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Oxidized isoquinolinoisoindolinone and benzazepinoisoindolinone alkaloids cores by convergent cyclisation processes: π-aromatic attack of thionium and oxonium species

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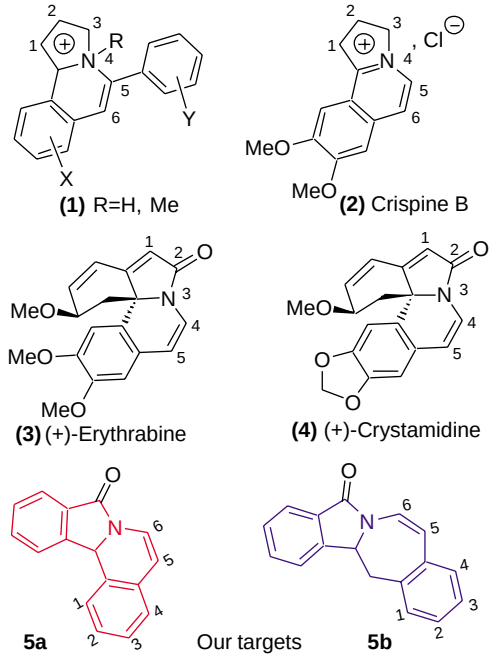
Abstract—An efficient methodology for synthesis of isoindoloisoquinoline **5a** and isoindolobenzazepine **5b** in oxidized forms as tetracyclic alkaloids cores are reported from *N*-bromoethylphthalimide (**6**) or phthalic anhydride and 2-phenylthioethylamine (**8**) in a five- or six-step sequence, respectively, in overall very good yields. The key step of this methodology is based on an intramolecular π-cationic cyclization of the thionium ion species. Alternatively, another four-step route was explored and based in an ultimate step on the cyclodehydration of an aldehyde functionality, which used as intermediate in the latest strategy, via the oxonium ion cation.

1. Introduction

The pyrrolo[2,1-*a*]isoquinoline skeleton is a structural motif common to a large and diverse family of natural products, which shown a remarkable array of biological activity.[1] The latter includes for example the so popular marine lamellarins,[2] erythrina[3] and aporhoedane[4] (including protoberberines) families, which produced a plethora of structures with profound important properties. In contrary, pyrrolo[2,1-*a*]isoquinoline motif with an olefinic moiety at α and β positions of the nitrogen atom of the isoquinoline nucleus (Scheme 1), as respectively, in iminium salts (**1**),[5] crispine B (**2**),[6] (+)-erythrabine (**3**)[7] and (+)-crystamidine (**4**)[8] are few explored. Some of unnatural compounds of type **1** are patented and have been reported to possess antidepressant activity.[5] Crispine B (**2**) is one of alkaloid products isolated from extracts of *Carduus crispus L.* which have been used in Chinese folk medicine for the treatment of cold, stomachache and rheumatism. The further screening of this compound for its inhibitory effect on the growth of some human-cancer lines in vitro by the SRB method showed that this product have significant cytotoxic activity.[6] Elsewhere, other study have reveled the existence of (+)-erythrabine (**3**) and (+)-crystamidine (**4**) together in nature, which were thought for long time to be artifacts.[7] While structures **3** and **4** as the sole erythrina alkaloids products with double bond at C_4–C_5 linkage, have not showed at this time any biological properties, they are useful intermediates



Scheme 1. Selected examples of clinical important natural and non natural pyrrolo[2,1-*a*]isoquinolines (**1**–**4**) and our targets **5a**,**b**.

Keywords: Isoindole; Isoquinoline; Benzazepine; Thionium ion; Oxonium ion; *N*-Acyliminium ion; Cyclization; α-Amidoalkylation; Pummerer; Alkaloid.
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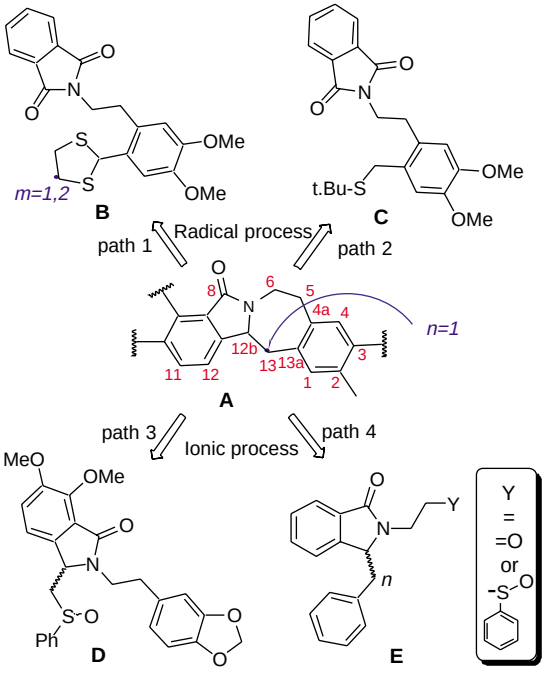
in organic synthetic chemistry, especially in the elaboration of other erythrina alkaloids products exemplified by erysotrine,[9] 8-oxoerythrinine,[10] and both of enantiomers of 3-demethoxyerythratidinone.[11] Furthermore, the azepinic homologues of the oxidized pyrrolo[2,1-*a*]isoquinoline have been reported to constitute a valuable platform to access easily homoerythrinan alkaloids as 2,7-dihydro-homoerysotrine and 3-epischelhammericine.[12]

Most of the hitherto reported syntheses of these type of compounds rely on a small number of strategies; the sulfur chemistry constitute an important one of them and in this case the ring closure was executed by radical or ionic process as shown in Scheme 2. In fact, if we consider the formation of the azepine ring system as in aporhoedanes (protoberberines), erythrinan, and homoerythrinan alkaloids for examples, the radical approaches have relied on the generation of the C_{12b}–C_{13} bond from appropriate imide-thioacetal **B** (path 1)[13] or imide-thioether **C** (path 2)[14] by photocyclization followed by deketalisation or oxidative formation with $Pb(OAc)_4$, respectively. In the ionic process, the sulfur-directed 5-exo selective aryl radical cyclization onto an enamide functionality using the tandem Bu_3SnH/AIBN followed by the Pummerer type-cyclization was also operated. During these processes, the ring closure involves the formation of the C_{13}–C_{13a} bond via the π-cyclization of the thionium ion generated from the sulfoxide **D** in acid conditions (path 3).[15]



