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Highly regioselective synthesis of glycospiro heterocycles through 1,3-dipolar cycloaddition reaction

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ABSTRACT

A highly regio-selective synthesis of novel glycospiropyrrolidines has been accomplished by 1,3-dipolar cycloaddition (1,3-DC) reaction. A unique dipolarophile derived from galactose has been reacted with azomethine ylide generated from 1,2-diketones and secondary aminoacids to give the corresponding spiro glycoheterocycles in good yields. The structures were assigned by 2D NMR spectra and the regio- and stereochemical outcome of the cycloadducts was established by a single crystal X-ray analysis.

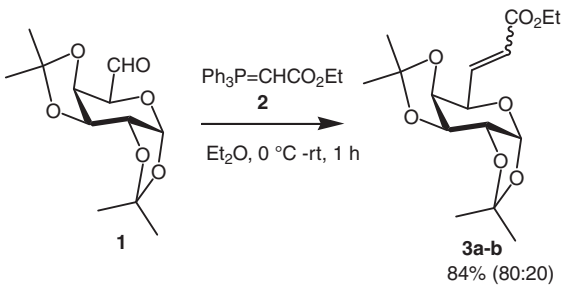
The surge of interest for carbohydrate-derived heterocycles[1] is due to their potential biological significance and pharmaceutical applications.[2] Recently, several studies have demonstrated that the carbohydrate-based heterocycles have shown a diverse range of bioactivities such as anti-influenza (H1N1),[3] antitumor,[4] anti-HIV,[5] antimicrobial,[6] and anticancer,[7] thereby making these compounds a particularly important subject for study. The diversity of biological activity and the ever-growing new application of these compounds have stimulated a great deal of interest in regard to their synthesis.

1,3-DC reaction of azomethine ylide is a powerful tool for the synthesis of a variety of natural products[8] containing a pyrrolidine structure. Although many investigations have been made to exploit carbohydrate as a template for 1,3-DC reaction involving azide,[9] nitrone,[10] and nitrile oxide,[11] there are only very few reports involving azomethine ylide[12] in the literature and the synthetic utility of azomethine ylide reaction has not been well exploited in carbohydrate chemistry. Hence, there arises a need to synthesize carbohydrate-fused heterocyclic systems through 1,3-DC reaction using azomethine ylide as a dipole.

In continuation of our research in the field of 1,3-dipolar cycloaddition reaction,[13] herein we report a highly efficient protocol for the synthesis of sugar-derived spiropyrrolidines through 1,3-DC reaction from D-galactose. 1,2:3,4-diisopropylidene-D-galactopyranose[14] on oxidation[15] gave the corresponding aldehyde **1** which on Wittig olefination[16] with the phosphorus ylide **2** derived from ethylbromoester gave the conjugated ester **3** in a 80:20 diastereomeric ratio with the predominant formation of *E* isomer (Scheme 1). These diastereomers were separated by column chromatography to give pure compounds **3a** and **3b** in good yield. The structure and geometry of the olefinic ester **3a** and **3b** were deduced on the basis of ^{1}H NMR spectral data where the coupling constant for **3a** (J = 15.9 Hz) and **3b** (J = 11.7 Hz) of vinylic protons confirmed a *trans* (*E*) and *cis* (*Z*) geometry of the products, respectively.

These dipolarophiles **3a** and **3b** when reacted with azomethine ylide generated from acenaphthequinone **4a** and sarcosine **5a** in refluxing toluene under Dean–Stark reaction conditions, furnished the cycloadducts[17] **6a** and **6b** in good yields (88–92%) in a highly regioselective and stereoselective manner[18] through an intermolecular 1,3-dipolar cycloaddition reaction (Scheme 2).

We then studied the solvent effects on the cycloaddition reaction for the synthesis of **6a** and **6b**. Interestingly, the reaction pro-



Scheme 1. Synthesis of glycoacrylate **3a–b**.

