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A new synthetic procedure to spiro[cyclohexane-1,3′-indoline]-2′,4-diones

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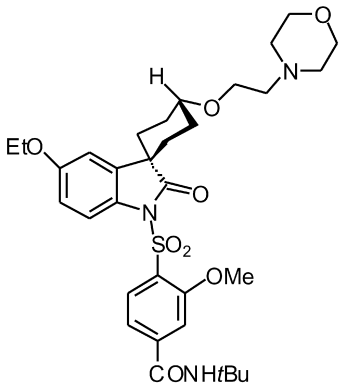
Abstract—A new synthetic pathway to spiro[cyclohexane-1,3′-indoline]-2′,4-diones was found starting from 3-chloromethylene-2-indolones **1** and Danishefsky's diene **2**. Their synthesis consists of several steps involving the formation of the cycloadducts, the 6-chloro-4-trimethylsilyloxy-2-methoxyspiro[cyclohex-3-en-1,3′-indolin]-2′-one derivatives, transformed into spiro[cyclohexa-2,5-dien-1,3′-indoline]-2′,4-diones *via* 6-chloro-spiro[cyclohex-2-en-1,3′-indoline]-2′,4-dione intermediates. The reduction of spiro[cyclohexa-2,5-dien-1,3′-indoline]-2′,4-diones gave spiro[cyclohexane-1,3′-indoline]-2′,4-diones **7**. Using a 'one pot reaction', starting from **1** and **2**, compounds **7** were obtained in satisfactory overall yield. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Much work[1] was carried out in our laboratory on the reactivity and synthetic potential of substituted methylene-2-indolones, particularly on [4+2]π cycloaddition reactions of 3-chloromethylene-2-indolones with several dienes.[2] As a further development of our continuing studies in this field, we now report on a new synthetic pathway for the straightforward and effective preparation of derivatives of spiro[cyclohexane-1,3′-indoline]-2′,4-dione **7**,**8** through their spiro-cyclohexene and/or cyclohexadiene derivatives.

Different synthetic strategies for the preparation of spiro [cyclohexane-1,3′-indolin]-2′-ones are known[3] but the introduction of the keto function on C-4 of the cyclohexane ring is not obvious. The synthesis of spiro[cyclohexane-1,3′-indoline]-2′,4-dione nucleus is of general interest. For example, the highly potent and selective vasopressin V2-receptor antagonist SR 121463 A contains a hydroxy group at the 4-position. The importance of the above compound is extensively documented by recent literature,[4] mostly in patents, and the synthetic approaches reported for its preparation made use of the corresponding keto compound reduced to the 4-hydroxy derivative.



SR 121463 A

Two different synthetic strategies were known for the preparation of spiro[cyclohexane-1,3′-indolin]-2′,4-dione ring i.e. starting either from a preexisting 4-oxo protected cyclohexyl derivative or from an oxindole. Two examples of the first type were reported: one from tetrahydrospiro [cylohexane-1,4′-isoquinoline]-1′,3′,4-triones using sodium hypochlorite in basic conditions.[4i,j] Alternatively, Fischer indolization of cyclohexylcarbohydrazides using Brunner reaction was used.[4e] When an oxindole was the starting material, the condensation reactions with protected 1,5-dihalopentan-3-one[4a,g] or with acrylate were followed by Dieckmann condensation of the resulting diester, hydrolysis and decarboxylation[4b,c,k,l] to obtain the cyclohexane ring.

Based on our previous experience on the reactivity of 3-chloromethylene-2-indolones **1**[2] in the cycloaddition reaction using Danishefsky's diene **2** which allows

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functionalization of the cyclohexane ring with an oxygen atom,[5] we were able to prepare compounds **7**,**8** through the unsaturated spiro[cyclohexene- and cyclohexadiene-1,3′-indoline]-2′,4-diones. Although the monounsaturated spiro compounds are known,[6] to our knowledge, the spiro cyclohexadiene derivatives have never been prepared. Interestingly, even if the final spiroketones **7** were prepared through many intermediates, which may be isolated in some cases, the one-pot synthesis was successfully performed. Furthermore, starting from 3-chloromethylene-2-indolone functionalized at the methylenic carbon, it is possible to introduce a further substituent on the cyclohexyl ring.

2. Results and discussion

The cycloaddition reaction of **1a** with Danishefsky's diene **2** using standard conditions (i.e. CH_2Cl_2, $EtAlCl_2$, 25°C),[2] resulted in decomposition of the diene. The reaction was successful when **1a** and **2** were heated in refluxing toluene. The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of two cycloadducts **3a** and **3′a** (2:3 ratio). By purification on silica gel of the crude reaction mixture, only transformation products of the primary cycloadducts were isolated. In fact, a small amount of spiro compound **4** was isolated accompanied by a major amount of biphenyl derivatives **5a**,**5b** (Scheme 1). Their formation is explained by silica gel-catalyzed hydrolysis of the silyl group on the primary cycloadducts **3a/3′a** giving the corresponding keto derivatives which, on methanol elimination, were transformed into the unsaturated ketone **4**. However, compound **4** is relatively unstable and equilibrates to the corresponding enol, thus favouring spontaneous chloride elimination and opening of the heterocyclic ring by addition of water or methanol to the carbonyl group giving the biphenyl compounds **5a** and **5b**, respectively. This pathway is in agreement with the mechanism already reported for the formation of biphenyl derivatives from chlorospirocyclohexeneindolones obtained from dienes different from **2**.[2] It has to be emphasised that in this case the formation of the biphenyl compound does not require the use of an added base because the aromatization of the diene intermediate is easy and spontaneous.

The isolation of spiroketone was possible following a different strategy. In fact compound **7a** was obtained in 57% overall yield using the 'one pot reaction' consisting in several steps described below which can be monitored by ^{1}H NMR spectroscopy. The cycloaddition reaction of **1a** and **2** was performed as described above, but operating in a sealed tube. Then, to the reaction mixture was added a catalytic amount of *p*-toluenesulfonic acid and heating was continued. The reaction resulted in the formation of the semiquinone **6a** (Scheme 1). Compound **6a** was not isolated and was directly hydrogenated with hydrogen and Pd/C at room temperature and 1 atm. The purification of the crude reaction mixture on silica gel gave two fractions containing a minor amount of the biphenyl derivatives **5c**,**5d** (about 20%, variable ratio) and the stable saturated ketone **7a**, respectively. All attempts to purify intermediate **6a** by column chromatography resulted in its transformation into a mixture of the biphenyl derivatives **5**. The formation of compounds **5c**,**5d**, bearing a methoxy group, is explained by considering that **5a** and **5b** are easily eterified by methanol and *p*-TSA in anhydrous conditions. Based on these and previous results, we can affirm that the cycloaddition reaction is regioselective, that a *trans* relationship between the chlorine atom and the carbonyl group of oxindole exists[2] and that the formation of two diastereomers **3/3′a** is ascribed to the use of a mixture of geometrical isomers **2**. Obviously, their formation is not relevant in view of the final outcome.

