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Asymmetric Synthesis of New Diastereomerically Pure Spiro Oxindolopyrrolizidines and Oxindolopyrrolidines via Cycloaddition Reactions of Azomethine Ylides and Menthol-Driven *Trans*-Cinnamic

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ABSTRACT

Chiral pyrrolidines and pyrrolizidines with spirooxindole ring systems are the central skeletons for numerous alkaloids and pharmacologically important compounds. Gelesmine, pseudotabersonine, formosanine, isoformosanine, morroniside and mitraphylline are some of the alkaloids containing spirooxindole ring systems. Derivatives of spirooxindole find very wide biological applications as anti microbials, anti-inflammatory, antitumourals, antibiotic agents and inhibitors of human NK-1 receptors. An efficient one-pot three-component procedure for the synthesis of new chiral spirooxindolopyrrolidines/pyrrolizidines with highly regio and diastereo-enantio, selective from 1,3-dipolar cycloaddition of azomethineylides and chiral menthol-driven *trans*-cinnamic are described. The mechanism of the reaction is discussed on the basis of the assignment of the absolute configuration of one of the cycloaddition products, which obtained by single crystal X-ray analysis. The process is occurred at reflux temperature in ethanol as green solvent and in the absence of any bidentate chelating Lewis acids.

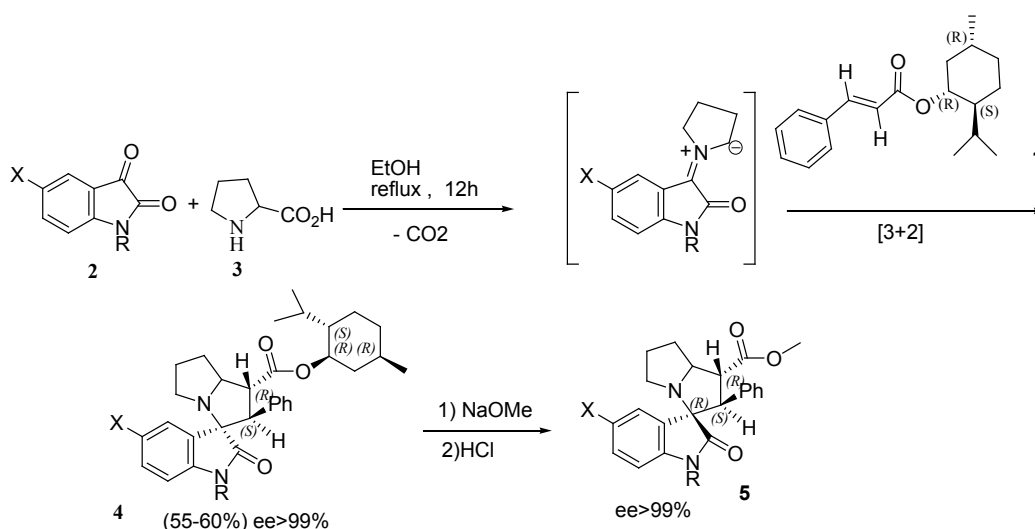
Keyword: Spirooxindole ring, 1,3-Dipolar cycloaddition, Isatins, L-proline, Asymmetric Synthesis.

1. INTRODUCTION

Functionalized pyrrolidines and pyrrolizidines with spirooxindole ring systems are the central skeletons for numerous alkaloids and pharmacologically important compounds [1]. Gelesmine, pseudotabersonine, formosanine, isoformosanine, morroniside and mitraphylline are some of the alkaloids containing spiroox-

indole ring systems [2]. Derivatives of spirooxindole find very wide biological applications as anti microbials, anti-inflammatory, antitumourals, antibiotic agents and inhibitors of human NK-1 receptors [3]. 1,3-Dipolar cycloaddition reaction is an efficient method for the construction of heterocyclic units in a highly regio- and

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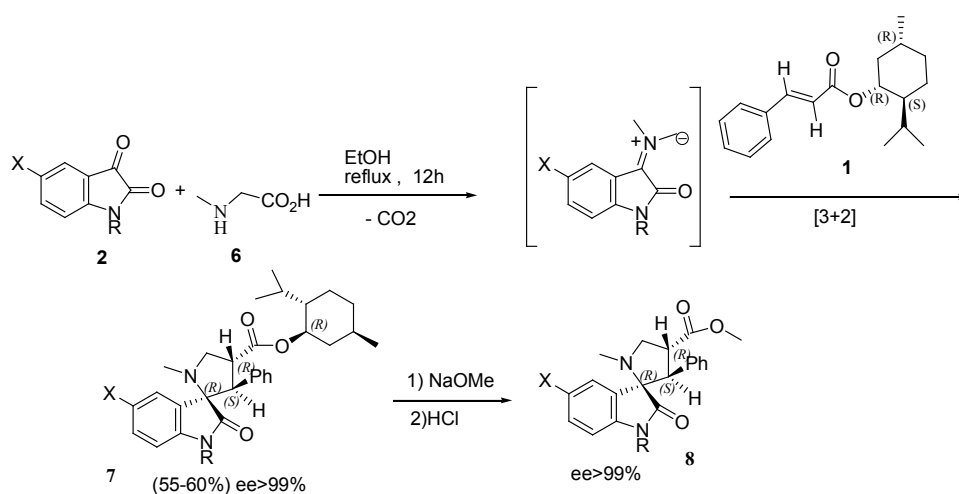


Scheme 1: Synthesis of chiral spirooxindolopyrrolidines 4.

stereo- selective manner [4]. Chiral pyrrolidines are extensively found as significant skeleton of numerous biologically relevant alkaloids [5] and are of considerable interest in medicinal chemistry [6]. On the other hand, chiral pyrrolizidines have a long history for attracting the interest of synthetic chemists because of wide distribution in nature and variegated biological activities [7]. Hence, various derivatives of this important class of spiro compounds have been synthesized [8]. But, only a few derivatives of chiral spirooxindolopyrrolizidine have been prepared. The reported methods suffer from many limitations, such as using toxic solvents in reflux condition and the absence of

enantiomeric purity [9].

Based on the literature procedure [10] grric and coworkers synthesized a series of diastereomerically pure new spirooxindolopyrrolidines/pyrrolizidines using a 1,3-dipolar cycloaddition reaction of the chairmenthyl acrylate with non-stabilized azomethine ylides which was generated in situ by the decarboxylative condensation of isatins with L-proline or sarcosine. We decided to synthesize a series of diastereomerically pure new spirooxindolopyrrolidines/pyrrolizidines using a three component reaction involving 1,3-dipolar cycloaddition reactions. Since Padwa performed the first diastereofacial selective 1,3-dipolar



Scheme 2: Synthesis of chiral spirooxindolopyrrolidines 7.

cycloaddition reaction using a chiral azomethineylide, asymmetric 1,3-dipolar cycloaddition reaction azomethineylide in presence of chiral auxiliaries, it has received much attention. In this report, at first we prepared chiral non-racemic dipolarophiles from the reaction of cinnamic acid with pure menthol as achiral auxiliary. Then the reactions were carried out in a one-pot and proceeded through a 1,3-dipolar cycloaddition reaction of the chiral dipolarophiles with non-stabilized azomethineylides which was generated in situ by the decarboxylative condensation of isatins with L-proline or sarcosine. Based on the literature procedure [11], the chiral auxiliary menthyl cinnamate 1, was easily prepared from reaction of cinnamic acid with thionylchlorid; and then was reacted readily with chiral menthol to provide chiral non-racemic menthylcinnamate 1. Three component reactions between this chiral non-racemic dipolarophile 1, isatin derivatives 2 and L-proline 3 or sarcosine 6 were carried out in ethanol at reflux temperature with excellent yields. As shown in Scheme 1 and 2, condensation of compounds 2 and 3 (or 6) after decarboxylation leading to the non-stabilized azomethineylide stereogenic centers in one step. Consequently, eight different stereoisomers could have been produced. But by using this strategy only diastereoisomer 4 (or 7) were obtained purely in

high total yield and high optical purity as shown by TLC, GC-MS and NMR analysis (Schemes 1 and 2). After this, other derivatives of this new chiral spirooxindolo (pyrrolizidine/pyrrolizidine) were synthesized. The results are summarized in Table 1.

