbon at δ=13.1 ppm (CH_3) and a quaternary carbon at 143.0 ppm characteristic of a six membered spirolactone.[6b,c] It should be noted that in CH_2Cl_2 at reflux, the cyclization became nonselective and lead to a mixture of nonseparable products, including the *Z*-**17** (29%), the *E*-**17** (58%), and the six membered ring spirolactone **16** (13%) in 38% over isolated yield. The ^{1}H NMR spectra of *E*-**17** exhibits a multiplet of the methyl protons (δ=1.75 ppm, $J_{H(CH3)-H4}$=2.3 Hz, $J_{H(CH3)-H4'}$=2.3 Hz, $J_{vicinal}$=7.0 Hz) and a quartet of doublet for the vinylic proton H_a (δ=4.76 ppm, $J_{Ha-H4'}$=2.3 Hz, $J_{Ha-H(CH3)}$=7.0 Hz). We noticed the absence of any coupling between H_4 and H_a protons. The stereochemistry of the double bond was demonstrated by performing NOE difference experiments on lactones **17**.

2.2. Synthesis of chiral spirobutyrolactone derivatives

Having established the facility of acids **7a–g** to provide interesting spirolactones in good yields and under catalytic amount of Ag_2CO_3, we envisioned whether this process might be extended for the preparation of chiral nonracemic γ-methylene-γ-butyrolactones. The *R*- and *S*-α-methylbenzylamines were chosen as examples for this study.

The conditions previously employed for the condensation of primary amines, i.e., stirring diethyl α-bromohomophthalate **3** in acetonitrile at room temperature, with either *R*- or *S*-α-methylbenzylamine, failed to give the desired phthalimidine cyclization products, with only starting material being systematically recovered. It was therefore apparent that the extra steric hindrance in the system, with the addition of an extra methyl group in the α position to the nitrogen of the amine, compared to benzylamine, was sufficient to stop cyclization from occurring.

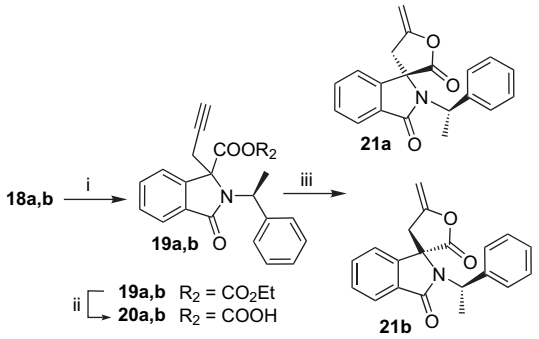
After intensive screening of the reaction conditions, for example, reaction temperatures, additives (K_2CO_3, NaH, and $NaNH_2$), and solvents (toluene, THF, and solvent-free), we found that cyclization could be achieved by using 4 equiv of *R*- or *S*-α-methylbenzylamine in solvent-free conditions at room temperature for 4 days. This gave (in the case of *S*-α-methylbenzylamine) the desired compounds **18a** and **18b** in a 1.8/1 mixture of nonseparable stereoisomers in an acceptable yield of 50% (Scheme 8).



Scheme 8. Reagents and conditions: *S*-α-methylbenzylamine, rt, 4 days, 50%.

Next, alkylation of **18** followed by saponification of **19** under the same operating methods previously used to obtain acids **7** afforded a mixture of nonseparable products in 71% overall yield for the two stages.

Finally, the phthalimidine carboxylic acids **20a**,**b** were subjected to the above optimized silver-catalyzed spirolactonization conditions. We were pleased to see that the 5-*exo* process was still effective with these sterically more demanding substrates, giving a chromatographically separable mixture of diastereomers (**21b/21a** 2/1) in 87% yield (Scheme 9).



Scheme 9. Reagents and conditions: (i) K_2CO_3, propargyl bromide, CH_3CN, reflux, 12 h, 86%; (ii) (a) NaOH, EtOH/H_2O, rt, 2 h; (b) aqueous 1 M HCl, 0 °C, 89%; (iii) Ag_2CO_3, toluene, 80 °C, 84%.

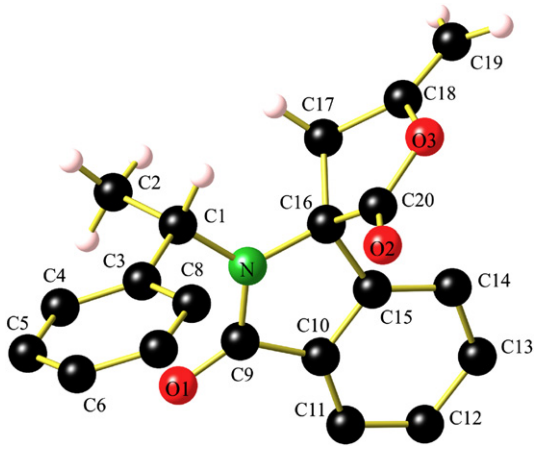


Figure 3. Molecular structure of **21b**. The hydrogen atoms of the aryl rings are omitted for clarity.

Single-crystal X-ray structure elucidation[19] on the major (more polar) diastereomer **21b** unambiguously established the relative configuration and, hence, the stereochemistry of the spirocenter C-16 as *R** (Fig. 3).

3. Conclusion

In summary, a highly efficient spirocyclization reaction of γ-acetylenic carboxylic acids was developed in the isoindolone series by using Ag_2CO_3 as a simple commercially available catalyst in toluene at 80 °C. The carboxylic substrates were very easily prepared from simple precursors and the cyclization reactions selectively afforded the corresponding 5-alkylidene-spirobutyrolactones. Further investigations will be devoted to the synthesis of halo spiro-γ-butyrolactones, as well as applications in analogous natural product syntheses.

4. Experimental part

4.1. 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. Gas chromatography–mass spectrometry (GC–MS) was performed with a GC apparatus equipped with a 25 m capillary column, at 90 °C for 2 min, then 10 °C/min up to 290 °C. 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. Abbreviations: dd=doublet of doublet, m=multiplet, s=singlet, d=doublet, q=quartet, t=triplet, br s=broad singlet, DCM=dichloromethane. Silver carbonate was purchased from Sigma–Aldrich. Tetrahydrofuran was dried by distillation from sodium/benzophenone. Dichloromethane was dried by distillation from calcium hydride, toluene was distilled from sodium and acetonitrile was dried by distillation from P_2O_5.

4.2. Typical procedure of primary amine condensation

To an ice chilled solution of diethyl α-bromophthalate **1** (2 g, 6.34 mmol) in dry acetonitrile (50 mL) was added under argon, primary amines **4a–g** (12.7 mmol) diluted in 10 mL of acetonitrile. The mixture was stirred at room temperature for 8 h. The salt that formed was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (dichloromethane/acetone 90/10).

4.2.1. 2-Benzyl-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (*5a*)

This product was prepared according to our previous work.[16b]

4.2.2. 2-(4-Methoxybenzyl)-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (*5b*)

Yellow liquid; yield: 84%; IR (ν, cm^{-1}, $CHCl_3$) 1693, 1747; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.94 (t, J=7.0 Hz, 3H), 3.50 (s, 3H), 3.92–3.99 (m, 3H), 4.61 (s, 1H), 5.15 (d, J=15.0 Hz, 1H), 6.56–6.60 (m, 2H), 6.90–6.94 (m, 2H), 7.23–7.28 (m, 2H), 7.54–7.65 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.1 (CH_3), 44.4 (CH_2), 55.2 (CH_3), 61.0 (CH_2), 62.0 (CH), 114.1 (2CH), 122.6 (CH), 124.0 (CH), 128.3 (Cq), 129.1 (CH), 129.8 (2CH), 131.7 (Cq), 131.8 (CH), 139.3 (Cq), 159.2 (Cq), 168.0 (CO), 168.5 (CO). Anal. Calcd for $C_{19}H_{19}NO_4$ (325.37): C, 70.14; H, 5.89; N, 4.30. Found: C, 70.37; H, 6.02; N, 4.50.