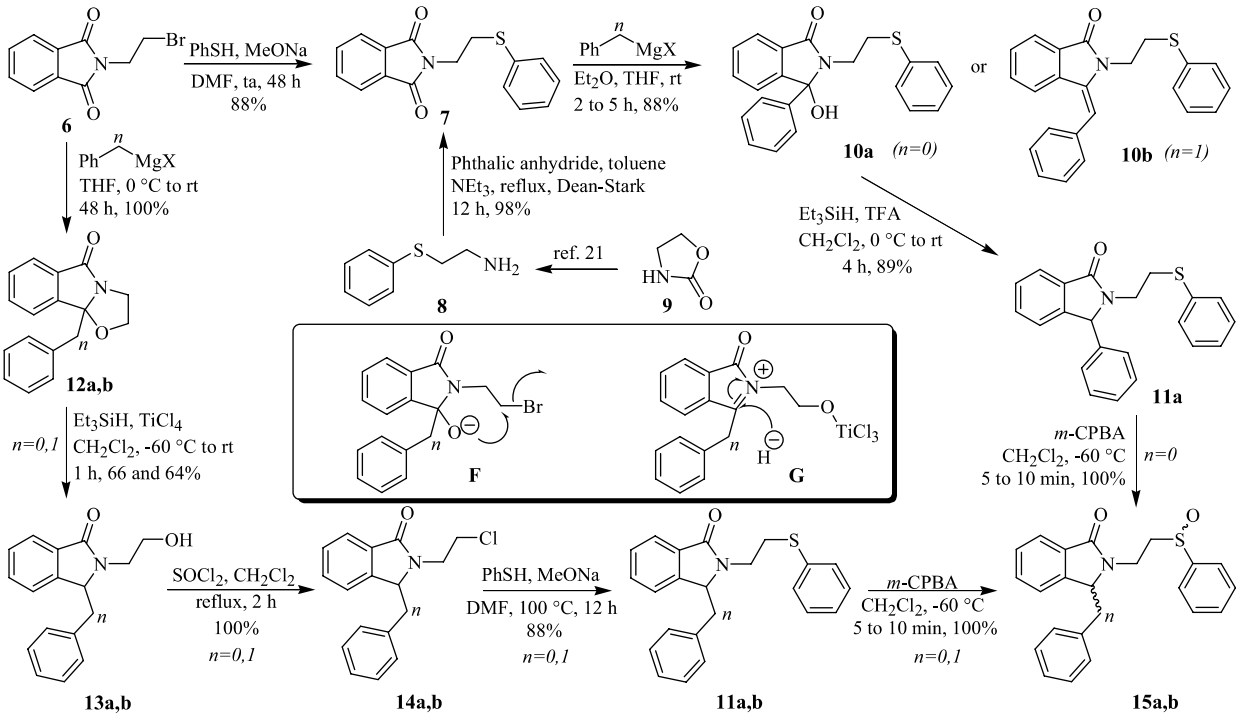
Scheme 2. Retrosynthetic scheme leading to isoindoloisoquinoline (**5a**, $n=0$) and related isoindolobenzazepine (**5b**, $n=1$).

2. Results and discussion

In our laboratory we are interested in the development of synthetic methodologies towards original aza-heterocyclic systems containing isoindole, isoquinoline and/or benzazepine moieties with promising pharmaceutical activities. In this sense, we have recently explored the utility of *N*-phenylthioalkylimides as remarkable synthons for the synthesis of various aza-fused [1,3]thiazines,[16,17] [1,3]thiazepines,[17] [1,3]thiazocinones in racemic,[17,18] or chiral[18] forms as well as isoindolo[2,1-*b*]isoquinolines alkaloids cores and their corresponding thio-bridged systems.[19] These compounds are obtained by the tandem thiocyclization/π-cationic cyclization of *N*-acyliminium ion in acidic conditions,[16,17] α-amidoalkylation/Friedel-Crafts type-cyclization[18] and finally Pummerer reaction/*N*-acyliminium ion cyclization.[19] In all these methodology, the phenylthio group was incorporated in the final structure except during the formation of the isoindolo[2,1-*b*]-isoquinoline alkaloid core in which the phenylthio group was eliminated in an ultimate stage by reduction.[19]

In our search for new synthetic applications for *N*-phenylthioalkylimides, we wish to report herein our finding in this area by using the *N*-acyliminium ion chemistry in combination with the Pummerer cyclization. So with the above considerations in hand, we speculated that the oxidized tetracyclic alkaloids frameworks **5a**,**b** might conceivably be constructed by formation of the C_{4a}–C_5 bond through electrophilic cyclization of the sulfoxide derivatives **E** (path 4 in Scheme 2). Interestingly, the Pummerer reaction seemed to be particularly well adapted for driving this plan since the cyclized Pummerer product which bear a phenylthio group at exocyclic position on the C_5 (Scheme 2) could produce efficaciously in concise manner saturated tetracyclic alkaloids cores or oxidized tetracyclic systems **5a**,**b** as in Scheme 1 by C-S linkage reduction or oxidative thiophenol elimination, respectively.

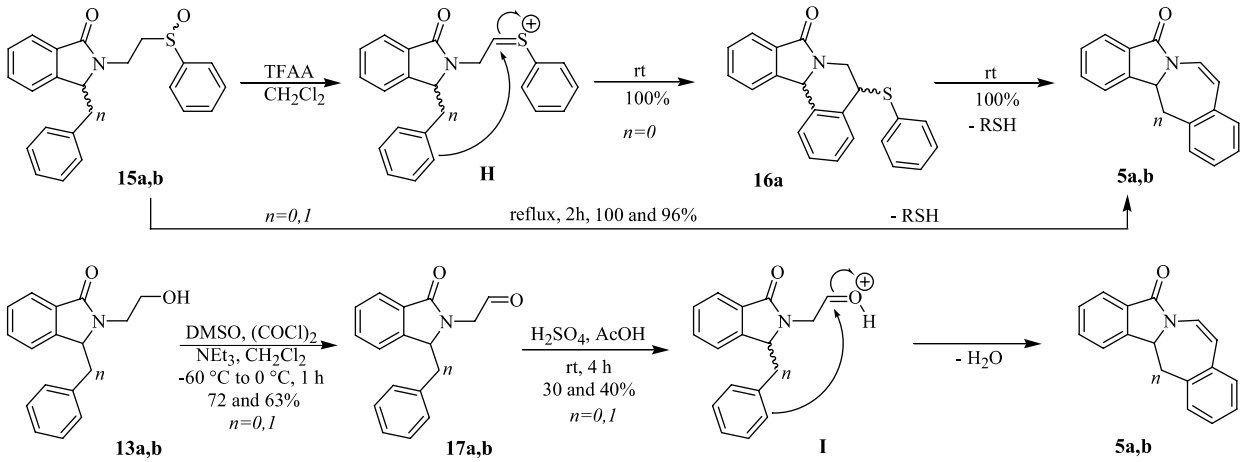
As a starting point of our study, the *N*-phenylthioethyl-α-phenyl(or benzyl)lactam derivatives **11a**,**b**, as sulfoxides precursors, constitutes a valuable target molecules (Scheme 3). We expected to obtain these products in a three-step sequence from the commercially available *N*-bromoethylphthalimide (**6**). So the halide (**6**) was *S*-alkylated with slight excess (1.2 equiv) of thiophenol in alkaline medium in 88% yield.[17,20] This product was also obtained in high yield of 98% in an alternative pathway from phthalic anhydride and the known 2-phenylthioethylamine[21] by the thermal amino-anhydride condensation in refluxing toluene in the presence of a catalytic amount of dry triethylamine under azeotropic removal of water.[22] Regioselective carbophilic addition onto the resulted phthalimide derivative **7** was performed with a large excess of Grignard reagents (RMgX with RX=PhBr and BnCl) in analogy to our precedent reports (i.e., RMgX, Et_2O, THF, room temperature, 2–5 h)[16] and afforded α-phenyl-α-hydroxylactam **10a** in 88% yield. In the case of the use of benzylmagnesium chloride, however, the changes operated in the experimental part notably in the work-up procedure (acidic or neutral conditions), no traces of α-benzyl-α-hydroxylactam were detected in the reaction mixture but only the enamidone **10b** as the consequence of the dehydration reaction of the latter α-hydroxylactam was isolated in good yield (96%). Because of the apparition of a stereogenic centre adjacent to the nitrogen atom, the ^1H NMR spectra of α-phenyl-α-hydroxylactam **10a** showed the magnetically non-equivalence of the methylene protons (–N–CH_2–) of the phenylthioethyl group, which appears as a classical AB system. Finally, the expected



Scheme 3. Sequential pathways leading to 2,3-dihydro-2-(2-phenylsulfanylethyl)-3-phenylisoindol-1-one (**15a**) and 3-benzyl-2-(2-phenylsulfanylethyl)-2,3-dihydroisoindol-1-one (**15b**) as thionium ions precursors.

