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Chiral Induction in Cycloaddition Reactions of Azomethine Ylides to Synthesis of New Enantiomerically Pure Spiro Oxindolopyrrolizidines

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ABSTRACT

An efficient one-pot three-component procedure for the synthesis of new chiral spiro-oxindolopyrrolizidines with highly regio-, diastereo-, and enantioselective from 1,3-dipolar cycloaddition of azomethine ylides and optically pure active cinamoyl oxazolidinone are described. The process occurs at room temperature in aqueous ethanol as green solvent and in the absence of any bidentate chelating Lewis acids. The oxazolidinone chiral auxiliary has been attached to the dipolarophile and removed from the cycloadducts in a non-destructive method. 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 X-ray single crystal structure analysis, and theoretical calculations.

Keyword: Proline; Spirooxindole; Oxazolidinone; Oxazolidinone chiral; Chiral pyrrolidines.

1. INTRODUCTION

Chiral pyrrolidines are extensively found as significant skeleton of numerous biologically relevant alkaloids [1] and are of considerable interest in medicinal chemistry [2]. Also, spiro- oxindolopyrrolidines systems like horsfiline [3], elacomine [4], alstonisine [5] and etc. [6] are core structure of a number of natural alkaloids with most productive biological applications. On the other hands, chiral pyrrolizidines have a long history for attractive the interest of synthetic chemists because of wide distribution in nature and variegated biological activities [7]. Because of pyrrolizidine frameworks can be considered as fused pyrrolidines, therefore can be expected that chiral spirooxindolopyrrolizidine supply more opportunity for the development wide spectrum of variety biological activity [8]. Hence, various derivatives of this important class of spiro compounds have been synthesized [9]. But only a few derivatives of chiral spirooxindolopyrrolizidine have been prepared. The

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reported methods suffer from many limitations, such as requiring multi steps reactions, using toxic solvents in reflux condition, lack of generality and diversity, remaining of chiral auxiliary in products or producing byproduct after its removal [10].

As a result of above reasons and in continuation of our work on synthesis of spirooxindoles [9, 11], we decided to synthesize a series of enantiomerically pure new spirooxindolo-pyrrolizidines using a three-component reaction involving 1,3-dipolar cycloadditions of appropriate azomethineylides with olefins which makes possible the simultaneous formation of up to four stereocenters in cycloaddact [12]. In this report, at first the chiral auxiliary, cinamoyl oxazolidinone 1, was easily prepared from reaction of readily available (S)-phenylglycinol with diethyl carbonate [13]; and then, after deprotonation of this with n-BuLi, react readily with cinamoyl chloride to provide chiral non-racemic cinamoyl oxazolidinone 1 [14]. Afterwards, the reactions were carried out in mild condition, at room temperature, in aqueous ethanol and in the absence of any bidentate chelating Lewis acids [15] through a one-pot three-component 1,3-dipolar cycloaddition reaction of the chiral dipolarophiles **1** with non-stabilized azomethineylides **2** which was generated in situ by the decarboxylative condensation of isatins **3** with proline **4**. After removal of oxazolidinone chiral auxiliary, new chiral spirooxindolopyrrolizidines were obtained in excellent yield and high enantiomeric excess (Scheme 1).

2. EXPERIMENTAL

2.1. General

Melting points were determined on an electrothermal 9100 apparatus and are uncorrected. Mass spectral data were obtained from a FINNIGAN-MAT 8430 and Agilet 5937 and mass spectrometer operating at 70 eV. ^{1}H, ^{13}C, DEPT, (H-H)-COSY, HMQC, HMBC, NOESY, ROESY spectra were recorded on a BRUKER DRX-300 MHz instrument in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a Bomen FT-IR-MB-series instrument. The single crystal X-ray data set was collected on a STOE IPDSII two-circle diffract meter.

2.2. Experimental details and data for compounds 5a-i

General methods: A mixture of isatin derivatives **3** (1 mmol), proline **4** (1 mmol, 0.115 g) and chiral cinamoyl oxazolidinone **1** (1 mmol, 0.293 g) was dissolved in EtOH (80%) (5 mL) and stirred at room temperature for about 5 h. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure, the products (**5a-i**) were obtained in high yields and high purity (only one diastereomer was obtained); and for future purification, were washed with cold EtOH.