In order to evaluate the possibility to functionalize the cyclohexyl ring with a second substituent, oxindole **1b** bearing an ethoxycarbonyl group on the methylene carbon was reacted with **2** (Scheme 2). The cycloaddition reaction was slower than with **1a** and gave a mixture of cycloadducts **3b**. The ^{1}H NMR spectrum was very complicated and the instability of the cycloadducts made it impossible to assign all signals. Of relevance, four signals in the δ 5.25–5.02 region associated with H-6 were present in 1:6:1:2 ratio.

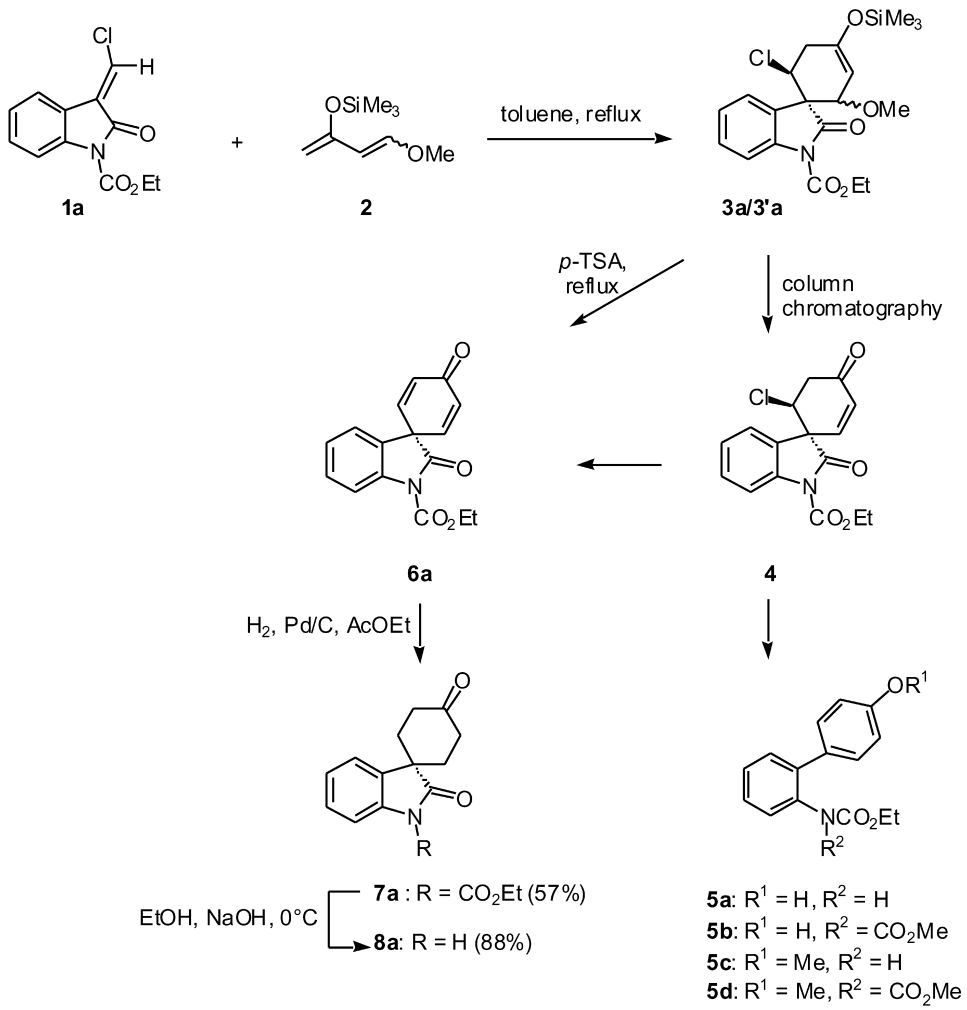
The mixture of cycloadducts **3b** was heated with *p*-toluenesulfonic acid giving compound **6b** (51%) which is more stable than **6a** and could be purified by column chromatography.

As for the synthesis of **7a**, a one-pot reaction procedure was considered starting from **1b** and **2**. Cycloadducts **3b** were obtained which were transformed into **6b** then hydrogenated. However, the catalytic reduction of compound **6b** is more complicated than the reduction of **6a** both considering the possibility to obtain a diastereomeric mixture of saturated compounds **7′** and because of the presence of the ethoxycarbonyl group which has caused the formation of by-products. For this reason, this reaction has been extensively studied (Table 1). The reduction of pure **6b** in ethyl acetate gave as the main products two diastereomers **7b** and **7′b** (Table 1, entry 1) which were partially deprotected at the nitrogen atom giving **8b** and **8′b** during chromatographic separation using AcOEt/cyclohexane as the eluent, as by-products, a mixture of the isomeric unsaturated alcohols **10a** and **10′a** and traces of **11** were also obtained (Scheme 2). The formation of compounds **10/10′a** can be explained by considering a partial reduction of the semiquinoid ring giving intermediate **9** (see below), and further reduction at its keto function. The mixture of allylic alcohols **10/10′a** could be reduced to **11**. The hydrogenation of the crude reaction mixture containing **6b** (Table 1, entries 2 and 3) resulted in the formation of intermediate **9**, compounds **7/7′b** and the alcohols **10/10′a**. The distribution of these compounds depends on the hydrogenation solvent. When toluene (entry 3) was used, the main product was the

Table 1. Reduction of unsaturated ketones **6b** and **9**

Compound	Method	**7b/7′b** yield (ratio)	**9** yield (%)	**10/10′**: yield (ratio)	**11**: yield
6b[a]	A[c]	60 (75:25)	–	**a**: 15 (20:80)	3.6
6b[b]	A[c]	30 (75:25)	7.5	**a**: 13.7 (20:80)	–
6b[b]	B[c]	20 (75:25)	24	**a**: 11 (20:80)	–
9	C[c]	–	–	**b**: 98 (60:40)	–

[a] Pure compound.
[b] Crude reaction mixture.
[c] A: H_2, Pd/C, AcOEt; B: H_2, Pd/C, toluene; C: $NaBH_4$, $CeCl_3$, EtOH, −78°C.