2. EXPERIMENTAL

General melting point was recorded on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a mattson 1000 FTIR. ^1H , ^{13}C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with CDCl_3 as solvent at 300.1 MHz.

Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an electron energy of 70 eV. isatin derivatives, proline, were obtained from Fluka (Buchs, Switzerland) and were used without further purification, and *trans*-cinnamic acid derived from the menthol were obtained via synthesized.

General procedure

To a magnetically stirred solution of an isatin derivatives (2) (1 mmol), proline (3) or sarcosine (6) (1 mmol) and *trans*-cinnamic acid derived from the men-

Table 1: Synthesis of chiral spirooxindolopyrrolizidines 4, 7.

Entry	R	X	Product	4 ^a		7	
				Yield (%) ^b	$[\alpha]_D^{25c}$	Yield (%) ^b	$[\alpha]_D^{25c}$
1	H	H	A	70	-5.4	65	-4.2
2	H	Br	B	75	-6.2	72	-4.3
3	H	NO ₂	C	72	-5.8	65	-4.7
4	Me	H	D	65	-5.4	60	-4.4
5	Me	Br	E	70	-5.2	65	-4.5
6	Me	NO ₂	F	67	-5.7	60	-4.4
7	Et	H	G	65	-5.2	60	-4.2
8	Et	Br	H	65	-5.7	62	-4.7
9	Et	NO ₂	I	72	-5.1	65	-4.3

^(a)The reaction was carried out in the ratio of 1/2/3/ 1:1:1; ^(b) Isolated yield based on substituted isatins; ^(c) $[\alpha]_D^{25}$ (c 1, CH_2Cl_2).

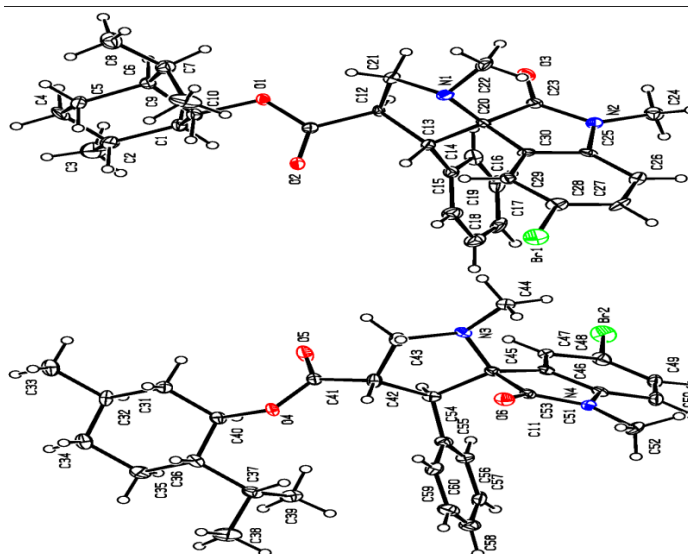


Figure 1: The ORTEP diagram of one of the two crystallographic independent molecules in the asymmetric unit of 7g is shown. Thermal ellipsoids are at 30% probability level.

thol (1) (1 mmol), as chiral auxiliaries in 10 mL EtOH was added dropwise at reflux temperature. Then, the reaction mixture was stirred for 12 h. The solvent was then removed under reduced pressure and the residue was separated by column chromatography (silica gel, Merck 230-400 mesh) using n-hexane–ethyl acetate (90:10) as eluent.

3. RESULT AND DISCUSSIONS

The structures of cycloaddition products were assigned by their elemental analysis including, IR, ^1H NMR, ^{13}C NMR, Mass spectral data, HMQC, and COSY NMR. Observation of three characteristic singlet at about (47.6, 53.0 and 61.3) in the ^{13}C NMR spectra of 4 is consistent with formation new pyrrolidine cyclic. The stereochemistry and the correct structure of this isomer and other derivatives were determined by ^1H NMR, ^{13}C NMR, IR, Mass, HMQC, and (H, H)-COSY. For example, the ^1H NMR spectrum of 4a exhibits a triplet signal at $\delta = 2.60$ ppm, a multiple at $\delta = 3.58$ and a multiple at $\delta = 4.07$ -4.22 ppm which are related to Hb, Hc and Ha protons respectively. Also DEPT 135° showed signals, corresponding to three (CH) carbons that were directly bonded to Hb, Hc and Ha in the region 47.6, 53.1 and 61.3 respectively. In HMQC

spectrum of cycloadduct 4a, the positions of three protons (Ha, Hb, and Hc) that were directly bonded to these carbon atoms (CH) were assigned. Accordingly, the exact chemical shifts of these protons ($\delta\text{Ha} = 4.02$ -4.22, $\delta\text{Hb} = 2.60$, $\delta\text{Hc} = 3.58$) were assigned by means of (H-H)-COSY spectrum. Stereochemistry of the 4a has been assigned from ROESY spectrum. Absence of any correlation between Ha and Hb in the ROESY spectrum shows that the Hb hydrogen could be *trans* to Ha. But an intense contour between Hc and Ha shows these two hydrogen are *trans* to each other's. This is also confirmed from the NOE between them. Therefore, the correct stereochemistry could be as shown in Scheme 1.

The ^1H NMR spectrum of 7g exhibits a triplet signal at $\delta = 3.64$ ppm and a doublet at $\delta = 4.14$ ppm which are related to Hb and Ha protons respectively. Also DEPT 135° of 7g showed signals, corresponding to three (CH) carbons that were directly bonded to Hb, Hc and Ha in the region 52.5, 66.5 and 72.6 respectively. Stereochemistry of the 7g has been assigned from ROESY NMR spectrum. Absence of any correlation between Ha and Hb in the ROESY spectrum shows that the Hb hydrogen could be *trans* to Ha. This is also confirmed from the NOE between them. Therefore, the correct stereochemistry could be as shown in Scheme 2. The absolute configuration

of spirooxindole 7g was determined by single crystal X-ray analysis (Figure 1).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4a): White powder, mp 143°C, yield 70%, $[\alpha]_D$ -5.4 (c 1, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1616(C=O), 1719(C=O), 3432 (NH); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.26-1.69 (9H, m, CH and CH₂), 1.88-2.05(5H, m, CH and CH₂), 2.55(1H, m, CH), 2.60 (1H, t, ³J_{HH}=8.4 Hz, CH), 3.58 (1H, m, CH), 4.07-4.22 (2H, m, 2CH), 6.91-7.49 (9H, m, Ar-H), 8.38 (1H, s, NH); ¹³CNMR (300.1 MHz, CDCl₃); 16.3, 20.6, 21.8 (3C, 3CH₃), 24.2, 26.4, 30.9 (3C, 3CH₂), 27.2, 33.9, 38.7 (3C, 3CH₂), 47.6, 53.0, 61.3 (3C, 3CH), 71.9 (1C), 74.6 (1C, OCH), 110.5, 122.2, 126.3, 129.5, 139.6 (5C, 5CH), 127.5, 128.5 (4C, 4CH), 129.0, 140.6, 141.7 (3C), 169.5, 179.2 (2C, 2C=O); MS, 486 (M⁺, 5), 200 (M⁺- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + C₄H₇N), 70).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4b): White powder, mp 198°C, yield 75%, $[\alpha]_D$ -6.2 (c 1, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1616(C=O), 1719(C=O), 3430 (NH); ¹HNMR (300.1 MHz, CDCl₃); 0.78 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.32-1.75 (9H, m, CH, CH₂), 1.79-2.16 (5H, m, CH, CH₂), 2.55 (1H, m, CH), 2.62-2.66 (1H, m, CH), 3.58 (1H, m, CH), 4.22-4.26 (2H, m, 2CH), 7.35-7.93 (8H, m, Ar-H), 8.36 (1H, s, NH); ¹³CNMR (300.1 MHz, CDCl₃); 16.4, 20.6, 21.8 (3C, 3CH₃), 24.1, 26.4, 30.9 (3C, 3CH₂), 27.2, 33.9, 38.7 (3C, 3CH₂), 47.6, 53.1, 61.3 (3C, 3CH), 71.9 (1C), 74.7 (1C, OCH), 110.7, 121.2, 133.0, 139.6 (4C, 4CH), 127.5, 128.5 (4C, 4CH), 128.0, 129.0, 140.6, 141.7 (4C), 169.5, 179.2 (2C, 2C=O); MS, 531(M⁺, 6), 245 (M⁺- Ph(CH)₂COOmenthyl, 100), 176 (M⁺- (Ph(CH)₂COOmenthyl + C₄H₇N), 75).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methyl-cyclohexyl)-5-bromo-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4c):