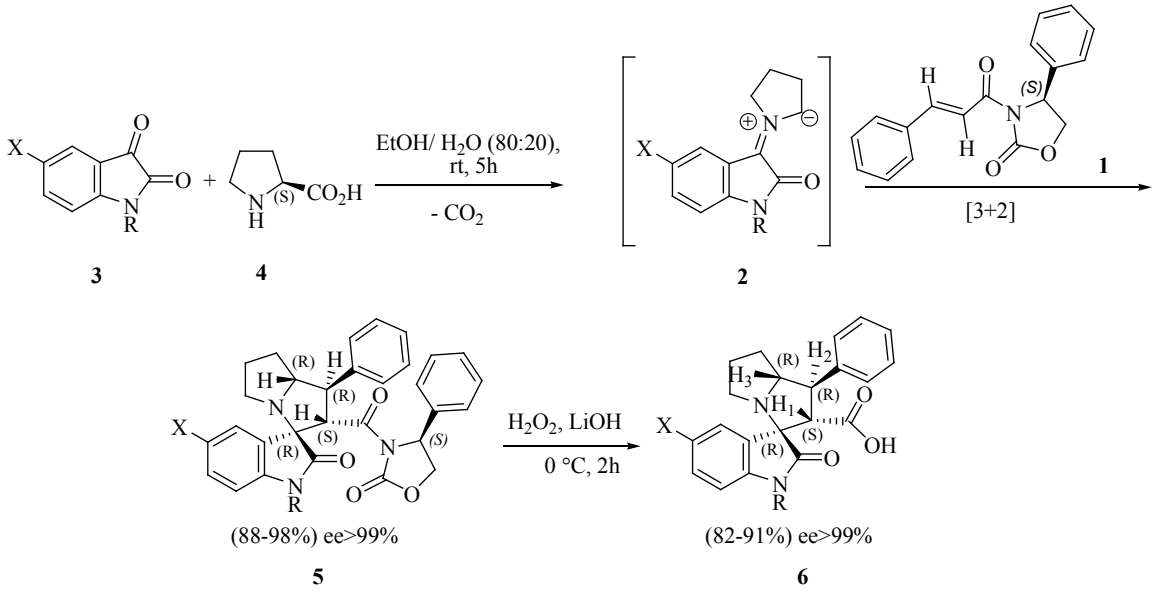
2.3. Experimental details and data for compounds 6a-i

General methods: Substrate **5** (1 mmol) was dissolved in a mixture of THF: H_2O (4:1) at 0°C and LiOH (3 equiv) was added and then H_2O_2 (3 mmol) in THF (2 mL) was added dropwise at 0°C over 10 min. The reaction mixture was stirred for an additional 2 hours and then evaporated. Water (5 mL) was added to the mixture and then extracted with EtOAc (3× 10 mL). The organic phase was separated, and washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo to afford pure products of **6**.

3. RESULTS AND DISCUSSION

As shown in Scheme 1, condensation of compounds **3** and 4 after decarboxylation leading to the non-stabilized azomethineylides **2**. The [3+2] cycloaddition of chiral dipolarophiles **1** with these, ylides produced new chiral spirooxindoldes 5 with four stereogenic centers in one step. Consequently, eight different stereoisomers could have been produced. But by using this strategy only diastereoisomer 5 were obtained purely in high total yield and high optical purity as shown by NMR (Scheme 1). After this, for study of diversity and generality of this method other derivates of new chiral spirooxindolopyrrolizidine were synthesized. The results are summarized in Table 1.

The structures of cycloaddition products were assigned by their elemental analysis including, IR, ^{1}HNMR, ^{13}CNMR and Mass spectral data. Observation of two characteristic doublets and triplet with $^{3}J_{HH}$ of about 9Hz in the ^{1}HNMR spectra of **5** and **6** is con-



Scheme 1: *Asymmetric synthesis of new chiral spirooxindolopyrrolizidines* **5**, **6**.

sistent with formation new pyrrolizidine cyclic. The absolute configuration of one of the products **5e** was determined based an X-ray crystallographic analysis [16] as 5R (spiro carbon C_7), 6S (C_{21}), 7R (C_{14}), 8R (C_{13}) which is shown in Figure 1.