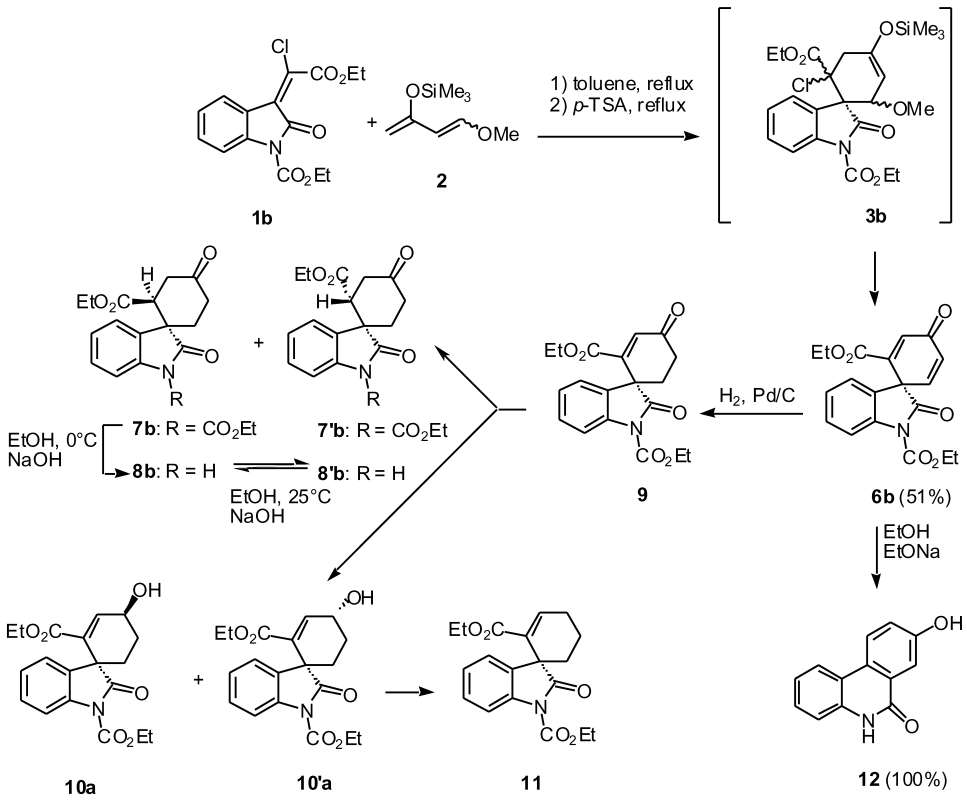
Scheme 1.

unsaturated ketone **9**. Minor amounts of **10/10′a** and **7/7′b** were formed. Instead, by working with ethyl acetate (entry 2) the main compounds were **7/7′b** besides **9** and **10/10′a**.

Both to confirm the structure of alcohols **10/10′a** and most of all to evaluate the possibility to change their diastereomeric ratio, sodium borohydride was used in the presence of $CeCl_3$ at −78°C as the reductant starting from **9** (Scheme 3). This gave a mixture of the two diastereomers **10b/10′b** (60:40 ratio), deprotected at the nitrogen atom. Comparing the ^{1}H NMR spectrum ($CDCl_3$) of this mixture (**10b**: H-4, δ 4.70–4.60; **10′b**: H-4, δ 4.60–4.50) with the spectrum of the crude reaction mixture derived from the *N*-deprotection reaction (see below) of a mixture of compounds **10a/10′a** obtained via the catalytic reduction, it was found that **10b** is the major isomer in the first case (**10b/10′b**, 60:40 from **9** and $NaBH_4$) and **10′b** is the major one via *N*-deprotection of **10a/10′a** (**10b/10′b**, 20:80). These data show the possibility to favour one diastereomer with respect to the other by suitable selection of the reducing agent.

Deprotection at the nitrogen atom in **7a**, **7b/7′b** and **10a/10′a**, was done with ethanol and a base. The use of triethylamine was unsuccessful as well as the use of sodium ethoxide which gave only degradation products. The use of sodium hydroxide in ethanol at 0°C for 1 h afforded deprotection of the nitrogen atom. In the case of **7a** (Scheme 1) and of a mixture of **10a/10′a** (Scheme 3) the corresponding *NH* compounds **8a** and **10b/10′b** were isolated. The results of the deprotection of pure **7b** or **7′b** were found to be dependent on reaction time and temperature (Scheme 2). After 1 h the corresponding isomeric *NH* compounds **8b** and **8′b** were obtained, respectively. Instead, by prolonging the reaction time a partial isomerization at C-2 occurred. Starting from pure **7b** or **7′b** after 24 h at 25°C a mixture of compounds **8b** and **8′b** in 60:40 and 25:75 ratio, respectively, was detected by ^{1}H NMR. By reacting **6b** with EtOH in the presence of a catalytic amount of EtONa, phenanthridinone **12** was isolated in quantitative yield via biphenyl derivative and its cyclization by reaction of the nitrogen atom with the ester function (Scheme 2).

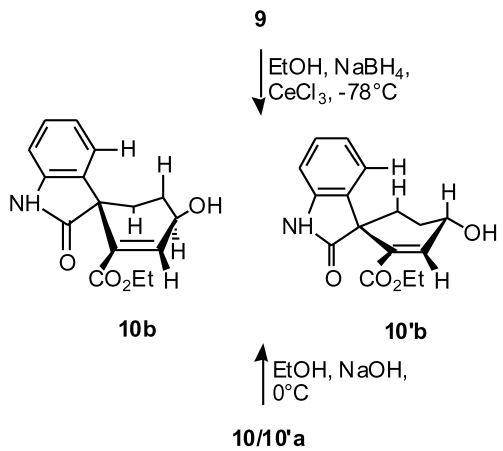
The structures of all compounds were determined on the basis of NMR experiments and all signals were unequivocally assigned. Significant ^{1}H NMR signals for the minor cycloadduct **3a** are an AB and an ABX system (δ 5.12, 3.97, J=4.8 Hz, H-2, H-3; δ 4.76, 3.03, 2.75, J=18.1, 8.1, 6.2 Hz, H-6, H-5, H′-5) and for the main cycloadduct **3′a** three signals at δ 5.04 (bs, H-2), δ 4.55–4.40 (m, H-6, H-3) and δ 2.73–2.61 (m, H-5, H′-5), respectively. Because of the cycloadduct instability it was impossible to perform a



Scheme 2.