Yellow powder, mp 163°C, yield 72%, $[\alpha]_D$ -5.8 (c 1, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1616(C=O), 1722(C=O), 3431 (NH); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH}=7 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.29-1.67 (9H, m, CH and CH₂), 1.77-2.19 (5H, m, CH and CH₂), 2.56 (1H, m, CH), 2.62-2.66 (1H, m, CH), 3.58 (1H, m, CH), 4.21-4.24 (2H, m, 2CH), 7.21-7.73 (8H, m, Ar-H), 8.35 (1H, s, NH); ¹³CNMR (300.1 MHz, CDCl₃); 16.3, 20.5, 21.8 (3C, 3CH₃), 24.1, 26.7, 30.9 (3C, 3CH₂), 27.2, 33.9, 38.7 (3C, 3CH₂), 47.6, 53.0, 61.3 (3C, 3CH), 71.9 (1C), 74.6 (1C, OCH), 109.6, 121.1, 133.2, 139.6 (4C, 4CH), 127.5, 128.6 (4C, 4CH), 128.1, 129.0, 140.6, 141.7 (4C), 169.3, 179.2 (2C, 2C=O); MS, 564, 566 (M⁺, M⁺+2, 5), 278, 280 (M⁺, M⁺+2- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + Br + C₄H₇N) + 1, 40).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4d): Yellow powder, mp 155°C, yield 65%, $[\alpha]_D$ -5.4 (c 1, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1616(C=O), 1719(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.76 (3H, d, ³J_{HH}=7.1 Hz, CH₃), 0.86 and 0.88 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.29-1.66 (9H, m, CH and CH₂), 1.77-2.15 (5H, m, CH and CH₂), 2.56 (1H, m, CH), 2.60 (1H, t, ³J_{HH}=8.4 Hz, CH), 3.25 (3H, s, NCH₃), 3.58 (1H, m, CH), 4.21-4.25 (2H, m, 2CH), 6.95-7.59 (9H, m, Ar-H); ¹³CNMR (300.1 MHz, CDCl₃); 16.5, 20.7, 21.8 (3C, 3CH₃), 24.1, 26.4, 30.9 (3C, 3CH₂), 27.2, 33.9, 38.6 (3C, 3CH₂), 42.2 (1C, NCH₃), 47.7, 53.0, 61.7 (3C, 3CH), 71.9 (1C), 74.6 (1C, OCH), 110.5, 121.2, 126.3, 129.5, 139.6 (5C, 5CH), 127.5, 128.5 (4C, 4CH), 129.1, 140.6, 141.7 (3C), 169.5, 179.2 (2C, 2C=O); MS, 500 (M⁺, 8), 214 (M⁺- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + C₄H₇N + Me)+1, 77).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-1-methyl-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4e): Yellow powder, mp 174°C, yield 70%, $[\alpha]_D$ -5.2 (c 1, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1619(C=O), 1720(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 0.87 and

0.89 (6H, 2d, $^3J_{\text{HH}}=7$ Hz, 2 CH₃), 1.33-1.77 (9H, m, CH and CH₂), 1.79-2.17 (5H, m, CH and CH₂), 2.55 (1H, m, CH), 2.62-2.67 (1H, m, CH), 3.25 (3H, s, NCH₃), 3.58 (1H, m, CH), 4.20-4.26 (2H, m, 2CH), 7.35-7.94 (8H, m, Ar-H); ¹³CNMR (300.1 MHz, CDCl₃); 16.2, 20.5, 22.8 (3C, 3CH₃), 24.3, 26.6, 30.9 (3C, 3CH₂), 27.4, 33.9, 38.7 (3C, 3CH₂), 42.1 (1C, NCH₃), 47.6, 53.1, 61.3 (3C, 3CH), 71.6 (1C), 74.6 (1C, OCH), 109.9, 122.0, 133.1, 139.6 (4C, 4CH), 127.5, 128.5 (4C, 4CH), 128.0, 129.0, 140.6, 141.7 (4C), 169.9, 180.4 (2C, 2C=O); MS, 545(M⁺, 3), 259 (M⁺- Ph(CH)₂COOmenthyl, 100), 190 (M⁺- (Ph(CH)₂COOmenthyl + C₄H₇N), 70).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-5-bromo-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4f): Yellow powder, mp 193°C, yield 67%, [α]_D^{-5.7} (c 1, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1619(C=O), 1720(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, $^3J_{\text{HH}}=7.1$ Hz, CH₃), 0.86 and 0.88 (6H, 2d, $^3J_{\text{HH}}=7$ Hz, 2 CH₃), 1.29-1.67 (9H, m, CH and CH₂), 1.77-2.20 (5H, m, CH and CH₂), 2.54 (1H, m, CH), 2.62-2.66 (1H, m, CH), 3.24 (3H, s, NCH₃), 3.59 (1H, m, CH), 4.21-4.25 (2H, m, 2CH), 7.21-7.80 (8H, m, Ar-H); ¹³CNMR (300.1 MHz, CDCl₃); 16.7, 20.4, 21.8 (3C, 3CH₃), 24.4, 26.8, 30.9 (3C, 3CH₂), 27.2, 33.9, 38.7 (3C, 3CH₂), 42.1 (1C, NCH₃), 47.6, 53.0, 61.3 (3C, 3CH), 71.9 (1C), 74.6 (1C, OCH), 110.7, 122.1, 133.0, 139.8 (4C, 4CH), 127.6, 128.7 (4C, 4CH), 128.2, 129.0, 140.6, 141.7 (4C), 169.5, 179.9 (2C, 2C=O); MS 578, 580 (M⁺, M⁺+2, 7), 292, 294 (M⁺, M⁺+2- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + Br + C₄H₇N + Me) + 2, 49).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4g): Yellow powder, mp 137°C, yield 65%, [α]_D^{-5.2} (c 0.01, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1616(C=O), 1722(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, $^3J_{\text{HH}}=7$ Hz, CH₃), 0.87 and 0.89 (6H, 2d, $^3J_{\text{HH}}=7$ Hz, 2 CH₃), 1.29-1.65 (9H, m, CH and CH₂), 1.37 (3H, t, $^3J_{\text{HH}}=7.2$ Hz, CH₃), 1.79-2.15 (5H, m, CH and CH₂), 2.55 (1H, m, CH), 2.60 (1H, t, $^3J_{\text{HH}}=8.4$ Hz, CH), 3.58 (1H, m, CH), 3.88 (2H, q, $^3J_{\text{HH}}=7.2$ Hz, NCH₂), 4.15-