4.2.3. 2-Allyl-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (*5c*)

This product was prepared according to our previous work.[16a]

4.2.4. 2-(Furan-2-ylmethyl)-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (*5d*)

Yellow solid; yield: 90%; mp 98–100 °C; IR (ν, cm^{-1}, $CHCl_3$) 1694, 1747; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.28 (t, J=7.1 Hz, 3H), 5.15–4.34 (m, 2H), 4.44 (d, J=15.6 Hz, 1H), 4.99 (s, 1H), 5.32 (d, J=15.6 Hz, 1H), 6.28–6.31 (m, 2H), 7.33–7.34 (m, 1H), 7.46–7.59 (m, 3H), 7.82–7.86 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 14.1 (CH_3), 37.7 (CH_2), 61.5 (CH), 62.1 (CH_2), 109.0 (CH), 110.4 (CH), 122.7 (CH), 124.0 (CH), 129.1 (CH), 131.4 (Cq), 131.9 (CH), 139.2 (Cq), 142.7 (CH), 149.7 (Cq), 167.9 (2CO). Anal. Calcd for $C_{16}H_{15}NO_4$ (285.30): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.52; H, 5.32; N, 5.02.

4.2.5. 2-(1,5-Dimethyl-1H-pyrrol-2-ylmethyl)-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (*5e*)

This product was prepared according to our previous work.[16c]

4.2.6. 3-Oxo-2-(thiophen-2-ylmethyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**5f**)

This product was prepared according to our previous work.[16b]

4.2.7. 3-Oxo-2-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**5g**)

This product was prepared according to our previous work.[16a]

4.2.8. Ethyl 3-oxo-2-(1-phenylethyl) isoindoline-1-carboxylate (**18a** and **18b**)

The ester diastereoisomers were inseparable and characterized together. Yellow liquid; yield: 50%; IR (ν, cm^{-1}, $CHCl_3$) 1680, 1730; ^1H NMR (200 MHz, $CDCl_3$, 25 °C).

Min: δ 0.90 (t, J=7.0 Hz, 3H), 1.72 (d, J=7.8 Hz, 3H), 3.49–3.75 (m, 2H), 5.10 (s, 1H), 5.40 (q, J=7.0 Hz, 1H), 7.06–7.32 (m, 4H), 7.34–7.51 (m, 4H), 7.69–7.82 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.4 (CH_3), 17.7 (CH_3), 52.1 (CH), 61.3 (CH), 61.5 (CH_2), 121.9 (CH), 123.7 (CH), 127.6 (CH), 127.9 (2CH), 128.1 (2CH), 128.9 (CH), 131.7 (CH), 132.2 (Cq), 139.6 (Cq), 139.8 (Cq), 168.6 (C=O), 168.8 (C=O).

Maj: ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.19 (t, J=7.0 Hz, 3H), 1.66 (d, J=7.0 Hz, 3H), 4.07–4.18 (m, 2H), 4.68 (s, 1H), 5.68 (q, J=7.0 Hz, 1H), 7.16–7.23 (m, 4H), 7.31–7.47 (m, 4H), 7.69–7.82 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.8 (CH_3), 17.2 (CH_3), 51.2 (CH), 60.9 (CH), 61.8 (CH_2), 121.8 (CH), 123.8 (CH), 127.3 (2CH), 127.7 (CH), 128.6 (2CH), 129.9 (CH), 131.8 (CH), 132.1 (Cq), 139.7 (Cq), 139.9 (Cq), 168.4 (C=O), 169.3 (C=O). Anal. Calcd for $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.59; H, 6.14; N, 4.62.

4.3. Alkylation with propargyl bromide (1-bromo-2-butyne)

To a mixture of **5**, **9**, **18** (8.23 mmol), potassium carbonate (1.25 g, 9.05 mmol), and 50 mL of acetonitrile was added propargyl bromide (1-bromo-2-butyne for preparing compound **14**) (9.87 mmol). The reaction mixture was refluxed over-night. The cooled resulting suspension was filtered off. The filtrate was concentrated in vaccuo, diluted with water, and extracted with dichloromethane (3×30 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 75/25) to give the phthalimidines **6**, **10**, **14**, and **19**.

4.3.1. 2-Benzyl-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**6a**)

White solid; yield: 91%; mp 86–88 °C; IR (ν, cm^{-1}, $CHCl_3$) 1695, 1733; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 1.00 (t, J=7.1 Hz, 3H), 1.71 (t, J=2.3 Hz, 1H), 3.08 (dd, J=2.3 Hz, J=17.2, 1H), 3.21 (dd, J=2.3 Hz, J=17.2, 1H), 3.58–3.64 (m, 1H), 3.75–3.90 (m, 1H), 4.63 (d, J=15.6, 1H), 4.94 (d, J=15.6 Hz, 1H), 7.27–7.34 (m, 3H), 7.38–7.50 (m, 3H), 7.53–7.63 (m, 2H), 7.90–7.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 13.5 (CH_3), 24.8 (CH_2), 44.3 (CH_2), 62.2 (CH_2), 69.8 (Cq), 72.0 (CH), 77.0 (Cq), 121.2 (CH), 123.9 (CH), 127.5 (CH), 128.3 (2CH), 128.9 (2CH), 129.4 (CH), 129.5 (Cq), 132.2 (CH), 136.6 (Cq), 143.5 (Cq), 169.3 (2CO). Anal. Calcd for $C_{21}H_{19}NO_3$ (333.39): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.92; H, 5.60; N, 4.32.

4.3.2. 2-(4-Methoxybenzyl)-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**6b**)

Yellow liquid; yield: 88%; IR (ν, cm^{-1}, $CHCl_3$) 1696, 1732; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.94 (t, J=7.0 Hz, 3H), 1.70 (t, J=2.3 Hz, 1H), 3.05 (dd, J=2.3 Hz, 17.2 Hz, 1H), 3.16 (dd, J=2.3 Hz, 17.2 Hz, 1H) 3.61–3.70 (m, 1H), 3.77 (s, 3H), 3.80–3.90 (m, 1H), 4.58 (d, J=15.6 Hz, 1H), 4.86 (d, J=15.6 Hz, 1H), 6.79–6.83 (d, J=8.6 Hz, 2H), 7.32 (d, J=8.6 Hz, 2H), 7.43–7.54 (m, 3H), 7.86–7.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.4 (CH_3), 24.7 (CH_2), 43.9 (CH_2), 55.2 (CH_3), 62.3 (CH_2), 69.7 (Cq), 72.0 (CH+Cq), 113.6 (2CH), 121.9 (CH), 123.8 (CH), 128.6 (Cq), 129.4 (CH), 129.7 (2CH), 131.8 (Cq), 132.1 (CH), 143.5 (Cq), 159.0 (Cq), 169.3 (CO), 169.4 (CO). Anal. Calcd for $C_{22}H_{21}NO_4$ (363.42): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.52; H, 5.70; N, 3.74.

4.3.3. 2-Allyl-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**6c**)

This product was prepared according to our previous work.[16a]

4.3.4. 2-(Furan-2-ylmethyl)-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**6d**)

Yellow solid; yield: 93%; mp 104–106 °C; IR (ν, cm^{-1}, $CHCl_3$) 1698, 1731; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.99 (t, J=7.0 Hz, 3H), 1.65 (t, J=2.6 Hz, 1H), 3.17 (dd, J=2.6 Hz, J=17.2 Hz, 1H), 3.28 (dd, dd, J=2.6 Hz, J=17.2 Hz, 1H), 3.75–3.84 (m, 1H), 3.92–3.98 (m, 1H), 4.65 (d, J=16.0, 1H), 4.90 (d, J=16.0 Hz, 1H), 6.27–6.29 (m, 1H), 6.30–6.33 (m, 1H), 7.30–7.31 (m, 1H), 7.42–7.51 (m, 3H), 7.85 (d, J=6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 13.6 (CH_3), 24.6 (CH_2), 36.7 (CH_2), 62.5 (CH_2), 69.7 (Cq), 71.8 (CH), 76.6 (Cq), 109.3 (CH), 110.6 (CH), 121.2 (CH), 123.9 (CH), 129.4 (CH), 131.6 (Cq), 132.2 (CH), 142.1 (CH), 143.2 (Cq), 149.8 (Cq), 168.7 (CO), 169.3 (CO). Anal. Calcd for $C_{19}H_{17}NO_4$ (323.35): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.32; H, 5.36; N, 4.32.