NOESY experiment to assign the spatial proximity between chlorine atom and the methoxy group. The formation of intermediate **4** is evidenced by the presence of an AB system (δ 6.45, 6.35, J=9.8 Hz, H-2, H-3) and an AMX system (δ 4.62, 3.73, 2.97, J=16.8, 13.3, 5.1 Hz, H-6, H-5, H′-5). The transformation into **6a** resulted in simplification of the ^{1}H NMR spectrum (AB system at δ 6.66, 6.53, J=10.3 Hz). Finally, compound **7a** is characterized by the presence of multiplets in the 3.27–2.19 region.

The stereochemistry assigned to compound **7b** was confirmed considering the large $J_{2,3}$ value (14.5 Hz) of H-2 (δ 3.37) which confirms its axial position on the cyclohexyl ring. Furthermore, a positive Overhauser effect (NOESY experiment) was observed between H-2 and H-4′. Instead, no NOE was detected in the case of the *N*-deprotected diastereomer **8′b**.



Scheme 3.

The configuration of compound **10b**, in which the OH group is in the equatorial position and *trans* with respect to the carbonyl function of the oxindole nucleus, was assigned by a NOE experiment. Spatial proximity between H-6 (δ 1.9) and H-4 (δ 4.3) was observed in agreement with the axial position of H-4. Furthermore, the axial proton H-5 (δ 1.69) has a positive Overhauser effect with the H-4′ (δ 7.10 region) of the indole ring, the OH proton at δ 5.32 and H-6 at δ 1.55. Diastereomer **10′b** shows spatial proximity between H-6 (δ 1.58) and H-4 (δ 4.37), thus confirming their axial disposition. As a consequence, the hydroxy group is in the equatorial position *cis* to the carbonyl group. A positive Overhauser effect was also observed between H-6 and H-4′ (δ 6.95). On the basis of the above correlations between the *N*-protected compounds **10a/10′a** and their *NH* compounds **10b/10′b**, both the NMR signals and configuration of compounds **10a/10′a** was unequivocally assigned.

In conclusion, we have found a new and useful one-pot synthesis of spiro[cyclohexane-1,3′-indoline]-2′,4-diones starting from Danishefsky's diene **2** and 3-chloromethylene-2-indolones **1**. The possibility to obtain the cyclohexene and cyclohexadiene intermediates was also confirmed. The functionaliztion of the C-2 position of the cyclohexane ring can be achieved starting from compounds **1** functionalization at the double bond both with a chlorine atom and an other group.

3. Experimental

3.1. General

Melting points are uncorrected. IR spectra of the nujol mulls were measured using NaCl Plate. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, with $CHCl_3$ as internal standard. Coupling constants (*J*) are given in Hz. Oxindoles **1a**,**1b**[1b] are known compounds.

3.2. General procedures for the cycloaddition reaction

Method a. Under nitrogen atmosphere, oxindole **1a** (503 mg, 2 mmol) and diene **2** (450 mg, 2.6 mmol) were dissolved in anhydrous toluene (5 mL). After heating at reflux, the solution turned brown. The reaction was monitored by ^{1}H NMR from which the formation of a mixture of cycloadducts **3a**/**3′a** in about 2:3 ratio was evidenced. After 7 h, the solvent was evaporated and the crude reaction mixture was chromatographed on silica gel (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) giving cycloadduct **4** (31.7 mg, 5.2%) and a mixture of the main biphenyl derivatives **5a**,**5b** (200 mg).

Method b. In a sealed tube, oxindole **1** (2 mmol) and diene **2** (0.45 g, 2.6 mmol) were dissolved in anhydrous toluene (5 mL). After heating at reflux (**1a**: 7 h; **1b**: 24 h), the solution was cooled, the tube was opened and a catalytic amount of *p*-TSA was added. The reaction was refluxed and monitored by ^{1}H NMR until the disappearance of signals of intermediates **3**,**4** (12 h). After solvent evaporation, the crude reaction mixture was chromatographed or was used directly for the reduction reaction. The chromatography (pentane/CH_2Cl_2, 1:0 to 0:1) of the reaction mixture (126 mg) obtained from **1a** gave four fractions containing respectively **5c** (17 mg), **5d** (13 mg), **5a** (26 mg) and **5b** (20 mg). The crude reaction mixture from **1b**, chromatographed with pentane/Et_2O (1:0 to 0:1), gave pure **6b** (363 mg, 51%).

3.2.1. Ethyl 6-chloro-4-trimethylsilyloxy-2-methoxy-2′-oxospiro[cyclohex-3-en-1,3′-indoline]-1′-carboxylate 3a/3′a. Mixture of compounds.

Compound **3a**. δ_H 7.98–7.08 (4H, m, Ph), 5.12 (1H, d, *J*=4.8 Hz, H-2), 4.76 (1H, dd, *J*=8.1, 6.2 Hz, H-6), 4.55–4.40 (2H, m, OCH_2), 3.97 (1H, d, *J*=4.8 Hz, H-3), 3.24 (3H, s, OMe), 3.03 (1H, dd, *J*=18.1, 6.2 Hz, H-5), 2.73–2.61 (1H, m, H′-5), 1.44 (3H, t, *J*=7.0 Hz, OCH_2*Me*), 0.29 (9H, s, SiMe).

Compound **3′a**. ^{1}H NMR δ_H 7.98–7.08 (m, 4H, Ph), 5.04 (1H, sbr, H-2), 4.55–4.40 (4H, m, OCH_2, H-6, H-3), 3.15 (3H, s, OMe), 2.73–2.61 (2H, m, H-5, H′-5), 1.46 (3H, t, *J*=7.3 Hz, OCH_2*Me*), 0.30 (9H, s, SiMe).

