Toward the improvement of the tandem halide displacement/amide coupling spiro-cyclization as a new route to γ-lactam and pyrroloisoquinoline templates

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ABSTRACT

Two efficient and rapid accesses to spiro-oxindole entities bearing an imide function were presented, and their performance was compared. The key components are N-substituted α-bromoacetamides to reach these derivatives in tandem process. The resulting spiro-imides from these methodologies were regioselectively reduced into corresponding N-acyliminium precursors, which were subsequently submitted to an intramolecular cyclization to provide pentacyclic spiro-oxindole architecture analogues to pteropodine and spirotryprostatin-B alkaloids with high diastereoselective control.

1. Introduction

Spiro-oxindole cores are present in numerous alkaloids of biological interest, including the treatment of cancer. Among them, horsfiline (**1a**) and coerulescine (**1b**) (Scheme 1) isolated, respectively, from the roots of the Malaysian tree *Horsfieldia superba*,[1] and blue canary grass *Phalaris coerulescens*,[2] constitute representative examples. Some unnatural spiro-oxindoles such as **2** turn out to be potent as aldose reductase inhibitors, antihyperglycemic agents,[3] and to be efficient for the treatment of allergic inflammatory diseases.[4] Other complex systems (Scheme 1) exemplified by pteropodine (**3**) and its stereoisomers are produced by *Uncaria tomentosa*, which has been used for decades in traditional South American medicine[5] and currently used across North America. The high interest of these products may also be explained by their anti-inflammatory[6] and cytoprotection[7] activities attributed in term to the presence of the pentacyclic spiro-oxindole scaffold in their architectures. Finally, spirotriprostatin B (**4**) is another sophisticated pentacyclic alkaloid from the spiro-oxindole family, which can be isolated from the fermentation broth of *Aspergillus fumigatus*, and has been shown to be efficient against some mammalian cancer cells.[8]
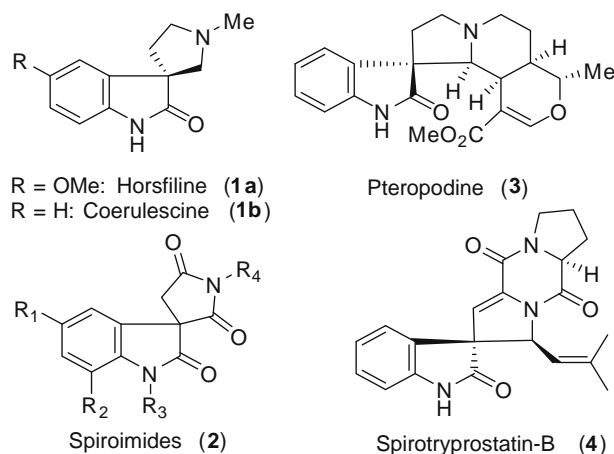
Scheme 1. Representative natural and unnatural active spiro-oxindoles.

In view of the therapeutic potential of these structures as well as the synthetic challenges they raise by the formation of the attractive and key spiro junction to a pyrrolidine ring, considerable efforts are continuously being made to synthesize them.[9] In this line, different strategies have been developed and include (i) an oxidative rearrangement of substituted tetrahydro-β-carbolines,[10] (ii) an intramolecular Mannich reaction of tryptophans,[11] (iii) a MgI₂-promoted ring expansion of spiro-oxindoles,[12] and (iv) an