N-phenylthioethyl-α-phenyllactam derivative **11a** was obtained in an ultimate stage from α-phenyl-α-hydroxy-lactam **10a** by removing the hydroxyl function with 2 equiv of triethylsilane and a large excess of TFA as hydride and proton sources, respectively. After 4 h of the reaction at room temperature, the excepted α-phenyllactam derivative **11a** was isolated in good yield (89%). Finally, the Pummerer thionium ion precursor **15a** was reached easily in quantitative yield by *m*-CPBA oxidation of **11a** in dry dichloromethane at −60 °C. The latter was isolated as uncoloured oil as a mixture of inseparable two diasteromers in 54/46 ratio. In addition, to avoid the formation of the non expected sulfone derivative, 1 equiv of *m*-CPBA and few minutes of reaction were necessary (in general only 5–10 min).

Because of this strategy was not general (all tentative to accede α-benzyllactam derivative **11b** have failed), our attention was turned to explore another approach starting again from *N*-bromoethylphthalimide (**6**). The choice of this sequence was based on two considerations: first, the oxazole ring in the oxazoloisoindolone tricyclic system might give the isoindolone ring equipped with alcohol function and aryl or aralkyl group at suitable positions, respectively. Second, the oxazoloisoindolone tricyclic system might limitated the proportion of the enamidone function, which could be formed after the ring cleavage according to the Meyers reports.[23] Thus, treatment of halide **6** with 1.2 equiv of Grignard reagents (RMgX with RX=PhBr and BnCl) in analogy to the procedure described above in dry THF over 48 h gave the tricyclic oxazoloisoindolones **12a**[24] and **12b** in quantitative yields. The formation of these products resulted from the regioselective carbophilic addition of RMgX onto one carbonyl group of the imide function followed by an intramolecular nucleophilic substitution of the bromine atom with oxygen anion as shown in the intermediate **F** (Scheme 3). These oxazoloisoindolones **12a** and **12b** were then converted easily to the *N*-hydroxy-alcohol derivatives **13a**,**b** by triethylsilane reduction as described above for **11a** in 66 and 64% yields, respectively. In these cases, the reaction occurred at −60 °C in dry dichloromethane and in the presence of $TiCl_4$ as catalyst instead of TFA used above during the transformation of **10a** into **11a**. Herein, $TiCl_4$ coordinates efficaciously the oxygen atom of the oxazole ring in **12a**,**b** inducing the formation of the *N*-acyliminium intermediate **G** (Scheme 3), which easily reduced by the hydride anion. Interestingly, the reaction proceeded cleanly and in the case of the reductive-cleavage of **12b** ($n=1$), no traces of the byproduct as *N*-hydroxy-ethyl-3-benzylidene were isolated. The above alcohol derivatives **13a**,**b** were treated with 1.5 equiv of thionyl chloride under reflux of dichloromethane for 2 h and the resulting halide **14a**,**b**, obtained in quantitative yields, were *S*-alkylated in accordance with the procedure described above for the synthesis of *N*-(2-phenylthioethyl)phthalimide (**7**) to give after chromatography purification (using SiO_2 column with a mixture of cyclohexane–AcOEt (4/1) as eluent) *N*-(2-phenylthioethyl)isoindolone derivatives **11a**,**b** in 88% yield in both cases. The reaction was slower then the one used for the production of the imide **7**. Consequently, the heat at 100 °C for 12 h was necessary for complete transformation of halides **14a**,**b** into corresponding sulfides **11a**,**b**. The requisite sulfoxides **15a**,**b** were then obtained by using same procedure reported above for oxidation of **11a** into **15a**. The latter **15a** and its benzyl isomer **15b** were isolated after short reaction times, which in general do not exceed 10 min, in quantitative yield for each case. Furthermore, these sulfoxides were isolated as a mixture of two diastereomers in comparable ratio of about 55/45.



Scheme 4. The π-cationic cyclization of sulfoxides **15a**,**b** and corresponding formyl derivatives **17a**,**b** into isoindolinones **5a**,**b** under acidic conditions.

Taking into account that sulfoxides similar to **15a**,**b** (see also intermediate **D** in Scheme 2) have been reported in the literature to constitute excellent precursors for the Pummerer type-cyclization,[19,26] the sulfoxide **15a** obtained above as a model substrate was subjected to TFAA at room temperature under Pummerer conditions (Scheme 4). The expected cyclization was readily induced by the intermediary of the thionium species **H**; and after 30 min of reaction, 5,12*b*-dihydro-5-phenylthioisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**16a**) was formed as a mixture of two diastereomers in 56/44 ratio (*cis* and *trans* isomers). The purification of the product by short column chromatography gives pure **16a** as uncoloured oil in quantitative yield. Similarly, cyclization of sulfoxide **15b** was also occurred under identical conditions (quantitative yield) and, interestingly, furnished directly the benzazepine product 12*b*,13-tetrahydrobenzo[4,5]azepino[2,1-*a*]isoindol-8-one (**5b**) via the intermediacy of the expected and 'non-isolated' 5-phenylthio-5,6,12*b*,13-tetrahydrobenzo-[4,5]azepino[2,1-*a*]isoindol-8-one (**16b**) followed by spontaneous lost of thiophenol. In order to isolate the cyclized sulfure **16b**, other cyclization protocols, notably under lower temperature, diluted solution, other solvent, etc…, have failed in all cases. Furthermore, this product **5b** and its isoquinoline derivative **5a** were also obtained in one-step procedure by heating **15a**,**b** and TFAA on refluxing dichloromethane for 2 h in 100 and 96% yields, respectively. In addition, exposition of neat sulfure **16a** at laboratory atmosphere or in dichloromethane for 3 h at room temperature produces quantitatively the oxidized product **5a**.

In an alternative pathway, compounds **5a** and **5b** could be obtained in two-steps starting from the more accessible *N*-hydroxyethylisoindolinones **13a** and **13b** (Scheme 4). This strategy commences with the oxidation of alcohols **13a**,**b** into corresponding acetaldehydes **17a**,**b**. The Swern reaction conducted at −60 to 0 °C for 1 h in dichloromethane seemed to be more practical since this protocol delivered straightforwardly, cleanly and with appreciable yields (72 and 63%, respectively) the expected *N*-isoindol-2-ylacetaldehydes **17a** ($n=0$) and **17b** ($n=1$), candidates for the final cyclization step (Scheme 4). In the case of *N*-isoindol-2-ylacetaldehyde possessing an benzyl appendage **17b** ($n=1$), no traces of *N*-phthalimidin-2-ylethanol and/or *N*-phthalimidin-2-ylacetaldehyde as by products were observed even when the temperature was raised (up to room temperature) and the reaction time prolonged (up to 2 h).