3.2.2. Ethyl 6-chloro-2′,4-dioxospiro[cyclohex-2-en-1,3′-indoline]-1′-carboxylate 4. Mp 145°C (Et_2O). [Found: C, 60.00; H, 4.52; N, 4.31. $C_{16}H_{14}ClNO_4$ requires: C, 60.18; H, 4.42; N, 4.39]; ν_{max} 1750, 1720, 1680 cm^{-1}; δ_H 8.00 (1H, d, *J*=8.2 Hz, H-6′), 7.51–7.18 (3H, m, Ph), 6.54 (1H, d, *J*=9.8 Hz, H-2), 6.35 (1H, d, *J*=9.8 Hz, H-3), 4.62 (1H, dd, *J*=13.3, 5.1 Hz, H-6), 4.50 (2H, q, *J*=7.1 Hz, OCH_2), 3.73 (1H, dd, *J*=16.8, 13.3 Hz, H-5), 2.97 (1H, dd, *J*=16.8, 5.1 Hz, H′-5), 1.47 (3H, t, *J*=7.1 Hz, OCH_2*Me*).

3.2.3. Ethyl (4′-hydroxybiphenyl-2-yl)carbamate 5a. Mp 113°C (Et_2O/pentane). [Found: C, 69.89; H, 5.84; N, 5.39. $C_{15}H_{15}NO_3$ requires: C, 70.01; H, 5.88; N, 5.45]; ν_{max} 3400–3100, 1690 cm^{-1}; δ_H 8.09 (1H, d, *J*=8.1 Hz, Ph), 7.37–7.06 (3H, m, Ph), 7.22 (2H, *J*=8.7 Hz, Ph′), 6.94 (2H, *J*=8.7 Hz, Ph′), 6.65 (1H, br, NH, exch.), 6.00 (1H, br, OH, exch.), 4.19 (2H, q, *J*=7.1 Hz, OCH_2), 1.26 (3H, t, *J*=7.1 Hz, OCH_2*Me*).

3.2.4. Methyl (*N*-ethoxycarbonyl-4′-hydroxybiphenyl-2-yl)carbamate 5b. Mp 134°C (Et_2O). [Found: C, 64.68; H, 5.38; N, 4.37. $C_{17}H_{17}NO_5$ requires: C, 64.74; H, 5.44; N, 4.44]; ν_{max} 3400–3100, 1760 cm^{-1}; δ_H 7.50–7.10 (4H, m, Ph), 7.16, (2H, *J*=8.7 Hz, Ph′), 6.85 (2H, *J*=8.7 Hz, Ph′), 5.50 (1H, s, OH, exch.), 4.12 (2H, q, *J*=7.3 Hz, OCH_2), 3.66 (3H, s, OMe), 1.14 (3H, t, *J*=7.3 Hz, OCH_2*Me*); δ_C 14.2, 54.2, 63.6, 115.7, 128.0, 128.8, 128.9, 129.8, 130.2, 130.9, 136.0, 140.2, 153.2, 153.9, 156.3.

3.2.5. Ethyl (4′-methoxybiphenyl-2-yl)carbamate 5c. Oil. [Found: C, 70.78; H, 6.28; N, 5.13. $C_{16}H_{17}NO_3$ requires: C, 70.82; H, 6.32; N, 5.16]; ν_{max} 3390, 1720 cm^{-1}; δ_H 8.15 (1H, d, *J*=8.1 Hz, Ph), 7.48–7.06 (3H, m, Ph), 7.28 (2H, d, *J*=8.7 Hz, Ph′), 7.03 (2H, d, *J*=8.7 Hz, Ph′), 6.65 (1H, br, NH, exch.), 4.19 (2H, q, *J*=6.9 Hz, OCH_2), 3.89 (3H, s, OMe), 1.28 (3H, t, *J*=6.9 Hz, OCH_2*Me*). $M^{+\cdot}$: 271.

3.2.6. Methyl (*N*-ethoxycarbonyl-4′-methoxybiphenyl-2-yl)carbamate 5d. Oil. [Found: C, 65.58; H, 5.77; N, 4.20. $C_{18}H_{19}NO_5$ requires: C, 65.63; H, 5.82; N, 4.25]; ν_{max} 1780, 1740 cm^{-1}; δ_H 7.50–7.20 (4H, m, Ph), 7.22 (2H, d, *J*=8.8 Hz, Ph′), 6.93 (2H, d, *J*=8.8 Hz, Ph′), 4.12 (2H, q, *J*=7.0 Hz, OCH_2), 3.84 (3H, s, OMe), 3.66 (3H, s, OMe), 1.14 (3H, t, *J*=7.0 Hz, OCH_2*Me*); δ_C 14.3, 54.0, 55.5, 63.3, 114.1, 128.1, 128.8, 128.9, 129.8, 130.9, 131.1, 136.3, 140.2, 152.9, 153.5, 159.4.

3.2.7. Ethyl 2′,4-dioxospiro[cyclohexa-2,5-dien-1,3′-indoline]-1′-carboxylate 6a. ν_{max} 1760, 1720, 1660 cm^{-1}; δ_H 8.01 (1H, d, *J*=7.7 Hz, Ph), 7.51–7.18 (3H, m, Ph), 6.66 (2H, d, *J*=10.3 Hz, H-2, H-6), 6.53 (2H, d, *J*=10.3 Hz, H-3, H-5), 4.50 (2H, q, *J*=7.0 Hz, OCH_2), 1.49 (3H, t, *J*=7.0 Hz, OCH_2*Me*); δ_C 14.5, 56.4, 64.5, 116.5, 124.9, 125.5, 126.0, 130.6, 131.7, 139.9, 143.3, 150.7, 169.7, 185.2.

3.2.8. Diethyl 2′,4-dioxospiro[cyclohexa-2,5-dien-1,3′-indoline]-1′,2-dicarboxylate 6b. Mp 108°C (Et_2O). [Found: C, 64.15; H, 4.78; N, 3.89. $C_{19}H_{17}NO_6$ requires: C, 64.22; H, 4.82; N, 3.94]; ν_{max} 1771, 1731, 1668 cm^{-1}; δ_H 8.04 (1H, d, *J*=8.4 Hz, Ph), 7.48–6.91 (3H, m, Ph), 7.44 (1H d, *J*=1.4 Hz, H-3), 6.65 (1H, d, *J*=9.9 Hz, H-6), 6.52 (1H, dd, *J*=9.9, 1.4 Hz, H-5), 4.53 (2H, q, *J*=7.0 Hz, OCH_2), 4.20–4.03 (2H, m, OCH_2), 1.49 (3H, t, *J*=7.0 Hz, OCH_2*Me*), 1.14 (3H, t, *J*=7.0 Hz, OCH_2*Me*); δ_C 14.0, 14.6, 56.2, 62.7, 64.3, 116.6, 123.6, 125.7, 125.9, 129.5, 130.4, 137.2, 140.7, 143.8, 144.6, 150.9, 163.9, 170.2, 186.0.