4.3.5. 2-(1,5-Dimethyl-1H-pyrrol-2-ylmethyl)-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**6e**)

Brown solid; yield: 81%; mp 142–144 °C; IR (ν, cm^{-1}, $CHCl_3$) 1691, 1734; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.95 (t, J=7.1 Hz, 3H), 1.63 (t, J=2.3 Hz, 1H), 2.1 (s, 3H), 3.02 (dd, J=2.3 Hz, J=17.2, 1H), 3.25 (dd, J=2.3 Hz, J=17.2, 1H), 3.45 (s, 3H), 3.54–3.70 (m, 1H), 3.78–3.94 (m, 1H), 4.49 (d, J=15.6 Hz, 1H), 5.05 (d, J=15.6 Hz, 1H), 5.73 (d, J=3.1 Hz, 1H), 5.93 (d, J=3.1 Hz, 1H), 7.31–7.38 (m, 1H), 7.45–7.56 (m, 2H), 7.83–7.87 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 12.4 (CH_3), 13.5 (CH_3), 23.8 (CH_2), 30.5 (CH_3), 35.7 (CH_2), 62.2 (CH_2), 68.9 (Cq), 71.3

(CH, Cq), 105.1 (CH), 109.2 (CH), 120.5 (CH), 123.8 (CH), 124.7 (Cq), 129.2 (CH), 130.3 (Cq), 131.7 (Cq), 132.1 (CH), 143.6 (Cq), 168.6 (CO), 168.9 (CO). Anal. Calcd for $C_{21}H_{22}N_2O_3$ (350.42): C, 71.98; H, 6.33; N, 7.99. Found: C, 71.91; H, 6.36; N, 7.91.

*4.3.6. 3-Oxo-1-(prop-2-ynyl)-2-(thiophen-2-ylmethyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**6f**)*

Yellow solid; yield: 86%; mp 113–115 °C; IR (ν, cm^{-1}, $CHCl_3$) 1696, 1731; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.98 (t, J=7.0 Hz, 3H), 1.73 (t, J=2.3 Hz, 1H), 3.17–3.19 (m, 2H), 3.74–3.79 (m, 2H), 4.86 (d, J=15.6 Hz, 1H), 5.07 (d, J=15.6 Hz, 1H), 6.87–6.91 (m, 1H), 7.03–7.05 (m, 1H), 7.18–7.21 (m, 1H), 7.43–7.53 (m, 3H), 6.82–6.89 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.6 (CH_3), 25.1 (CH_2), 38.9 (CH_2), 62.4 (CH_2), 69.8 (Cq), 72.2 (Cq), 76.9 (CH), 121.4 (CH), 123.9 (CH), 125.8 (CH), 126.4 (CH), 127.5 (CH), 129.4 (CH), 131.5 (Cq), 132.2 (CH), 139.1 (Cq), 143.3 (Cq), 168.8 (CO), 169.1 (CO). Anal. Calcd for $C_{19}H_{17}NO_3S$ (339.42): C, 67.24; H, 5.05; N, 4.13. Found: C, 67.45; H, 5.09; N, 4.32.

*4.3.7. 3-Oxo-1,2-(di-prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**6g**)*

Yellow solid; yield: 89%; mp 100–102 °C; IR (ν, cm^{-1}, $CHCl_3$) 1701, 1734; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.17 (t, J=7.0 Hz, 3H), 1.80 (t, J=2.35 Hz, 1H), 2.25 (t, J=2.3 Hz, 1H), 3.34–3.37 (m, 2H), 4.08–4.19 (m, 2H), 4.38 (dd, J=2.3 Hz, 18.0 Hz, 1H), 4.53 (dd, J=2.3 Hz, 18.0 Hz, 1H), 7.49–7.60 (m, 3H), 7.84–7.88 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.7 (CH_3), 25.2 (CH_2), 30.0 (CH_2), 62.5 (CH_2), 69.6 (Cq), 72.2 (Cq), 72.6 (Cq), 76.8 (CH), 77.7 (CH), 121.3 (CH), 123.9 (CH), 129.5 (CH), 131.2 (Cq), 132.5 (CH), 143.0 (Cq), 168.1 (C=O), 169.3 (C=O). Anal. Calcd for $C_{17}H_{15}NO_3$ (281.31): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.66; H, 5.60; N, 4.92.

*4.3.8. 3-Oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**10**)*

White solid; yield: 80%; mp 169–171 °C; IR (ν, cm^{-1}, $CHCl_3$) 1712, 1738; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 1.20 (t, J=7.0 Hz, 3H), 2.00 (t, J=2.3 Hz, 1H), 2.56 (dd, J=2.3 Hz, J=16.4, 1H), 3.23 (dd, J=2.3 Hz, J=16.4, 1H), 4.05–4.26 (m, 2H), 6.73–6.90 (br s, 1H), 7.45–7.61 (m, 3H), 7.75 (d, J=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 13.8 (CH_3), 29.5 (CH_2), 62.7 (CH_2), 66.7 (Cq), 72.3 (Cq), 76.6 (CH), 122.8 (CH), 124.1 (CH), 129.8 (CH), 131.0 (Cq), 131.9 (CH), 143.8 (Cq), 169.3 (CO), 169.5 (CO). Anal. Calcd for $C_{14}H_{13}NO_3$ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.92; H, 5.50; N, 5.93.

*4.3.9. 2-Benzyl-1-(but-2-ynyl)-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**14**)*

Yellow liquid; yield 92%; IR (ν, cm^{-1}, $CHCl_3$) 1692, 1730; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.79 (t, J=7.0 Hz, 3H), 1.32 (s, 3H), 2.97 (s, 2H), 3.47–3.58 (m, 1H), 3.65–3.76 (m, 1H), 4.56 (d, J=15.4 Hz, 1H), 4.78 (d, J=15.4 Hz, 1H), 7.05–7.16 (m, 3H), 7.21–7.43 (m, 5H), 7.75–7.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 2.8 (CH_3), 13.2 (CH_3), 24.9 (CH_2), 44.1 (CH_2), 61.7 (CH_2), 70.0 (Cq), 71.4 (Cq), 79.1 (Cq), 121.0 (CH), 123.3 (CH), 126.9 (CH), 127.7 (2CH), 128.2 (2CH), 128.8 (CH), 131.3 (Cq), 131.7 (CH), 136.5 (Cq), 143.5 (Cq), 168.9 (C=O), 169.0 (C=O). Anal. Calcd for $C_{21}H_{20}NO_3$ (334.40): C, 75.43; H, 6.03; N, 4.19. Found: C, 75.25; H, 6.12; N, 4.08.

*4.3.10. 3-Oxo-2-(1-phenyl-ethyl)-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid ethyl ester (**19a** and **19b**)*

The ester diastereoisomers were inseparable and characterized together. Brown solid; yield 86%; mp 67–69 °C; IR (ν, cm^{-1}, $CHCl_3$) 1696, 1730.

Min: ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.17 (t, J=7.0 Hz, 3H), 1.55 (t, J=2.3 Hz, 1H), 1.98 (d, J=7.0 Hz, 3H), 2.98–3.15 (m, 2H), 4.02–4.13 (m, 2H), 4.78 (q, J=7.0 Hz, 1H), 7.27–7.35 (m, 4H), 7.40–7.55 (m, 4H), 7.79–7.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.8 (CH_3), 20.1 (CH_3), 25.7 (CH_2), 54.4 (CH), 62.4 (CH_2), 70.5 (Cq), 72.2 (Cq), 77.1 (CH), 121.2 (CH), 123.5 (CH), 127.2 (CH), 127.7 (2CH), 128.1 (2CH), 129.3 (CH), 131.7 (CH), 132.6 (Cq), 141.7 (Cq), 143.0 (Cq), 169.1 (CO), 169.5 (CO).

Maj: ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.74 (t, J=7.0 Hz, 3H), 1.78 (t, J=2.3 Hz, 1H), 2.01 (d, J=7.0 Hz, 3H), 3.19–3.22 (m, 2H), 3.49–3.86 (m, 2H), 4.75 (q, J=7.0 Hz, 1H), 7.27–7.35 (m, 4H), 7.40–7.55 (m, 4H), 7.79–7.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.1 (CH_3), 20.1 (CH_3), 25.0 (CH_2), 55.7 (CH), 62.1 (CH_2), 71.8 (Cq), 72.0 (Cq), 77.3 (CH), 120.9 (CH), 123.5 (CH), 127.2 (CH), 127.6 (2CH), 128.1 (2CH), 129.2 (CH), 131.9 (CH), 132.7 (Cq), 141.7 (Cq), 143.4 (Cq), 169.3 (CO), 169.6 (CO). Anal. Calcd for $C_{22}H_{21}NO_3$ (347.42): C, 76.06; H, 6.09; N, 4.03. Found: C, 75.92; H, 6.00; N, 4.12.