Taking into account that Brönsted acid (HCO_2H, AcOH, H_2SO_4 and PTSA)[27,28] or Lewis acid ($ZnCl_2$ and $BF_3\cdot Et_2O$)[28a] are reported to induce cyclization of appropriate amidoacetals to tetrahydroisoquinolines[27] and isoindolobenzazepines,[28] we then proceeded to apply this method to the synthesis of dihydroisoquinoline **5a** and oxidized benzazepine **5b** directly from acetaldehydes **17a** and **17b**. Among all attempts used for cyclization of acetaldehydes **17a**,**b** into our targets **5a**,**b**, the tandem AcOH/H_2SO_4 in 1/2 ratio constitutes the best cyclodehydration combination for achieving this reaction with, however, low yields (30 and 40%, respectively). In this process, the oxidized alkaloids cores **5a**,**b** were formed via the intermediacy of the oxonium cation **I** followed by the dehydration of the tricyclic secondary alcohol obtained by the Friedel-Crafts reaction.

The structure elucidation of the cyclized products **5a**,**b** as well as all compounds intermediates was based on their spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR including NOE difference and DEPT experiments) as well as their microanalyses.

The ^{1}H NMR analyses indicated that in the isoindolones structures **5a** and **5b**, the angular protons appear as singlet at $\delta=5.86$ ppm for **5a** and a doublet of doublet at $\delta=5.08$ ppm for **5b** with coupling constant of $J=7.0$, 3.1 Hz characteristics of an AMX system. These latter absorb downfield compared to the same protons of their acetaldehydes congeners **17a** ($\delta=5.65$ ppm) and **17b** ($\delta=4.96$ ppm), respectively. The same profile was also observed for these protons in comparison to the ones of their sulfoxides precursors, with however, a big difference on the chemical shift values which are $\Delta\delta=+0.44$ ppm and $\Delta\delta=+0.39$ ppm in favour of the cyclized products **5a** and **5b**, to the detriment of the sulfoxides **15a** and **15b**. Interestingly, when the comparison was done with minor form of **15a** and **15b**, respectively, only a little difference ($\delta=5.73$ ppm for **15a** and $\delta=5.01$ ppm for **15b** in their

minor forms) was observed. Especially diagnostic was also the appearance of one olefinic proton with coupling constant of $J=7.8$ Hz for **5a** and $J=14.1$ Hz for **5b** at $\delta=6.20$ and 6.10 ppm, respectively. These latter appear as a doublet in each case characteristic of an AB system and constitutes ultimately the consequence of the intramolecular cyclization of **15a**,**b** into **5a**,**b**.

Furthermore, the key feature in the ^{13}C NMR spectra of **5a** and **5b**, was the appearance of fifteen signals in the aromatic regions. One of these disappears in the corresponding DEPT program spectra in comparison to spectra of their precursors **15a**,**b** or **17a**,**b** as the consequence of the π-cationic cyclization process.

Finally, these observations are in agreement with the fact that C_{4a}–C_5 and C_5–C_6 bonds, formed during the tandem π-cyclization/elimination process, have the same effect on the absorbance of the $C_{12b}H$ angular and the olefinic C_5H and C_6H protons absorbance as well as the C_5, C_6 and C_{12b} carbon signals. These results are also in agreement with previous reports dealing on analogous compounds.[28]

3. Conclusion

In summary, we have shown that imide **7** could generate in two-steps α-phenyllactam **11a** by successive Grignard carbophilic addition and α-hydroxylactam triethylsilane reduction mediated by an *N*-acyliminium cation. Because of the benzyl equivalent of α-phenyllactam **11a** could not obtained by this procedure, another approach using the bicyclic lactams chemistry in a four-step sequence was used successfully. In these conditions, α-substituted isoindolones **11a** and **11b** were isolated in an overall good yield from the readily available *N*-(2-bromoethyl)phthalimide (**6**) by the tandem Grignard addition/SN_2 *O*-cyclisation → oxazoline cleavage → alcohol chlorination and finally the nucleophilic chloride displacement with phenylthio anion. In the last step, the *m*-CPBA oxidation of **11a** and **11b** lead to the expected thionium ion precursors **15a** and **15b** cleanly, in very short times, and in quantitative yields.

Treatment of the latter sulfoxides **15a**,**b** under Pummerer conditions produced efficiently in high yields the cyclized isoindoloisoquinoline derivative **16a** while corresponding benzazepine component **16b** was instable and cyclized directly into the requisite tricyclic product **5b**. Taking advantage from this behavior, the alkaloids cores **5a** and **5b**, were then obtained in comparable high yields in a one-pot procedure from corresponding sulfoxides **15a**,**b** when the Pummerer-type cyclization was operated under refluxing dichloromethane. Alternatively, these targets **15a**,**b** were also obtained, with however, lower yields, from the formyl intermediates **17a**,**b** under acid influence. During this transformation the reaction involves an initial arylation of oxonium ion, followed by spontaneous water elimination. This, is resulted from the likely and unstable secondary alcohol adduct as the resulting product of the ring closure into isoindolones fused to isoquinoline ring **5a** and benzazepine ring **5b**.

4. Experimental

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 (300 MHz) instrument in deuteriochloroform unless other indicated solvent and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Ascending thin-layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapour. Mass spectral measurements were recorded on a AEI MS 902 S spectrophotometer. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mont-Saint-Aignan, France.

4.1.1. *N*-(2-Phenylthioethyl)phthalimide (7). *Method A*. To a stirred solution, under an atmosphere of dry argon, of thiophenol (1.32 g, 12 mmol) in 15 mL of dry DMF was added (65 mg, 12 mmol) of sodium methoxide. After stirring for 40 min at room temperature, *N*-bromoethyl-phthalimide (**6**, 2.52 g, 10 mmol) was added slowly dropwise over a period of 5 min. The mixture was then allowed to react at the ambient temperature for 48 h (monitored by TLC using CH_2Cl_2/cyclohexane as eluent) and hydrolysed by crushed ice. The solution was filtered off and the solid was recrystallized from dry ethanol to give the expected imide **7**. In the case of the solid is not formed, the solution was extracted three times with diethyl ether, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The oily residue was passed through short Celite column and recrystallized in the second time from dry ethanol to give the above imide **7** in 88% yield. *Method B*. A mixture of 2-phenylthioethylamine (**8**, 1.53 g, 10 mmol), phthalic anhydride (1.48 g, 10 mmol) and two drops of dry triethylamine in toluene (50 mL) was refluxed with a Dean–Stark apparatus for 12 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was dissolved into CH_2Cl_2 (50 mL), washed with 5% HCl solution then with a 10% $NaHCO_3$ solution and then with water. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and recrystallization of the residue from dry ethanol gave the desired imide **7** in 98% yield; mp = 69 °C (lit.[17], isolated as oil in 69% yield); IR (KBr) $\tilde{\nu}_{max}=1712\ cm^{-1}$ (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.19 (t, 2H, $J=7.0$ Hz, C–CH_2–S), 3.90 (t, 2H, $J=7.0$ Hz, N–CH_2–C), 7.19–7.23 (m, 2H, aromatic), 7.36–7.41 (m, 3H, aromatic), 7.64–7.71 (m, 2H, phthalimide), 7.74–7.82 (m, 2H, phthalimide); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 37.5, 123.3, 126.4, 129.1, 129.6, 132.0, 134.1, 134.9, 168.2; MS (EI): $m/z=283$ [M^+]. Anal. Calcd for $C_{16}H_{13}NO_2S$ (283.35): C, 67.82; H, 4.62; N, 4.94. Found. C, 67.78, H, 4.42, N, 4.78.