4.22 (2H, m, 2CH), 7.21-7.73 (9H, m, Ar-H); ¹³CNMR (300.1 MHz, CDCl₃); 11.7 (1C, CH₃), 16.8, 20.6, 21.5 (3C, 3CH₃), 24.3, 26.6, 30.9 (3C, 3CH₂), 27.4, 33.9, 38.7 (3C, 3CH₂), 36.1 (1C, NCH₂), 47.5, 53.1, 61.7 (3C, 3CH), 71.8 (1C), 74.9 (1C, OCH), 109.9, 122.2, 126.4, 129.5, 139.6 (5C, 5CH), 127.5, 128.5 (4C, 4CH), 129.1, 140.6, 141.7 (3C), 166.5, 177.8 (2C, 2C=O); MS, 514 (M⁺, 9), 228 (M⁺- Ph(CH)₂COOmenthyl, 100), 159 (M⁺- (Ph(CH)₂COOmenthyl + C₄H₇N), 68).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-1-ethyl-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4h): Yellow powder, mp 158°C, yield 65%, [α]_D^{-5.7} (c 0.01, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1625(C=O), 1718(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.77 (3H, d, $^3J_{\text{HH}}=6.9$ Hz, CH₃), 0.87 and 0.89 (6H, 2d, $^3J_{\text{HH}}=7.1$ Hz, 2 CH₃), 1.34 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, CH₃), 1.36-1.77 (9H, m, CH and CH₂), 1.79-2.08 (5H, m, CH and CH₂), 2.58 (1H, m, CH), 2.62-2.66 (1H, m, CH), 3.58 (1H, m, CH), 3.85 (2H, q, $^3J_{\text{HH}}=7.1$ Hz, NCH₂), 4.22-4.26 (2H, m, 2CH), 7.30-7.91 (8H, m, Ar-H); ¹³CNMR (300.1 MHz, CDCl₃); 11.9 (1C, CH₃), 16.3, 20.5, 21.9 (3C, 3CH₃), 24.2, 26.4, 30.7 (3C, 3CH₂), 27.2, 33.9, 39.0 (3C, 3CH₂), 36.1 (1C, NCH₂), 47.5, 53.3, 61.3 (3C, 3CH), 71.9 (1C), 74.9 (1C, OCH), 112.1, 122.5, 133.1, 139.9 (4C, 4CH), 127.5, 128.7 (4C, 4CH), 128.0, 129.1, 140.7, 141.9 (4C), 169.7, 179.9 (2C, 2C=O); MS, 559 (M⁺, 4), 273 (M⁺- Ph(CH)₂COOmenthyl, 100), 158 (M⁺- (Ph(CH)₂COOmenthyl + C₄H₇N + NO₂), 73).

(1's,2's)-((1s,2s,5s)-2-isopropyl-5-methylcyclohexyl)-5-bromo-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydro spiro[indoline-3,3'-pyrrolizine]-2'-carboxylate (4i): Yellow powder, mp 187°C, yield 72%, [α]_D^{-5.3} (c 0.01, CH₂Cl₂); IR(KBr)($\tilde{\nu}$ max, cm⁻¹): 1616(C=O), 1720(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.75 (3H, d, $^3J_{\text{HH}}=7$ Hz, CH₃), 0.87 and 0.89 (6H, 2d, $^3J_{\text{HH}}=7.1$ Hz, 2 CH₃), 1.32 (3H, t, $^3J_{\text{HH}}=7.2$ Hz, CH₃), 1.35-1.67 (9H, m, CH, CH₂), 1.79-2.09 (5H, m, CH, CH₂), 2.56 (1H, m, CH), 2.62-2.66 (1H, m, CH), 3.55 (1H, m, CH), 3.84 (2H, q, $^3J_{\text{HH}}=7.1$ Hz, NCH₂), 4.21-4.24 (2H, m, 2CH), 7.21-7.73 (8H, m, Ar-H); ¹³CNMR (300.1 MHz, CDCl₃); 11.6 (1C, CH₃), 16.3, 20.6, 21.9 (3C, 3CH₃), 24.1, 26.6, 30.7 (3C, 3CH₂),

27.2, 33.9, 38.7 (3C, 3CH₂), 36.2 (1C, NCH₂), 47.6, 53.0, 61.3 (3C, 3CH), 71.9(1C), 74.6(1C, OCH), 111.6, 121.1, 133.2, 139.6 (4C, 4CH), 127.5, 128.6 (4C, 4CH), 128.1, 129.2, 140.6, 142.0 (4C), 169.3, 181.2 (2C, 2C=O); MS 592, 594 (M⁺, M⁺+2, 8), 306, 308 (M⁺, M⁺+2- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + Br + C₄H₇N + Et) + 1, 70).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-1'-methyl-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7a): Yellow powder, yield 65 %; IR(KBr) (ν_{max}, cm⁻¹): 1609(C=O), 1711(C=O), 3430(NH); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.26-1.69 (9H, m, CH and CH₂), 2.16 (3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), 4.56-4.60(1H, m, OCH), 6.63-7.55 (9H, m, Ar-H), 8.84(1H, s, NH); ¹³CNMR (75 MHz, CDCl₃); 16.3, 20.6, 21.8 (3C, 3CH₃), 24.2, 26.4, 30.9 (3C, 3CH₂), 35.2 (1C, NCH₃), 43.9 (1C, 1CH₂), 60.8, 65.4, (2C, 2CH), 74.2(1C), 74.6 (1C, OCH), 110.5, 122.2, 126.3, 129.5, 139.6 (5C, 5CH), 127.5, 128.5 (4C, 4CH), 129.0, 140.6, 141.7 (3C), 169.5, 179.2 (2C, 2C=O). MS, 460 (M⁺, 4), 174 (M⁺- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + C₂H₅N), 60).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-1'-methyl-5-nitro-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7b): Yellow powder, yield 72 %; IR(KBr) (ν_{max}, cm⁻¹): 1615(C=O), 1721(C=O), 3420(NH); ¹HNMR (300.1 MHz, CDCl₃); 0.78 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.32-1.75 (9H, m, CH, CH₂), 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), 4.57-4.60(1H, m, OCH), 6.63-7.55 (8H, m, Ar-H), 8.84(1H, s, NH); ¹³CNMR (75 MHz, CDCl₃); 16.4, 20.6, 21.8 (3C, 3CH₃), 24.1, 26.4, 30.9 (3C, 3CH₂), 35.2 (1C, NCH₃), 43.9 (1C, 1CH₂), , 60.8, 65.4, (2C, 2CH), 71.9 (1C), 74.7 (1C, OCH), 110.7, 121.2, 133.0, 139.6 (4C, 4CH), 127.5, 128.5 (4C, 4CH), 128.0,129.0 140.6, 141.7 (4C), 169.5, 179.2 (2C, 2C=O). MS, 505(M⁺, 7), 219 (M⁺- Ph(CH)₂COOmenthyl, 100), 176 (M⁺- (Ph(CH)₂COOmenthyl + C₂H₅N), 82).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-5-bromo-1'-methyl-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7c): Yellow powder, yield 65 %; IR(KBr) (ν_{max}, cm⁻¹): 1612(C=O), 1707(C=O), 3427(NH); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH}=7 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.29-1.67 (9H, m, CH and CH₂), 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), 4.56-4.60(1H, m, OCH), 6.62-7.55 (8H, m, Ar-H), 8.84(1H, s, NH); ¹³CNMR (75 MHz, CDCl₃); 16.3, 20.5, 21.8 (3C, 3CH₃), 24.1, 26.7, 30.9 (3C, 3CH₂), 35.2 (1C, NCH₃), 43.9 (1C, 1CH₂), 60.8, 65.4, (2C, 2CH), 74.2(1C), 74.6 (1C, OCH), 109.6, 121.1, 133.2, 139.6 (4C, 4CH), 127.5, 128.6 (4C, 4CH), 128.1,129.0 140.6, 141.7 (4C), 169.3, 179.2 (2C, 2C=O). MS 539, 541(M⁺, M⁺+2, 8), 251, 253 (M⁺, M⁺+2- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + Br + C₂H₅N) + 1, 48).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-1,1'-dimethyl-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7d): Yellow powder, yield 60 %; IR(KBr)(ν_{max}, cm⁻¹): 1608(C=O), 1717(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.76 (3H, d, ³J_{HH}=7.1 Hz, CH₃), 0.86 and 0.88 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.29-1.66 (9H, m, CH and CH₂), 2.16(3H, s, NMe), 3.14(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), , 4.56-4.60(1H, m, OCH), 6.63-7.55 (9H, m, Ar-H); ¹³CNMR (75 MHz, CDCl₃); 16.5, 20.7, 21.8 (3C, 3CH₃), 24.1, 26.4, 30.9 (3C, 3CH₂), 35.2 (1C, NCH₃), 42.2 (1C, NCH₃), 43.9 (1C, 1CH₂), 60.8, 65.4, (2C, 2CH), 74.2(1C), 74.6 (1C, OCH), 110.5, 121.2, 126.3, 129.5, 139.6 (5C, 5CH), 127.5, 128.5 (4C, 4CH), 129.1, 140.6, 141.7 (3C), 169.5, 179.2 (2C, 2C=O). MS, 474 (M⁺, 8), 188 (M⁺- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + C₂H₅N + Me)+1, 70).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-1,1'-dimethyl-5-nitro-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7e): Yellow powder, yield 65 %; IR(KBr) (ν_{max}, cm⁻¹): 1603(C=O), 1717(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7

