Tetrahedron Letters 53 (2012) 854–858

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# An expedient diastereoselective synthesis of pyrrolidinyl spirooxindoles fused to sugar lactone via [3+2] cycloaddition of azomethine ylides

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ARTICLE INFO

*Article history:*
Received 3 August 2011
Revised 30 November 2011
Accepted 7 December 2011
Available online 14 December 2011

*Keywords:*
1,3-Dipolar cycloaddition
Azomethine ylide
Pyrrolidinyl-spirooxindoles
α,β-Unsaturated sugar lactones

ABSTRACT

Synthesis of pyrrolidinyl-spirooxindoles fused to sugar lactone has been achieved by a one pot three component 1,3-dipolar cycloaddition (1,3-DC) reaction. A unique dipolarophile (α,β-unsaturated lactone) derived from D-glucose/D-galactose reacted with azomethine ylide generated in situ from isatin/*N*-substituted isatin and secondary amino acids (sarcosine/proline/piperidine-2-carboxylic acid) to give the corresponding cycloadducts in good yield. The cycloaddition was found to be highly regio- and diastereoselective.



In recent years, synthesis of new substituted spirooxindole derivatives[1] has attracted the attention of synthetic organic chemists due to their remarkable biological activity.[2,3] Moreover spirooxindole frame work has been found as core structure of many pharmacological agents and alkaloids,[4] such as horsifiline, spirotryprostatine A and B, pteropodine, isopteropodine (Fig. 1). It is an important structural motif which acts as potent non-peptide inhibitor of the p53–MDM2 interaction.[5,6]

Developing efficient synthetic methods for the synthesis of oxindoles derivatized at $C_3$ with spirocarbocycles, spiroheterocycles, spirolactones, and spirocyclic ethers are particularly important in organic synthesis. Among the different synthetic strategies, 1,3-dipolar cycloaddition reaction of azomethine ylide[7] plays a key role in the construction of spirooxindoles.[8]

1,3-DC reaction of azomethine ylide is a powerful tool for the synthesis of a variety of natural products[9] containing a pyrrolidine structure. And it has been widely used as an important carbon–carbon bond forming reaction. 1,3-DC reactions of nitrone,[10] nitrile oxide[11] and azide[12] with carbohydrate scaffolds are well known in the literature, whereas only very few reports are available involving azomethine ylide[13] with carbohydrates. To the best of our knowledge, there is no report in the literature on the synthesis of pyrrolidinyl spirooxindoles fused to sugar lactone through 1,3-DC reaction.

As part of our ongoing research in the area of 1,3-dipolar cycloaddition[14] herein we report a short and efficient protocol for the synthesis of sugar lactone fused pyrrolidinyl-spirooxindole derivatives through 1,3-DC reaction of azomethine ylide with α,β-unsaturated lactones (**1a**, **1b**) derived from D-glucose and D-galactose.[15]

In a prototype experiment, the reaction of dipolarophile **1a** with azomethine ylide generated in situ from *N*-methyl isatin and proline in refluxing toluene under Dean–Stark reaction conditions, afforded the cycloadduct **9**[16] in good yields (88%) with high regio- and stereoselectivities through an intermolecular 1,3-DC reaction