4.2. General procedure for Grignard addition onto *N*-(2-phenylthioethyl)phthalimide (7)

To a well stirred and cold solution of imide (**7**, 2.83 g, 10 mmol) under dry nitrogen atmosphere in a mixture of

anhydrous diethyl ether and anhydrous THF (40 mL) was added slowly in dropwise, over a period of 30 min, a 0.5 M solution of Grignard reagent (phenylmagnesium bromide or benzylmagnesium chloride (15 mmol)) in dry THF. After 2–5 h of reaction at room temperature, the reaction was hydrolysed under stirring with water (40 mL) then with 0.5 M NH_4Cl solution (40 mL), and the solution was passed through Celite. After separation, the organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization of the reaction residue from a dry ethanol give α-hydroxylactam **10a** or enamidone **10b** in yields of 88 and 96%, respectively.

4.2.1. 3-Hydroxy-3-phenyl-2-(2-phenylthioethyl)-2,3-dihydroisoindol-1(2*H*)-one (10a). This product was isolated as white prisms in 88% yield and melted at 150 °C; IR (KBr) $\tilde{\nu}_{max}=3313$ (OH), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.61–2.79 (m, 1H, CH_2–CH_2), 2.94–3.12 (m, 2H, CH_2–CH_2), 3.44–3.64 (m, 1H, CH_2–CH_2), 4.48 (s broad, 1H, OH), 7.02–8.39 (m, 13H, aromatic), 7.59–8.68 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.7, 39.1, 122.9, 123.4, 126.0, 126.1, 126.3, 128.5, 128.7, 128.8, 129.1, 129.7, 130.1, 133.1, 135.2, 138.4, 149.9, 168.2; MS (EI): $m/z=361$ [M^+]. Anal. Calcd for $C_{22}H_{19}NO_2S$ (361.11): C, 73.10; H, 5.30; N, 3.88. Found. C, 73.00; H, 5.12; N, 3.63.

4.2.2. (*E*)-3-Benzylidene-1,2-dihydro-2-(phenylthioethyl)-1*H*-isoindol-1-one (10b). This product was isolated as a yellow oil in 88% yield after chromatograph on silica gel column using a mixture of diethyl acetate–hexane (3/7) as eluent; IR (neat) $\tilde{\nu}_{max}=3019$ and 2976 (CH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.28 (dd, 2H, $J=7.5$, 7.1 Hz, CH_2–CH_2), 4.13 (dd, 2H, $J=7.5$, 7.1 Hz, CH_2–CH_2), 6.41 (s, 1H, CH=C), 7.16–7.23 (m, 1H, aromatic), 7.27–7.35 (m, 4H, aromatic), 7.38–7.46 (m, 6H, aromatic), 7.48–7.53 (m, 2H, aromatic), 7.78 (d, 1H, $J=8.4$ Hz, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 39.4, 110.3, 123.3, 123.4, 126.7, 128.0, 128.8, 129.3, 129.5, 129.7, 129.9, 129.7, 130.3, 131.8, 135.1, 135.2, 135.3, 136.1, 166.7; MS (EI): $m/z=357$ [M^+]. Anal. Calcd for $C_{23}H_{19}NOS$ (357.12): C, 77.28; H, 5.36; N, 3.92. Found. C, 77.04; H, 5.12; N, 3.87.

4.2.3. 2,3-Dihydro-3-phenyl-2-(2-phenylthioethyl)-isoindol-1-one (11a). To a solution of 3-hydroxy-3-phenyl-2-(2-phenylthioethyl)-2,3-isoindol-1-one (**10a**, 1.80 g, 5 mmol) in 30 mL of dry dichloromethane, was added on stirring and cooling at 0 °C dropwise 5 mL of TFA. After 5 min of reaction, triethylsilane (1.53 mL, 10 mmol) dissolved in 10 mL of anhydrous dichloromethane was added slowly over a period of 5 min. After 4 h of the reaction at room temperature, the solvent was evaporated under reduced pressure. The oily residue was diluted with 30 mL of dichloromethane and 30 mL of saturated sodium hydrogenocarbonate solution. The organic layer was separated, washed twice with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization of the reaction residue from a dry ethanol give α-phenyllactam **11a** in 89% yield as white crystals; mp = 120 °C; IR (KBr) $\tilde{\nu}_{max}=3009$ and 2985 (CH), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97–3.05 (m, 1H, CH_2–CH_2), 3.10–3.31 (m, 2H, CH_2–CH_2), 3.93–4.07 (m, 1H, CH_2–CH_2), 5.52 (s, 1H, CH), 7.04–7.33 (m, 11H, aromatic), 7.42–7.46 (m, 2H, aromatic), 7.82–7.95 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.5, 40.2, 65.6, 123.2, 123.6, 126.1, 127.8, 128.5, 128.9, 129.1, 129.2, 131.4, 132.0, 135.3, 136.9, 146.4, 168.9; MS (EI): $m/z=345$ [M^+]. Anal. Calcd for $C_{22}H_{19}NOS$ (345.46): C, 76.49; H, 5.54; N, 4.05. Found. C, 76.21; H, 5.38; N, 3.79.

4.3. General procedure for Grignard addition onto *N*-(2-bromoethyl)phthalimide (6)

To a well stirred and cold solution (0 °C) of halide (**6**, 6 g, 22.5 mmol) under dry argon atmosphere in anhydrous THF (150 mL) was added slowly in dropwise, over a period of 30 min, a 0.5 M solution of Grignard reagent (phenylmagnesium bromide or benzylmagnesium chloride (1.2 equiv, 27 mmol)) in dry THF. After 48 h of reaction at room temperature, the reaction mixture was hydrolysed under stirring with cold water (100 mL) then passed through a short column of Celite. After separation, the organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization of the reaction residue from a dry ethanol or cyclohexane/diethyl ether gave oxazoline derivatives **12a** or **12b** in quantitative yield.