*4.4. Preparation of acids **7**, **11**, **15**, and **20***

To an ice chilled solution of the esters **6**, **10**, **14**, and **19** (4 mmol) in 20 mL of ethanol was added sodium hydroxide solution (0.32 g, 8 mmol in 5 mL of water). The reaction mixture was stirred for 15 min concentrated in vaccuo, diluted with water, and washed with dichloromethane. The aqueous layer was acidified with 10% hydrochloric acid solution to pH=1. The aqueous layer was extracted with dichloromethane (3×30 mL). The organic phase was dried over $MgSO_4$, filtered then concentrated under reduced pressure to give the corresponding acids **7**, **11**, **15**, and **20** who were used without purification in the following steps.

*4.4.1. 2-Benzyl-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**7a**)*

White solid; yield: 93%; mp 86–88 °C; IR (ν, cm^{-1}, $CHCl_3$) 1691, 1730, 3307; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 1.62 (t, J=2.3 Hz, 1H), 2.92 (dd, J=2.3 Hz, J=17.2, 1H), 3.14 (dd, J=2.3 Hz, J=17.2 Hz, 1H), 4.62 (d, J=15.6 Hz, 1H), 4.79 (br s, 1H), 4.91 (d, J=15.6 Hz, 1H), 7.09–7.24 (m, 4H),

7.32–7.36 (m, 2H), 7.46–7.60 (m, 2H), 7.84 (d, J=6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 24.9 (CH_2), 45.1 (CH_2), 70.4 (Cq), 72.1 (Cq), 76.7 (CH), 121.6 (CH), 124.1 (CH), 127.5 (CH), 128.2 (2CH), 128.7 (2CH), 129.6 (CH), 131.3 (Cq), 132.4 (CH), 136.0 (Cq), 143.1 (Cq), 169.9 (CO), 172.1 (CO). Anal. Calcd for $C_{19}H_{15}NO_3$ (305.34): C, 74.74; H, 4.95; N, 4.59. Found: C, 74.82; H, 5.02; N, 4.78.

*4.4.2. 2-(4-Methoxybenzyl)-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**7b**)*

White solid; yield: 91%; mp 134–136 °C; IR (ν, cm^{-1}, $CHCl_3$) 1692, 1730, 3308; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.63 (t, J=2.3 Hz, 1H), 2.93 (dd, J=2.3 Hz, J=17.2, 1H), 3.18 (dd, J=2.3 Hz, J=17.2, 1H), 3.71 (s, 3H), 4.58 (d, J=14.8 Hz, 1H), 4.89 (d, J=14.8 Hz, 1H), 6.74–6.78 (m, 2H), 7.15 (br s, 1H), 7.28–7.32 (m, 2H), 7.52–7.57 (m, 3H), 7.81–7.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 24.5 (CH_2), 43.7 (CH_2), 54.6 (CH_3), 69.9 (Cq), 71.3 (Cq), 77.2 (CH), 113.0 (2CH), 121.1 (CH), 122.9 (CH), 128.6 (CH), 128.7 (Cq), 128.7 (Cq), 129.5 (2CH), 131.3 (Cq), 131.5 (CH), 143.4 (Cq), 158.2 (Cq), 168.8 (CO), 170.3 (CO). Anal. Calcd for $C_{20}H_{17}NO_4$ (335.36): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.70; H, 5.12; N, 4.08.

*4.4.3. 2-Allyl-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**7c**)*

This product was prepared according to our previous work.[16a]

*4.4.4. 2-(Furan-2-ylmethyl)-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**7d**)*

Yellow solid; yield: 72%; mp 104–106 °C; IR (ν, cm^{-1}, $CHCl_3$) 1700, 1722, 3405; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 1.54 (t, J=2.3 Hz, 1H), 3.01 (dd, J=2.3 Hz, J=17.2, 1H), 3.20 (dd, J=2.3 Hz, J=17.2, 1H), 4.59 (d, J=14.4 Hz, 1H), 4.89 (d, J=14.4 Hz, 1H), 6.22–6.29 (m, 2H), 6.43 (br s, 1H), 7.37–6.51 (m, 4H), 7.76 (d, J=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 24.8 (CH_2), 36.9 (CH_2), 69.9 (Cq), 71.1 (CH), 76.1 (Cq), 108.9 (CH), 110.2 (CH), 121.4 (CH), 123.3 (CH), 128.9 (CH), 131.8 (CH), 134.6 (Cq), 141.7 (CH), 143.3 (Cq), 149.9 (Cq), 168.5 (CO), 170.6 (CO). Anal. Calcd for $C_{17}H_{13}NO_4$ (295.30): C, 69.15; H, 4.44; N, 4.74. Found: C, 70.07; H, 4.41; N, 4.78.

*4.4.5. 2-(1,5-Dimethyl-1H-pyrrol-2-ylmethyl)-3-oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**7e**)*

Yellow solid; yield: 98%; mp 144–146 °C; IR (ν, cm^{-1}, $CHCl_3$) 1691, 1734, 3307; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.64 (t, J=2.3 Hz, 1H), 1.82 (s, 3H, CH_3), 2.99 (dd, J=2.3 Hz, J=17.2, 1H), 3.22 (dd, J=2.3 Hz, J=17.2, 1H), 3.31 (s, 3H), 4.53 (d, J=16.4 Hz, 1H), 5.06 (d, J=16.4 Hz, 1H), 5.53 (d, J=3.3 Hz, 1H), 5.93 (d, J=3.3 Hz, 1H), 7.40–7.63 (m, 3H), 7.84 (d, J=7.8 Hz, 1H), 8.14 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 12.6 (CH_3), 24.3 (CH_2), 31.0 (CH_3), 36.5 (CH_2), 66.4 (Cq), 69.5 (Cq), 77.1 (CH), 105.2 (CH), 110.1 (CH), 121.4 (CH), 124.7 (CH), 124.9 (Cq), 130.2 (CH), 131.5 (Cq), 132.3 (Cq), 132.9 (CH), 143.8 (Cq), 169.4 (CO), 173.8 (CO). Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.37): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.76; H, 5.71; N, 8.68.

*4.4.6. 3-Oxo-1-(prop-2-ynyl)-2-(thiophen-2-ylmethyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**7f**)*

Yellow solid; yield: 97%; mp 131–133 °C; IR (ν, cm^{-1}, $CHCl_3$) 1695, 1724, 3302; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 1.68 (t, J=2.3 Hz, 1H), 3.11 (dd, J=2.3 Hz, J=17.2, 1H), 3.22 (dd, J=2.3 Hz, J=17.2, 1H), 4.84 (d, J=15.6 Hz, 1H), 5.12 (d, J=15.6 Hz, 1H), 6.83–6.87 (m, 1H), 7.06–7.16 (m, 2H), 7.46–7.63 (m, 3H), 7.83–7.87 (m, 1H), 8.26 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 25.4 (CH_2), 39.6 (CH_2), 70.4 (Cq), 72.2 (CH), 76.6 (Cq), 121.8 (CH), 124.0 (CH), 125.8 (CH), 126.5 (CH), 127.8 (CH), 129.7 (CH), 131.3 (Cq), 132.5 (CH), 138.7 (Cq), 143.1 (Cq), 169.3 (CO), 172.0 (CO). Anal. Calcd for $C_{17}H_{13}NO_3S$ (311.36): C, 65.58; H, 4.21; N, 4.50. Found: C, 65.57; H, 4.31; N, 4.54.

*4.4.7. 3-Oxo-1,2-(di-prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**7g**)*

Yellow solid; yield: 72%; mp 127–129 °C; IR (ν, cm^{-1}, $CHCl_3$) 1701, 1730, 3308; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.82 (t, J=2.3 Hz, 1H), 2.27 (t, J=2.3 Hz, 1H), 3.34 (dd, J=2.3 Hz, 18.0 Hz, 1H), 3.42 (dd, J=2.3 Hz, 18.0 Hz, 1H), 5.51 (s, 2H), 6.82 (br s, 1H), 7.51–7.65 (m, 3H), 7.83–7.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 25.3 (CH_2), 30.4 (CH_2), 70.1 (Cq), 72.4 (Cq), 73.0 (Cq), 76.8 (CH), 77.4 (CH), 121.7 (CH), 124.0 (CH), 129.7 (CH), 130.8 (Cq), 132.7 (CH), 143.1 (Cq), 169.0 (C=O), 171.5 (C=O). Anal. Calcd for $C_{15}H_{11}NO_3$ (253.26): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.00; H, 4.41; N, 3.32.