Hz, 2 CH₃), 1.33-1.77 (9H, m, CH and CH₂), 2.16(3H, s, NMe), 3.15(3H, s, NMe), 3.43(1H, m, CH), 3.65 (1H, t, ³J_{HH}=10 Hz, CH), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.45(1H, m, CH), 4.56-4.60(1H, m, OCH), 6.63-7.55 (8H, m, Ar-H); ¹³CNMR (75 MHz, CDCl₃); 16.2, 20.5, 22.8 (3C, 3CH₃), 24.3, 26.6, 30.9 (3C, 3CH₂), 74.6 (1C, OCH), 26.3 (1C, NCH₃), 35.1 (1C, NCH₃), 43.9 (1C, 1CH₂), 60.9, 65.3, (2C, 2CH), 73.8(1C), 109.9, 122.0, 133.1, 139.6(4C, 4CH), 127.5, 128.5 (4C, 4CH), 128.0, 129.0, 140.6, 141.7 (4C), 169.9, 180.4 (2C, 2C=O). MS, 519(M⁺, 5), 233 (M⁺- Ph(CH)₂COOmenthyl, 100), 190 (M⁺- (Ph(CH)₂COOmenthyl + C₂H₅N), 60).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-5-bromo-1,1'-dimethyl-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7f): Yellow powder, yield 65 %; IR(KBr)($\tilde{\nu}_{\max}$, cm⁻¹): 1613(C=O), 1714(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH}=7.1 Hz, CH₃), 0.86 and 0.88 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.29-1.67(9H, m, CH and CH₂), 2.16(3H, s, NMe), 3.14(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 4.15 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), 4.56-4.60(1H, m, OCH), 6.63-7.50 (8H, m, Ar-H); ¹³CNMR (75 MHz, CDCl₃); 16.7, 20.4, 21.8 (3C, 3CH₃), 24.4, 26.8, 30.9 (3C, 3CH₂), 35.2 (1C, NCH₃), 43.9 (1C, 1CH₂), 60.8, 65.4, (2C, 2CH), 74.2(1C), 74.6 (1C, OCH), 110.7, 122.1, 133.0, 139.8 (4C, 4CH), 127.6, 128.7 (4C, 4CH), 128.2, 129.0, 140.6, 141.7 (4C), 169.5, 179.9 (2C, 2C=O). MS 553, 555 (M⁺, M⁺+2, 7), 266, 268 (M⁺, M⁺+2- Ph(CH)₂COOmenthyl, 100), 131 (M⁺- (Ph(CH)₂COOmenthyl + Br + C₂H₅N + Me) + 2, 49).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-1-ethyl-1'-methyl-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7g): Yellow powder, yield 60 %; IR(KBr)($\tilde{\nu}_{\max}$, cm⁻¹): 1605(C=O), 1710(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.79 (3H, d, ³J_{HH} = 7 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7 Hz, 2 CH₃), 1.07 (3H, t, ³J_{HH}=7.5 Hz, CH₃), 1.29-1.65 (9H, m, CH and CH₂), 2.15(3H, s, NMe), 3.44(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 3.68 (2H, q, ³J_{HH}=7.5 Hz, CH₂), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.44(1H, m, CH), 4.56-4.60(1H, m, OCH), 6.63-7.55 (9H, m, Ar-H); ¹³CNMR (75 MHz, CDCl₃); 12.3 (1C, CH₃), 16.8, 20.6, 21.5 (3C, 3CH₃), 24.3, 26.6, 30.9 (3C, 3CH₂), 35.2 (1C, NCH₃),

36.1 (1C, NCH₂), 43.7 (1C, 1CH₂), 60.8, 65.3, (2C, 2CH), 74.1(1C), 74.9 (1C, OCH), 109.9, 122.2, 126.4, 129.5, 139.6 (5C, 5CH), 127.5, 128.5 (4C, 4CH), 129.1, 140.6, 141.7 (3C), 166.5, 177.8 (2C, 2C=O). MS, 488 (M⁺, 5), 202(M⁺- Ph(CH)₂COOmenthyl, 100), 159 (M⁺- (Ph(CH)₂COOmenthyl + C₂H₅N), 75).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-1-ethyl-1'-methyl-5-nitro-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7h): Yellow powder, yield 62 %; IR(KBr)($\tilde{\nu}_{\max}$, cm⁻¹): 1609(C=O), 1717(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.77 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7.1 Hz, 2 CH₃), 1.08 (3H, t, ³J_{HH}=7.1 Hz, CH₃), 1.36-1.77 (9H, m, CH and CH₂), 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.63 (1H, t, ³J_{HH}=10 Hz, CH), 3.69 (2H, q, ³J_{HH}=7.1 Hz, CH₂), 4.13 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), 4.56-4.60(1H, m, OCH), 6.65-7.49 (8H, m, Ar-H); ¹³CNMR (75 MHz, CDCl₃); 12.3 (1C, CH₃), 16.3, 20.5, 21.9 (3C, 3CH₃), 24.2, 26.4, 30.7 (3C, 3CH₂), 35.2 (1C, NCH₃), 36.1 (1C, NCH₂), 43.9 (1C, 1CH₂), 61.3, 65.4, (2C, 2CH), 74.2(1C), 74.9 (1C, OCH), 112.1, 122.5, 133.1, 139.9 (4C, 4CH), 127.5, 128.7 (4C, 4CH), 128.0, 129.1, 140.7, 141.9 (4C), 169.7, 179.9 (2C, 2C=O); MS, 533 (M⁺, 4), 247 (M⁺- Ph(CH)₂COOmenthyl, 100), 158 (M⁺- (Ph(CH)₂COOmenthyl + C₂H₅N + No₂), 73).

(2'S,3'R,4'S)-2-isopropyl-5-methylcyclohexyl-5-bromo-1-ethyl-1'-methyl-2-oxo-4'-phenylspiro[indoline-3,2'-pyrrolidine]-3'-carboxylate (7i): Yellow powder, yield 65 %; IR(KBr)($\tilde{\nu}_{\max}$, cm⁻¹): 1612(C=O), 1719(C=O); ¹HNMR (300.1 MHz, CDCl₃); 0.75 (3H, d, ³J_{HH} = 7 Hz, CH₃), 0.87 and 0.89 (6H, 2d, ³J_{HH}=7.1 Hz, 2 CH₃), 1.06 (3H, t, ³J_{HH}=7.5 Hz, CH₃), 1.35-1.67 (9H, m, CH, CH₂), 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 3.64 (2H, q, ³J_{HH}=7.5 Hz, CH₂), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), 4.56-4.60(1H, m, OCH), 6.63-7.55 (8H, m, Ar-H); ¹³CNMR (75 MHz, CDCl₃); 12.1 (1C, CH₃), 16.3, 20.6, 21.9 (3C, 3CH₃), 24.1, 26.6, 30.7 (3C, 3CH₂), 35.5 (1C, NCH₂), 36.2 (1C, NCH₂), 43.9 (1C, 1CH₂), 60.7, 65.4, (2C, 2CH), 74.1(1C), 74.6(1C, OCH), 111.6, 121.1, 133.2, 139.6 (4C, 4CH), 127.5, 128.6 (4C, 4CH), 128.1, 129.2, 140.6, 142.0 (4C),

169.3, 181.2 (2C, 2C=O); MS 567, 569 (M^+ , M^{+2} , 5), 280, 282 (M^+ , M^{+2} - Ph(CH)₂COOmenthyl, 100), 131 (M^+ - (Ph(CH)₂COOmenthyl + Br + C₂H₅N + Et) + 1, 85).