4.3.1. 2,3-Dihydro-9*b*-phenyloxazolo[2,3-*a*]isoindol-5-(9*bH*)-one (12a). This product was isolated as yellow-white solid in quantitative yield and melted at 146 °C (lit.[24], 148–150 °C); IR (KBr) $\tilde{\nu}_{max}=3012$ and 2995 (CH), 1689 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.19–3.35 (m, 1H, CH_2–CH_2), 4.06–4.20 (m, 2H, CH_2–CH_2), 4.32–4.44 (m, 1H, CH_2–CH_2), 7.21–7.65 (m, 8H, aromatic), 7.75–7.88 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.6, 70.3, 100.5, 123.6, 123.7, 124.4, 125.8, 125.9, 128.9, 129.0, 130.2, 131.2, 133.6, 138.0; MS (EI): $m/z=251$ [M^+]. Anal. Calcd for $C_{16}H_{13}NO_2$ (251.09): C, 76.48; H, 5.21; N, 5.57. Found. C, 76.22; H, 5.06; N, 5.39.

4.3.2. 9*b*-Benzyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5-(9*bH*)-one (12b). This product was isolated as yellow solid in quantitative yield and melted at 53 °C (decomposition); IR (KBr) $\tilde{\nu}_{max}=3021$ and 2987 (CH), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72–2.92 (m, 1H, CH_2–CH_2), 3.16 (d, 1H, $J=14.0$ Hz, CH_2–C), 3.38 (d, 1H, $J=14.0$ Hz, CH_2–C), 3.85–4.05 (m, 3H, CH_2–CH_2), 7.20–7.36 (m, 5H, aromatic), 7.44–7.62 (m, 3H, aromatic), 7.69–7.72 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.0, 43.2, 69.9, 100.6, 122.7, 124.2, 127.0, 128.1, 130.1, 130.7, 133.1, 135.2, 138.1, 147.1, 173.9; MS (EI): $m/z=265$ [M^+]. Anal. Calcd for $C_{17}H_{15}NO_2$ (265.31): C, 76.96; H, 5.70; N, 5.28. Found. C, 76.79; H, 5.54; N, 5.11.

4.4. General procedure for cleavage-reduction of oxazoloisoindolones (12a,b)

To a cold (−60 °C) and stirred solution of oxazoloisoindolone (**12a**) or (**12b**) (10 mmol) in 40 mL of dry dichloromethane, was added dropwise (15 mL, 15 mmol) of 1.0 M $TiCl_4$ solution in dry THF. After 10 min of reaction under stirring, triethylsilane (4.58 mL, 30 mmol) dissolved

in 10 mL of anhydrous dichloromethane was added slowly by syringe over a period of 2 min. The reaction mixture was allowed to reach gradually room temperature during 30 min and allowed to react again for an additional 30 min. After addition of 30 mL saturated NH_4Cl solution and 30 mL of dichloromethane, the organic layer was separated, washed twice with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (1/1) as eluent give the expected alcohol derivative (**13a**) or (**13b**) in 66 and 64% yields, respectively.

4.4.1. 2-(2-Hydroxyethyl)-2,3-dihydro-3-phenylisoindol-1-one (13a). This product was isolated as a white solid in 66% yield and melted at 99 °C (methanol/water) (lit.[25], 110–112 °C); IR (KBr) $\tilde{\upsilon}_{max}=3401$ (OH), 3009 and 2986 (CH), 1702 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.98–3.11 (m, 1H, CH_2–CH_2), 3.63–3.85 (m, 2H, CH_2–CH_2), 3.87–3.97 (m, 1H, CH_2–CH_2), 4.41 (s broad, 1H, OH), 5.67 (s, 1H, CH), 7.09–7.79 (m, 9H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.3, 61.7, 66.2, 123.2, 123.6, 127.8, 128.5, 128.9, 129.3, 131.2, 132.1, 136.8, 146.6, 170.2; MS (EI): $m/z=235$ [M^+-H_2O]. Anal. Calcd for $C_{16}H_{15}NO_2$ (253.11): C, 75.87; H, 5.97; N, 5.53. Found. C, 75.63; H, 5.81; N, 5.34.

4.4.2. 3-Benzyl-2-(2-hydroxyethyl)-2,3-dihydroisoindol-1-one (13b). This product was isolated as an uncolourless oil in 64% yield; IR (neat) $\tilde{\upsilon}_{max}=3397$ (OH), 3015 and 2990 (CH), 1673 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.86 (dd, 1H, $J=14.1$, 7.8 Hz, CH_2–CH), 3.37–3.57 (m, 2H, CH_2–CH_2), 3.86 (t, 2H, $J=5.5$ Hz, CH_2–CH_2), 3.95–4.07 (m, 1H, CH_2–CH_2), 4.91 (dd, 1H, $J=7.8$, 4.7 Hz, CH–CH_2), 6.85–6.94 (m, 1H, aromatic), 7.02–7.12 (m, 2H, aromatic), 7.23–7.27 (m, 3H, aromatic), 7.35–7.47 (m, 2H, aromatic), 7.71–7.79 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 44.6, 62.0, 62.3, 123.0, 123.6, 127.2, 128.3, 128.6, 129.6, 131.3, 131.8, 135.9, 145.3, 169.9; MS (EI): $m/z=249$ [M^+-H_2O]. Anal. Calcd for $C_{17}H_{17}NO_2$ (267.32): C, 76.38; H, 6.41; N, 5.24. Found. C, 76.06; H, 6.21; N, 5.06.

4.5. General procedure for chlorination of alcohols (13a,b)

To a stirred solution of 5 mmol of alcohol **13a** or **13b** in 40 mL of dry dichloromethane under argon atmosphere was added slowly 1.5 equiv of freshly distilled thionyl chloride (0.56 mL, 0.89 g, 7.5 mmol) and the mixture was allowed to react at reflux for 2 h. After cooling and concentration under vacuo, the oily residue was diluted with dry dichloromethane and treated with charcoal. The concentration of the solution under reduced pressure give suitable aliphatic halide **14a** or **14b** in quantitative yield.

4.5.1. 2-(2-Chloroethyl)-2,3-dihydro-3-phenylisoindol-1-one (14a). This product was isolated as an orange oil in quantitative yield; IR (neat) $\tilde{\upsilon}_{max}=3012$ and 2988 (CH), 1689 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.16–3.30 (m, 1H, CH_2–CH_2), 3.51–3.62 (m, 1H, CH_2–CH_2), 3.71–3.83 (m, 1H, CH_2–CH_2), 4.14–4.27 (m, 1H, CH_2–CH_2), 5.72 (s, 1H, CH), 7.10–7.96 (m, 9H, aromatic); MS (EI): $m/z=271$ [M^+]. Anal. Calcd for $C_{16}H_{14}ClNO$ (271.74): C, 70.72; H, 5.19; N, 5.15. Found. C, 70.39; H, 5.01; N, 4.92.

4.5.2. 3-Benzyl-2-(2-chloroethyl)-2,3-dihydroisoindol-1-one (14b). This product was isolated as an uncolourless oil in quantitative yield; IR (neat) $\tilde{\upsilon}_{max}=3021$ and 2979 (CH), 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (dd, 1H, $J=14.1$, 7.8 Hz, CH_2–CH), 3.38–3.60 (m, 2H, CH_2–CH_2 and CH_2–CH), 3.68–3.89 (m, 2H, CH_2–CH_2), 4.31–4.44 (dt, 1H, $J=5.5$, 4.7 Hz, CH_2–CH_2), 5.06 (dd, 1H, $J=7.8$, 4.7 Hz, CH–CH_2), 6.91–6.99 (m, 1H, aromatic), 7.02–7.14 (m, 2H, aromatic), 7.19–7.34 (m, 3H, aromatic), 7.36–7.50 (m, 2H, aromatic), 7.75–7.84 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 42.5, 42.6, 61.6, 123.1, 123.7, 127.2, 128.4, 128.7, 129.5, 131.4, 131.6, 135.7, 145.2, 168.8; MS (EI): $m/z=285$ [M^+]. Anal. Calcd for $C_{17}H_{16}ClNO$ (285.77): C, 71.45; H, 5.64; N, 4.90. Found. C, 71.20; H, 5.36; N, 4.61.