*4.4.8. 3-Oxo-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**11**)*

White solid; yield: 65%; mp 163–165 °C; IR (ν, cm^{-1}, $CHCl_3$) 1712, 1724, 3301; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 1.96 (t, J=2.3 Hz, 1H), 2.60 (dd, J=2.3 Hz, J=16.4, 1H), 3.19 (dd, J=2.3 Hz, J=16.4, 1H), 7.05 (br s, 1H), 7.38–7.54 (m, 2H), 7.62 (d, J=7.0 Hz, 1H), 7.71 (d, J=7.0 Hz, 1H), 8.22 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 39.7 (CH_2), 65.9 (Cq), 73.6 (Cq), 78.8 (CH), 122.5 (CH), 122.7 (CH), 129.1 (CH), 132.0 (CH), 132.1 (Cq), 144.6 (Cq), 169.1 (CO), 171.3 (CO). Anal. Calcd for $C_{12}H_9NO_3$ (215.21): C, 66.97; H, 4.22; N, 6.51. Found: C, 66.80; H, 4.31; N, 6.64.

*4.4.9. 2-Benzyl-1-(but-2-ynyl)-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid (**15**)*

White solid; yield: 88%; mp 98–100 °C; IR (ν, cm^{-1}, $CHCl_3$) 1692, 1735, 3155; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 1.34 (s, 3H), 2.86 (dd, J=2.3 Hz, 16.9 Hz, 1H), 3.00 (dd, J=2.3 Hz, 16.9 Hz, 1H), 4.54 (d, J=15.8 Hz, 1H), 4.91 (d, J=15.4 Hz, 1H), 6.13 (br s, 1H), 7.05–7.19 (m, 3H), 7.26–7.32 (m, 2H), 7.40–7.53 (m, 3H), 7.75–7.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 3.21 (CH_3), 25.0 (CH_2), 45.2 (CH_2), 71.1 (Cq), 71.6 (Cq), 79.7 (Cq), 121.7 (CH), 123.8 (CH), 127.3 (CH), 128.0 (2CH), 128.5 (2CH), 129.4

(CH), 131.3 (Cq), 132.3 (CH), 136.5 (Cq), 143.5 (Cq), 170.0 (C=O), 172.0 (C=O). Anal. Calcd for $C_{20}H_{17}NO_3$ (319.36): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.12; H, 5.32; N, 4.50.

4.4.10. 3-Oxo-2-(1-phenyl-ethyl)-1-(prop-2-ynyl)-2,3-dihydro-1H-isoindole-1-carboxylic acid (**20a** and **20b**)

The acid diastereoisomers were inseparable and characterized together. White solid; yield 89%; mp 83–85 °C; IR (ν, cm^{-1}, $CHCl_3$) 1694, 1730, 3308.

Min: ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.50 (t, J=2.3 Hz, 1H), 1.99 (d, J=7.0 Hz, 3H), 2.94–3.26 (m, 2H), 4.74 (q, J=7.0 Hz, 1H), 7.18–7.25 (m, 4H), 7.43–7.58 (m, 4H), 7.76–7.80 (m, 1H), 8.41 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 20.2 (CH_3), 25.3 (CH_2), 56.3 (CH), 72.1 (Cq), 72.2 (Cq), 77.1 (CH), 121.5 (CH), 123.6 (CH), 127.6 (CH), 127.8 (2CH), 128.2 (2CH), 129.5 (CH), 131.8 (CH), 132.6 (Cq), 141.6 (Cq), 142.8 (Cq), 169.6 (CO), 172.4 (CO).

Maj: ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.72 (t, J=2.3 Hz, 1H), 1.95 (d, J=7.0 Hz, 3H), 2.94–3.26 (m, 2H), 4.74 (q, J=7.0 Hz, 1H), 7.18–7.25 (m, 4H), 7.43–7.58 (m, 4H), 7.76–7.80 (m, 1H), 8.41 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 19.2 (CH_3), 25.5 (CH_2), 53.9 (CH), 70.7 (Cq), 72.4 (Cq), 77.2 (CH), 121.2 (CH), 123.7 (CH), 127.3 (CH), 127.9 (2CH), 128.1 (2CH), 129.4 (CH), 132.2 (CH), 132.3 (Cq), 140.5 (Cq), 143.3 (Cq), 169.5 (CO), 172.0 (CO). Anal. Calcd for $C_{20}H_{17}NO_3$ (319.36): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.10; H, 5.32; N, 4.28.

4.5. Typical procedure of the spirolactonization reaction

A mixture of acetylenic acid **7** or **20** (1 mmol), Ag_2CO_3 (5 mol %) in degassed toluene (5 mL) was stirred under argon atmosphere at 80 °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 lactone **8** or **21**.

4.5.1. 2′-Benzyl-5-methylidene-4,5-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (**8a**)

White solid; yield: 100%; mp 112–114 °C; IR (ν, cm^{-1}, $CHCl_3$) 1684, 1703; ^1H NMR (200 MHz, $CDCl_3$): δ 2.86 (d, J=16.4 Hz, 1H), 3.13 (dt, J=2.3 Hz, 16.4 Hz, 1H), 4.19 (d, J=15.6 Hz, 1H), 4.49 (t, J=2.3 Hz, 1H), 4.98 (t, J=2.3 Hz, 1H), 5.33 (d, J=15.6 Hz, 1H), 7.18–7.28 (m, 5H), 7.41–7.58 (m, 3H), 7.90–7.94 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.0 (CH_2), 44.3 (CH_2), 69.0 (Cq), 91.7 (CH_2), 120.5 (CH), 124.4 (CH), 127.5 (2CH), 127.8 (CH), 128.8 (2CH), 130.0 (CH), 130.1 (Cq), 132.9 (CH), 136.6 (Cq), 143.5 (Cq), 151.0 (Cq), 168.7 (CO), 170.6 (CO). Anal. Calcd for $C_{19}H_{15}NO_3$ (305.34): C, 74.74; H, 4.95; N, 4.59. Found: C, 74.72; H, 5.02; N, 4.70.

4.5.2. 2′-(4-Methoxybenzyl)-5-methylidene-4,5-dihydrospiro-[furan-1′,3-isoindol-3′-one]-2-one (**8b**)

White solid; yield: 89%; mp 117–119 °C; IR (ν, cm^{-1}, $CHCl_3$) 1683, 1702; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.87 (d, J=16.4 Hz, 1H), 3.18 (dt, J=2.3 Hz, J=16.4 Hz, 1H), 3.78 (s, 3H), 4.19 (d, J=15.6 Hz, 1H), 4.51 (t, J=2.3 Hz, 1H), 5.00 (t, J=2.3 Hz, 1H), 5.27 (d, J=15.6 Hz, 1H), 6.80–6.88 (m, 2H), 7.15–7.25 (m, 2H), 7.42–7.47 (m, 1H), 7.52–7.60 (m, 2H), 7.91–7.98 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 34.9 (CH_2), 43.6 (CH_2), 55.1 (CH_3), 68.9 (Cq), 91.6 (CH_2), 114.1 (2CH), 120.4 (CH), 124.3 (CH), 128.5 (Cq), 129.0 (2CH), 129.9 (CH), 130.2 (Cq), 132.9 (CH), 143.6 (Cq), 151.1 (Cq), 159.2 (Cq), 168.5 (CO), 170.7 (CO). Anal. Calcd for $C_{20}H_{17}NO_4$ (335.36): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.70; H, 5.16; N, 4.20.

4.5.3. 2′-Allyl-5-methylidene-4,5-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (**8c**)

White solid; yield: 80%; mp 104–106 °C; IR (ν, cm^{-1}, $CHCl_3$) 1684, 1703; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 3.00 (d, J=16.4 Hz, 1H), 3.51 (dt, J=2.3 Hz, J=16.4 Hz, 1H), 4.00 (dd, J=16.2, J=6.0 Hz, 1H), 4.29 (dd, J=16.2, J=6.0 Hz, 1H), 4.56 (t, J=2.3 Hz, 1H), 4.98 (t, J=2.3 Hz, 1H), 5.13–5.21 (m, 2H), 5.77–5.90 (m, 1H), 7.37–7.40 (m, 1H), 7.45–7.54 (m, 2H), 7.80 (d, J=7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 33.6 (CH_2), 42.3 (CH_2), 67.5 (Cq), 90.7 (CH_2), 117.3 (CH_2), 119.4 (CH), 123.3 (CH), 129.0 (CH), 129.4 (Cq), 131.8 (CH), 131.9 (CH), 142.6 (Cq), 150.0 (Cq), 167.0 (CO), 170.1 (CO). Anal. Calcd for $C_{15}H_{13}NO_3$ (255.28): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.70; H, 5.21; N, 5.38.