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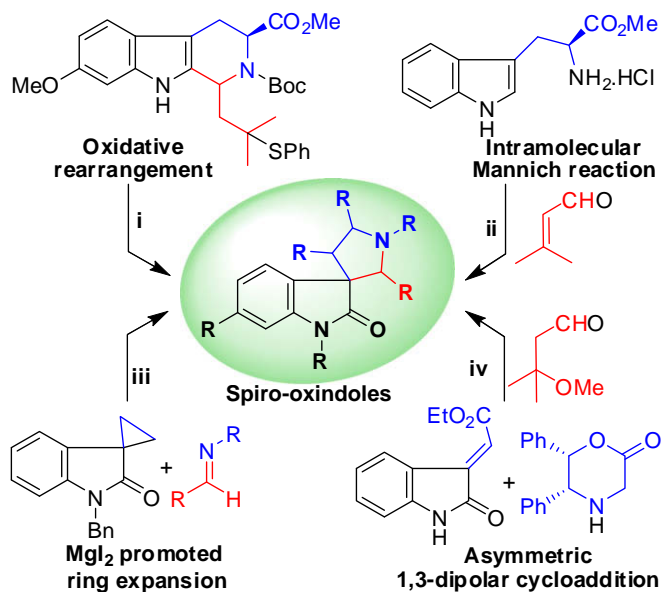
Scheme 2. Popular approaches for the synthesis of spiro-oxindole cores.

Scheme 3. Retrosynthetic scheme leading to tricyclic and pentacyclic spiro-oxindole cores 2, 8, and 9.

asymmetric 1,3-dipolar cycloaddition of functionalized methylidene-oxindoles[13] (Scheme 2).

2. Results and discussion

Because there are few strategies amenable to these spiro-systems as potential candidates for novel therapeutic agents, the development of new and straightforward routes for their production is therefore quite desirable. In the preliminary report, we have explored a synthetic potential of N-alkyl α-bromoacetamides of type 5 in tandem sequences to provide high functionalized γ-lactams and bis-spiro-imides by reaction with activated olefins[14] and malonates,[15] respectively. In the continuation of this work, we now explore another chapter on the engagement of these α-bromoacetamides 5 for the synthesis of the tricyclic spiro-imides 2 using two pathways (Scheme 3). Path A may prove to be a reaction between the N-alkyl α-bromoacetamides 5 and the dimethyl 2-(2-nitrophenyl)malonates 6 followed ultimately by the tandem nitro-reduction/amino-ester cyclization. As for path B, this time, the tandem process may be considered between the N-alkyl α-bromoacetamides 5 and the ethyl oxindole-carboxylate 7. In both cases, the common point is the acidic property of the methylene proton of substrates 6 and 7. Furthermore, we also demonstrate the synthetic utility of these spiro-systems 2 as remarkable precursors of N-acyliminium species to build new pentacyclic spiro-oxindole cores 8 and 9 with promising biological profiles.

Our investigation was initiated by the synthesis in a two-step sequence of the quaternary nitro-imides 12a,b, as the key reagents in pathway A from dimethyl malonate (10) and o-nitrofluorobenzenes 11a,b (Scheme 4).[16] So, the reaction of 10 with 11a,b using known procedure[17] afforded the nitro-diester derivatives 6a,b in average yields of 60%. The crucial cyclization, which was based on the tandem nucleophilic substitution/peptide coupling of 6a,b with N-benzyl-α-bromoacetamide (5: n = 1, Ar = Ph) proceeded in THF/NaH at reflux. Under these conditions, the expected products 12a,b were isolated in low and moderate yields of 39% and 55%, respectively, calculated from the purified mixture containing the starting materials 6a,b which were very difficult to be eliminated. The behavior of the latter reaction also remains the same whatever the changes made on the reaction conditions. This is probably due to the steric hindrance of the corresponding anions of nitro-diesters 6a,b.[18]
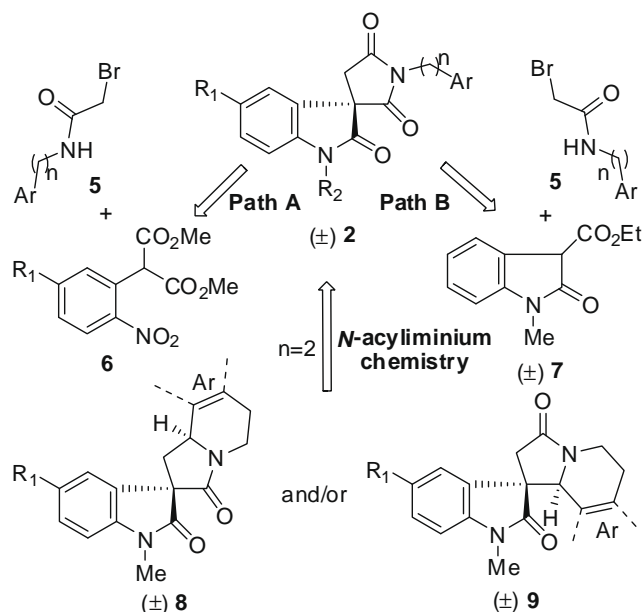
Finally, the synthesis of the spiro-center was achieved by the reduction of the nitro function using iron powder in acetic acid to provide, via spontaneous amino-ester condensation, the tricyclic spiro-oxindoles 2a,b in 40% and 7% yields, respectively.

This strategy produced very low yields, notably those concerning the formation of an oxindole ring of spiro-imides 2a,b despite the simplicity and the cheaper reagents used, allied to the difficulties encountered during the purification of certain intermediates. We then turned our attention to path B in which the oxindole nucleus constitutes the starting material. So, we synthesized the ethyl N-methyloxindole-carboxylate (7) using a modified known procedure (Scheme 5).[19] This substrate was then engaged to react with various N-substituted α-bromoacetamides 5 under basic conditions.[14,15] In a 'one-pot' procedure, the reaction led to the expected spiro-imides 2c–g in satisfactory to good yields. These products were secured by obtaining an X-ray structure of the representative product 2c (n = 1, Ar = Ph; Scheme 5).[20] Interestingly, from the results summarized in Table 1, the tandem reaction seems to be
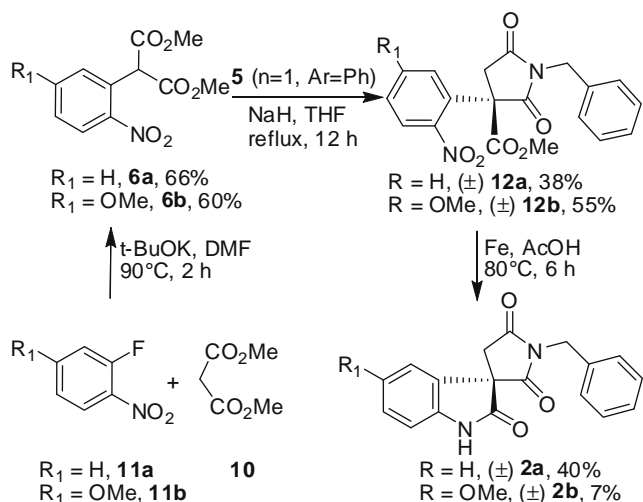
Scheme 4. Synthesis of spiro-oxindoles 2a,b using pathway A.
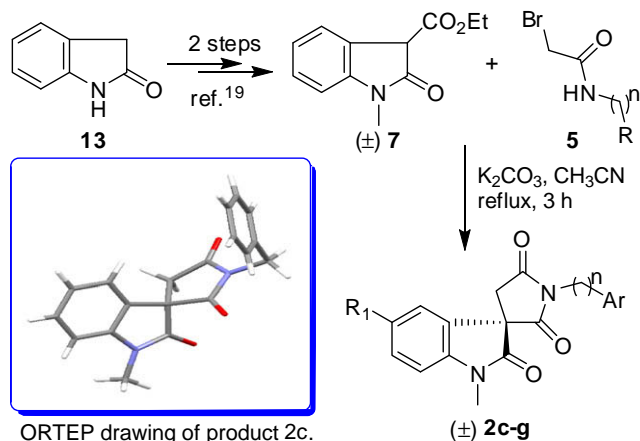
Scheme 5. Scheme leading to spiro-imides **2c**–**g** using pathway B and the ORTEP drawing of product **2c**.

Table 1
Synthesis of spiro-imides **2c**–**g** using pathway B[a]

Entry	n Value	Aryl (Ar)	Product	Yield[b] (%)
1	1	Ph	**2c**	84
2	2	Ph	**2d**	80
3	2	4-MeO-Ph	**2e**	63
4	2	3,4-(MeO)$_2$-Ph	**2f**	73
5	2	Indol-3-yl	**2g**	58

[a] The reaction was conducted in CH$_3$CN at reflux.
[b] Isolated yield.

effective and general; in addition, it readily tolerates both the methoxy substituent and the presence of a hetero-aromatic ring such as indole. This clearly demonstrates the power of this approach (path B) in comparison to that used in path A, which is also known.

In the second part of this work, we next decided to investigate the reactivity of the spiro-imides of type **2** particularly by examining their behavior when using N-acyliminium chemistry. These are of interest since the transformation could target the racemate pen-
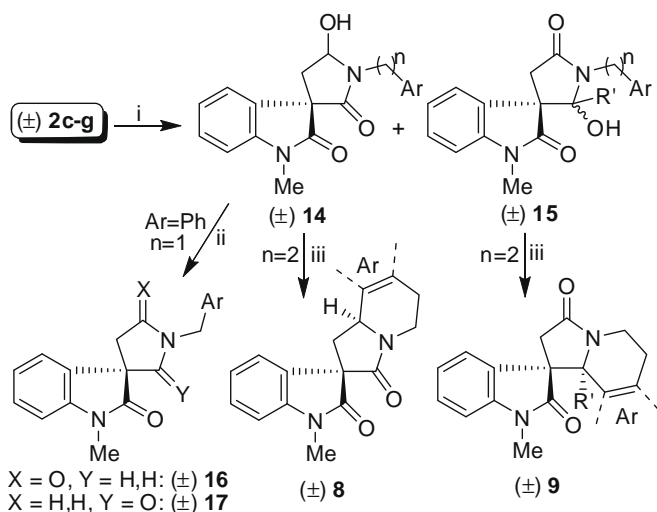
Scheme 6. Reactivity of spiro-imides **2c**–**d** leading to spiro-oxindole-lactams **16**, **17** and pentacyclic spiro-oxindoles **8**, **9**. Reagents and conditions: (i) LiEt$_3$BH, CH$_2$Cl$_2$, −60 °C or PhMgBr, CH$_2$Cl$_2$, 0 °C to rt ; (ii) TFA, Et$_3$SiH, CH$_2$Cl$_2$, reflux; (iii) see conditions in Table 2.
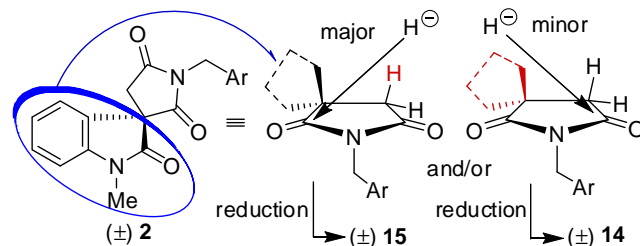

Figure 1. Regioselectivity of the reduction of spiro-imide (±)-**2** into hydroxy-lactams (±)-**14** and (±)-**15**.

tacyclic spiro-oxindoles **8** and **9**, as aromatic analogues of the bio-active alkaloid pteropodine (**3**, Schemes 1 and 6).

At the outset, the reduction of the imide function was carried out using LiEt$_3$BH as reducing agent in dry CH$_2$Cl$_2$ at −60 °C (the reaction was monitored by TLC) to provide the hydroxy-lactams **14** (R′ = H) and **15** (R′ = H) in yields ranging from 67% to 99%. In the case of spiro-imide **2d**, the reaction was incomplete (Table 2). The two regioisomers **14** and **15** were obtained in a range of 5/4 to 9/1 ratios in favor of hydroxy-lactam **15**, and were easily separated by flash chromatography on silica gel column using a mixture of AcOEt/CH$_2$Cl$_2$ as the eluent. This regioselectivity was first confirmed chemically by the reduction of the hydroxy-lactams using standard conditions (e.g., TFA, Et$_3$SiH in CH$_2$Cl$_2$)[21] to give the corresponding lactams **16** and **17** in 66% and 68% yields, respectively. On the other hand, the reaction of spiro-imide **2d** with bulky nucleophile (e.g., PhMgBr, CH$_2$Cl$_2$, 0 °C to rt) allowed us to obtain the hydroxy-lactam **15** (R′ = Ph) in only 18% yield (entry 3, Table 2)[22] regioselectively, despite the increase in the steric hindrance. These results are similar to those pointed out by numerous groups[23] including us.[24] In those studies, a model similar to that represented in Figure 1 was proposed initially in the Speckamp group for the reduction of related N-substituted imides.

Because there is no body of literature on hydroxy oxindole-spi-ropyrrolidines regarding the reactivity of these functionalities in acidic medium,[25] the behavior of α-hydroxy spiro-lactams **14** and **15** bearing different aromatic nucleophiles was examined under the influence of acid. For a better comparison of the results, only the nature of the aryl (Ar) group attached to the N-position of the succinimide nucleus in hydroxy spiro-lactam substrates **14** and **15** was changed. In this perspective, two protocols were tested using two types of acids such as Lewis acid (BF$_3$·OEt$_2$, LA) and Brønsted acid (TFA, BA), the most used in the literature for this purpose[23] (Table 2).

At the outset of our investigations, the major hydroxy spiro-lactam regioisomer **15** (n = 2), obtained as a mixture of two diastereoisomers in 1:1 ratio, was chosen as a test compound for the intramolecular α-amidoalkylation cyclization (Scheme 6). Here, the treatment of the N-acyliminium precursor **15d** with an excess of BF$_3$·OEt$_2$ in CH$_2$Cl$_2$ at room temperature for 12 h (Table 2, entry 2) gave the cyclized product **9d** in only 38% yield after chromatographic purification and separation of the starting material. Interestingly this product, **9d**, was obtained in 83% yield without traces of the starting material, when the hydroxy-lactam **15d** was treated with TFA at the same temperature and in the same solvent (Table 2, entry 2). In parallel studies, the behavior under acid conditions of the hydroxy-lactam **14d**, obtained as a single diastereoisomer and for which the stereochemistry is not yet determined, was considered. Thus, **14d** with TFA under conditions as outlined above led to the formation of the spiro-cyclic product **8d** in 56% yield accompanied with small amounts of the starting material **14d**.

Encouraged by the above results using both acids (LA or BA), we extended the process to a variety of π-aromatic nucleophiles

Table 2
Results of the two-step synthesis of the pentacyclic spiro-oxindole structures **8** and **9**

Entry	Substrate-**2**	Group R′	Yield[a]-**14** + **15** (%)	Ratio[b]-**15**/**14**	Acidic conditions	Yield[a]-**9** (%)	Yield[a]-**8** (%)
1	**2c**	H	97	5/4	—	—	—
2	**2d**	H	99	4/1	BF$_3$·Et$_2$O	38[c] (35)[d]	56[c]
					TFA	83[e]	—
3	**2d**	Ph	18 (45)[d]	—	BF$_3$·Et$_2$O	nr[c]	—
					TFA	54[f]	—
4	**2e**	H	67	9/1	BF$_3$·Et$_2$O	—	92[c]
					TFA	18[e]	—
5	**2f**	H	77	7/3	BF$_3$·Et$_2$O	49[g]	86[c]
					TFA	decomp[e]	—
6	**2g**	H	86	4/1	BF$_3$·Et$_2$O	—	11[c]
					TFA	60[e]	—

[a] Isolated yield.
[b] Determined by ^{1}H NMR analysis of the crude mixture.
[c] BF$_3$·OEt$_2$ (2 equiv), CH$_2$Cl$_2$, rt, 12 h; nr: no reaction.
[d] Recovered starting material.
[e] TFA (5 equiv), rt, 12 h.
[f] TFA (5 mL for 1 mmol of the hydroxy-lactam), rt, 2 days.
[g] BF$_3$·OEt$_2$ (9 equiv), CH$_2$Cl$_2$, rt, 2 days.

such as phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, and indol-3-yl (Tables 1 and 2). The results are tabulated in Table 2. This clearly shows that the reaction of hydroxy-lactams **15d–g** under the protocols outlined above is effective in both cases. However, the best results were obtained when a BA was used. In this context, the reaction is complete, and the desired spiro-oxindoles **9d–h** constitute the sole reaction products in low to good yields but with high diastereoselectivity.[26] These results could be explained by the steric hindrance due to the contiguous quaternary center, implying the use of harsher conditions for the intramolecular α-amido-alkylation reaction. Under these conditions, it was also possible to isolate in 54% yield the cyclic compound **9h** (R′ = Ph) bearing two contiguous quaternary centers (Table 2, entry 3). Furthermore, in the case of the more reactive 3,4-dimethoxyphenyl N-acyliminium ion precursor **15f**, the use of an LA gave the polycyclic spiro-system **9f** in 49% yield, while the use of BA led to the formation of an inseparable complex mixture probably due to the partial or total deprotection of the methoxy groups (Table 2, entry 5). Importantly, using the cyclization protocol delineated in Scheme 6 (LA) from hydroxyl spiro-lactams **14d–g** (R′ = H) as the minor regioisomers proved successful, thanks to the lower steric hindrance. In all these cases, the reaction provided the pentacyclic compounds **8d–g** (R′ = H) in low (11%; Table 2, entry 6) to excellent (92%; Table 2, entry 4) yields. For these

substrates, no additional cyclization conditions were tested. Finally, from these results, we can conclude that the reaction occurred by direct attack on the N-acyliminium ion intermediates **A** and **B** (Fig. 2) by the π-aromatic systems tethered to the nitrogen atom of the pyrrolidinone ring, to produce the pentacyclic pyrrolo-isoquinoline spiro-oxindoles **8** and **9**.

The relative stereochemistry of the newly formed stereocenters of the pentacyclic spiro-oxindoles **8** and **9** could be confirmed by NMR experiments (Fig. 2). In the case of product **9** it was firstly attributed by the chemical shift of the H$_{10′}$-proton, which appeared as a singlet or a doublet signal around δ = 6 ppm in ^{1}H NMR spectra in all cases. This chemical shift value is most likely due to the anisotropic effect of the carbonyl function on C$_2$-position, showing a *syn* relationship between the amide function onto the oxindole nucleus and the benzyl group of the newly created stereocenter. For instance, the stereoselectivity was secured by NOE experiments done on component **9d** with a 600 MHz NMR apparatus,[27] showing an important effect between H$_{4′}$- and H$_{10b′}$-protons. These studies confirm that the proton H$_{10b′}$ is on the same side than the aromatic ring of the oxindole moiety (Fig. 2). The same stereoselectivity was also observed earlier by Hiemstra and Speckamp for related structures.[25] In addition, we can assume that for the same reasons the preferred approach of the nucleophile would be from the less hindered oxindole side, that is, in our case the amide one (Fig. 2). Similarly, the NOE experiments performed in this case on product **8f** have shown a correlation between the H$_{10b′}$- and H$_{4′}$-protons, confirming that the aromatic ring was trapped by the N-acyliminium intermediate **B** from the same side of the amide function of the oxindole ring.

3. Conclusion

In this Letter, we have successfully introduced a new and expedient synthetic entry to spiro-imides of type **2** containing succinimide which is relevant to biological systems. Requiring only three operations from a ubiquitous and commercially available starting material (oxindole), this sequence culminated in the last step with the tandem halide displacement/amide coupling spiro-cyclization, which extends our recent findings in this area.

The spiro-cyclic systems containing an imide function obtained with this protocol were then used as valuable templates to provide, as application, spiro-oxindoles containing γ-lactams by two successive regioselective reductions. The hydroxy spiro-oxindole-lactams obtained as intermediates in this way were additionally
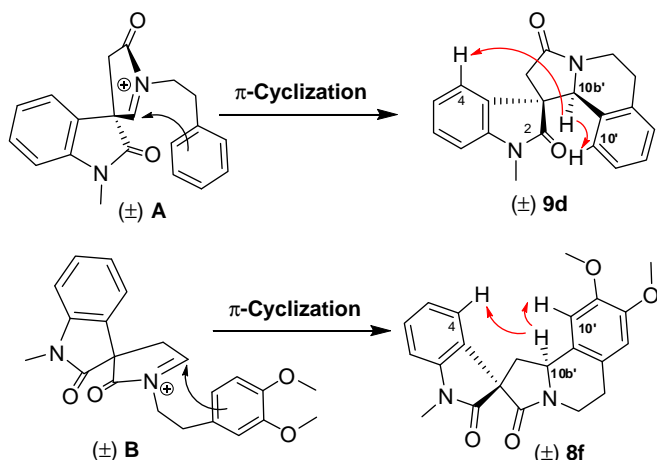

Figure 2. Stereoselective outcome of the intramolecular N-acyliminium cyclization into the racemate pentacyclic systems **8** and **9**.

treated in acidic medium (Lewis and Brønsted acids), and provided spiro-oxindolopyrroloisoquinolines via stable *N*-acyliminium species with high stereocontrol.

Finally, we anticipate that the transformations developed in this project, particularly the access to spiro-oxindoles containing γ-lactams, will find further applications in total synthesis of bioactive alkaloids. These systems are currently under investigation in our group, and the results will be reported soon in full account.

Acknowledgments

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26. *Typical procedure for the synthesis of pentacyclic spiro-oxindoles* **8** *and* **9**: BF₃·OEt₂ (50 μL, 0.36 mmol) or TFA (70 μL, 0.7 mmol) was added at rt to a solution of hydroxy-lactam **14** or **15** (0.18 mmol) in CH₂Cl₂ (2 mL). After 12 h of the reaction, the solution was cooled to 0 °C and quenched carefully by addition of an aqueous saturated solution of NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL), the organic layers were combined, dried over MgSO₄, and evaporated to dryness. The residue was then purified by chromatography on silica gel column using a mixture of AcOEt/cyclohexane as eluent. Data for a representative pentacyclic spiro-oxindole product **9d**: ¹H NMR (200 MHz, CDCl₃): 2.61–2.85 (m, 1H), 2.75 (d, 1H, *J* = 16.4 Hz), 3.01 (s, 3H), 2.86–3.21 (m, 2H), 3,01 (d, 1H, *J* = 16.4 Hz), 4.50 (dd, 1H, *J* = 3.3 and 12.5 Hz), 5.21 (s, 1H), 6.06 (d, 1H, *J* = 7.0 Hz), 6.83 (d, 2H, *J* = 7.8 Hz), 7.07 (d, 2H, *J* = 3.9 Hz), 7.17–7.46 (m, 3H). ¹³C NMR (50 MHz, CDCl₃): 25.8, 28.9, 37.3, 41.3, 53.9, 64.0, 108.5, 122.9, 123.3, 123.6, 126.1, 127.4, 128.9, 129.5, 131.9, 135.4, 144.3, 170.5, 176.1.
27. NMR spectra were recorded on an INOVA 600 Varian spectrometer in CDCl₃ solution. Chemical shifts (δ) are quoted in ppm, and are referenced to the tetramethylsilane (TMS) as the internal standard. The COSY and NOESY-1D techniques were used for the assignment of ¹H–¹H relationships and the determination of relative configuration. The HSQC and HMBC techniques were used throughout for the assignment of the ¹H–¹³C relationships.