3.3. General procedure for the reduction reaction

Compound **6b** (537 mg, 1.5 mmol) or the crude reaction

mixture obtained as reported above (method b), was dissolved into AcOEt or toluene (20 mL) and Pd/C (10%, 1 mmol reagent: 0.1 mmol catalyst) was added and hydrogenated at 25°C and 1 atm. After 3 h the reaction was checked by ^{1}H NMR to control the disappearance of signals of compound **6**. The catalyst was filtered. When AcOEt has been used as the solvent, the solution was washed with a solution of $NaHCO_3$ and the organic layer was dried over Na_2SO_4. After solvent evaporation, the crude reaction mixture was chromatographed on silica gel (CH_2Cl_2/Et_2O, 1:0 to 0:1). Depending on the starting material and the reaction solvent a different distribution of compounds was found. From **1a** and AcOEt: two fractions were isolated containing respectively compounds **5c**,**5d** (about 20%, variable ratio) and spiro-keton **7a** (57%); from pure **6b** and AcOEt: compound **11** (108 mg, 3.6%), a mixture of **7b/7′b** (260 mg, 75:25, 60%) and **10a/10′a** (83 mg, 15%, 20:80); from **1b** and toluene: three fractions containing respectively compound **9** (24%), **7b/7′b** (20%), **10/10′a** (11%); from **1b** and AcOEt: three fractions containing respectively compound **9** (7.5%), **7b/7′b** (30%), **10/10′a** (13.7%). Diastereomers **10a/10′a** were not separable. The mixture of isomers **7b/7′b** can be partially separated by column chromatography (AcOEt/cyclohexane, 1:1). In this case a partial deprotection of nitrogen atom was observed giving compounds **8b/8′b**.

3.4. Reduction of 9 with $NaBH_4$

Compound **9** (124 mg, 0.35 mmol) was dissolved in EtOH (10 mL) and the solution was cooled at −78°C. $CeCl_3{\cdot}7H_2O$ (156.5 mg, 0.42 mmol) was added and the stirring was continued for 10 min.. A suspension of $NaBH_4$ (13.2 mg, 0.35 mmol) in EtOH (3 mL) was dropped in 5 min. After 1.30 h a saturated solution of NH_4Cl was added until pH 7. EtOH was evaporated and the aqueous solution was extracted with CH_2Cl_2 (2×10 mL). The organic layers were dried over Na_2SO_4. The ^{1}H NMR of the crude reaction mixture revealed the presence of two isomers **10b/10′b** in a 60:40 ratio. The crude reaction mixture was chromatographed on silica gel (pentane/Et_2O, 1:0 to 0:1) giving pure compound **10b** (25 mg, 25%) and a mixture of isomers **10/10′b** (73 mg, 73%). The separation of diastereomeric compounds **10/10′b** was done as described below.

3.5. *N*-Deprotection of compounds 7a, 7b/7′b and 10a/10′a

Pure compounds **7a**, **7b**, **7′b** or a mixture of **10a/10′a** (0.5 mmol) was dissolved in EtOH (3 mL). The solution was cooled at 0°C with stirring and NaOH (0.5 mmol, 20 mg) was added. After 1 h the solvent was evaporated and the crude reaction mixture was taken up with CH_2Cl_2 (5 mL). The organic layer was washed with HCl (10%, 5 mL). After drying over Na_2SO_4 the solution was concentrated giving *N*-deprotected compound. Compounds **8a** (93 mg, 88%), **8b** (105 mg, 73%), and **8′b** (107 mg, 75%), were obtained after recrystallization. A mixture of **10b/10′b** (93 mg, 65%) was obtained from **10a/10′a**. The mixture of **10b/10′b** was taken up with CH_2Cl_2 giving pure compound **10b**. Starting from pure **7b** or **7′b** and operating at 25°C for 24 h, the ^{1}H NMR analyses revealed a partial isomerization at C-2 (from **7b**: **8b/8′b**, 60:40; from **7′b**: **8b/8′b**, 25:75).

3.5.1. Ethyl 2′,4-dioxaspiro[cyclohexane-1,3′-indoline]-1′-carboxylate 7a and *NH*-derivative 8a. *Compound* **7a**. Mp 110°C (Et_2O). [Found: C, 66.85; H, 5.82; N, 4.74. $C_{16}H_{17}NO_4$ requires: C, 66.89; H, 5.96; N, 4.88]; ν_{max} 1730, 1710, 1680 cm^{-1}; δ_H 7.96 (1H, d, *J*=8.2 Hz, Ph), 7.42–7.22 (3H, m, Ph), 4.52 (2H, q, *J*=7.0 Hz, OCH_2), 3.27–3.21 (2H, m, H-3, H-5), 2.54–2.52 (2H, m, H′-3, H′-5), 2.39–2.10 (4H, m, H-2, H-6), 1.50 (3H, t, *J*=7.0 Hz, OCH_2*Me*); δ_C 14.3, 34.3, 36.7, 45.6, 63.7, 115.4, 122.3, 125.1, 128.8, 132.2, 138.4, 150.9, 177.4, 210.0.

Compound **8a**. Mp 192°C (Et_2O). Lit.[4j] 200°C (AcOH). [Found: C, 72.46; H, 6.12; N, 6.45. $C_{13}H_{13}NO_2$ requires: C, 72.54; H, 6.09; N, 6.51]; ν_{max} 3200–3100, 1680 cm^{-1}; δ_H 8.80–8.40 (1H, br, NH, exch.), 7.34–6.96 (4H, m, Ph), 3.31–3.09 (2H, m, H-3, H-5), 2.60–2.47 (2H, m, H′-3, H′-5), 2.26–2.19 (4H m, H-2, H-6); δ_C 33.5, 36.9, 46.0, 110.2, 122.7, 122.9, 128.4, 133.7, 140.1, 181.9, 210.7.