(1'S,2'R,3R)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5a): Yellow oil, yield 95 %, [α]_D-1.2 (c 0.005, CHCl₃); IR(KBr)(ν max, cm⁻¹): 1663(C=O), 1717(C=O), 3430(NH), 3232-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.67-1.79 (2H, m, CH₂), 1.89-1.91 (2H, m, CH₂), 2.38 (1H, m, CH), 2.99 (1H, m, CH), 3.67 (1H, t, ³J_{HH}=9 Hz, CH), 3.96 (1H, m, CH), 4.44 (1H, d, ³J_{HH}=9 Hz, CH), 6.81-7.88 (9H, m, Ar-H), 8.37 (1H, s, NH), 10.42 (1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); 27.9, 28.7, 29.3 (3C, 3CH₂), 37.6, 55.4, 67.1 (3C, 3CH), 71.6(1C), 121.1, 126.5, 127.8, 128.2, 132.5 (5C, 5CH), 125.1, 127.9 (4C, 4CH), 125.7, 138.2, 143.0 (3C), 173.2, 177.9 (2C, 2C=O). MS, 364 (M^+ , 7), 303 (M^+ -CO₂H, 100), 200 (M^+ -Ph(CH)₂CO₂H, 85), 131 (M^+ - (Ph(CH)₂CO₂H + C₄H₇N), 55).

(1'S,2'R,3R)-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5b): Yellow oil, yield 95 %, [α]_D-1.3 (c 0.005, CHCl₃); IR(KBr)(ν max, cm⁻¹): 1669(C=O), 1725(C=O), 3432(NH), 3230-3375 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.66-1.79 (2H, m, CH₂), 1.89-1.91 (2H, m, CH₂), 2.39 (1H, m, CH), 2.98 (1H, m, CH), 3.67 (1H, t, ³J_{HH}=9 Hz, CH), 3.96 (1H, m, CH), 4.44 (1H, d, ³J_{HH}=9 Hz, CH), 6.88-7.99 (8H, m, Ar-H), 8.22 (1H, s, NH), 10.57 (1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); 27.8, 28.7, 29.2 (3C, 3CH₂), 37.6, 55.3, 67.2 (3C, 3CH), 71.6(1C), 121.1, 127.8, 128.2, 132.5 (4C, 4CH), 125.1, 127.9 (4C, 4CH), 125.6, 138.2, 140.5, 143.0 (4C), 173.2, 176.2 (2C, 2C=O). MS 393 (M^+ , 6), 348 (M^+ - CO₂H, 100), 245 (M^+ - Ph(CH)₂COOH, 77), 131 (M^+ - (Ph(CH)₂COOH + C₄H₇N + NO₂) + 1, 50).

(1'S,2'R,3R)-5-bromo-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5c): Yellow oil, yield 90 %, [α]_D-1.7 (c 0.005, CHCl₃); IR(KBr)(ν max, cm⁻¹): 1663(C=O), 1719(C=O), 3422(NH), 3215-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.67-1.79 (2H, m, CH₂),

1.87-1.98 (2H, m, CH₂), 2.39 (1H, m, CH), 2.97 (1H, m, CH), 3.67 (1H, t, ³J_{HH}=9.1 Hz, CH), 3.98 (1H, m, CH), 4.41 (1H, d, ³J_{HH}=9.1 Hz, CH), 6.81-7.88 (8H, m, Ar-H), 8.37 (1H, s, NH), 10.41 (1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); 27.9, 28.7, 29.3 (3C, 3CH₂), 37.6, 55.4, 67.1 (3C, 3CH), 71.6(1C), 121.1, 127.8, 128.2, 132.5 (4C, 4CH), 125.1, 127.9 (4C, 4CH), 125.7, 138.2, 140.4, 143.0 (4C), 173.2, 176.2 (2C, 2C=O); MS, 426, 428 (M^+ , M^{+2} , 5), 381, 383 (M^+ , M^{+2} - Ph(CH)₂COOH, 100), 278, 280 (M^+ , M^{+2} - Ph(CH)₂COOH, 70), 131 (M^+ - (Ph(CH)₂COOH + Br + C₄H₇N), 45).

(1'S,2'R,3R)-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5d): Yellow oil, yield 95%, [α]_D-1.4 (c 0.005, CHCl₃); IR(KBr)(ν max, cm⁻¹): 1666(C=O), 1717(C=O), 3217-3390 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.68-2.01 (4H, m, 2CH₂), 2.62 (1H, m, CH), 3.23 (1H, m, CH), 3.27 (3H, s, NMe) 3.73 (1H, t, ³J_{HH}=9 Hz, CH), 4.13 (1H, m, CH), 4.55 (1H, d, ³J_{HH}=9 Hz, CH), 6.86-7.48 (9H, m, Ar-H), 10.55(1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); ¹³CNMR (300.1 MHz, CDCl₃); 27.8, 28.7, 29.3 (3C, 3CH₂), 42.4(1c, NMe), 37.8, 54.6, 67.1 (3C, 3CH), 71.6(1C), 121.2, 126.4, 127.8, 128.1, 132.5 (5C, 5CH), 125.2, 127.9 (4C, 4CH), 125.7, 138.2, 143.0 (3C), 173.1, 178.7 (2C, 2C=O); MS, 362 (M^+ , 6), 317 (M^+ - CO₂H, 100), 214 (M^+ - Ph(CH)₂COOH, 82), 131 (M^+ - (Ph(CH)₂COOH + C₄H₇N + Me) + 1, 55).

(1'S,2'R,3R)-1-methyl-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5e): Yellow oil, yield 93%, [α]_D-1.5 (c 0.005, CHCl₃); IR(KBr)(ν max, cm⁻¹): 1663(C=O), 1720(C=O), 3255-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.75-2.03 (4H, m, 2CH₂), 2.67 (1H, m, CH), 3.24 (1H, m, CH), 3.27 (3H, s, NMe) 3.73 (1H, t, ³J_{HH}=9.1 Hz, CH), 4.11 (1H, m, CH), 4.56 (1H, d, ³J_{HH}=9.1 Hz, CH), 6.96-7.56 (8H, m, Ar-H), 10.68(1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); ¹³CNMR (300.1 MHz, CDCl₃); 27.8, 28.6, 28.3 (3C, 3CH₂), 42.4(1C, NMe), 36.7, 53.6, 67.1 (3C, 3CH), 71.6(1C), 121.2, 127.8, 128.2, 132.5 (4C, 4CH), 125.2, 127.9 (4C, 4CH), 125.7, 138.4, 141.1, 143.0 (4C), 172.9, 179.1 (2C, 2C=O); MS, 408 (M^+ , 4), 363

(M⁺- CO₂H, 100), 260 (M⁺- Ph(CH)₂COOH, 78), 131 (M⁺- (Ph(CH)₂COOH + C₄H₇N + NO₂+ Me) +1, 53).

(1'S,2'R,3R)-5-bromo-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5f): Yellow oil, yield 90%, [α]_D-1.4 (c 0.005, CHCl₃); IR(KBr)(ν_{max}, cm⁻¹): 1685(C=O), 1727(C=O), 3255-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.68-2.01 (4H, m, 2CH₂), 2.62 (1H, m, CH), 3.23 (1H, m, CH), 3.27 (3H, s, NMe), 3.73 (1H, t, ³J_{HH}=9 Hz, CH), 4.13 (1H, m, CH), 4.55 (1H, d, ³J_{HH}=9 Hz, CH), 6.86-7.48 (8H, m, Ar-H), 10.55(1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); 27.8, 28.7, 29.3 (3C, 3CH₂), 42.4(1C, NMe), 37.7, 54.6, 67.1 (3C, 3CH), 71.6(1C), 121.1, 127.9, 128.2, 132.5 (5C, 5CH), 125.2, 127.8 (4C, 4CH), 125.7, 139.1, 140.6, 143.1 (3C), 172.8, 179.3 (2C, 2C=O); MS, 440, 442 (M⁺, M⁺+2, 6), 395, 397 (M⁺, M⁺+2- CO₂H, 100), 292, 294 (M⁺, M⁺+2- Ph(CH)₂COOH, 65) 131 (M⁺- (Ph(CH)₂COOH + Br + C₄H₇N + Me) + 2, 54).