4.6. General procedure for *S*-alkylation of *N*-chloroethylisoindolones (14a,b)

The procedure is identical to that used for synthesis of *N*-(2-phenylthioethyl)phthalimide (**7**). After 12 h of reaction at 100 °C, the reaction mixture was cold and diluted with water (30 mL) and diethyl ether (30 mL). The organic layer was separated, washed twice with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (4/1) as eluent gave the expected sulfure (**11a**) or (**11b**) in 88% yield in both cases.

4.6.1. 2,3-Dihydro-3-phenyl-2-(2-phenylthioethyl)isoindol-1-one (11a). The characteristics of this component, obtained in 88% yield, are identical to that reported above in Section 4.2.3

4.6.2. 3-Benzyl-2,3-dihydro-2-(2-phenylthioethyl)-isoindol-1-one (11b). This product was not isolated in pure form (impurities do not exceed 5%). The product obtained as an orange oil in 88% yield (determined by GC–MS coupling) was used in the next without other purification; IR (neat) $\tilde{\upsilon}_{max}=3017$ and 2988 (CH), 1694 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.75 (dd, 1H, $J=13.3$, 7.8 Hz, CH_2–CH), 3.15–3.50 (m, 4H, CH_2–CH_2 and CH_2–CH), 4.15–4.28 (m, 1H, CH_2–CH_2), 4.87 (dd, 1H, $J=7.8$, 4.7 Hz, CH_2–CH), 6.85–6.91 (m, 3H, aromatic), 7.08–7.29 (m, 6H, aromatic), 7.31–7.47 (m, 4H, aromatic), 7.71–7.80 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.9, 31.8, 38.4, 61.2, 122.9, 123.5, 126.3, 127.1, 128.2, 128.5, 128.7, 129.1, 129.4, 131.1, 131.9, 135.2, 135.7, 145.0, 168.5; MS (EI): $m/z=359$ [M^+]. Anal. Calcd for $C_{23}H_{21}NOS$ (359.49): C, 76. 85; H, 5.89; N, 3.90. Found. C, 76.55; H, 5.63; N, 3.68.

4.7. General procedure for oxidation of *N*-phenylthioethylisoindolone derivatives (11a,b)

To a solution of sulfides **11a**,**b** (1 mmol) in 10 mL of dry dichloromethane was added in one portion under vigorous stirring at −60 °C a solution of *m*-CPBA (0.18 g, 1 mmol) in dry dichloromethane (10 mL). After 2–5 min of reaction

at this temperature and an additional 5 min at room temperature, the mixture was alkalinised with a saturated solution of $NaHCO_3$ (15 mL). The organic layer after separation, was dried over $MgSO_4$, concentrated under reduced pressure, and the residue was passed through short silica gel column using a mixture of cyclohexane–AcOEt (1/2) as eluent to give the expected cyclic sulfoxides **15a** or **15b** as inseparable two diastereosomers in quantitative yield.

4.7.1. 2,3-Dihydro-2-(2-phenylsulfanylethyl)-3-phenylisoindol-1-one (15a). This product was isolated as a mixture of two diastereomers (54/46) as a white solid in quantitative yield; IR (KBr) $\tilde{\upsilon}_{max}=3009$ and 2986 (CH), 1698 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.83–2.94 (m, 2×1H, CH_2–CH_2, mixture), 3.07–3.51 (m, 2×2H, CH_2–CH_2, mixture), 3.91–4.18 (m, 2×1H, CH_2–CH_2, mixture), 5.42 (s, 1H, CH of minor isomer), 5.73 (s, 1H, CH of major isomer), 7.08–7.18 (m, 2×2H, aromatic, mixture), 7.21–7.62 (m, 2×11H, aromatic, mixture), 7.76–7.92 (m, 2×1H, aromatic, mixture); MS (EI): $m/z=361$ [M^+]. Anal. Calcd for $C_{22}H_{19}NO_2S$ (361.11): C, 73.10; H, 5.30; N, 3.88. Found. C, 73.04; H, 5.11; N, 3.65.

4.7.2. 3-Benzyl-2-(2-phenylsulfanylethyl)-2,3-dihydroisoindol-1-one (15b). This product was isolated as a mixture of two diastereomers (55/45) as a white solid in quantitative yield; IR (KBr) $\tilde{\upsilon}_{max}=3012$ and 2990 (CH), 1693 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.79–2.92 (m, 1H, CH_2–CH of major isomer), 2.96–3.08 (m, 1H, CH_2–CH of minor isomer), 3.22–3.53 (m, 2×3H, CH_2–CH_2 and CH_2–CH, mixture), 3.68–3.89 (m, 2×1H, CH_2–CH, mixture), 4.11–4.31 (m, 2×1H, CH_2–CH_2, mixture), 4.69 (dd, 1H, $J=8.6$, 4.7 Hz, CH of minor isomer), 5.01 (dd, 1H, $J=7.8$, 4.6 Hz, CH of major isomer), 6.80–7.12 (m, 2×2H, aromatic, mixture), 7.16–7.89 (m, 2×12H, aromatic, mixture); MS (EI): $m/z=375$ [M^+]. Anal. Calcd for $C_{23}H_{21}NO_2S$ (375.13): C, 73.57; H, 5.64; N, 3.73. Found. C, 73.36; H, 5.49; N, 3.61.

4.8. General procedure for Swern oxidation of *N*-hydroxyethylisoindolone derivatives (13a,b)

To a mixture of oxalyl chloride (1.01 mL, 11.83 mmol, 3.15 equiv) in 15 mL of anhydrous dichloromethane and cooled at −60 °C was added dropwise dry DMSO (1.33 m, 18.78 mmol, 5 equiv) and the mixture stirred at −60 °C for 15 min. A solution of *N*-hydroxyethylisoindolone derivatives (**13a**,**b**, 3.75 mmol, 1 equiv) in 30 mL of anhydrous dichloromethane was then added slowly and the resulting solution stirred at same temperature for 1 h, at which time triethylamine (2.80 mL, 19.9 mmol, 5.3 equiv) was added and the reaction mixture was allowed to warm to 0 °C. After hydrolysis with saturated sodium hydrogenocarbonate solution, the solution was then concentrated under reduced pressure. The residue was redissolved in dichloromethane, washed twice with water, brine, dried over Na_2SO_4, and concentrated to dryness in vacuo. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (2/3) as eluent give the expected formyl derivative (**17a**) or (**17b**) in acceptable yield.