Interestingly, the chiral auxiliary in these compounds were removed easily with hydrogenperoxide, LiOH and cleanly produced products **6** in quantitated yield [17] (Scheme 1). But in contrast to this removing method, reduction cleavage of this auxiliary with lithium borohydride yielded only 25% of corresponding product [10b]. The stereochemistry and the correct structure of this isomer and other derivatives were determined by ^{1}HNMR, ^{13}CNMR, IR, Mass, HMQC, and (H, H)-COSY. For example, the ^{1}HNMR spectrum of **6a** for exhibits a triplet signal at $\delta = 4.02$ ppm, a triplet at $\delta = 4.51$ and a doublet at $\delta = 4.96$ ppm which are related to H_2, H_3 and H_1 protons respectively. Also DEPT 135o showed signals, corresponding to three (CH) carbons that were directly bonded to H_3, H_2 and H_1 in the region 67.1, 29.3 and 37.6 respectively. In HMQC spectrum of cycloadduct exo-6a, the positions of three protons (H_3, H_2, and H_1) that were directly bonded to these carbon atoms (CH) were as-

Table 1: *The results of asymmetric synthesis of new chiral spirooxindolopyrrolizidines* **5**, **6**.

Entry	R	X	Product	5[a]		6	
				Yield (%)[b]	α (°)[c]	Yield (%)[b]	α (°)[c]
1	H	H	A	95	+260.5	98	+241.3
2	H	Br	B	93	+273.5	90	+342.1
3	H	NO_2	C	98	+256.7	98	+263.7
4	Me	H	D	89	+264.9	95	+283.2
5	Me	Br	E	90	+253.4	87	+282.8
6	Me	NO_2	F	95	+248.8	93	+301.4
7	Et	H	G	86	+261.7	88	+243.6
8	Et	Br	H	88	+267.5	91	+264.1
9	Et	NO_2	I	85	+294.4	88	+343.8

(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).

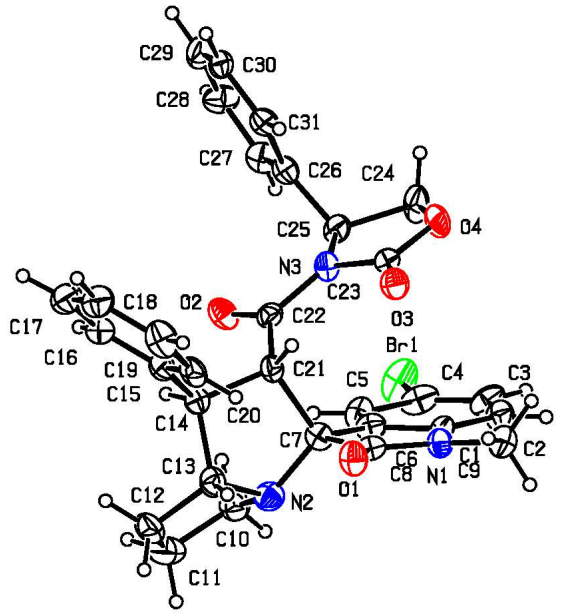


Figure 1: *ORTEP diagram of one of the four crystallographic independent molecules in the asymmetric unit of 5e. Thermal ellipsoids are at 30% probability level.*

signed. Accordingly, the exact chemical shifts of these protons (δH_3 = 3.67, δH_2 = 3.96, δH_1 = 4.44) were assigned by means of (H-H)-COSY spectrum. Stereochemistry of the exo-6a has been assigned from ROESY spectrum. Absence of any correlation between H_3 and H_2 in the ROESY spectrum shows that the H_2 hydrogen could be trans to H_3. But an intense contour between H_1 and H_3 shows these two hydrogen are cis to each others. This is also confirmed from the NOE between them. Therefore, the correct stereochemistry could be as shown in Scheme 1.

The AM1 calculated energy shows that there is a remarkably energy difference (about 2.5 kcal/mol) between the exo and endo transition state. Consequently, high level of stereochemistry can be the results of approach exo transition state in which azomethine ylides approach from re-face of the dipolarophile as shown in Figure 2 which is in good agreement with the experimentally observed X-ray crystallography of molecule **5e**.