4.5.4. 2′-(Furan-2-ylmethyl)-5-methylidene-4,5-dihydrospiro-[furan-1′,3-isoindol-3′-one]-2-one (**8d**)

Yellow solid; yield: 78%; mp 148–150 °C; IR (ν, cm^{-1}, $CHCl_3$) 1681, 1708; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.90 (d, J=16.2 Hz, 1H), 3.30 (d, J=16.2 Hz, 1H), 4.43 (dt, J=2.3 Hz, J=16.2 Hz, 1H), 4.52 (t, J=2.3 Hz, 1H), 4.98 (m, 2H), 6.27–6.30 (m, 2H), 7.35–7.37 (m, 1H), 7.40–7.49 (m, 3H), 7.81–7.83 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 34.5 (CH_2), 36.8 (CH_2), 68.4 (Cq), 91.6 (CH_2), 109.8 (CH), 110.9 (CH), 120.4 (CH), 124.4 (CH), 130.0 (CH+Cq), 133.0 (CH), 142.6 (CH), 143.9 (Cq), 149.0 (Cq), 151.3 (Cq), 168.2 (CO), 170.5 (CO). Anal. Calcd for $C_{17}H_{13}NO_4$ (295.30): C, 69.15; H, 4.44; N, 4.74. Found: C, 70.02; H, 4.50; N, 4.68.

4.5.5. 2′-(1,5-Dimethyl-1H-pyrrol-2-ylmethyl)-5-methylidene-4,5-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (**8e**)

Yellow solid; yield: 99%; mp 145–147 °C; IR (ν, cm^{-1}, $CHCl_3$) 1688, 1708; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.16 (s, 3H), 2.90 (d, J=16.4 Hz, 1H), 3.34–3.38 (m, 4H, 1H), 4.51 (t, J=2.3 Hz, 1H), 4.52 (d, J=15.6 Hz, 1H), 4.93 (t, J=2.3 Hz, 1H), 5.10 (d, J=15.6 Hz, 1H), 5.65 (d, J=3.9 Hz, 1H), 5.97 (d, J=3.9 Hz, 1H), 7.33–7.41 (m, 1H), 7.47–7.58 (m, 2H), 7.84–7.88 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 12.4 (CH_3), 30.2 (CH_3), 33.2 (CH_2), 35.7 (CH_2), 67.3 (Cq), 91.1 (CH_2), 105.2 (CH), 109.4 (CH), 120.28 (CH), 123.7 (Cq), 124.2 (CH), 129.8 (CH), 130.1 (Cq), 131.6 (Cq), 132.9 (CH), 144.5 (Cq), 151.0 (Cq), 167.8 (CO), 169.7 (CO).

Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.37): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.87; H, 5.61; N, 8.78.

4.5.6. 2′-(Thiophen-2-ylmethyl)-5-methylidene-4,5-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (**8f**)

Yellow solid; yield: 87%; mp 148–150 °C; IR (ν, cm^{-1}, $CHCl_3$) 1686, 1704; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.96 (d, J=16.4 Hz, 1H), 3.33 (dt, J=2.3 Hz, J=15.6 Hz, 1H), 4.50 (d, J=16.4 Hz, 1H), 4.57 (t, J=2.3 Hz, 1H), 5.03 (t, J=2.3 Hz, 1H), 5.38 (d, J=15.6 Hz, 1H), 6.91–6.95 (m, 1H), 7.01–7.03 (m, 1H), 7.23–7.25 (m, 1H), 7.43–7.47 (m, 1H), 7.51–7.58 (m, 2H), 7.89–7.95 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 35.0 (CH_2), 39.2 (CH_2), 68.8 (Cq), 91.8 (CH_2), 120.5 (CH), 124.4 (CH), 126.1 (CH), 126.8 (CH), 126.9 (CH), 129.9 (Cq), 130.0 (CH), 133.0 (CH), 139.2 (Cq), 143.6 (Cq), 151.1 (Cq), 168.1 (CO), 170.5 (CO). Anal. Calcd for $C_{17}H_{13}NO_3S$ (311.36): C, 65.58; H, 4.21; N, 4.50. Found: C, 65.64; H, 4.19; N, 4.48.

4.5.7. 2′-(Prop-2-ynyl)-5-methylidene-4,5-dihydrospiro-[furan-1′,3-isoindol-3′-one]-2-one (**8g**)

White solid; yield: 74%; mp 133–135 °C; IR (ν, cm^{-1}, $CHCl_3$) 1683, 1713; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.33 (t, J=2.3 Hz, 1H), 3.11 (d, J=16.4 Hz, 1H), 4.01 (dt, J=2.3 Hz, J=16.4 Hz, 1H), 4.13 (dd, J=2.3 Hz, J=18.0, H), 4.66 (t, J=2.3 Hz, 1H), 4.71 (dd, J=3.1 Hz, J=18.0 Hz, 1H), 5.08 (t, J=2.3 Hz, 1H), 7.37–7.40 (m, 1H), 7.44–7.63 (m, 3H), 7.85–7.87 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 29.7 (CH_2), 34.6 (CH_2), 68.4 (Cq), 73.8 (Cq), 77.4 (CH), 92.0 (CH_2), 120.4 (CH), 124.4 (CH), 129.6 (Cq), 130.1 (CH), 133.2 (CH), 143.6 (Cq), 151.1 (Cq), 167.6 (CO), 170.6 (CO). Anal. Calcd for $C_{15}H_{11}NO_3$ (253.26): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.00; H, 4.35; N, 5.58.

4.5.8. 2′-H-5-Methylidene-4,5-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (**13**)

The CH_2Cl_2 was used as solvent for this reaction. White solid; yield: 40%; mp 136–138 °C; IR (ν, cm^{-1}, $CHCl_3$) 1696, 1722; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 3.3 (d, J=16.4 Hz, 1H), 3.43 (dt, J=2.3 Hz, J=16.4, 1H), 4.66 (t, J=2.3 Hz, 1H), 5.08 (t, J=2.3 Hz, 1H), 6.65 (br, 1H), 7.46–7.50 (m, 1H), 7.57–7.63 (m, 2H), 7.86–7.92 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 37.5 (CH_2), 68.22 (Cq), 92.1 (CH_2), 120.9 (CH), 124.6 (CH), 130.2 (CH), 133.4 (CH), 134.0 (Cq), 143.4 (Cq), 151.3 (Cq), 169.3 (CO), 171.4 (CO). Anal. Calcd for $C_{12}H_9NO_3$ (215.21): C, 66.97; H, 4.22; N, 6.51. Found: C, 66.94; H, 4.19; N, 6.48.

4.5.9. 2′-Benzyl-6-methyl-3,4-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (**16**)

Gummy solid; yield: 34%; IR (ν, cm^{-1}, $CHCl_3$) 1682, 1709; ^1H NMR (300 MHz, $CDCl_3$): δ 1.68 (m, $J_{H(CH3)-H4}$=2.0 Hz, $J_{H(CH3)-H4'}$=2.0 Hz, $J_{H(CH3)-H5}$=2.3 Hz, 3H), 2.45–2.85 (m, 2H), 4.27 (d, J=15.6 Hz, 1H), 4.40 (m, J_{H5-H4}=2.0 Hz, $J_{H5-H(CH3)}$=2.3 Hz, $J_{H5-H4'}$=7.0 Hz, 1H), 5.39 (d, J=15.6 Hz, 1H), 7.16–7.28 (m, 5H), 7.41–7.56 (m, 3H), 7.90–7.93 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.1 (CH_3), 31.2 (CH_2), 41.4 (CH_2), 72.1 (Cq), 112.9 (CH), 122.33 (CH), 122.6 (CH), 126.5 (CH), 127.0 (2CH), 127.4 (CH), 127.7 (2CH), 129.2 (Cq), 130.5 (CH), 131.0 (Cq), 136.0 (Cq), 143.7 (Cq), 167.5 (CO), 170.9 (CO).