4.8.1. (1,3-Dihydro-1-oxo-3-phenylisoindol-2-yl)acetaldehyde (17a). This product was isolated as an uncolourless oil in 72% yield; IR (neat) $\tilde{\upsilon}_{max}=3010$ and 2987 (CH), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (d, 1H, $J=18.7$ Hz, CH_2), 4.71 (d, 1H, $J=18.7$ Hz, CH_2), 5.65 (s, 1H, CH), 7.07–7.19 (m, 3H, aromatic), 7.25–7.51 (m, 5H, aromatic), 7.87–7.91 (m, 1H, aromatic), 9.52 (s, 1H, CH=O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.4, 65.2, 123.3, 123.8, 127.7, 128.5, 129.1, 129.3, 130.6, 132.3, 136.1, 146.5, 169.0, 196.9; MS (EI): $m/z=251$ [M^+]. Anal. Calcd for $C_{16}H_{13}NO_2$ (251.09): C, 76.48; H, 5.21; N, 5.57. Found. C, 76.29; H, 5.11; N, 5.39.

4.8.2. (3-Benzyl-1,3-dihydro-1-oxoisoindol-2-yl)acetaldehyde (17b). This product was isolated as an uncolourless oil in 63% yield; IR (neat) $\tilde{\upsilon}_{max}=3014$ and 2992 (CH), 1698 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (dd, 1H, $J=14.1$, 7.0 Hz, CH_2–CH), 3.14 (dd, 1H, $J=14.1$, 6.3 Hz, CH_2–CH), 3.99 (d, 1H, $J=19.6$ Hz, CH_2), 4.62 (d, 1H, $J=19.6$ Hz, CH_2), 4.96 (dd, 1H, $J=7.0$, 6.3 Hz, CH–CH_2), 7.03–7.10 (m, 3H, aromatic), 7.12–7.55 (m, 5H, aromatic), 7.78–7.83 (m, 1H, aromatic), 9.52 (s, 1H, CH=O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.1, 51.3, 61.4, 122.9, 123.8, 127.3, 128.4, 128.7, 129.3, 131.1, 131.7, 135.9, 145.4, 169.0, 196.9; MS (EI): $m/z=265$ [M^+]. Anal. Calcd for $C_{17}H_{15}NO_2$ (265.11): C, 76.96; H, 5.70; N, 5.28. Found. C, 76.78; H, 5.43; N, 5.12.

4.9. General procedure for cyclodeshydratation of aldehydes 17a,b or Pummerer type-cyclization of sulfoxides 15a,b into cyclic isoindolone 5a,b

Method A: Cyclocondensation. To a stirred and cold solution of aldehydes (**17a**,**b**, 2 mmol) in 15 mL of glacial acetic acid was added dropwise concentrated sulphuric acid (96–98%, 30 mL). The mixture was stirred at room temperature for 4 h and neutralised carefully on cooling with addition dropwise of 30% ammonia solution. After extraction with dichloromethane and separation, the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated to dryness in vacuo. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (4/1) as eluent gave the expected cyclic product (**5a**) or (**5b**) in 30% and 40% yields. *Method B: Pummerer cyclization*. To a stirred solution of sulfoxides (**15a**,**b**, 2.77 mmol) in 45 mL of dry dichloromethane was added dropwise TFAA (6 mL, 42.6 mmol). After 2 h of reaction at reflux, the reaction mixture was washed successively with saturated sodium hydrogenocarbonate solution and brine. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and the residue was passed through short silica gel column using a mixture of cyclohexane–AcOEt (4/1) as eluent to give the expected cyclic product (**5a**) or (**5b**) in 100 and 96% yields, respectively.

4.9.1. Isoindolo[1,2-*a*]isoquinolin-8(12*bH*)-one (5a). This product was isolated as an orange solid in yields indicated above; mp=122 °C (ethanol/diethyl ether); IR (KBr) $\tilde{\upsilon}_{max}=$ 3009 (CH), 1703 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.86 (s, 1H, CH), 6.20 (d, 1H, $J=7.8$ Hz, CH=CH), 7.16–7.31 (m, 4H, aromatic), 7.52–7.71 (m, 3H, aromatic), 7.90 (dd, 2H, $J=6.3$, 7.8 Hz CH=CH+aromatic); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 57.8, 123.4, 123.9, 124.2, 124.6, 125.6, 126.9, 128.5, 128.6, 128.7, 129.2, 129.3, 132.1, 132.5, 134.5, 172.1; MS (EI): $m/z=233$ [M^+]. Anal. Calcd for $C_{16}H_{11}NO$ (233.08): C, 82.38; H, 4.75; N, 6.00. Found. C, 82.21; H, 4.66; N, 5.86.

4.9.2. 12*b*,13-Dihydrobenzo[4,5]azepino[2,1-*a*]isoind-ol-8-one (5b). This product was isolated as a white-yellow solid in yields indicated above; mp=110 °C (ethanol); IR (KBr) $\tilde{\upsilon}_{max}=3012$ (CH), 1701 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05 (dd, 1H, $J=14.1$, 7.0 Hz, CH_2–CH), 3.51 (dd, 1H, $J=14.1$, 3.1 Hz, CH_2–CH), 5.08 (dd, 1H, $J=7.0$, 3.1 Hz, CH–CH_2), 6.10 (d, 1H, $J=14.1$ Hz, CH=CH), 6.88–6.93 (m, 2H, aromatic), 7.05–7.52 (m, 6H, CH=CH+aromatic), 7.74 (d, 1H, $J=7.0$ Hz, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.0, 60.6, 109.9, 121.4, 122.4, 124.3, 127.0, 127.4, 129.0, 129.9, 130.8, 131.2, 133.0, 135.4, 135.9, 144.4, 165.8; MS (EI): $m/z=247$ [M^+]. Anal. Calcd for $C_{17}H_{13}NO$ (247.10): C, 82.38; H, 4.75; N, 6.00. Found. C, 82.21; H, 4.66; N, 5.86.

4.9.3. (*cis* and *trans*)-5,12*b*-Dihydro-5-phenylthioisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (16a). Following a procedure similar to that described above for the preparation of cyclic isoindolines **5a**,**b**, the sulfide **16a** as the Pummerer type-cyclization intermediate was isolated when the reaction was performed at room temperature for 30 min. After a similar work-up as above, this product, **16a**, was obtained as a mixture of two diastereomers in 56/44 ratio as uncolourless oil in quantitative yield; IR (neat) $\tilde{\upsilon}_{max}=3016$ and 2983 (CH), 1704 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.18 (dd, 1H, $J=14.1$, 9.4 Hz, CH_2–CHS, major isomer), 3.32 (dd, 1H, $J=14.1$, 5.5 Hz, CH_2–CHS, minor isomer), 4.31 (dd, 1H, $J=14.1$, 3.9 Hz, CH_2–CHS, major isomer), 4.44 (dd, 1H, $J=14.1$, 5.5 Hz, CH_2–CHS, minor isomer), 4.48 (s, 1H, CH, major isomer), 5.67 (s, 1H, CH, minor isomer), 6.33 (dd, 1H, $J=9.4$, 3.9 Hz, SCH–CH_2, major isomer), 6.47 (d, 1H, $J=5.5$ Hz, SCH–CH_2, minor isomer), 6.97–7.41 (m, 2×13H, aromatic, mixture), 7.83–7.96 (m, 2×1H, aromatic, mixture); MS (EI): $m/z=233$ [M^+-PhSH].

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