3.5.2. Diethyl 2′,4-dioxospiro[cyclohexane-1,3′indoline]-1′,2-dicarboxylate 7b/7′b and *NH*-derivatives 8b/8′b. *Compound* **7b**. Mp 120°C (AcOEt/*i*Pr_2O). [Found: C, 66.30; H, 6.20; N, 3.98. $C_{19}H_{21}NO_6$ requires: C, 66.46; H, 6.16; N, 4.08]; ν_{max} 1780, 1750, 1710 cm^{-1}; δ_H 7.96 (1H, d, *J*=7.8 Hz, Ph), 7.41–7.22 (3H, m, Ph), 4.54 (2H, q, *J*=7.0 Hz, OCH_2), 4.01–3.84 (2H, m, OCH_2), 3.53 (1H, *J*=14.5, 14.1 Hz, H-3), 3.37 (1H, *J*=14.1, 3.8 Hz, H-2), 2.70 (1H, dd, *J*=14.5, 3.8 Hz, H′-3), 3.34–3.23 (1H, m, H-5), 2.41 (1H, d, *J*=15.4 Hz, H′-5), 2.18–1.95 (2H, m, H-6), 1.49 (3H, t, *J*=7.0 Hz, OCH_2*Me*), 0.98 (3H, t, *J*=7.0 Hz, OCH_2*Me*); δ_C 14.0, 14.7, 34.9, 36.5, 39.9, 47.0, 50.8, 61.7, 63.9, 115.8, 121.7, 125.2, 129.3, 130.7, 139.6, 151.3, 170.5, 176.2, 207.7.

Compound **7′b**. Mp 128°C (AcOEt/*i*Pr_2O). [Found: C, 66.32; H, 6.21; N, 4.00. $C_{19}H_{21}NO_6$ requires: C, 66.46; H, 6.16; N, 4.08]; ν_{max} 1780, 1750, 1710 cm^{-1}; δ_H 8.05 (1H, d, *J*=8.1 Hz, Ph), 7.47–7.17 (3H, m, Ph), 4.53 (2H, q, *J*=7.0 Hz, OCH_2), 3.92–3.78 (2H, m, OCH_2), 3.59 (1H, dd, *J*=9.5, 8.4 Hz, H-2), 3.02–2.97 (2H, m, H-3), 2.74–2.63 (2H, m, H-5), 2.41–2.03 (2H, m, H-6), 1.50 (3H, t, *J*=7.0 Hz, OCH_2*Me*), 0.91 (3H, t, *J*=7.0 Hz, OCH_2*Me*); δ_C 13.7, 14.5, 33.9, 36.3, 39.3, 47.2, 48.9, 61.6, 63.9, 115.8, 123.7, 124.9, 129.4, 129.42, 139.6, 151.1, 170.2, 177.3, 207.5.

Compound **8b**. Mp 130°C (AcOEt/*i*Pr_2O). [Found: C, 66.80; H, 6.05; N, 4.73. $C_{16}H_{17}NO_4$ requires: C, 66.89; H, 5.96; N, 4.88]; ν_{max} 3200–3100, 1730, 1700 cm^{-1}; δ_H 7.84 (1H, br, NH, exch.), 7.28–6.89 (4H, m, Ph), 3.99–3.88 (2H, m, OCH_2), 3.65, (1H, t, *J*=13.9 Hz, H-3) 3.35 (1H, dd, *J*=13.9, 4.0 Hz, H-2), 2.68 (1H, dd, *J*=13.9, 4.0 Hz, H′-3), 3.44–3.26 (1H, m, H-5), 2.41 (1H, d, *J*=15.5 Hz, H′-5), 2.21–2.07 (2H, m, H-6), 0.99 (3H, t, *J*=7.0 Hz, OCH_2*Me*).

Compound **8′b**. Mp 157°C (AcOEt, *i*Pr_2O). [Found: C, 66.82; H, 6.03; N, 4.76. $C_{16}H_{17}NO_4$ requires: C, 66.89; H, 5.96; N, 4.88]; ν_{max} 3200–3100, 1730, 1700 cm^{-1}; δ_H 8.13 (1H, br, 1H, NH, exch.), 7.36–6.89 (4H, m, Ph), 4.16–3.83 (2H, m, OCH_2), 3.53 (1H, dd, *J*=10.6, 7.3 Hz, H-2), 3.03–2.98 (2H, m, H-3), 2.76–2.68 (2H, m, H-5), 2.38–2.03 (2H, m, H-6), 0.96 (3H, t, *J*=6.9 Hz, OCH_2*Me*); δ_C 14.0, 33.4, 36.8, 39.7, 46.8, 49.3, 61.6, 110.8, 122.9, 124.6, 129.3, 130.8, 141.3, 170.8, 181.4, 208.3.

3.5.3. Diethyl 2′,4-dioxospiro[cyclohex-2-ene-1,3′-indoline]-1′,2-dicarboxylate 9. Mp 80°C (iPr$_2$O/Et$_2$O). [Found: C, 63.67; H, 5.23; N, 3.88. $C_{19}H_{19}NO_6$ requires: C, 63.86; H, 5.36; N, 3.92]; ν_{max} 1780, 1760, 1720, 1680 cm^{-1}; δ_H 8.02 (1H, d, J=8.0 Hz, Ph), 7.46–7.08 (3H, m, Ph), 7.05 (1H, s, H-3), 4.53 (2H, q, J=7.0 Hz, OCH$_2$), 4.14–3.99 (2H, m, OCH$_2$), 3.00–2.60 (2H, m, H-5), 2.59–2.17 (2H, m, H-6), 1.50 (3H, t, J=7.0 Hz, OCH$_2$*Me*), 1.10 (3H, t, J=7.0 Hz, OCH$_2$*Me*); δ_C 13.9, 14.6, 33.1, 33.9, 50.7, 62.5, 64.1, 116.2, 122.8, 123.6, 125.1, 129.8, 130.0, 136.1, 139.7, 146.3, 151.2, 175.4, 198.1.