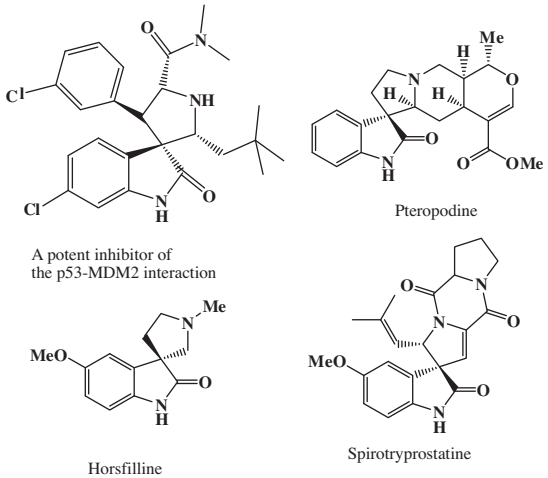


**Figure 1.** Naturally occurring and biologically active 3,3′-pyrrolidinyl-spirooxindole natural products.

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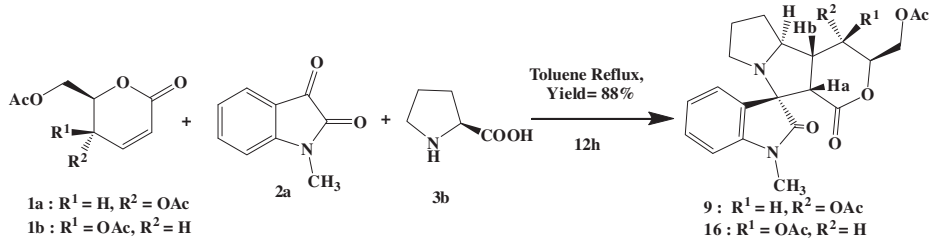
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.025




**Scheme 1.** Synthesis of sugar lactone fused spiropyrrolizidine oxindole.

(Scheme 1). The structure of the product was confirmed by spectroscopic and X-ray analyses.[17] A single product was isolated in all the cases and no trace of the other isomers formed even after prolonged reaction time. The crude $^{1}$H NMR spectra of the products confirmed the formation of single regio and stereoisomers.

The $^{1}$H NMR spectrum of compound **9** exhibited a characteristic singlet at $\delta$ 3.15 for $NCH_3$ protons of isatin and at $\delta$ 2.08, 2.12 for two acetyl protons of lactone which proved the incorporation of oxindole ring into sugar lactone. Moreover the characteristic doublet at $\delta$ 3.87 ($J$ = 11.7 Hz) for $H_a$ proton proved the formation of regioisomer **9**. If regioisomer **9A** had been formed, the $H_a$ proton would have appeared as a multiplet in the $^{1}$H NMR spectrum. The lactone carbonyl carbon and amide carbonyl carbon showed peaks at 176.7 and 170.6 ppm respectively in $^{13}$C NMR spectrum. These observed chemical shift values are in agreement with the structure of the compound **9**. Furthermore, the presence of