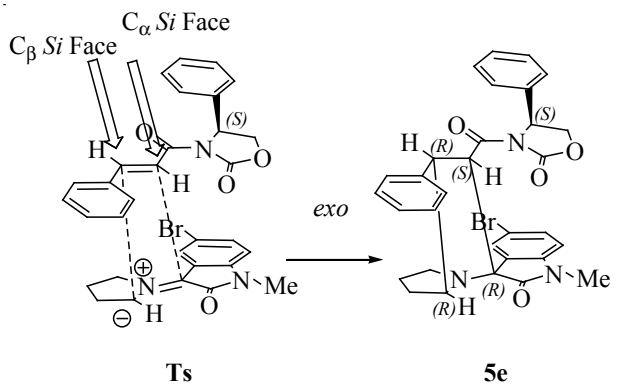


Figure 2: *Proposed models for endo/exo cycloaddition.*

Spectral data

(S)-3-((1'R,2'S,3R,7a'R)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3' pyrr olizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5a): white powder, mp 125-128°C, yield 95%, $[\alpha]_D$+260.5 (c 1, CH_2Cl_2); IR (KBr)(υ_{max}, cm^{-1}): 1614(C=O), 1716(C=O), 1782(C=O), 3432(NH); ^{1}HNMR (300 MHz, $CDCl_3$); 1.69-1.72 (2H, m, CH_2), 1.98-2.02 (2H, m, CH_2), 2.70 (1H, m, CH), 3.18 (1H, m, CH), 3.88-3.95 (2H, m, CH_2), 4.02 (1H, t, $^3J_{HH}$ = 9 Hz, CH), 4.51 (1H, m, CH), 4.95 (1H, d, $^3J_{HH}$ = 9 Hz, CH), 5.09 (1H, dd, $^2J_{HH}$ = 9 Hz, $^3J_{HH}$ = 3 Hz, CH), 6.95-7.50 (14H, m, Ar-H), 8.36 (1H, s, NH); ^{13}CNMR (75 MHz, $CDCl_3$); 24.4 (CH_2), 27.4 (CH_2), 29.7 (CH_2), 49.3 (CH), 53.3 (CH), 61.8 (CH), 57.9 (OCH_2), 70.2 (CHPh), 72.1 (spiro), 110.6, 121.1, 126.1, 126.8, 129.8, 140.2, 125.6, 128.6, 128.7, 129.1, 125.8, 128.5, 138.2, 143.0, 153.0 (C=O), 172.2 (C=O), 179.9 (C=O); MS, 493 (M^+, 6), 200 (100), 131 (70).

(S)-3-((1'R,2'S,3R,7a'R)-5-bromo-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5b): Yellow powder, mp 128°C, yield 93%, $[\alpha]_D$+273.5 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1614(C=O), 1720(C=O), 1779(C=O), 3420(NH); ^{1}HNMR (300 MHz, $CDCl_3$); 1.74-1.87 (2H, m, CH_2), 1.98-2.01 (2H, m, CH_2), 2.73 (1H, m, CH), 3.12 (1H, m, CH), 3.88-4.01 (2H, m, CH_2), 4.16(1H, t, $^3J_{HH}$ = 8.9 Hz, CH), 4.49 (1H, m, CH), 4.91 (1H, d, $^3J_{HH}$ = 8.9 Hz, CH), 5.18 (1H, m, CH), 6.86-7.15 (13H, m, Ar), 8.91 (1H, s, NH); ^{13}CNMR (75 MHz, $CDCl_3$); 24.3 (CH_2), 27.3 (CH_2), 29.8 (CH_2), 49.2 (CH), 53.1(CH), 61.7 (CH), 58.1 (OCH_2), 70.2 (CHPh), 72.1 (spiro), 112.4, 113.5, 126.8, 132.7, 140.0, 125.6, 128.6, 128.7, 129.1, 126.9, 127.8, 128.9 138.3, 142.4, 153.1 (C=O), 172.3 (C=O), 179.9 (C=O). MS 571 (M^+, 6), 573 (M^{+2}, 6), 278 (75), 280 (78), 131 (100).

(S)-3-((1'R,2'S,3R,7a'R)-5-nitro-2-oxo-1'-phe-

nyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5c): Yellow powder, mp 120-123°C, yield 98%, $[\alpha]_D$+256.7 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1615(C=O), 1719(C=O), 1780(C=O), 3431(NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.81-1.89 (2H, m, CH_2), 1.98-2.01 (2H, m, CH_2), 2.75 (1H, m, CH), 3.12 (1H, m, CH), 3.89-4.03 (2H, m, CH_2), 4.18 (1H, t, $^3J_{HH}$= 9 Hz, CH), 4.49 (1H, m, CH), 4.92 (1H, d, $^3J_{HH}$= 9 Hz , CH), 5.18 (1H, m, CH), 6.98-7.80 (13H, m, Ar-H), 8.91 (1H, s, NH); ^{13}CNMR (300.1 MHz, $CDCl_3$); 24.4, 27.4, 29.8 (3C, $3CH_2$), 49.2, 53.3, 61.8 (3C, 3CH), 57.9 (1C, OCH_2), 70.2 (1C, 1CHPh), 72.2 (1C), 112.5, 113.5, 126.9, 132.7, 140.1 (5C, 5CH), 125.6, 128.6, 128.7, 129.2 (8C, 8CH), 126.8, 127.9, 128.9 138.5, 142.4 (5C, 5CH), 153.1, 172.3, 179.2 (3C, 3C=O); MS 538 (M^+, 6), 245 (M+-$Ph(CH)_2COoxazolidyl$, 100), 131 (M+-($Ph(CH)_2COoxazolidyl$ + C_4H_7N + NO_2) + 1, 57).