(1'S,2'R,3R)-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5g): Yellow oil, yield 90%, [α]_D-1.2 (c 0.005, CHCl₃); IR(KBr)(ν_{max}, cm⁻¹): 1675(C=O), 1716(C=O), 3230-3423 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.36 (3H, t, ³J_{HH}=7.2 Hz, CH₃), 1.72-1.86 (2H, m, CH₂), 1.92-2.01 (2H, m, CH₂), 2.66 (1H, m, CH), 3.22(1H, m, CH), 3.81 (1H, t, ³J_{HH}=9.2 Hz, CH), 3.92 (2H, q, ³J_{HH}=7.2 Hz, CH₂), 4.12 (1H, m, CH), 4.57 (1H, d, ³J_{HH}=9.2 Hz, CH), 6.89-7.51 (9H, m, Ar-H), 10.55(1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); 12.0 (1C, CH₃), 27.9, 28.7, 29.3 (3C, 3CH₂), 35.3 (1C, NCH₂), 37.7, 54.6, 67.2 (3C, 3CH), 71.6(1C), 121.1, 126.5, 127.9, 128.2, 132.5 (5C, 5CH), 125.2, 127.8 (4C, 4CH), 125.7, 138.9, 143.1 (3C), 173.9, 180.2 (2C, 2C=O); MS, 376 (M⁺, 2), 331 (M⁺- CO₂H, 100), 228 (M⁺- Ph(CH)₂COOH, 55), 131 (M⁺- (Ph(CH)₂COOH + C₄H₇N + Et), 78).

(1'S,2'R,3R)-1-ethyl-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5h): Yellow oil, yield 93%, [α]_D-1.7 (c 0.005, CHCl₃); IR(KBr)(ν_{max},

cm⁻¹): 1663(C=O), 1721(C=O), 3232-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.36 (3H, t, ³J_{HH}=7.2 Hz, CH₃), 1.71-1.84 (2H, m, CH₂), 1.97-2.01 (2H, m, CH₂), 2.67(1H, m, CH), 3.21(1H, m, CH), 3.83 (1H, t, ³J_{HH}=9.3 Hz, CH), 3.92 (2H, q, ³J_{HH}=7.2 Hz, CH₂), 4.12 (1H, m, CH), 4.57 (1H, d, ³J_{HH}=9.3 Hz, CH), 6.95-7.59 (8H, m, Ar-H), 10.55(1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); 11.9 (1C, CH₃), 27.8, 28.7, 29.3 (3C, 3CH₂), 35.1 (1C, NCH₂), 37.7, 54.6, 67.1 (3C, 3CH), 71.6(1C), 121.1, 127.9, 128.2, 132.5 (4C, 4CH), 125.2, 127.8 (4C, 4CH), 125.7, 139.1, 140.5, 143.1 (4C), 172.8, 179.3 (2C, 2C=O); MS, 421 (M⁺, 4), 376 (M⁺- CO₂H, 100), 273 (M⁺- Ph(CH)₂COOH, 77), 158 (M⁺- (Ph(CH)₂COOH + C₄H₇N + NO₂), 37).

(1'S,2'R,3R)-5-bromo-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (5i): Yellow oil, yield 90%, [α]_D-1.3 (c 0.005, CHCl₃); IR(KBr)(ν_{max}, cm⁻¹): 1675(C=O), 1735(C=O), 3272-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.36 (3H, t, ³J_{HH}=7.1 Hz, CH₃), 1.72-1.82 (2H, m, CH₂), 1.97-2.01 (2H, m, CH₂), 2.68(1H, m, CH), 3.21(1H, m, CH), 3.85 (1H, t, ³J_{HH}=9.3 Hz, CH), 3.92 (2H, q, ³J_{HH}=7.1 Hz, CH₂), 4.18 (1H, m, CH), 4.53 (1H, d, ³J_{HH}=9.3 Hz, CH), 6.89-7.53 (8H, m, Ar-H), 10.55(1H, s, OH); ¹³CNMR (300.1 MHz, CDCl₃); 11.8 (1C, CH₃), 27.8, 28.9, 29.4 (3C, 3CH₂), 34.9 (1C, NCH₂), 37.8, 54.6, 67.1 (3C, 3CH), 71.6(1C), 121.1, 127.9, 128.4, 132.5 (4C, 4CH), 125.2, 127.7 (4C, 4CH), 125.5, 139.1, 140.7, 143.0 (4C), 172.9, 179.2 (2C, 2C=O); MS, 454, 456 (M⁺, M⁺+2, 3), 409, 411(M⁺, M⁺+2- CO₂H, 100), 306, 308 (M⁺- (Ph(CH)₂COOH), 69). 131 (M⁺- (Ph(CH)₂COOH + Br + C₄H₇N + Et) + 2, 48).

3'-cinnamoyl-1'-methyl-4'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (8a): Yellow powder, yield 85 %; IR(KBr)(ν_{max}, cm⁻¹): 1609(C=O), 1681(C=O), 3430(NH), 3280-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, ³J_{HH}=10 Hz, CH), 4.14 (1H, d, ³J_{HH}=10Hz CH), 4.43(1H, m, CH), 6.63-7.55 (9H, m, Ar-H), 8.84(1H, s, NH), 10.64(1H, s, OH); ¹³CNMR (75 MHz, CDCl₃); 35.2 (1C, NCH₃), 43.9 (1C, 1CH₂), 60.8, 65.4, (2C, 2CH), 74.2(1C), 121.1, 126.5, 127.8, 128.2, 132.5

(5C, 5CH), 125.1, 127.9 (4C, 4CH), 125.7, 138.2, 143.0 (3C), 173.2, 177.9 (2C, 2C=O).

3'-cinnamoyl-1'-methyl-5-nitro-4'-phenylspiro [indoline-3,2'-pyrrolidin]-2-one (8b): Yellow powder, yield 83 %; IR(KBr)($\tilde{\nu}_{\max}$, cm^{-1}): 1615(C=O), 1691(C=O), 3420(NH), 3322-3400 (OH); ^1H NMR (300.1 MHz, CDCl_3); 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 4.14 (1H, d, $^3J_{\text{HH}}=10\text{Hz}$ CH), 4.43(1H, m, CH), 6.63-7.55 (8H, m, Ar-H), 8.84(1H, s, NH), 10.64(1H, s, OH); ^{13}C NMR (75 MHz, CDCl_3); 35.2 (1C, NCH_3), 43.9 (1C, 1CH_2), 60.8, 65.4, (2C, 2CH), 74.2(1C), 121.1, 127.8, 128.2, 132.5 (4C, 4CH), 125.1, 127.9 (4C, 4CH), 125.6, 138.2, 140.5, 143.0 (4C), 173.2, 176.2 (2C, 2C=O).

5-bromo-3'-cinnamoyl-1'-methyl-4'-phenylspiro [indoline-3,2'-pyrrolidin]-2-one (8c): Yellow powder, yield 80 %; IR(KBr)($\tilde{\nu}_{\max}$, cm^{-1}): 1612(C=O), 1687(C=O), 3427(NH), 3272-3400 (OH); ^1H NMR (300.1 MHz, CDCl_3); 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 4.14 (1H, d, $^3J_{\text{HH}}=10\text{Hz}$ CH), 4.43(1H, m, CH), 6.62-7.55 (8H, m, Ar-H), 8.84(1H, s, NH), 10.57(1H, s, OH); ^{13}C NMR (75 MHz, CDCl_3); 35.2 (1C, NCH_3), 43.9 (1C, 1CH_2), 60.8, 65.4, (2C, 2CH), 74.2(1C), 121.1, 127.8, 128.2, 132.5 (4C, 4CH), 125.1, 127.9 (4C, 4CH), 125.7, 138.2, 140.4, 143.0 (4C), 173.2, 176.2 (2C, 2C=O).