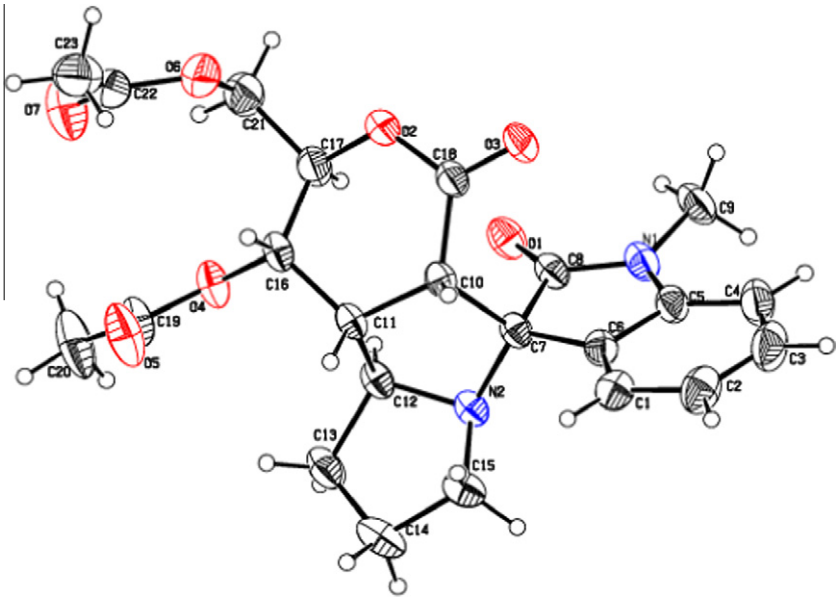



**Figure 2.** ORTEP diagram of **9**.

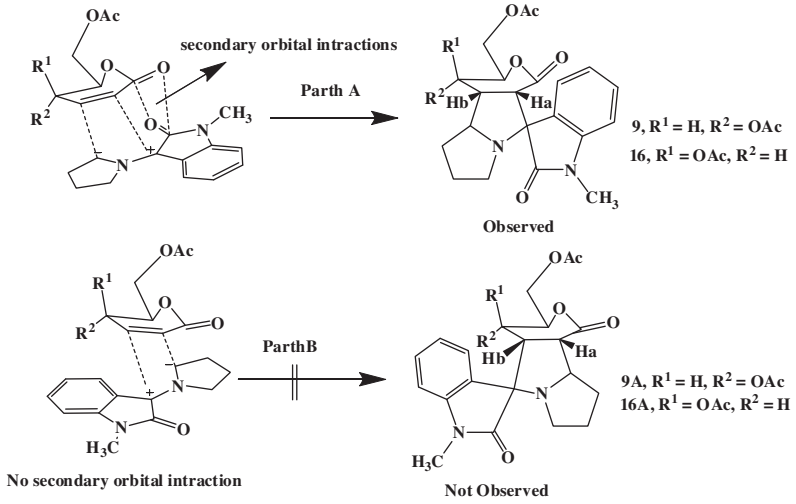



**Figure 3.** The possible regio chemical mode of approach of azomethine ylide to the dipolarophile.

molecular ion peak at $m/z$ 443.18 ($M^+$+1) in the mass spectrum confirmed the formation of the cycloadduct **9**. The stereochemistry of the product **9** was established by X-ray crystallography analysis as shown in Figure 2.[17]

The possible regiochemical mode of approach of azomethine ylide to the dipolarophile (**1a** and **1b**) is shown in Figure 3. In path A amide carbonyl group of azomethine ylide having secondary orbital interaction[18] with the lactone carbonyl group of dipolarophile whereas in path B such kind of secondary orbital interaction cannot take place. Hence path A is more favorable for regioselective formation of the cycloadduct **9**.

Similarly path C and path D in Figure 4 explain the stereochemical approach of dipole to the dipolarophile (**1a** and **1b**). The transition state TS1 of path C shows *exo* mode of approach of dipole to both faces of dipolarophile. Since dipole is having a steric repulsion with terminal acetoxymethyl[19] group in the unsaturated lactones in *Si* face it preferably attacks from the face opposite to that of the terminal acetoxymethyl group in unsaturated lactones.

Hence approach from the *Re* face is more favorable than *Si* face of dipolarophile. Transition state TS2 of path D would be less favorable due to dipolar repulsion between lactone carbonyl group of dipolarophile and amide carbonyl group of dipole. Hence dipole favorable approach is from *Re* face of dipolarophile through *exo* mode[19] for stereoselective formation of cycloadduct **9**. The acetate group at C-4 of lactone does not seem to play any role in controlling the direction of approach of dipole to the dipolarophile. Since the cycloaddition proceeded exclusively through *exo* mode, a single diastereomer was observed in all cases.

To study the effect of solvent on cycloaddition reaction, the reaction was carried out in different solvents and toluene was found to be the best to get the maximum yield of the products.

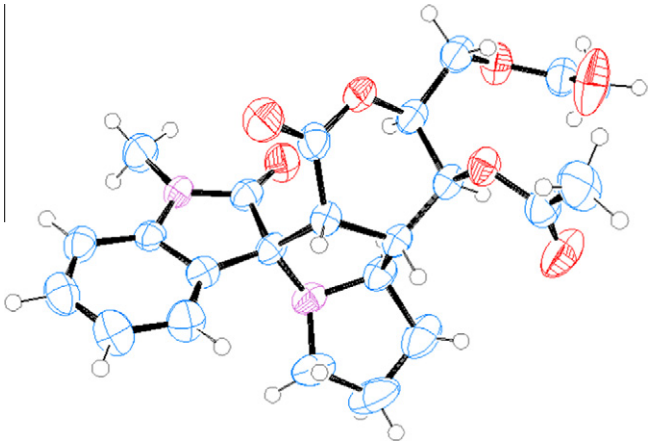


**Figure 5.** ORTEP diagram of **16**.

Having optimized reaction conditions, we investigated the scope of the reaction by reacting different 1,3-dipoles with the dipolarophiles (**1a** and **1b**). The reactions smoothly proceeded through [3+2] cycloaddition to give the corresponding cycloadducts in good yields. All the compounds were thoroughly characterized by $^1$H, $^{13}$C NMR, DEPT-135 and mass spectroscopic methods (Fig. 5, Table 1).