(S)-3-((1'R,2'S,3R,7a'R)-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5d): white powder, mp 189°C, yield 90%, $[\alpha]_D$+264.9 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1614(C=O), 1716(C=O), 1780(C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.75-1.85 (2H, m, CH_2), 1.98-2.02 (2H, m, CH_2), 2.71 (1H, m, CH), 3.20 (1H, m, CH), 3.25 (3H, s, NMe) 3.88-3.98 (2H, m, CH_2), 4.02 (1H, t, $^3J_{HH}$= 9 Hz, CH), 4.58 (1H, m, CH), 4.83 (1H, d, $^3J_{HH}$= 9 Hz, CH), 5.07 (1H, dd, $^2J_{HH}$= 9 Hz, $^3J_{HH}$= 4.2 Hz, CH), 6.95-7.50 (14H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 24.1, 26.5, 27.3 (3C, $3CH_2$), 42.2 (1C, NMe), 49.7, 53.3, 62.2 (3C, 3CH), 57.9 (1C, OCH_2), 70.5 (1C, 1CHPh), 72.9 (1C), 108.7, 121.3, 125.8, 126.8, 128.5, 140.0 (6C, 6CH), 125.9, 128.6, 128.7, 129.1 (8C, 8CH), 125.2, 127.5, 128.5, 138.1 (4C), 153.0, 172.2, 179.9 (3C, 3C=O); MS 507 (M+, 8), 214 (M+- $Ph(CH)_2COoxazolidyl$, 100), 131 (M+-($Ph(CH)_2COoxazolidyl$ + C_4H_7N + Me) + 1, 55).

(S)-3-((1'R,2'S,3R,7a'R)-5-bromo-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5e): white powder, mp 122°C, yield 90%, $[\alpha]_D$+253.4 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1613(C=O), 1711(C=O), 1781(C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.75-1.82 (2H, m, CH_2), 1.98-2.02 (2H, m, CH_2), 2.69 (1H, m, CH), 3.16 (1H, m, CH), 3.24 (3H, s, NMe) 3.88-3.94 (2H, m, CH_2), 4.11 (1H, t, $^3J_{HH}$= 8.9 Hz, CH), 4.53 (1H, m, CH), 4.77 (1H, d, $^3J_{HH}$= 8.9 Hz, CH), 5.14 (1H, dd, $^2J_{HH}$= 8.9 Hz, $^3J_{HH}$= 4.1 Hz, CH), 6.95-7.63 (13H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 24.2, 26.6, 27.2 (3C, $3CH_2$), 42.1 (1C, NMe), 49.6, 53.1, 62.3 (3C, 3CH), 58.0 (1C, OCH_2), 70.6 (1C, 1CHPh), 71.8 (1C), 110.2, 113.6, 126.8, 132.6, 140.1 (5C, 5CH), 125.8, 128.6, 128.7, 129.2 (8C, 8CH), 125.7, 127.4, 128.5, 138.1, 144.9 (5C), 153.0, 172.2, 177.9 (3C, 3C=O); MS 585, 587 (M+, M++2, 6), 292, 294 (M+, M++2- $Ph(CH)_2COoxazolidyl$, 67), 131 (M+- ($Ph(CH)_2COoxazolidyl$ + Br + C_4H_7N + Me) + 2, 100).

(S)-3-((1'R,2'S,3R,7a'R)-5-nitro-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5f): Yellow powder, mp 195°C, yield 92%, $[\alpha]_D$+248.8 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1614(C=O), 1721(C=O), 1779(C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.82-1.92 (2H, m, CH_2), 1.98-2.02 (2H, m, CH_2), 2.70 (1H, m, CH), 3.15 (1H, m, CH), 3.24 (3H, s, NMe) 3.88-3.98 (2H, m, CH_2), 4.12 (1H, t, $^3J_{HH}$= 9 Hz, CH), 4.53 (1H, m, CH), 4.76 (1H, d, $^3J_{HH}$= 9 Hz, CH), 5.14 (1H, dd, $^2J_{HH}$= 9 Hz, $^3J_{HH}$= 4.2 Hz, CH), 6.95-7.63 (13H, m, Ar-H); ^{13}CNMR (300.1 MHz, CCl_3); 24.2, 26.6, 27.2 (3C, $3CH_2$), 42.2 (1C, NMe), 49.6, 53.2, 61.3 (3C, 3CH), 58.0 (1C, OCH_2), 70.6 (1C, 1CHPh), 71.9 (1C), 111.2, 113.7, 126.8, 132.7, 140.3 (5C, 5CH), 125.8, 128.7, 128.8, 129.2 (8C, 8CH), 125.9, 127.5, 128.6, 138.2, 144.9 (5C), 153.1, 172.2, 178.9 (3C, 3C=O); MS 552 (M+, 6), 259 (M+- $Ph(CH)_2COoxazolidyl$, 100), 131 (M+-($Ph(CH)_2COoxazolidyl$ + C_4H_7N + NO_2+ Me) + 2, 60).

(S)-3-((1'R,2'S,3R,7a'R-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5g): Yellow powder, mp 103°C, yield 85%, $[\alpha]_D$+261.7 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1613(C=O), 1711(C=O), 1781 (C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.36 (3H, t, $^3J_{HH}$= 7.2 Hz, CH_3), 1.71-

1.84 (2H, m, CH_2), 1.97-2.01 (2H, m, CH_2), 2.67(1H, m, CH), 3.21(1H, m, CH), 3.85-3.98 (4H, m, $2CH_2$), 4.13 (1H, t, $^3J_{HH}$= 9.3 Hz, CH), 4.52 (1H, m, CH), 4.87 (1H, d, $^3J_{HH}$= 9.3 Hz, CH), 5.06 (1H, dd, $^2J_{HH}$= 9 Hz, $^3J_{HH}$= 4.2 Hz, CH), 6.89-7.52 (14H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 11.9 (1C, CH_3), 24.2, 27.2, 31.0 (3C, $3CH_2$), 35.0 (1C, NCH_2), 49.6, 53.3, 62.0 (3C, 3CH), 58.0 (1C, OCH_2), 70.1 (1C, 1CHPh), 72.0 (1C), 111.2, 121.1, 126.1, 126.7, 129.1, 140.2 (6C, 6CH), 125.6, 128.7, 128.9, 129.2 (8C, 8CH), 125.8, 128.5, 129.9, 138.3 (4C), 153.0, 172.2, 179.9 (3C, 3C=O); MS 521 (M+, 7), 228 (M+- $Ph(CH)_2$COoxazolidyl, 100), 131 (M+- ($Ph(CH)_2$COoxazolidyl + C_4H_7N + Et), 90).

(S)-3-((1'R,2'S,3R,7a'R)-5-bromo-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5h): Yellow powder, mp 135°C, yield 85%, $[\alpha]_D$+267.5 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1611(C=O), 1711(C=O), 1781(C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.37(3H, t, $^3J_{HH}$= 6.9 Hz, CH_3), 1.71-1.89 (2H, m, CH_2), 1.97-2.01 (2H, m, CH_2), 2.67-2.69 (1H, m, CH), 3.17-3.22 (1H, m, CH), 3.88-3.93 (4H, m, $2CH_2$), 4.12 (1H, t, $^3J_{HH}$= 9 Hz, CH), 4.51-4.57 (1H, m, CH), 4.87 (1H, d, $^3J_{HH}$= 9Hz , CH), 5.03-5.06 (1H, m, CH), 6.89-7.55 (13H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 11.9 (1C, CH_3), 24.2, 27.3, 30.8 (3C, $3CH_2$), 35.1 (1C, NCH_2), 49.6, 53.4, 61.9 (3C, 3CH), 58.1 (1C, OCH_2), 69.7 (1C, 1CHPh), 71.9 (1C), 109.2, 121.0, 126.1, 126.7, 129.8 (5C, 5CH), 125.6, 128.5, 128.6, 129.1 (8C, 8CH), 125.8, 128.7, 138.4, 140.4, 143.9 (5C), 153.8, 172.5, 178.1 (3C, 3C=O); MS 599, 601 (M+, M++2, 5), 306, 308 (M+, M++2- Ph(CH)2COoxazolidyl, 60), 131 (M+-($Ph(CH)_2$COoxazolidyl + Br + C_4H_7N + Et) + 1, 100).

(S)-3-((1'R,2'S,3R,7a'R)-5-nitro-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2'-ylcarbonyl)-4-phenyloxazolidin-2-one (5i): Yellow powder, mp 148°C, yield 88%, $[\alpha]_D$+249.4 (c 1, CH_2Cl_2); IR(KBr)(υ_{max}, cm^{-1}): 1614(C=O), 1711(C=O), 1781 (C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.39 (3H, t, $^3J_{HH}$= 7.1 Hz , CH_3), 1.71-1.90 (2H, m, CH_2), 1.97-2.01 (2H, m, CH_2), 2.68 (1H, m, CH), 3.20 (1H, m, CH), 3.89-3.95 (4H, m, $2CH_2$), 4.12 (1H, t, $^3J_{HH}$= 8.9 Hz, CH), 4.51-4.58 (1H, m, CH), 4.87 (1H, d, $^3J_{HH}$= 8.9Hz, CH), 5.02-5.07 (1H, m, CH), 6.89-7.55 (13H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 11.9 (1C, CH_3), 24.1, 27.3, 30.9 (3C, $3CH_2$), 35.1 (1C, NCH_2), 49.6, 53.3, 61.9 (3C, 3CH), 57.9 (1C, OCH_2), 69.6 (1C, 1CHPh), 71.9 (1C), 108.9, 121.0, 126.1, 126.7, 129.8 (5C, 5CH), 125.6, 128.5, 128.6, 129.1 (8C, 8CH), 125.9, 128.7, 138.3 140.4, 144.9 (5C), 152.7, 172.4, 178.1 (3C, 3C=O); MS 567 (M+, 7), 274 (M+- $Ph(CH)_2$COoxazolidyl, 100), 159 (M+- ($Ph(CH)_2$COoxazolidyl + C_4H_7N + NO_2), 55).

(1'R,2'S,3R,7a'R)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6a): Yellow oil, yield 98%, $[\alpha]_D$+241.3 (c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1663(C=O), 1717(C=O), 3430(NH), 3232-3400 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.67-1.79 (2H, m, CH_2), 1.89-1.91 (2H, m, CH_2), 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, $^3J_{HH}$= 9Hz, CH), 6.81-7.88 (9H, m, Ar-H), 8.37 (1H, s, NH), 10.42 (1H, s, OH); ^{13}CNMR (300.1 MHz, $CDCl_3$); 27.9, 28.7, 29.3 (3C), 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+-CO_2H, 100), 200 (M+-$Ph(CH)_2CO_2H$, 85), 131 (M+- ($Ph(CH)_2CO_2H$ + C_4H_7N), 55).

(1'R,2'S,3R,7a'R)-5-bromo-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6b): Yellow oil, yield 90%, $[\alpha]_D$+342.1 (c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1663(C=O), 1719(C=O), 3422(NH), 3215-3400 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.67-1.79 (2H, m, CH_2), 1.87-1.98 (2H, m, CH_2), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 27.9, 28.7, 29.3 (3C, $3CH_2$), 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- $Ph(CH)_2$COOH, 100), 278, 280 (M+, M++2- $Ph(CH)_2$COOH, 70), 131 (M+-

($Ph(CH)_2COOH$+ Br + C_4H_7N), 45).

(1'R,2'S,3R,7a'R)-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6c): Yellow oil, yield 98%, $[\alpha]_D$+263.7 (c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1669(C=O), 1725(C=O), 3432(NH), 3230-3375 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.66-1.79 (2H, m, CH_2), 1.89-1.91 (2H, m, CH_2), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 27.8, 28.7, 29.2 (3C, $3CH_2$), 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+- CO_2H, 100), 245 (M+- $Ph(CH)_2COOH$, 77), 131 (M+- ($Ph(CH)_2COOH$ + C_4H_7N + NO_2) + 1, 50).

(1'R,2'S,3R,7a'R)-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6d): Yellow oil, yield 95%, $[\alpha]_D$+283.2(c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1666(C=O), 1717(C=O), 3217-3390 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.68-2.01 (4H, m, $2CH_2$), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 27.8, 28.7, 29.3 (3C, $3CH_2$), 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+- CO_2H, 100), 214 (M+- $Ph(CH)_2COOH$, 82), 131 (M+- ($Ph(CH)_2COOH$ + C_4H_7N + Me) + 1, 55).

(1'R,2'S,3R,7a'R)-1-methyl-5-bromo-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6e): Yellow oil, yield 85%, $[\alpha]_D$+282.8(c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1685(C=O), 1727(C=O), 3255-3400 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.68-2.01 (4H, m, $2CH_2$), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 27.8, 28.7, 29.3 (3C, $3CH_2$), 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- CO_2H, 100), 292, 294 (M+, M++2- $Ph(CH)_2COOH$, 65), 131 (M+- ($Ph(CH)_2COOH$ + Br + C_4H_7N + Me) + 2, 54).

(1'R,2'S,3R,7a'R)-1-methyl-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6f): Yellow oil, yield 93%, $[\alpha]_D$+301.4(c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1663(C=O), 1720(C=O), 3255-3400 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.75-2.03 (4H, m, $2CH_2$), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 27.8, 28.6, 28.3 (3C, $3CH_2$), 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+- CO_2H, 100), 260 (M+- $Ph(CH)_2COOH$, 78), 131 (M+- ($Ph(CH)_2COOH$ + C_4H_7N + NO_2+ Me) +1, 53).

(1'R,2'S,3R,7a'R)-1-ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6g): Yellow oil, yield 85%, $[\alpha]_D$+243.6(c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1675(C=O), 1716(C=O), 3230-3423 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.36 (3H, t, $^3J_{HH}$= 7.2 Hz, CH_3), 1.72-1.86 (2H, m, CH_2), 1.92-2.01 (2H, m, CH_2), 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, CH_2), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 12.0 (1C, CH_3), 27.9, 28.7, 29.3 (3C, $3CH_2$), 35.3 (1C, NCH_2), 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+- CO_2H, 100), 228 (M+-

$Ph(CH)_2COOH$, 55), 131 (M+- ($Ph(CH)_2COOH$ + C_4H_7N + Et), 78).

(1'R,2'S,3R,7a'R)-1-ethyl-5-bromo-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6h): Yellow oil, yield 90%, $[\alpha]_D$+264.1(c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1675(C=O), 1735(C=O), 3272-3400 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.36 (3H, t, $^3J_{HH}$= 7.1 Hz, CH_3), 1.72-1.82 (2H, m, CH_2), 1.97-2.01 (2H, m, CH_2), 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, CH_2), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 11.8 (1C, CH_3), 27.8, 28.9, 29.4 (3C, $3CH_2$), 34.9 (1C, NCH_2), 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- CO_2H, 100), 306, 308 (M+-($Ph(CH)_2COOH$), 69). 131 (M+- ($Ph(CH)_2COOH$ + Br + C_4H_7N + Et) + 2, 48).

(1'R,2'S,3R,7a'R)-1-ethyl-5-nitro-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-carboxylic acid (6i): Yellow oil, yield 87%, $[\alpha]_D$+343.8(c 1, $CHCl_3$); IR(KBr)(υ_{max}, cm^{-1}): 1663(C=O), 1721(C=O), 3232-3400 (OH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.36 (3H, t, $^3J_{HH}$= 7.2 Hz, CH_3), 1.71-1.84 (2H, m, CH_2), 1.97-2.01 (2H, m, CH_2), 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, CH_2), 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); ^{13}CNMR (300.1 MHz, $CDCl_3$); 11.9 (1C, CH_3), 27.8, 28.7, 29.3 (3C, $3CH_2$), 35.1 (1C, NCH_2), 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+-CO_2H, 100), 273 (M+- $Ph(CH)_2COOH$, 77), 158 (M+-($Ph(CH)_2COOH$ + C_4H_7N + NO_2), 37).

4. CONCLUSIONS

We introduced a small library of new chiral spirooxindolopyrrolizidines through a one-pot three component reaction between available isatin derivatives, proline and chiral cinamoyl oxazolidinone in mild condition and environmentally friendly solvent of aqueous ethanol, in high yield and high optical purity. Removal of the chiral auxiliary was achieved easily without producing any byproducts. The structure of the products was elucidated using IR, Mass, one and two dimensional NMR techniques and X-ray single crystal analysis.

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16. X-ray data for 5e: $C_{31}H_{28}BrN_3O_4$, M = 586.46, triclinic system, space group P1, a = 10.1837(4), b = 15.3844(6), c = 17.7233(7) Å, α = 86.429(3), β = 81.529(3), γ = 77.831(3)º; V = 2683.31(19) Å3, Z = 4, Z' = 4, Dcalcd = 1.452 g c^{m-3}, μ(Mo-Kα)=1.575 m^{m-1}, crystal dimension of 0.28×0.25×0.15 mm. The X-ray diffraction measurement was made on a STOE IPDS-II diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by using SHELXS. The Data reduction and structure refinement was carried out with SHELXL using the X-STEP32 crystallographic software package [18]. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F2 values to final R1 = 0.1010, wR2 = 0.2554 and S = 1.034 with 1409 parameters using 23418 independent reflection (θ range = 2.07-29.19º). All hydrogen atoms were added in idealized positions.
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