3.5.4. Diethyl 4-hydroxy-2′-oxospiro[cyclohex-2-ene-1,3′-indoline]-1′,2-dicarboxylate 10a/10′a and *NH*-derivatives 10b/10′b. *Compound* **10a**. Minor isomer, mixture with **10′a**. δ_H (C_6D_6) 8.35 (1H, d, J=8.2 Hz, Ph), 7.57 (1H, d, J=3.2 Hz, H-3), 7.26–6.95 (2H, m, Ph), 6.63 (1H, d, J=6.2 Hz, Ph), 4.31–4.20 (3H, m, OCH$_2$, H-4), 3.79–3.69 (2H, m, OCH$_2$), 3.30–3.10 (1H, br, OH, exch.), 2.16–1.30 (4H, m, H-5, H-6), 1.16 (3H, t, J=7.2 Hz, OCH$_2$*Me*), 0.77 (3H, t, J=7.1 Hz, OCH$_2$*Me*); δ_C (C_6D_6) 13.7, 14.3, 27.2, 32.2, 50.3, 61.2, 63.3, 64.9, 115.8, 122.6, 124.8, 128.7, 131.3, 133.5, 140.3, 146.5, 151.8, 165.1, 177.5.

Compound **10′a**. Major isomer, mixture with **10a**. ν_{max} 3400, 1770, 1750, 1710 cm^{-1}; δ_H (C_6D_6) 8.42 (1H, d, J=8.0 Hz, Ph), 7.53 (1H, d, J=2.3 Hz, H-3), 7.26–6.95 (3H, m, Ph), 4.31–4.20 (3H, m, OCH$_2$, H-4), 3.79–3.69 (2H, m, OCH$_2$), 3.05–2.90 (1H, br, OH, exch.), 2.16–1.30 (4H, m, H-5, H-6), 1.15 (3H, t, J=7.1 Hz, OCH$_2$*Me*), 0.79 (3H, t, J=7.0 Hz, OCH$_2$*Me*); δ_C (C_6D_6) 13.7, 14.3, 27.0, 33.2, 50.7, 61.2, 63.3, 66.0, 115.7, 123.4, 124.7, 128.7, 130.9, 133.6, 140.1, 147.1, 151.9, 164.9, 177.5.

Compound **10b**. Mp 190°C (CH_2Cl_2). [Found: C, 66.67; H, 5.87; N, 4.82. $C_{16}H_{17}NO_4$ requires: C, 66.89; H, 5.96; N, 4.88]; ν_{max} 1710, 1707, 1680 cm^{-1}; δ_H (DMSO d_6) 10.35 (1H, s, NH, exch.), 7.20–6.83 (5H, m, Ph, H-3), 5.32 (1H, d, J=7.0 Hz, OH, exch.), 4.35–4.32 (1H, m, H-4), 3.88 (2H, q, J=7.0 Hz, OCH$_2$), 2.10–1.94 (1H, m, H-5), 1.94–1.80 (1H, m, H-6), 1.78–1.60 (1H, m, H′-5), 1.60–1.43 (1H, m, H′-6), 0.99 (3H, t, J=7.0 Hz, OCH$_2$*Me*); δ_C (DMSO d_6) 14.4, 27.6, 39.6, 50.4, 61.1, 65.6, 110.2, 121.7, 123.6, 128.6, 129.9, 135.5, 142.8, 148.4, 165.1, 181.4.

Compound **10′b**. Impure of **10b**. ν_{max} 1710, 1707, 1680 cm^{-1}; δ_H (DMSO d_6) 10.32 (1H, s, NH, exch.), 7.14–6.80 (5H, m, Ph, H-3), 5.29 (1H, d, J=5.1 Hz, OH, exch.), 4.42–4.22 (1H, m, H-4), 3.95–3.80 (2H, m, OCH$_2$), 2.00–1.90 (3H, m, H-5, H-6), 1.60–1.50 (1H, m, H′-6), 0.96 (t, J=7.3 Hz, 3H, OCH$_2$*Me*); δ_C (DMSO d_6) 14.4, 27.2, 31.8, 49.9, 60.9, 64.1, 110.1, 121.7, 123.1, 128.5, 129.7, 135.3, 143.0, 147.3, 165.5, 180.8.

3.5.5. Diethyl 2′-oxospiro[cyclohex-2-ene-1,3′-indoline]-1′,2-dicarboxylate 11. Mp 107°C (Et$_2$O). [Found: C, 66.37; H, 6.13; N, 3.99. $C_{19}H_{21}NO_5$ requires: C, 66.46; H, 6.16; N, 4.08]; ν_{max} 1760, 1700 cm^{-1}; δ_H (C_6D_6) 8.51 (1H, d, J=8.1 Hz, Ph), 7.38 (1H, dd, J=4.1, 4.0 Hz, H-3), 7.26–6.90 (3H, m, Ph), 4.26–4.19 (2H, m, OCH$_2$), 3.80–3.73 (2H, m, OCH$_2$), 2.04–1.92 (1H, m, H-6), 1.92–1.83 (2H, m, H-4), 1.60–1.30 (3H, m, H-5, H′-6), 1.14 (3H, t, J=7.1 Hz, OCH$_2$*Me*), 0.79 (3H, t, J=7.2 Hz, OCH$_2$*Me*); δ_C 13.8, 14.3, 17.2, 25.9, 35.0, 50.3, 60.7, 63.1, 115.7, 123.0, 124.3, 127.8, 128.2, 128.5, 140.4, 144.4, 152.2, 164.9, 177.2. $M^{+\cdot}$: 343.

3.5.6. 8-Hydroxy-5*H*-phenanthridin-6-one 12. Compound **6b** (32 mg, 0.09 mmol) was dissolved in EtOH (3 mL) and a catalytic amount of EtONa was added. The solution was stirred for 1 h at room temperature. The solvent was evaporated and the residue was taken up with AcOEt (5 mL) and washed with HCl (10%, 5 mL). The organic layer was separated and dried over Na_2SO_4. The crude reaction mixture was taken up with Et$_2$O. A solid was separated and filtered corresponding to compound **12** (21 mg, 100%). Mp 300°C dec. Lit.[7] 305°C (benzene/-methanol). [Found: C, 73.87; H, 4.23; N, 6.54. $C_{13}H_9NO_2$ requires: C, 73.92; H, 4.29; N, 6.63]; ν_{max} 1750, 1640 cm^{-1}; δ_H (DMSO d_6) 11.56 (1H, s, NH, exch.), 10.13 (1H, s, OH, exch.), 8.34 (1H, d, J=8.8 Hz, Ph), 8.24 (1H, d, J=7.7 Hz, Ph), 7.65 (1H, d, J=3.0 Hz, Ph), 7.59–6.17 (4H, m, Ph); δ_C (DMSO d_6) 112.2, 116.6, 118.7, 122.4, 122.8, 122.9, 125.2, 126.9, 127.9, 128.6, 135.9, 158.1, 161.3.

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