In conclusion, we have developed a simple and efficient protocol for the synthesis of pyrrolidinyl-spirooxindoles fused to sugar lactone through 1,3-dipolar cycloaddition methodology. This multicomponent reaction offers high yield of the products, with simple experimental procedure and formation of single regio and

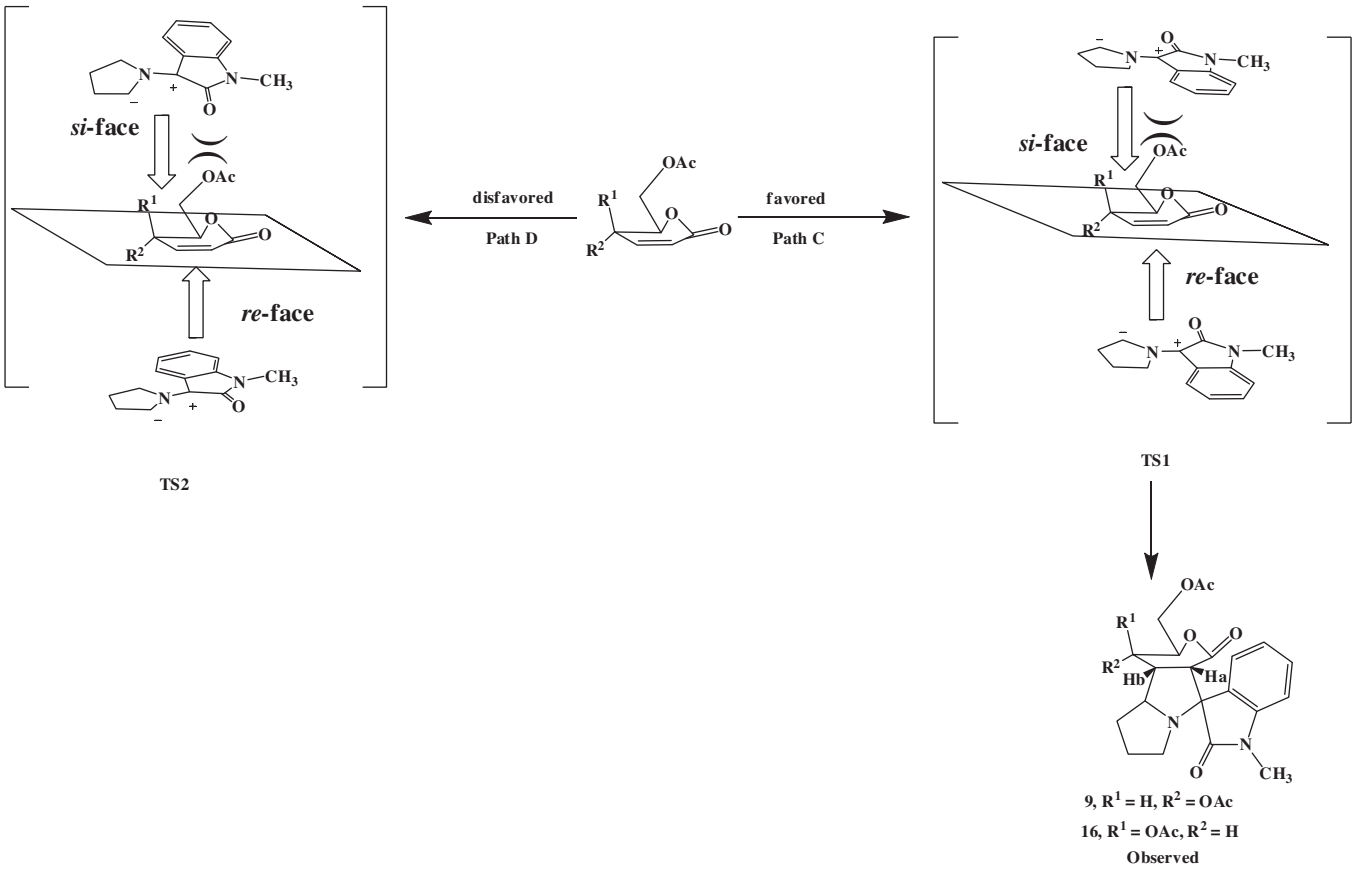
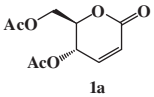
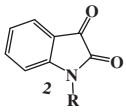
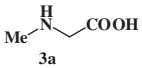
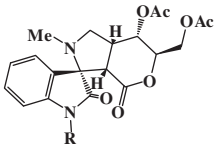
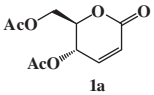
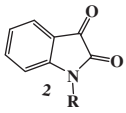
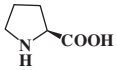
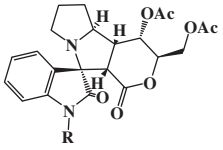
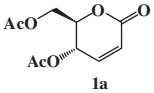
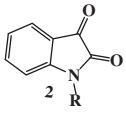
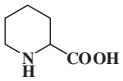
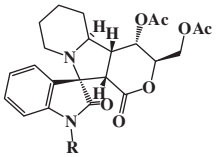
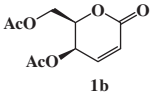
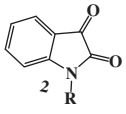
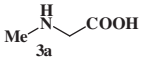
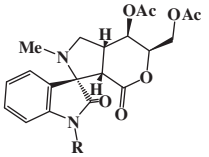
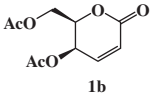
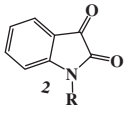
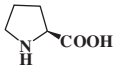
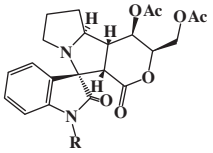
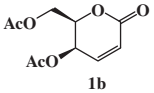
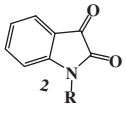
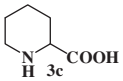
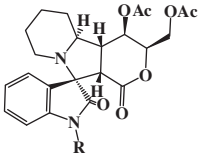



**Figure 4.** The possible stereo chemical mode of approach of azomethine ylide to the dipolarophile.

**Table 1**
Synthesis of 2,3′-pyrrolidinyl-spirooxindole derivatives

| Entry | Unsaturated sugar lactone | Isatin | Secondary amino acids | Time (h) | Product[a] | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  1a |  2 |  3a | 12 |  | R = H, 84%, 4<br>R = Me, 86%, 5<br>R = Et, 82%, 6<br>R = Bn, 784%, 7 |
| 2 |  1a |  2 |  3b | 12 |  | R = H, 84%, 8<br>R = Me, 88%, 9<br>R = Et, 80%, 10 |
| 3 |  1a |  2 |  3c | 12 |  | R = H, 80%, 11 |
| 4 |  1b |  2 |  3a | 12 |  | R = H, 86%, 12<br>R = Me, 88%, 13<br>R = Et, 84%, 14 |
| 5 |  1b |  2 |  3b | 12 |  | R = H, 86%, 15<br>R = Me, 87%, 16<br>R = Et, 83%, 17 |
| 6 |  1b |  2 |  3c | 12 |  | R = H, 84%, 18 |

[a] The products were characterized by IR, NMR, MS and elemental analysis.
[b] Isolated yield after purification.

stereoisomers. The biological activities of the synthesized compounds are currently under investigation, and further work in this direction is in progress.

## Acknowledgments

J.N. thanks Council of Scientific and Industrial Research (CSIR), New Delhi, India for the award of junior research fellowship (JRF). R.R. and J.N. thank DST (Project No. SR/S1/OC-51/2008), New Delhi for financial support and DST-FIST program for the NMR facility. The authors wish to thank Professors D. Velmurugan and S. Sundaramoorthy for single crystal X-ray data.

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16. **General procedure for the synthesis of pyrrolidinyl-spirooxindole derivatives:** To a solution of isatin/*N*-substituted isatin (1 equiv) and cyclic or acyclic secondary amino acid (1.4 equiv) in dry toluene, was added α,β-unsaturated sugar lactone (**1a**–**b**) under the nitrogen atmosphere. The solution was refluxed for 12 h in Dean–Stark apparatus to give the cycloadducts. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure. The crude product was extracted with dichloromethane. The organic layer was dried with anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified by column chromatography using hexane/EtOAc (7:3) as eluent.
(a) **((3*S*,3′*R*,4′*S*,4a′*R*,6′*R*,7′*S*,7a′*R*)-7′-Acetoxy-2′-methyl-2,4′-dioxo-2′,3a′,4′,6′,7′,7a′-hexahydro-1′*H*-spiro[indoline-3,3′-pyrano[4,3-*c*]pyrrole]-6′-yl)methyl acetate (4)**: Isolated yield: 84% (0.296 g) Synthesized from α,β-unsaturated sugar lactone **1a** (0.2 g, 0.087 mmol), isatin (0.129, 0.087 mmol), and sarcosine (0.117 g, 0.132 mmol),white solid. Mp = 115–116 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 2.06 (s, 3H), 2.12 (s, 3H), 2.15 (s, 3H), 3.01–3.06 (m, 1H), 3.40–3.49 (m, 1H), 3.55–3.61 (m, 1H), 3.70 (d, $J$ = 11.1 Hz, 1H), 4.21–4.25 (m, 1H), 4.40–4.46 (m, 1H), 5.21–5.24 (m, 1H), 5.31–5.34 (m, 1H), 6.79 (d, $J$ = 7.5 Hz, 1H), 7.07 (t, $J$ = 7.5 Hz, 1H), 7.18–7.28 (m, 2H), 8.58 (s, 1H). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 20.4, 26.6, 34.2, 35.2, 51.6, 53.6, 61.4, 65.2, 73.4, 74.8, 110.1, 123.1, 123.7, 128.5, 129.6, 141.4, 169.4, 169.6, 170.4, 177.7. IR (KBr) $\nu_{max}$: 1710, 1743, 3290 cm$^{-1}$. HRMS (ESI) $m/z$ [M+H]$^+$ calcd for $C_{20}H_{23}N_2O_7$ 403.1505, found 403.1509. Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.70; H, 5.51; N, 6.69. Found: C, 59.85; H, 5.63; N, 6.62. $[\alpha]_D^{27.3}$ +3.5 ($c$ 2.3, $CH_2Cl_2$).
(b) **((3S,3′*R*,4′*S*,4a′*R*,4b′*S*,9a′*S*)-4′-Acetoxy-1-methyl-1′,2-dioxo-3′,4′,4a′,4b′,5′,6′,7′,9a′-octahydro-1′*H*-spiro[indoline-3,9′-pyrano[4,3-*a*]pyrrolizine]-3′-yl)methyl acetate (9)**: Isolated yield: 88% (0.34 g) Synthesized from α,β-unsaturated sugar lactone **1a** (0.2 g, 0.087 mmol), *N*-methyl isatin (0.141 g, 0.087 mmol), and proline (0.151 g, 0.132 mmol), white solid. Mp = 164–165 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 1.54–1.57 (m, 1H), 1.84–1.97 (m, 2H), 1.93–1.96 (m, 1H), 2.08 (s, 3H), 2.12 (s, 3H), 2.58–2.62 (m, 1H), 2.71–2.80 (m, 1H), 2.95–3.01 (m, 1H), 3.15 (s, 3H), 3.87 (d, $J$ = 11.7 Hz, 1H), 4.24–4.29 (m, 1H), 4.40–4.51 (m, 2H), 5.40–5.41 (m, 2H), 6.84 (d, $J$ = 7.5 Hz, 1H), 7.09 (t, $J$ = 7.5 Hz, 1H), 7.33–7.38 (m, 2H). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 20.7, 25.2, 26.2, 28.9, 42.0, 48.5, 52.0, 61.5, 65.1, 65.5, 73.4, 74.1, 108.8, 122.8, 124.7, 127.3, 130.0, 144.4, 169.3, 169.8, 170.6, 176.7. IR (KBr) $\nu_{max}$: 1698, 1745 cm$^{-1}$. HRMS (ESI) $m/z$ [M+H]$^+$ calcd for $C_{23}H_{27}N_2O_7$ 443.1818, found 443.1824. Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.54; H, 5.99; N, 6.41. $[\alpha]_D^{26.7}$ +4 ($c$ 0.55, $CH_2Cl_2$).
(c) **((3S,3′*R*,4′*S*,4a′*R*,4b′*S*,10a′*S*)-4′-Acetoxy-1′,2-dioxo-1′,3′,4′,4a′,4b′,5′,6′,7′,8′,10a′-decahydrospiro[indoline-3,10′-pyrano[4,3-*a*]indolizine]-3′-yl)methyl acetate (11)**: Isolated yield: 80% (0.31 g) Synthesized from α,β-unsaturated sugar lactone **1a** (0.2 g, 0.087 mmol), isatin (0.129 g, 0.087 mmol), and piperidine-2-carboxylic acid (0.169, 0.132 mmol),white solid. Mp = 150–151 °C.$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 1.18–1.23 (m, 3H), 1.29 (s, 3H), 1.35–1.42 (m, 1H), 1.97 (s, 3H), 2.0–2.07 (m, 2H), 2.20–2.23 (m, 2H), 2.99–3.06 (m, 1H), 3.41–3.61 (m, 2H), 4.11–4.20 (m, 2H), 5.15–5.21 (m, 1H), 5.27–5.31 (m, 1H), 6.75 (d, $J$ = 7.5 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 7.09–7.20 (m, 2H), 7.90 (s, 1H). $^{13}$ C NMR ($CDCl_3$, 75 MHz): $\delta$ 19.2, 20.6, 23.7, 25.0, 32.3, 44.4, 44.6, 46.1, 61.7, 62.9, 64.5, 72.7, 73.7, 109.3, 123.5, 124.7, 128.8, 129.4, 140.9, 169.1, 169.7, 170.6, 178.3. IR (KBr) $\nu_{max}$: 1712, 1744, 3296 cm$^{-1}$. $m/z$ 442.17. Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.53; H, 5.98; N, 6.40. $[\alpha]_D^{27.1}$ +3.39 ($c$ 0.4, $CH_2Cl_2$).
**(d) ((3S,3a′*S*,6′*R*,7′*R*,7a′*R*)-7′-Acetoxy-2′-methyl-2,4′-dioxo-2′,3a′,4′,6′,7′,7a′-hexahydro-1′*H*-spiro[indoline-3,3′-pyrano[4,3-*c*]pyrrole]-6′-yl)methyl acetate (12)**: Isolated yield: 86% (0.3 g) Synthesized from α,β-unsaturated sugar lactone **1b** (0.2 g, 0.087 mmol), isatin (0.129 g, 0.087 mmol), and sarcosine (0.117 g, 0.132 mmol), white solid. m.p =110–111 °C.$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 2.08 (s, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 3.02–3.11 (m, 1H), 3.34–3.39 (m, 2H), 3.64 (d, $J$ = 11.1 Hz, 1H), 4.26–4.30 (m, 2H), 5.19–5.20 (m, 1H), 5.25–5.29 (m, 1H), 6.84 (d, $J$ = 7.5 Hz, 1H), 7.1 (t, $J$ = 7.5 Hz, 1H), 7.23–7.28 (m, 2H), 8.01 (s, 1H). $^{13}$ C NMR ($CDCl_3$, 75 MHz): $\delta$ 20.7, 20.8, 34.3, 38.5, 49.9, 55.9, 62.2, 66.6, 74.0, 74.8, 110.3, 123.4, 123.9, 128.7, 129.9, 141.5, 169.1, 169.9, 170.5, 177.7. IR (KBr) $\nu_{max}$: 1708, 1743, 3296 cm$^{-1}$. $m/z$ 402.14; Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.70; H, 5.51; N, 6.69. Found: C, 59.81; H, 5.58; N, 6.74. $[\alpha]_D^{27.6}$ +3.6 ($c$ 0.5, $CH_2Cl_2$).