4.5.10. 2′-Benzyl-5-eth-(Z)ylidene-4,5-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (E-**17**)

The lactone diastereoisomers were inseparable and characterized together. White solid; yield 38%; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (m, $J_{H(CH3)-H4}$=2.3 Hz, $J_{H(CH3)-H4'}$= 2.3 Hz, $J_{H(CH3)-Ha}$=7.0 Hz, 1H), 2.27 (qd, $J_{H4-H(CH3)}$= 2.3 Hz, $J_{H4-H4'}$=15.6 Hz, 1H), 3.08 (m, $J_{H4'-H(CH3)}$=2.3 Hz, $J_{H4'-Ha}$=2.3 Hz, $J_{H4'-H4}$=15.6 Hz, 1H), 4.18 (d, J=15.6 Hz, 1H), 4.76 (qd, $J_{Ha-H4'}$=2.3 Hz, $J_{Ha-H(CH3)}$=7.0 Hz, 1H), 5.30 (d, J=15.6 Hz, 1H), 7.18–7.28 (m, 5H), 7.40–7.55 (m, 3H), 7.90–7.94 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.3 (CH_3), 34.0 (CH_2), 43.3 (CH_2), 67.9 (Cq), 101.3 (CH), 119.6 (CH), 123.4 (CH), 126.5 (2CH), 126.8 (CH), 127.7 (2CH), 128.9 (CH), 129.3 (Cq), 131.8 (CH), 135.8 (Cq), 142.7 (Cq), 148.2 (Cq), 167.7 (CO), 169.9 (CO).

4.5.11. 2′-Benzyl-5-eth-(Z)ylidene-4,5-dihydrospiro[furan-1′,3-isoindol-3′-one]-2-one (Z-**17**)

^1H NMR (300 MHz, $CDCl_3$): δ 1.95–2.05 (m, J=2.3 Hz, J=7.0 Hz, 3H), 2.74–2.83 (m, 2H), 4.14 (d, J=16.4 Hz, 1H), 5.03–5.10 (m, 2.3 Hz, J=7.0 Hz, 1H) 5.50 (d, J=16.4 Hz, 1H), 7.23–7.29 (m, 5H), 7.53–7.64 (m, 3H), 7.92–7.97 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.3 (CH_3), 30.1 (CH_2), 44.6 (CH_2), 66.6 (Cq), 98.5 (CH), 121.5 (CH), 124.5 (CH), 127.2 (2CH), 127.5 (CH), 128.6 (2CH), 129.9 (CH), 130.7 (Cq), 132.4 (CH), 138.0 (Cq), 143.8 (Cq), 149.6 (Cq), 165.6 (CO), 168.6 (CO).

4.5.12. 2′-(1-Phenyl-ethyl)-5-methylidene-4,5-dihydrospiro-[furan-1′,3-isoindol-3′-one]-2-one (**21a** and **21b**)

Yield: 84%.

4.5.12.1. 2′-(1-Phenyl-ethyl)-5-methylidene-4,5-dihydrospiro-[furan-1′,3-isoindol-3′-one]-2-one (**21a**).

White solid; mp 123–125 °C; IR (ν, cm^{-1}, $CHCl_3$) 1678.6, 1704.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.97 (d, J=7.0 Hz, 3H), 2. 89 (d, J=16.4 Hz, 1H), 3.31 (dt, J=2.3 Hz, 16.4 Hz, 1H), 4.46 (q, J=7.0 Hz, 1H), 4.49 (t, J=2.3 Hz, 1H), 4.96 (t, J=2.3 Hz, 1H), 7.18–7.28 (m, 3H), 7.33–7.38 (m, 3H), 7.44–7.52 (m, 2H), 7.78–7.81 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 20.0 (CH_3), 34.8 (CH_2), 55.8 (CH), 70.5 (Cq), 91.9 (CH_2), 120.3 (CH), 124.1 (CH), 126.6 (2CH), 127.5 (CH), 128.7 (2CH), 130.0 (CH), 131.5 (Cq), 132.7 (CH), 141.6 (Cq), 143.2 (Cq), 151.0 (Cq), 168.5 (C=O), 171.2 (C=O). Anal. Calcd for $C_{20}H_{17}NO_3$ (319.36): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.12; H, 5.34; N, 4.44.

4.5.12.2. 2′-(1-Phenyl-ethyl)-5-methylidene-4,5-dihydrospiro-[furan-1′,3-isoindol-3′-one]-2-one (**21b**).

White solid; mp 160–162 °C; IR (ν, cm^{-1}, $CHCl_3$) 1691.1, 1702.0; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.73 (d, J=7.0 Hz, 3H), 2.68 (d, J=16.4 Hz, 1H), 3.03 (dt, J=2.3 Hz, 16.4 Hz, 1H), 4.39 (t,

J=2.3 Hz, 1H), 4.92 (t, J=2.3 Hz, 1H), 5.75 (q, J=7.0 Hz, 1H), 7.19–7.34 (m, 6H), 7.46–7.52 (m, 2H), 7.84–7.87 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 17.1 (CH_3), 34.4 (CH_2), 50.0 (CH), 67.8 (Cq), 91.5 (CH_2), 120.1 (CH), 124.4 (CH), 126.7 (2CH), 127.7 (CH), 128.7 (2CH), 129.9 (CH), 130.3 (Cq), 132.9 (CH), 140.8 (Cq), 144.4 (Cq), 151.2 (Cq), 168.6 (C=O), 172.0 (C=O). Anal. Calcd for $C_{20}H_{17}NO_3$ (319.36): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.09; H, 5.33; N, 4.34.

*4.5.12.3.3-(Prop-2-ynyl)-2,3-dihydro-isoindol-1-one (**12**).* White solid, yield 100%; mp 179–181 °C; IR (ν, cm^{-1}, $CHCl_3$) 1700; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 2.04 (t, J=2.3 Hz, 1H), 2.42 (ddd, J=2.3 Hz, J=7.8 Hz, J=17.1 Hz, 1H), 2.70 (ddd, J=2.3 Hz, J=5.4 Hz, J=17.1 Hz, 1H), 4.67 (dd, J=5.4 Hz, J=7.8, 1H), 6.66 (br s, 1H), 7.39–7.55 (m, 3H), 7.79 (d, J=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 25.2 (CH_2), 55.1 (CH), 71.3 (Cq), 77.2 (CH), 122.5 (CH), 124.0 (CH), 128.8 (CH), 132.1 (CH), 133.6 (Cq), 146.3 (Cq), 171.8 (C=O). Anal. Calcd for $C_{11}H_9NO$ (171.20): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.09; H, 5.33; N, 8.34.

Acknowledgements

The authors are grateful to Dr. V. Dalla for many fruitful discussions throughout the course of this work.