3'-cinnamoyl-1,1'-dimethyl-4'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (8d): Yellow powder, yield 83 %; IR(KBr)($\tilde{\nu}_{\max}$, cm^{-1}): 1608(C=O), 1687(C=O), 3250-3400 (OH); ^1H NMR (300.1 MHz, CDCl_3); 2.16(3H, s, NMe), 3.14(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 4.14 (1H, d, $^3J_{\text{HH}}=10\text{Hz}$ CH), 4.43(1H, m, CH), 6.63-7.55 (9H, m, Ar-H) 10.77(1H, s, OH); ^{13}C NMR (75 MHz, CDCl_3); 26.2 (1C, NCH_3), 35.2 (1C, NCH_3), 43.9 (1C, 1CH_2), 60.8, 65.4, (2C, 2CH), 74.2(1C), 121.2, 126.4, 127.8, 128.1, 132.5 (5C, 5CH), 125.2, 127.9 (4C, 4CH), 125.7, 138.2, 143.0 (3C), 173.1, 178.7 (2C, 2C=O).

3'-cinnamoyl-1,1'-dimethyl-5-nitro-4'-phenylspiro

[indoline-3,2'-pyrrolidin]-2-one (8e): Yellow powder, yield 80 %; IR(KBr)($\tilde{\nu}_{\max}$, cm^{-1}): 1603(C=O), 1677(C=O), 3272-3420 (OH); ^1H NMR (300.1 MHz, CDCl_3); 2.16(3H, s, NMe), 3.15(3H, s, NMe), 3.43(1H, m, CH), 3.65 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 4.14 (1H, d, $^3J_{\text{HH}}=10\text{Hz}$ CH), 4.45(1H, m, CH), 6.63-7.55 (8H, m, Ar-H), 10.67(1H, s, OH); ^{13}C NMR (75 MHz, CDCl_3); 26.3 (1C, NCH_3), 35.1 (1C, NCH_3), 43.9 (1C, 1CH_2), 60.9, 65.3, (2C, 2CH), 73.8(1C), 121.2, 127.8, 128.2, 132.5 (4C, 4CH), 125.2, 127.9 (4C, 4CH), 125.7, 138.4, 141.1, 143.0 (4C), 172.9, 179.1 (2C, 2C=O).

5-bromo-3'-cinnamoyl-1,1'-dimethyl-4'-phenylspiro [indoline-3,2'-pyrrolidin]-2-one (8f): Yellow powder, yield 85 %; IR(KBr)($\tilde{\nu}_{\max}$, cm^{-1}): 1613(C=O), 1685(C=O), 3272-3400 (OH); ^1H NMR (300.1 MHz, CDCl_3); 2.16(3H, s, NMe), 3.14(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 4.15 (1H, d, $^3J_{\text{HH}}=10\text{Hz}$ CH), 4.43(1H, m, CH), 6.63-7.50 (8H, m, Ar-H), 10.88(1H, s, OH); ^{13}C NMR (75 MHz, CDCl_3); 26.2 (1C, NCH_3), 35.2 (1C, NCH_3), 43.9 (1C, 1CH_2), 60.8, 65.4, (2C, 2CH), 74.2(1C), 121.1, 127.9, 128.2, 132.5 (5C, 5CH), 125.2, 127.8 (4C, 4CH), 125.7, 139.1, 140.6, 143.1 (3C), 172.8, 179.3 (2C, 2C=O).

3'-cinnamoyl-1-ethyl-1'-methyl-4'-phenylspiro [indoline-3,2'-pyrrolidin]-2-one (8g): Yellow powder, yield 87%; IR(KBr)($\tilde{\nu}_{\max}$, cm^{-1}): 1605(C=O), 1690(C=O), 3272-3400 (OH); ^1H NMR (300.1 MHz, CDCl_3); 1.07 (3H, t, $^3J_{\text{HH}}=7.5$ Hz, CH_3), 2.15(3H, s, NMe), 3.44(1H, m, CH), 3.64 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 3.68 (2H, q, $^3J_{\text{HH}}=7.5$ Hz, CH_2), 4.14 (1H, d, $^3J_{\text{HH}}=10\text{Hz}$ CH), 4.44(1H, m, CH), 6.63-7.55 (9H, m, Ar-H), 10.57(1H, s, OH); ^{13}C NMR (75 MHz, CDCl_3); 12.3 (1C, CH_3), 35.2 (1C, NCH_3), 35.5 (1C, NCH_2), 43.7 (1C, 1CH_2), 60.8, 65.3, (2C, 2CH), 74.1(1C), 121.1, 126.5, 127.9, 128.2, 132.5 (5C, 5CH), 125.2, 127.8 (4C, 4CH), 125.7, 138.9, 143.1 (3C), 173.9, 180.2 (2C, 2C=O).

3'-cinnamoyl-1-ethyl-1'-methyl-5-nitro-4'-phenylspiro [indoline-3,2'-pyrrolidin]-2-one (8h): Yellow powder, yield 85 %; IR(KBr)($\tilde{\nu}_{\max}$, cm^{-1}): 1609(C=O), 1681(C=O), 3300-3400 (OH); ^1H NMR (300.1 MHz, CDCl_3); 1.08 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, CH_3), 2.16(3H, s,

NMe), 3.43(1H, m, CH), 3.63 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 3.69 (2H, q, $^3J_{\text{HH}}=7.1$ Hz, CH₂), 4.13 (1H, d, $^3J_{\text{HH}}=10$ Hz CH), 4.43(1H, m, CH), 6.65-7.49 (8H, m, Ar-H), 10.59(1H, s, OH); ¹³CNMR (75 MHz, CDCl₃); 12.3 (1C, CH₃), 35.2 (1C, NCH₃), 35.4 (1C, NCH₂), 43.9 (1C, 1CH₂), 61.3, 65.4, (2C, 2CH), 74.2(1C), 121.1, 127.9, 128.2, 132.5 (4C, 4CH), 125.2, 127.8 (4C, 4CH), 125.7, 139.1, 140.5, 143.1 (4C), 172.8, 179.3 (2C, 2C=O).

5-bromo-3'-cinnamoyl-1-ethyl-1'-methyl-4'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (8i): Yellow powder, yield 83%; IR(KBr)($\bar{\nu}_{\text{max}}$, cm⁻¹): 1612(C=O), 1689(C=O), 3272-3400 (OH); ¹HNMR (300.1 MHz, CDCl₃); 1.06 (3H, t, $^3J_{\text{HH}}=7.5$ Hz, CH₃), 2.16(3H, s, NMe), 3.43(1H, m, CH), 3.64 (1H, t, $^3J_{\text{HH}}=10$ Hz, CH), 3.64 (2H, q, $^3J_{\text{HH}}=7.5$ Hz, CH₂), 4.14 (1H, d, $^3J_{\text{HH}}=10$ Hz CH), 4.43(1H, m, CH), 6.63-7.55 (8H, m, Ar-H), 10.67(1H, s, OH); ¹³CNMR (75 MHz, CDCl₃); 12.1 (1C, CH₃), 35.2 (1C, NCH₃), 35.5 (1C, NCH₂), 43.9 (1C, 1CH₂), 60.7, 65.4, (2C, 2CH), 74.1(1C), 121.1, 127.9, 128.4, 132.5 (4C, 4CH), 125.2, 127.7 (4C, 4CH), 125.5, 139.1, 140.7, 143.0 (4C), 172.9, 179.2 (2C, 2C=O).

4. CONCLUSIONS

Because of wide distribution in nature and variegated biological activities, chiral pyrrolizidines alkaloids are very attractive synthetic targets. For the reason that a pyrrolizidine can be viewed as a fused pyrrolidine, thus method employed for the formation of pyrrolidine rings can be used to construct the pyrrolizidine ring system. So, the asymmetric 1,3-Dipolar cycloaddition reaction of azomethine yields, including pyrrolidine derivatives, with olefins can be useful method for the synthesis of chiral pyrrolizidines. On the other hand, oxindoles also are structural key moieties in many bioactive substances and it is interesting that systematic investigation has shown that if this moiety is joined to the pyrrolizidine or pyrrolidine ring through a spiro atom at C-3, the resulting compounds show an increased spectrum of biological activity. As a result we have found a tri-component synthetic method for the preparation of some oxindoles

derivatives of potential synthetic interest. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

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