(e) **((3S,3′*R*,4′*R*,4a′*R*,4b′*S*,9a′*S*)-4′-Acetoxy-1-methyl-1′,2-dioxo-3′,4′,4a′,4b′,5′,6′,7′,9a′-octahydro-1′*H*-spiro[indoline-3,9′-pyrano[4,3-*a*]pyrrolizine]-3′-yl)methyl acetate (16)**: Isolated yield: 87% (0.338 g) Synthesized from α,β-unsaturated sugar lactone **1b** (0.2 g, 0.087 mmol), *N*-methyl isatin (0.141 g, 0.087 mmol), and proline (0.151 g, 0.132 mmol), white solid. Mp = 158–159 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 1.84–1.85 (m, 1H), 1.97–2.00 (m, 2H), 2.11 (s, 3H), 2.12 (s, 3H), 2.21–2.23 (m, 1H), 2.56–2.64 (m, 1H), 2.71–2.81(m, 2H), 3.15 (s, 3H), 3.78 (d, $J$ = 11.4 Hz, 1H), 4.21–4.24 (m, 1H), 4.27–4.31 (m, 2H), 5.21–5.13 (m, 1H), 5.37–5.40 (m, 1H), 6.85 (d, $J$ = 7.8 Hz, 1H), 7.09 (t, $J$ = 7.5 Hz, 1H), 7.33–7.36 (m, 2H). $^{13}$ C NMR ($CDCl_3$, 75 MHz): $\delta$ 20.8, 20.9, 24.2, 26.3, 27.8, 46.4, 48.0, 49.6, 62.2, 66.5, 66.7, 73.9, 75.3, 108.8, 122.7, 124.9, 127.1, 130.1, 144.6, 169.3, 170.1, 170.5, 176.7. IR (KBr) $\nu_{max}$: 1745, 1698 cm$^{-1}$. $m/z$ 442.19. Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.33; H, 5.82; N, 6.41. $[\alpha]_D^{26.9}$ +1.78 ($c$ 0.3, $CH_2Cl_2$).
(f) **((3S,3′*R*,4′*R*,4a′*R*,4b′*S*,10a′*S*)-4′-Acetoxy-1′,2-dioxo-1′,3′,4′,4a′,4b′,5′,6′,7′,8′,10a′-decahydrospiro[indoline-3,10′-pyrano[4,3-*a*]indolizine]-3′-yl)methyl acetate (18)**: Isolated yield: 84% (0.326 g) Synthesized from α,β-unsaturated sugar lactone **1b** (0.2 g, 0.087 mmol), isatin (0.129 g, 0.087 mmol), and piperidine-2-carboxylic acid (0.169 g, 0.132 mmol), white solid. mp = 157–158 °C.$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 1.19–1.25 (m, 2H), 1.25–1.28 (m, 1H), 1.45–1.46 (m, 1H), 1.68 (s, 3H), 2.02 (s, 3H), 2.04–2.08 (m, 1H), 2.21–2.18 (m, 2H), 2.32–2.35 (m, 1H), 2.84–2.90 (m, 1H), 2.95–3.02 (m, 1H), 3.52–3.58 (m, 1H), 4.12–4.26 (m, 2H), 4.91–4.96 (m, 1H), 5.11–5.14 (m, 1H), 6.77 (d, $J$ = 7.5 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 7.15–7.21 (m, 2H), 8.23 (s, 1H). $^{13}$ C NMR ($CDCl_3$, 75 MHz): $\delta$ 19.2, 19.7, 22.5, 24.1, 31.2, 44.3, 44.5, 47.4, 61.1, 61.5, 64.9, 72.8, 74.0, 108.8, 122.3, 123.0, 127.9, 128.5, 140.2, 168.2, 168.6, 169.6, 176.4. IR (KBr) $\nu_{max}$: 1712, 1746, 3297 cm$^{-1}$. HRMS (ESI) $m/z$ [M+H]$^+$ calcd or $C_{23}H_{27}N_2O_7$ 443.1818, found 443.1820. Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.51; H, 5.86; N, 6.40. $[\alpha]_D^{27.1}$ + 1.10 ($c$ 0.35, $CH_2Cl_2$).
17. The detailed X-ray crystallographic data (CCDC numbers for **9** and **16** are 827985 and 822189 respectively) are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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