References and notes

1. (a) Kupchan, S. M.; Britto, R. W.; Ziegler, M. P.; Gilmore, C. J.; Restivo, R. G.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 1335; (b) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1975**, 1539; (c) Niwa, M.; Iguchi, M.; Yamamura, S. *Chem. Lett.* **1975**, 655; (d) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1975**, 4395; (e) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560; (f) Mason, C. P.; Edwards, K. R.; Carlson, R. E.; Pignatello, J.; Gleason, F. K.; Wood, J. M. *Science (Washington, D.C.)* **1982**, *215*, 400; (g) Jellal, A.; Grimaldi, J.; Santelli, M. *Tetrahedron Lett.* **1984**, 3179; (h) Hirota, A.; Nakagawa, M.; Hirota, A. *Agric. Biol. Chem.* **1991**, *55*, 1187; (i) Anderson, J. E.; Ma, W.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1992**, *55*, 71.
2. For recent reviews on γ-lactone, see: (a) Negishi, E. I.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707; (b) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377; (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; (d) He, Ch.; Li, Z. *Eur. J. Org. Chem.* **2006**, *19*, 4313.
3. For the use of gold catalyst see: (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J. P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112; (b) Harkat, H.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273; (c) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; Van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979.
4. For the use of silver catalysts see: (a) Castaner, J.; Pascual, J. *J. Chem. Soc.* **1968**, 3962; (b) Willioard, P. G.; Jong, T. T.; Porwoll, J. P. *J. Org. Chem.* **1984**, *49*, 736; (c) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447; (d) Kinsman, R.; Lathbury, D.; Vermon, V.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243; (e) Huang, P. Q.; Zhou, W. S. *Tetrahedron: Asymmetry* **1991**, *2*, 875; (f) Dai, W.; Katzenellenbogen, A. *J. Org. Chem.* **1991**, *56*, 6893; (g) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1994**, *35*, 3525; (h) Westermann, B.; Dubbrke, S. *Liebigs Ann. Recueil* **1997**, 375; (i) Dalla, V.; Pale, P. *New J. Chem.* **1999**, *23*, 803; (j) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533; (k) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019; (l) Anastasia, L.; Xu, C.; Negishi, E. I. *Tetrahedron Lett.* **2002**, *43*, 5673; (m) Haga, Y.; Okazaki, M.; Shuto, Y. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 2183; (n) Oh, C. O.; Yi, H. J.; Lee, J. H. *New J. Chem.* **2007**, *31*, 835.
5. For the use of mercury catalysts, see: (a) Ref. 1e. (b) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114; (c) Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459; (d) Yamamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 582; (e) Ref. 1h; (f) Sofia, M. J.; Katzenellenbogen, J. A. *J. Org. Chem.* **1984**, *50*, 2331; (g) Spencer, R. W.; Tam, T. F.; Thomas, E.; Robinson, W. J.; Krantz, A. *J. Am. Chem. Soc.* **1986**, *108*, 5589.
6. For the use of rhodium catalysts, see: (a) Marder, T. B.; Chan, D. M.-T.; Fultz, W. C.; Calabrese, J. C.; Mibtein, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1885; (b) Chan, D. M.-T.; Marder, T. B.; Mibtein, D.; Taylor, N. J. *J. Am. Chem. Soc.* **1987**, *109*, 6385; (c) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.* **2000**, *607*, 97.
7. For the use of palladium catalysts, see: (a) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323; (b) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753; (c) Negishi, E. I.; Kotora, M. *Synthesis* **1997**, 121; (d) Tsuda, T.; Ohashi, Y.; Nagahama, N.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 2650; (e) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 967; (f) Mandai, T.; Ohta, K.; Baba, N.; Kawada, M.; Tsuji, J. *Synlett* **1992**, 671; (g) Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron Lett.* **1992**, *33*, 2811; (h) Bouyssi, D.; Goré, J.; Balme, G.; Louis, D.; Wallach, J. *Tetrahedron Lett.* **1993**, *34*, 3129; (i) Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2123; (j) Cavicchioli, M.; Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron Lett.* **1996**, *37*, 1429.
8. Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353.
9. (a) Anzini, M.; Capelli, A.; Vomero, S.; Giorgi, G.; Langer, T.; Bruni, G.; Romero, M. R.; Basile, A. S. *J. Med. Chem.* **1996**, *39*, 4275; (b) Gotor, V.; Limeres, F.; Garcia, R.; Bayod, M.; Brieva, R. *Tetrahedron: Asymmetry* **1997**, *8*, 995.
10. Goa, K. I.; Heel, R. C. *Drugs* **1986**, *32*, 48.
11. (a) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779; (b) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346 and references cited therein; (c) Grigg, R.; Basher Sarker, M. A. *Tetrahedron* **2006**, *62*, 10332; (d) Paquette, L. A. *Aust. J. Chem.* **2004**, *57*, 17; (e) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533; (f) Kisel, V. M.; Kostyrko, E. O.; Kovtunenko, V. A. *Chem. Heterocycl. Comp.* **2002**, *38*, 1295; (g) Singh, S. B.; Zink, D. L.; Huber, J.; Genilloud, O.; Salazar, O.; Diez, M. T.; Basilio, A.; Vicente, F.; Byrne, K. M. *Org. Lett.* **2006**, *8*, 5449; (h) Michaut, M.; Santelli, M.; Parrain, J. L. *Tetrahedron Lett.* **2003**, *44*, 2157; (i) Zhang, W.; Pugh, G. *Tetrahedron.* **2003**, *59*, 4237; (j) Michaut, M.; Santelli, M.; Parrain, J. L. *J. Organomet. Chem.* **2000**, *606*, 93; (k) Martin-Lopez, M. J.; Bermejo, F. *Tetrahedron* **1998**, *54*, 12379.
12. (a) Zhang, X.; Shiraishi, Y.; Hirai, T. *Org. Lett.* **2007**, *9*, 5039; (b) Lee, M. H.; Wu, J.-S.; Lee, J. W.; Jung, J. H.; Kim, J. S. *Org. Lett.* **2007**, *9*, 2501; (c) Soh, J. H.; Swamy, K. M. K.; Kim, S. K.; Kim, S.; Lee, S.-H.; Yoon, J. *Tetrahedron Lett.* **2007**, *48*, 5966; (d) Zhang, X.; Shiraishi, Y.; Hirai, T. *Tetrahedron Lett.* **2007**, *48*, 5455; (e) Bae, S.; Tae, J. *Tetrahedron Lett.* **2007**, *48*, 5389; (f) Zhang, M.; Gao, Y.-H.; Li, M.-Y.; Yu, M.-X.; Li, F.-Y.; Li, L.; Zhu, M.-W.; Zhang, J.-P.; Yi, T.; Huang, C.-H. *Tetrahedron Lett.* **2007**, *48*, 3709; (g) Xiang, Y.; Tong, A.-J.; Jin, P.-Y.; Ju, Y. *Org. Lett.* **2006**, *8*, 2863; (h) Xiang, Y.; Tong, A.-J. *Org. Lett.* **2006**, *8*, 1549; (i) Zheng, H.; Qian, Z.-H.; Xu, L.; Yuan, F.-F.; Lan, L.-D.; Xu, J.-G. *Org. Lett.* **2006**, *8*, 859; (j) Kwon, J. Y.; Jang, Y. J.; Lee, Y. J.; Kim, K. M.; Seo, M. S.; Nam, W.; Yoon, J. *J. Am. Chem. Soc.* **2005**, *127*, 10107.
13. (a) Wu, J.-S.; Hwang, I.-C.; Kim, K. S.; Kim, J. S. *Org. Lett.* **2007**, *9*, 907; (b) Ko, S.-K.; Yang, Y.-K.; Tae, J.; Shin, I. *J. Am. Chem. Soc.* **2006**, *12*, 14150; (c) Yang, Y.-K.; Yook, K.-J.; Tae, J. *J. Am. Chem. Soc.* **2005**, *127*, 16760; (d) Dujols, V.; Ford, F.; Czarnik, A. W. *J. Am. Chem. Soc.* **1997**, *119*, 7386.
14. Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, S. *J. Med. Chem.* **1992**, *35*, 4613.
15. (a) Tranchant, M. J.; Moine, C.; Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Tetrahedron Lett.* **2006**, *47*, 4477; (b) Ben Othman, R.;

Fousse, A.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825; (c) Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335; (d) Akué-Gédu, R.; Al Akoum Ebrik, S.; Witczak-Legrand, A.; Fasseur, D.; El Ghammarti, S.; Couturier, D.; Decroix, B.; Othman, M.; Debacker, M.; Rigo, B. *Tetrahedron* **2002**, *58*, 9239.

16. (a) Ben Othman, R.; Othman, M.; Decroix, B. *Tetrahedron* **2008**, *64*, 559; (b) Othman, M.; Pigeon, P.; Decroix, B. *Tetrahedron* **1998**, *54*, 8737; (c) Othman, M.; Decroix, B. *Synth. Commun.* **1996**, *26*, 2803.
17. Couture, A.; Deniau, E.; Ionescu, D.; Grandclaudon, P. *Tetrahedron Lett.* **1998**, *39*, 2319.
18. Phthalimidine **9** could be prepared by using BBr_3 (more toxic then TFA) according to our previous work (see Ref. 16c).
19. Crystal data for **21b** $C_{20}H_{17}NO_3$ (193 K): orthorombic, $P2_12_12_1$, a=6.963(2), b=13.324(5), c=17.853(6) Å, $\alpha=\beta=\gamma=90°$, wavelength: 0.71073 Å, V=1656.3(10) Å^3, Z=4, D_c=1.281 Mg/m^3, 14435 reflections, 2921 unique reflections; 2422 with $I>2\sigma(I)$; structure refined by full-matrix least-squares on F^2 to give final indices R_1=0.0588 and wR_2=0.1493 (all data). Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 646997 for compound **21b**. Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk.