

STUDIES ON (1*S*)-*N*-(1-PHENYLETHYL)PHTHALIMIDE: SYNTHESIS OF BOTH CHIRAL SPIRO INDANE AND BENZAZEPINE DERIVATIVES

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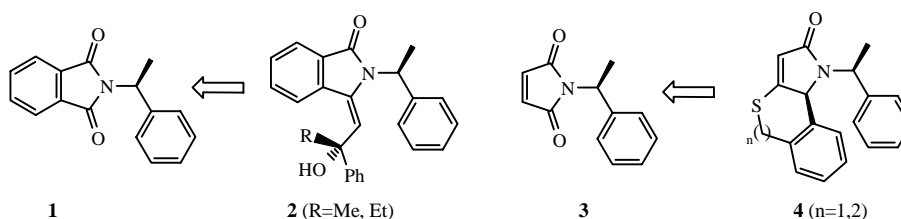
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**Abstract** – Chiral spiro indane and benzazepine compounds in isoindolinone series were prepared easily by  $\pi$ -cationic cyclization of the *N*-acyliminium ions (**5-9**) or the acylium ion (**17**) precursors with trifluoroacetic acid or aluminum trichloride, respectively. The stereochemistry and the ratio of diastereomeric mixtures observed during these process were also discussed.

## Introduction

*N*-Acyliminium ions have been shown to be highly important species in organic synthesis.<sup>1</sup> Also, for stereoselective syntheses of aza-compounds and aza-containing natural products, application of *N*-acyliminium cation intermediates in the crucial carbon-carbon bond formation in an intermolecular and intramolecular manner is well established.<sup>1,2</sup>

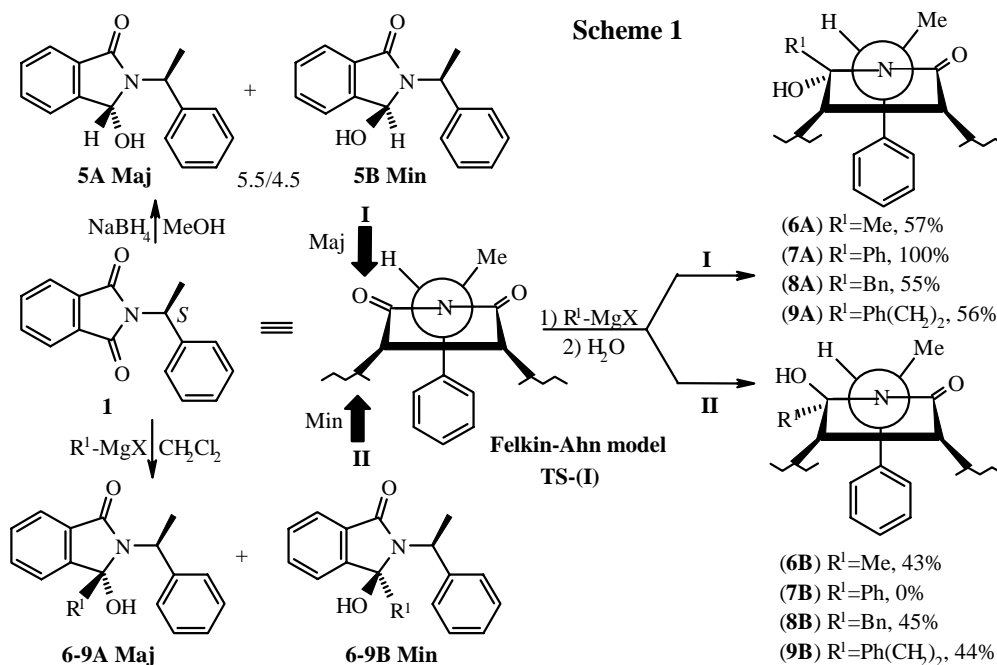


As an extension of our work in this field, allied with our interest in the development of synthetic approaches to diversely chiral heterocyclic compounds containing isoindolinone or pyrrolidinone moieties, we have recently reported the preparation of chiral aza-analogues of *senkyunolide-E* (**2**) in three steps from phthalimide derivative (**1**) by successive organolithium addition, Meyer-Schuster rearrangement and Grignard reaction.<sup>3</sup> More recently, we focused our interest on the synthesis of chiral

pyrroloisothiochroman (**4**,  $n=1$ ) and pyrrolobenzo[*d*]thiepine (**4**,  $n=2$ ),<sup>4</sup> starting from the maleimide synthon (**3**) by sulfurization, regioselective reduction followed by  $\pi$ -cationic cyclization, to apply to these original molecules an exhaustive pharmaceutical investigation. In this paper, we wish to report full our studies concerning the reactivity of (1*S*)-*N*-(1-phenylethyl)phthalimide (**1**) towards nucleophiles followed by subsequent cyclization of the resulting hydroxylactams and carboxylic acids derivatives.

## Result and discussion

As highlighted in Scheme 1, the enantiopure substrate (**1**) described earlier by us<sup>3</sup> was subjected to reduction and carbophilic addition in order to study the influence of the steric and electronic effects in both reduction-addition and further cyclization steps.



Actually, reduction of the carbonyl group of the imide function was carried out with large excess of sodium borohydride in dry methanol at  $-5-0^\circ\text{C}$ . The reaction was accomplished in 30 min, by regular addition of an ethanolic hydrochloric acid solution according to our precedent report,<sup>5</sup> and afforded in 92% yield a 5.5/4.5 mixture of two diastereomers. These products were separated by fractional crystallization (FC) or preparative TLC (hexane/ether : 1/9) and were assigned as **5A** and **5B**, respectively. On the other hand, the addition of Grignard reagents ( $\text{R}^1\text{-MgX}$  with  $\text{R}^1\text{-X} = \text{Me-I}$ ,  $\text{Ph-Cl}$ ,  $\text{PhCH}_2\text{-Br}$ ,  $\text{Ph}(\text{CH}_2)_2\text{-Br}$ ) onto imide (**1**) give after aqueous hydrolysis<sup>6</sup>  $\alpha$ -hydroxy lactams (**6-9**) with moderate to good yields (65-88%). It is worth mentioning that when the reaction was hydrolyzed by an aqueous acidic solution, other significant competing process like the dehydration of hydroxy lactam into enamide for example took place giving a complex mixture of inseparable products.

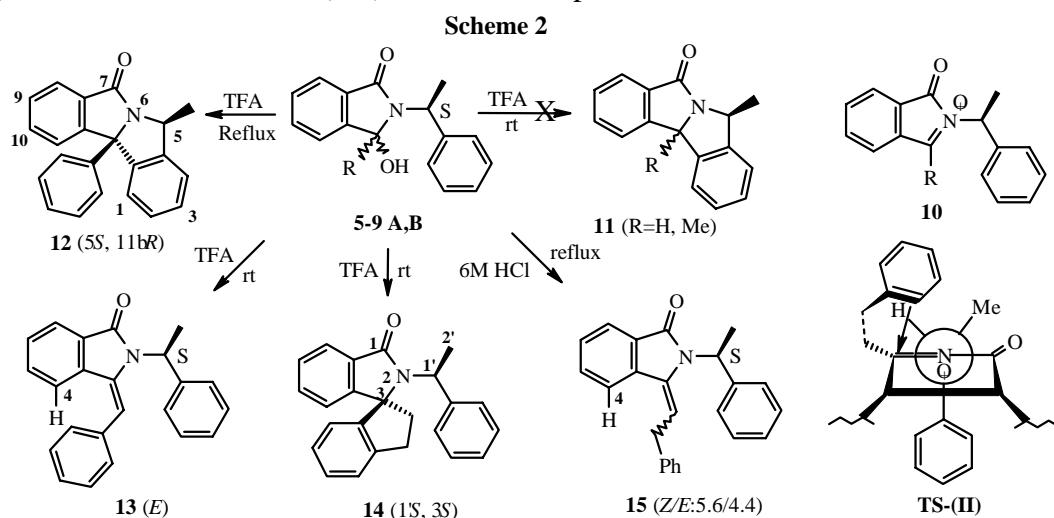
Interestingly, the results highlighted in Scheme 1 show that the reaction proceeded with moderate to high diastereoselectivity depending on the  $\text{R}^1$  group in the Grignard reagent. These facts could be rationalized by assuming that reduction and carbophilic addition reactions proceeded probably through Felkin-Ahn

like model as in the transition state **TS-(I)** (Scheme 1) in which the steric hindrance of the methylbenzyl group induces a diastereofacial discrimination during the approach of the incoming nucleophile. Consequently, exclusive nucleophilic addition product (**7A**) (88%) was obtained with phenylmagnesium chloride, whereas methylmagnesium iodide, benzylmagnesium bromide and phenylethylmagnesium bromide gave  $\alpha$ -hydroxy lactams (**6**) (86%), (**8**) (65%) and (**9**) (67%) which showed respectively a 5.7/4.3, 5.5/4.5 and 5.6/4.4 mixture of two diastereomers inseparable by column chromatography. These observations were comparable with our previously reported study in chiral succinimide series.<sup>4</sup>

Taking into account that the products (**5-9**) could give access to endocyclic *N*-acyliminium ion intermediate (**10**) (Scheme 2) precursors of isoindoloisoindolinone core (**11**) as an attractive target, they were subjected to the general  $\pi$ -cationic cyclization condition (trifluoroacetic acid, room temperature).<sup>7</sup>

Under these conditions, **5-7A,B** were recovered unreacted accompanied in the case of **5A,B** and **6A,B** with some epimerization in the favor of the major isomer (**A**). Interestingly, under harsher acid conditions (neat TFA at reflux) **7A** led to the expected cycle (**12**) in 18% yield accompanied with some resinification of the starting material. This product which shows a *cis*-relationship between methyl and phenyl groups is similar to that obtained (racemic form) earlier as a major diastereomer (16%) from the corresponding racemate 3-hydroxy-3-phenyl-2-(1-phenylethyl)isoindolin-1-one.<sup>8</sup>

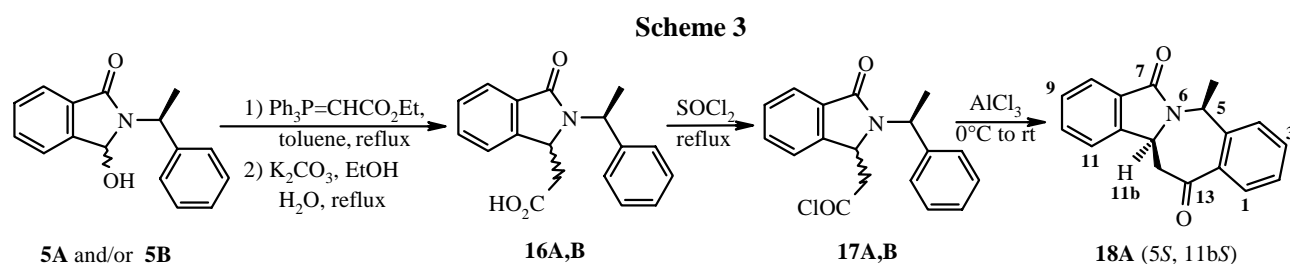
Similarly, **8A,B** led to only the stable enamide compound (**13**) (84%) resulting from the dehydration of the hydroxy lactams (**8A,B**). However, the application of this process to **9A,B** provided a cyclized spiro lactam instead of the expected isoindoloisoindolinone (**11**) (R=-(CH<sub>2</sub>)<sub>2</sub>-Ph), as the single diastereomer (**14**) (63%). Alternatively, the dehydrated phenylethylidenephthalimidine product (**15**), homologous of the enamide (**13**), was obtained as a 5.6/4.4 (*Z/E*) mixture, inseparable by chromatography, in 78% yield when an hydrochloric acid solution (6*M*) was used as a proton source.



Evidence of the *Z/E* geometry of olefin part in enamides (**13** and **15**) was performed from the <sup>1</sup>H NMR spectral data. For benzylidene (**13**) for example, the lone alkene proton appears at  $\delta=5.86$  ppm while the aromatic proton H<sub>4</sub> appears as a doublet at  $\delta=6.40$  ppm. The shielding effect of the latter proton is

comparable to the one observed for related stereoisomers.<sup>9</sup> Based on these values we assert that the benzyldene side chain in **13** has a *s-cis* conformation and *E* configuration. Finally, under same considerations, the *Z* and *E* stereomers of the phenylethylidene (**15**) were unambiguously assigned.

A high degree of the stereocontrol observed in the synthesis of the spiro indene (**14**) could be rationalized in terms of a Felkin-Ahn like transition state (Scheme 2). In fact, in the **TS-(II)** the  $\pi$ -system attack the iminium cation from the upper side of the phenyl group at the  $\alpha$ -position of the stereocenter to produce the adduct (**14**) as a single diastereomer. These results were in accordance with *N*-acyliminium ion cyclizations onto  $\pi$ -aromatics,<sup>4</sup> oxygen atom<sup>10,11</sup> or olefins. Some relevant examples of the latter process have been reviewed recently by Speckamp.<sup>1,2</sup> The relative stereochemistry of **14** was also confirmed by its <sup>1</sup>H-NMR spectral characteristics which were identical to the one obtained in a racemate form (*SS* and *RR*) as a major isomer by Bahajaj *et al.*<sup>11</sup> From these considerations, we can infer the (1'*S*, 3*S*) absolute configuration for the spiro indane (**14**) ( $[\alpha]_D^{25} = +121^\circ$  (c 0.5 M, CH<sub>2</sub>Cl<sub>2</sub>)).



Our next concern was the cyclization of acetic acid derivative (**16**) by Friedel-Crafts reaction. Thus, the conversion of diastereopure  $\alpha$ -hydroxy lactam (**5A** or **5B**) or a diastereomeric mixture of **5A,B** to acetic acid derivative (**16**) was accomplished by applying the elegant tandem Wittig type condensation/alkaline hydrolysis, followed with an acidic treatment.<sup>12</sup> At this stage, it is important to note that this reaction occurred with good diastereoselectivity. Actually, the acids (**16**) are isolated as white crystalline materials in 68% yield and showed a 84/16 mixture of two diastereomers. A tentative of separation by FC have not give satisfactory results but led only to an enriched 92/8 diastereomeric mixture of **16A,B**. This mixture was then treated with thionyl chloride in dichloromethane at reflux and the resulting acid chloride **17** under  $\pi$ -cationic cyclization using aluminum trichloride (99.99%) as catalyst gave the expected ketone (**18**) (68%) in an equivalent diastereomeric ratio. This mixture was chromatographed without success but pure diastereomer (**18A**) ( $[\alpha]_D^{25} = +67^\circ$  (c 0.3 M, CH<sub>2</sub>Cl<sub>2</sub>)) was obtained by recrystallization from ethanol. Because the difficulty encountered in our course to obtain good monocystals during the recrystallization of **18A**, its stereochemistry cannot be determined by X-Ray analysis. However, the absolute configuration of the new chiral center at the H<sub>11b</sub>-position for ketone (**18A**) was determined by NOE experiments. In fact, when the angular proton H<sub>11b</sub> (dd at  $\delta = 5.10$  ppm) was irradiated a significant NOE affect was detected for the proton H<sub>5</sub> (q at  $\delta = 5.87$  ppm). These results prove clearly the *cis* orientation of H<sub>11b</sub> and H<sub>5</sub> as shown in Scheme 3. This indicates also that the isoindolobenzoazepinone (**18A**) have a (5*S*, 11*bS*) configuration.

**Conclusion:** In summary, we have demonstrated in this paper that (1*S*)-*N*-(1-phenylethyl)phthalimide (**1**) substrate constitutes an excellent precursor into both chiral spiro indane and benzazepine in isoindolinone series using *N*-acyliminium ion and acylium ion cyclizations, respectively.

## EXPERIMENTAL

Melting points are uncorrected. The IR spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrophotometer. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform solution unless otherwise noted and chemical shifts (δ) are expressed in ppm relative to internal TMS. 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 vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. Optical rotations were measured with a Perkin Elmer 251 polarimeter in a 10 cm cell at 20°C. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M<sup>t</sup>. S<sup>t</sup>. Aignan, France. MS spectral measurements were recorded on a MS 902 S spectrometer.

**(1'*S*, 3*R* and 1'*S*, 3*S*)-2,3-Dihydro-3-hydroxy-2-(1'-phenylethyl)-1*H*-isoindol-1-ones (5A,B).** To a mixture of (1'*S*)-*N*-(1-phenylethyl)phthalimide (**1**) (1.26 g, 5 mmol) in dry methanol (40 mL) at -5-0°C was added sodium borohydride (0.94 g, 25 mmol) by portions (5 min). To this mixture was added 5 drops of ethanolic hydrochloric acid solution at regular intervals of 10 min. The reaction was monitored by TLC using CH<sub>2</sub>Cl<sub>2</sub> as eluent. After the end of the reaction (30 min), the excess of sodium borohydride was decomposed by careful addition of cold water (15 mL) and 10 % hydrochloric acid until pH=4. Sodium hydrogen carbonate was added and the solvent was evaporated. The residue was triturated with water and brine and the solid was separated by filtration, washed with water and dried. The resulting solid was separated by fractional crystallization or preparative TLC by using a mixture of hexane/ether (1/9) to furnish pure α-hydroxy lactams (**5A** and **5B**) in a 5.5/4.5 ratio and 92% yield.

**Major isomer (5A):** mp 118.5°C; [α]<sub>D</sub>=+51° (c 0.8 M, CH<sub>2</sub>Cl<sub>2</sub>); IR: 3279 (OH), 1682 (C=O) cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 1.82 (d, *J*=6.0 Hz, 3H, CH<sub>3</sub>), 2.79 (s, 1H, OH), 5.34 (q, *J*=6.0 Hz, 1H, N-CH), 5.91 (s, 1H, O-CH), 7.23-7.69 (m, 9H, H<sub>aromatic</sub>); MS (EI, 70 eV) *m/z*: 253 (M<sup>+</sup>); *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>2</sub>: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.85; H, 5.66; N, 5.35.

**Minor isomer (5B):** mp 165°C; [α]<sub>D</sub>=-71° (c 0.9 M, CH<sub>2</sub>Cl<sub>2</sub>); IR: 3265 (OH), 1689 (C=O) cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 1.78 (d, *J*=6.0 Hz, 3H, CH<sub>3</sub>), 3.33 (s, 1H, OH), 5.49 (s, 1H, O-CH), 5.55 (q, *J*=6.0 Hz, 1H, N-CH), 7.23-7.54 (m, 9H, H<sub>aromatic</sub>); MS (EI, 70 eV) *m/z*: 253 (M<sup>+</sup>); *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>2</sub>: C, 75.87 ; H, 5.97 ; N, 5.53. Found: C, 75.80 ; H, 5.72 ; N, 5.41.

**General procedure for synthesis of α-hydroxy lactams (6-9A,B) by Grignard reaction.** To a well stirred and cold solution (0°C) of (1'*S*)-*N*-(1-phenylethyl)phthalimide (**1**) (1.26 g, 5 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> or ether (30 mL) was added slowly and dropwise 6 mmol of a commercially available Grignard reagent (R<sup>1</sup>-MgX with R<sup>1</sup>=Me, Ph and Bn) or a freshly prepared Ph(CH<sub>2</sub>)<sub>2</sub>MgBr. After 1 h of reaction at 0°C, the reaction was allowed to stir for an additional 3 h at rt. After water hydrolysis (40 mL) under

stirring, the solution was passed through celite. After separation, the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo*. Recrystallization of the reaction residue from a mixture of ether/hexane gave hydroxy lactams (**6-9A,B**) in a range of 65-88% yields.

**(1'S, 3R and 1'S, 3S)-2,3-Dihydro-3-hydroxy-3-methyl-2-(1'-phenylethyl)-1H-isoindol-1-ones (6A,B)**. This compound was prepared in a yield of 86% as a 5.7/4.3 ratio of two diastereomers, mp 69-73°C (mixture); IR: 3256 (OH), 1682 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (Major):  $\delta$  1.79 (d,  $J = 7.5$  Hz, 3H,  $\text{CH}_3$ ), 3.92 (s, 3H,  $\text{CH}_3$ ), 4.15 (s, 1H, OH), 4.91 (q,  $J = 7.5$  Hz, 1H, CH), 7.10-7.18 (m, 3H,  $\text{H}_{\text{aromatic}}$ ), 7.21-7.61 (m, 6H,  $\text{H}_{\text{aromatic}}$ ); MS (EI, 70 eV)  $m/z$ : 249 ( $\text{M}^+ - \text{H}_2\text{O}$ ); *Anal.* Calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}_2$ : C, 76.38; H, 6.41; N, 5.24. Found: C, 76.19; H, 6.22; N, 5.18.

**(1'S, 3S)-2,3-Dihydro-3-hydroxy-3-phenyl-2-(1'-phenylethyl)-1H-isoindol-1-one (7A)**. This compound was prepared in a yield of 88% as a single diastereomer, mp 138°C;  $[\alpha]_{\text{D}}^{25} +19^\circ$  (c 0.7 M,  $\text{CH}_2\text{Cl}_2$ ); IR: 3218 (OH), 1687 (C=O);  $^1\text{H}$ -NMR:  $\delta$  1.88 (d,  $J=7.4$  Hz, 3H,  $\text{CH}_3$ ), 4.75 (q,  $J=7.4$  Hz, 1H, N-CH), 6.78-7.60 (m, 14H,  $\text{H}_{\text{aromatic}}$ ); MS (EI, 70 eV)  $m/z$ : 329 ( $\text{M}^+$ ); *Anal.* Calcd for  $\text{C}_{22}\text{H}_{19}\text{NO}_2$ : C, 80.22; H, 5.81; N, 4.25. Found: C, 80.09; H, 5.72; N, 4.16.

**(1'S, 3R and 1'S, 3S)-2,3-Dihydro-3-benzyl-3-hydroxy-2-(1'-phenylethyl)-1H-isoindol-1-ones (8A,B)**. This compound was prepared in a yield of 65% as a 5.5/4.5 mixture of two diastereomers, mp 126-129°C (mixture); IR: 3279 (OH), 1656 (C=O);  $^1\text{H}$ -NMR (Major):  $\delta$  1.84 (d,  $J=8.0$  Hz, 3H,  $\text{CH}_3$ ), 2.56 (d,  $J=13.4$  Hz, 1H, Ph- $\text{CH}_2$ ), 2.77 (s, 1H, OH), 3.41 (d,  $J=13.4$  Hz, 1H, Ph- $\text{CH}_2$ ), 4.98 (q,  $J=8.0$  Hz, 1H, N-CH), 6.49-7.54 (m, 14H,  $\text{H}_{\text{aromatic}}$ ); MS (EI, 70 eV)  $m/z$ : 325 ( $\text{M}^+ - \text{H}_2\text{O}$ ); *Anal.* Calcd for  $\text{C}_{23}\text{H}_{21}\text{NO}_2$ : C, 80.44; H, 6.16; N, 4.08. Found: C, 80.09; H, 6.06; N, 4.00.

**(1'S, 3R and 1'S, 3S)-2,3-Dihydro-3-hydroxy-3-(2-phenylethyl)-2-(1'-phenylethyl)-1H-isoindol-1-ones (9A,B)**. This compound was obtained in a yield of 67% as a 5.6/4.4 ratio of two diastereomers, mp 135-137°C; IR: 3283 (OH), 1664 (C=O);  $^1\text{H}$ -NMR (Major):  $\delta$  1.84 (d,  $J=7.0$  Hz, 3H,  $\text{CH}_3$ ), 2.13-2.24 (m, 4H, Ph- $\text{CH}_2\text{-CH}_2$ ), 4.78 (q,  $J=7.0$  Hz, N-CH), 6.80-7.60 (m, 14H,  $\text{H}_{\text{aromatic}}$ ); MS (EI, 70 eV)  $m/z$ : 339 ( $\text{M}^+ - \text{H}_2\text{O}$ ); *Anal.* Calcd for  $\text{C}_{24}\text{H}_{23}\text{NO}_2$ : C, 80.64; H, 6.48; N, 3.92. Found: C, 80.39; H, 6.32; N, 3.89.

**General procedure for treatment of hydroxylactams (7-9A,B) with neat TFA or HCl 6M.** A solution of hydroxy lactams (**7-9A,B**) (10 mmol) in 15 mL of trifluoroacetic acid (or 6M aqueous HCl (25 mL) for synthesis of olefin (**15**)) was stirred over night at rt (or reflux) (the reaction was monitored by TLC). The solution was concentrated *in vacuo*, diluted with  $\text{CH}_2\text{Cl}_2$ , washed successively with a saturated sodium hydrogen carbonate solution, then with water and was dried over magnesium sulfate and filtered. The solution was concentrated under reduced pressure and the residue was recrystallized or chromatographed to furnish **12**, **13**, **14** or **15**.

**(5S, 11<sub>b</sub>R)-5,11<sub>b</sub>-Dihydro-5-methyl-11<sub>b</sub>-phenyl-7H-isoindolo[1,2-a]isoindol-7-one (12)**. This compound was isolated after chromatography on silica gel column, using a mixture of ethyl acetate and hexane (4/1) as eluent, as a single diastereomer (*cis*) in 18% yield, mp 142°C (lit.,<sup>8</sup> mp 151-153°C for a racemate);  $[\alpha]_{\text{D}}^{25} +115^\circ$  (c 0.5 M,  $\text{CH}_2\text{Cl}_2$ ); MS (EI, 70 eV)  $m/z$ : 311 ( $\text{M}^+$ ); *Anal.* Calcd for  $\text{C}_{22}\text{H}_{17}\text{NO}$ : C, 84.86; H, 5.50; N, 4.50. Found: C, 84.67; H, 5.38; N, 4.36.

**(1'S)-(E)-3-Benzylidene-2,3-dihydro-2-(1'-phenylethyl)-1H-isoindol-1-one (13).** This compound was isolated by recrystallization from ethanol in a yield of 84%, mp 243°C;  $[\alpha]_D^{25} = +98^\circ$  (c 0.8 M, CH<sub>2</sub>Cl<sub>2</sub>); IR: 1715 (C=O), 1654 (C=C); <sup>1</sup>H-NMR:  $\delta$  1.43 (d,  $J=8.0$  Hz, 3H, CH<sub>3</sub>), 4.51 (q,  $J=8.0$  Hz, 1H, N-CH), 5.86 (s, 1H, C=CH), 6.40 (d,  $J=6.4$  Hz, 1H, H<sub>4</sub>), 6.80-7.80 (m, 13H, H<sub>aromatic</sub>); <sup>13</sup>C-NMR:  $\delta$  18.1 (CH<sub>3</sub>), 42.2 (CH<sub>2</sub>), 123.2 (CH), 123.2 (CH), 126.5 (CH), 130.0 (CH), 130.2 (CH), 130.5 (CH), 130.8 (CH), 131.5 (CH), 136.5 (C), 137.1 (C), 142.0 (C), 169.2 (CO); MS (EI, 70 ev)  $m/z$ : 325 (M<sup>+</sup>); *Anal.* Calcd for C<sub>23</sub>H<sub>19</sub>NO: C, 84.90; H, 5.88; N, 4.30. Found: C, 84.77; H, 5.67; N, 4.10.

**(1'S, 3S)-2-(1'-Phenylethyl)-spiro(indane-1,3-isoindol)-1-one (14).** This compound was obtained by recrystallization from ethanol in a yield of 63%, mp 202°C (lit.,<sup>8</sup> mp 200-203°C for a racemate);  $[\alpha]_D^{25} = +121^\circ$  (c 0.5 M, CH<sub>2</sub>Cl<sub>2</sub>); IR: 1679 (C=O); <sup>1</sup>H-NMR:  $\delta$  1.22 (d,  $J=6.7$  Hz, 3H, CH<sub>3</sub>), 2.42-2.65 (m, 4H, CH<sub>2</sub>-CH<sub>2</sub>), 3.26 (q,  $J=6.7$  Hz, 1H, N-CH), 6.80-7.80 (m, 13H, H<sub>aromatic</sub>); <sup>13</sup>C-NMR:  $\delta$  18.1 (CH<sub>3</sub>), 35.5 (CH<sub>2</sub>), 43.0 (CH<sub>2</sub>), 59.5 (CH), 73.8 (C), 121.2 (CH), 122.4 (CH), 123.1 (CH), 123.2 (CH), 126.2 (CH), 127.0 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (2CH), 130.0 (C), 131.2 (CH), 139.5 (C), 143.1 (C), 146.0 (C), 148.8 (C), 150.2 (C), 170.6 (CO); MS (EI, 70 ev)  $m/z$ : 339 (M<sup>+</sup>); *Anal.* Calcd for C<sub>24</sub>H<sub>21</sub>NO: C, 84.92; H, 6.23; N, 4.12. Found: C, 84.70; H, 6.18; N, 4.58.

**(1'S)-(Z+E)-2,3-Dihydro-3-phenylethylidene-2-(1'-phenylethyl)-1H-isoindol-1-ones (15).** This product was isolated after chromatography on silica gel column (CH<sub>2</sub>Cl<sub>2</sub>/hexane: 7/3) as a mixture of two isomers (5.6/4.4: Z/E) in a yield of 78%, mp 115-119°C (mixture); IR: 1706 (C=O), 1651 (C=C); <sup>1</sup>H-NMR (Major):  $\delta$  1.39 (d,  $J=8.2$  Hz, 3H, CH<sub>3</sub>), 3.90 (d, 2H,  $J=7.8$  Hz, CH<sub>2</sub>-CH=), 4.53 (q,  $J=8.2$  Hz, 1H, N-CH), 5.92 (t, 1H,  $J=7.8$  Hz, C=CH-CH<sub>2</sub>) (5.41 ppm *E* isomer), 6.92-8.05 (m, 14H, H<sub>aromatic</sub>); MS (EI, 70 ev)  $m/z$ : 339 (M<sup>+</sup>); *Anal.* Calcd for C<sub>24</sub>H<sub>21</sub>NO: C, 84.92; H, 6.23; N, 4.12. Found: C, 84.59; H, 6.09; N, 4.08.

**(1'S, 3R and 1'S, 3S)-2,3-Dihydro-2-(1'-phenylethyl)-1H-isoindol-1-one-3-acetic acids (16A,B).** A mixture of **5A** and/or **5B** (1.5 g, 5.9 mmol) and ethoxycarbonylmethylidene triphenylphosphorane (2.48 g, 7.1 mmol) in 50 mL of toluene was refluxed for 12 h. After concentration, the residue was added to ethanol (30 mL), potassium carbonate (0.92 g, 8.26 mmol) and water (10 mL). After 2 h of reflux, the solution was concentrated *in vacuo*, dissolved in 50 mL of water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x30 mL). The cold aqueous layer was acidified with 10% HCl to pH=2. The resulting precipitate was filtered off then recrystallized from ethanol to give **16A,B** as a 84/16 ratio of two diastereomers in 68% yield, mp 168°C; IR: 3433 (OH), 1724 (C=O), 1636 (C=C); <sup>1</sup>H-NMR (Major):  $\delta$  1.79 (d,  $J=6.0$  Hz, 3H, CH<sub>3</sub>), 2.13 (dd,  $J=16.6$  and 4.1 Hz, 1H, CH<sub>2</sub>CO<sub>2</sub>H), 2.44 (dd,  $J=16.6$  and 4.1 Hz, 1H, CH<sub>2</sub>CO<sub>2</sub>H), 5.10 (dd,  $J=9.4$  and 4.1 Hz, 1H, CH<sub>2</sub>-CH), 5.50 (q,  $J=6.0$  Hz, 1H, N-CH), 7.24-7.88 (m, 9H, H<sub>aromatic</sub>), 9.3 (s, 1H, CO<sub>2</sub>H); <sup>13</sup>C-NMR:  $\delta$  18.1 (CH<sub>3</sub>), 38.2 (CH<sub>2</sub>), 50.1 (CH), 56.2 (CH), 122.3 (CH), 124.5 (CH), 126.1 (CH), 127.5 (CH), 128.1 (CH), 129.1 (CH), 132.5 (CH), 138.5 (C), 140.1 (C), 147.2 (C), 168.0 (CO), 173.5 (CO); MS (EI, 70 ev)  $m/z$ : 295 (M<sup>+</sup>); *Anal.* Calcd for C<sub>18</sub>H<sub>17</sub>NO<sub>3</sub>: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.06; H, 5.66; N, 4.57.

**(5*S*, 11<sub>b</sub>*S*)-5,7,11<sub>b</sub>,13-Tetrahydro-5-methylisoindolo[1,2-*d*]benzazepine-7,13(12*H*)-dione (18A).** To a stirred suspension of **16A,B** (1.3 g, 4.4 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was treated slowly with freshly distilled thionyl chloride (0.63 g, 5.28 mmol) and the mixture was heated under reflux for 2 h. After cooling, the solution was concentrated *in vacuo* and the residue was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (35 mL). The mixture was treated with aluminium trichloride (99.99%) (0.88 g, 6.6 mmol) over a period of 10 min at -5-0°C. After 1 h of reaction at this temperature and 3 h at rt, the solution was poured onto cold water and decanted. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the organic layers were washed with water, brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the ketone (**18**) as a 96/4 ratio of two diastereomers (68%). The resulting solid after recrystallization from ethanol give pure **18A**, mp 189°C; [α]<sub>D</sub> = +67° (c 0.3 M, CH<sub>2</sub>Cl<sub>2</sub>); IR: 1678 (C=O); <sup>1</sup>H-NMR: δ 1.63 (d, *J*=8.0 Hz, 3H, CH<sub>3</sub>), 2.92 (dd, *J*=8.0 and 12.0 Hz, CO-CH<sub>2</sub>), 3.54 (dd, *J*=6.0 and 12.0 Hz, CO-CH<sub>2</sub>), 5.10 (dd, *J*=6.0 and 8.0 Hz, 1H, CH<sub>2</sub>-CH), 5.87 (q, *J*=8.0 Hz, 1H, N-CH), 7.24-7.80 (m, 8H, H<sub>aromatic</sub>); <sup>13</sup>C-NMR: δ 23.1 (CH<sub>3</sub>), 49.2 (CH<sub>2</sub>), 51.1 (CH), 55.0 (CH), 122.1 (CH), 125.2 (CH), 128.4 (CH), 129.1 (CH), 130.5 (CH), 132.0 (C), 133.5 (CH), 134.2 (CH), 138.0 (CH), 140.2 (C), 146.2 (C), 149.4 (C), 168.4 (CO), 202.2 (CO); MS (EI, 70 ev) *m/z*: 277 (M<sup>+</sup>); *Anal.* Calcd for C<sub>18</sub>H<sub>15</sub>NO<sub>2</sub>: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.75; H, 5.38; N, 4.97.

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