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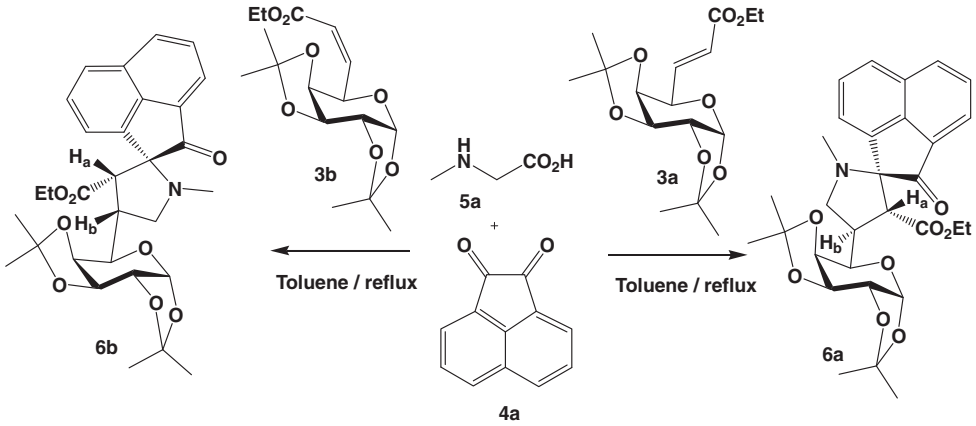


Scheme 2. Synthesis of glycopyrrolidine.

Table 1
Effect of solvent on the yield of reaction

Solvent	Temperature (°C)	Time		Yield[a] (%)	
		6a	6b	6a	6b
Toluene	Reflux	4	5	92	88
Benzene	Reflux	8	8	57	52
CH_3CN	Reflux	6	6	76	78
CH_3OH	Reflux	10	12	30	34
DMF	110	12	12	16	12
1,4-Dioxane	90	8	8	18	12

[a] Isolated yield in percentage.

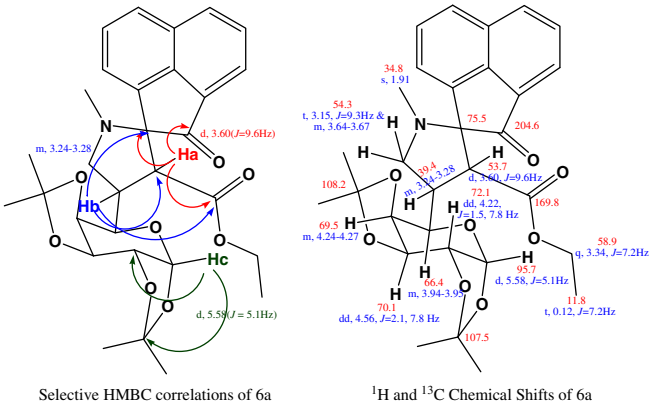


Figure 1. HMBC correlation of **6a**.

Table 2
Synthesis of galactopyranoyl-derived spiroheterocycles through [3+2] cycloaddition reaction

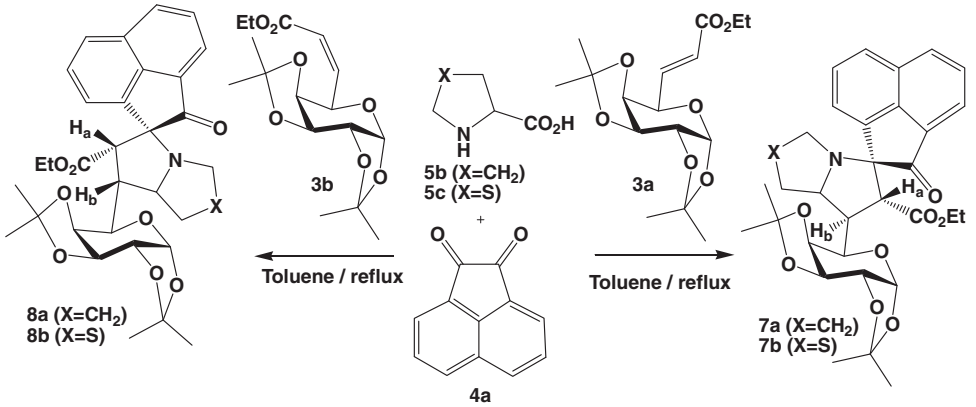
Entry	Product[a]	Time (h)	Yield[b] (%)
1	**7a**	4.5	86
2	**8a**	5.0	78
3	**7b**	4.0	82
4	**8b**	5.0	76
5	**9a**	4.0	84
6	**9b**	4.5	86
7	**10a**	5.5	82
8	**11a**	5.5	84
9	**10b**	4.5	88
10	**11b**	5.0	86

[a] Reaction carried out with toluene/reflux.
[b] Isolated yields of pure products.

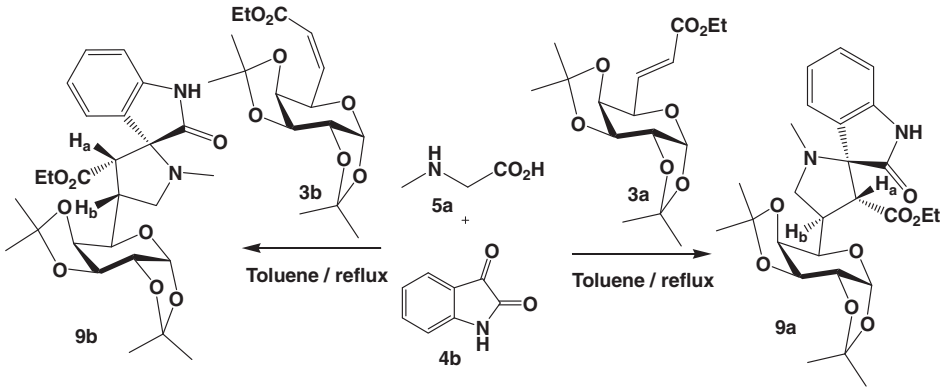
ceeded more efficiently in toluene than in benzene or other solvents (Table 1). The structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, DEPT 135, HMBC, and HRMS.

The ^{1}H NMR spectrum of diastereomers **6a** and **6b** showed a doublet at δ 3.60 (J = 9.6 Hz) and 3.24 (J = 6.9 Hz), respectively, for the H_a proton, which clearly showed the stereo- and regiochemistry of the cycloaddition reaction.

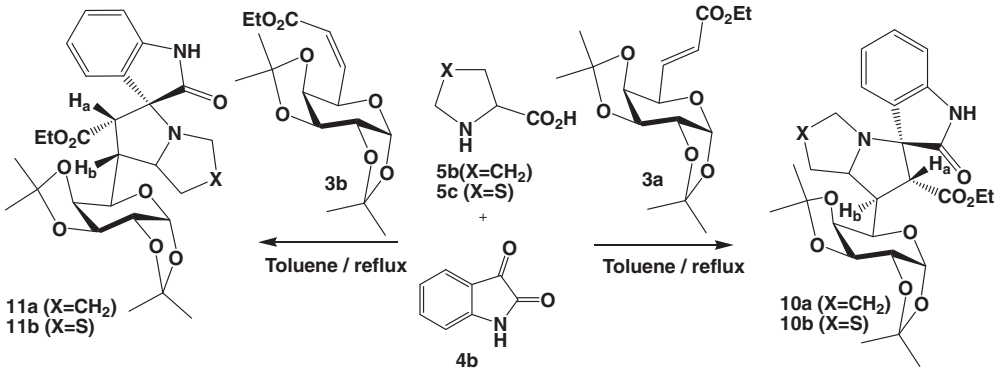
In the H–H COSY spectrum of **6a**, the proton at δ 3.60 (H_a) showed a correlation with the proton at δ 3.26 (H_b), whereas the peak at δ 3.26 (H_b) showed a H–H COSY correlation with the peak at δ 3.95 (Gal-C_5-H) and the peaks at δ 3.15 and δ 3.65 (diastereotropic –CH_2–), which clearly indicated that the signals at δ 3.60 are



Scheme 3. Synthesis of glycopyrrolizidines.



Scheme 4. Synthesis of glycopyrrolizidines.



Scheme 5. Synthesis of spirooxindolopyrrolizidines.

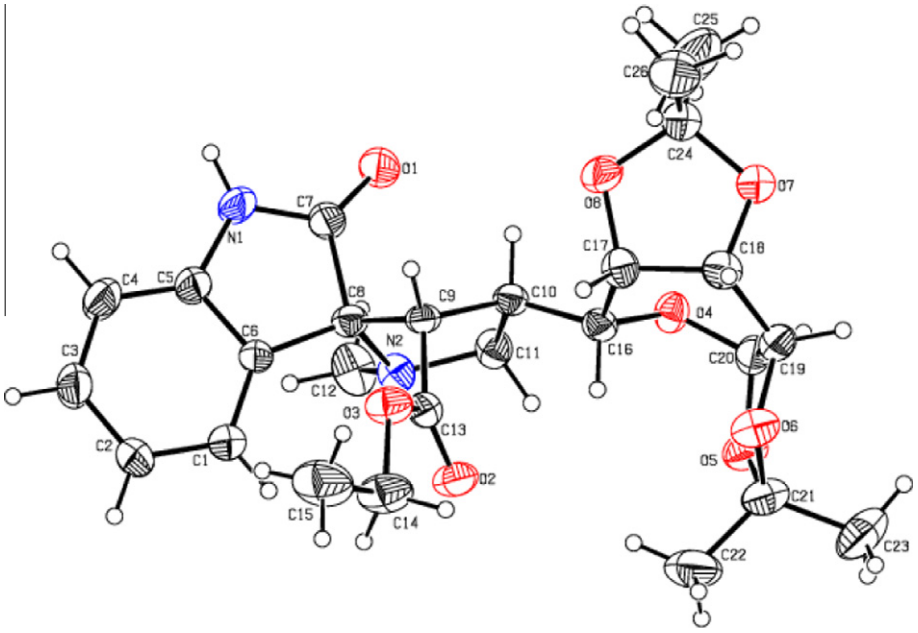


Figure 2. ORTEP diagram of **9b**.

due to the H_a proton and δ 3.26 is due to the H_b proton. The doublet at δ 3.60 (J = 9.6 Hz) and the multiplet at δ 3.26 have an HMBC contour (Fig. 1) with carbons at 169.8 ppm (ester carbonyl carbon) and 75.5 ppm (spiro carbon) which further confirmed the δ values of the H_a and H_b protons, respectively.

Furthermore, the presence of a molecular ion peak at m/z 537 (M^+) in the mass spectrum confirmed the structure of the cycloadduct **6a**.

The same reaction was carried out with cyclic amino acid L-proline **5b** and thiazolidine-4-carboxylic acid **5c** in order to obtain a

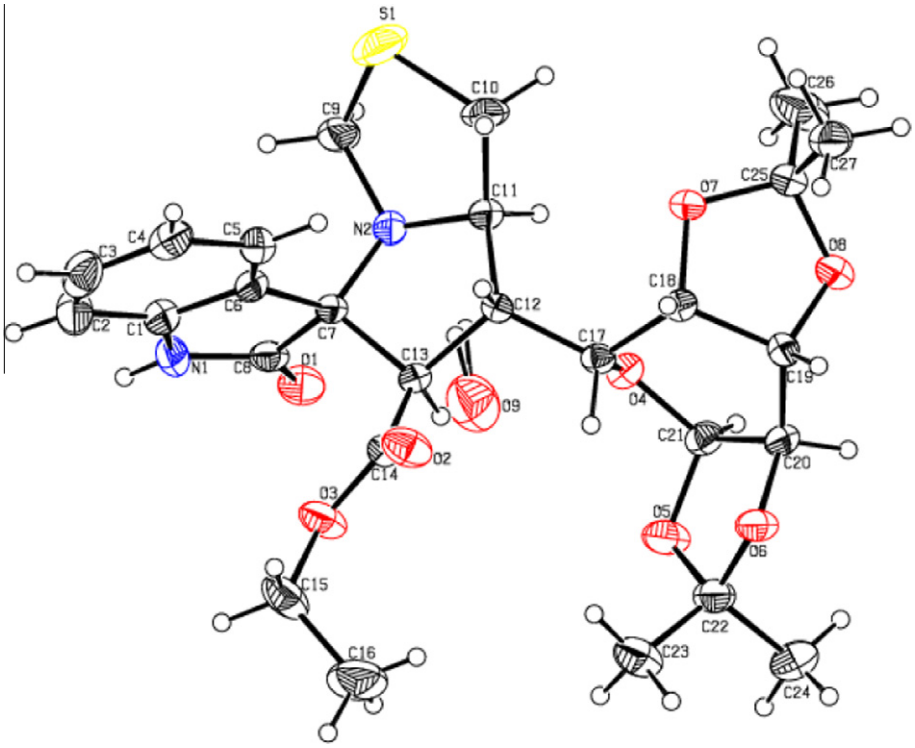


Figure 3. ORTEP diagram of **10b**.

glycospiropyrrolizidines and pyrrolothiazoles,[19] respectively (Scheme 3, Table 2). The structures of the products (**7** and **8**) were confirmed by spectroscopic techniques.

In order to further extend the scope of the reaction, the dipole generated from isatin **4b** (a diketone) and the secondary amino acids **5a–c** reacted with **3a** and **3b** to give novel sugar-derived spirooxindolopyrrolidines (Scheme 5), pyrrolizidines, and pyrrolothiazoles in good yields,[20] respectively (Scheme 4 and 5, Table 2). The structures of the products (**9–11**) were also confirmed by spectroscopic techniques. The ^{1}H NMR spectrum of **9a** exhibited a doublet at δ 3.57 (J = 9.0 Hz) for the H_a proton, which clearly showed the regio- and stereo chemistry of the cycloaddition reaction.

Finally, the regio- and stereochemical outcome of the cycloaddition reaction was confirmed by a single crystal X-ray analysis[21] of the cycloadducts **9b** (Fig. 2) and **10b** (Fig. 3).

In conclusion, we have developed a simple and efficient protocol for the synthesis of sugar-derived heterocycles containing pyrrolidines, pyrrolizidines, and pyrrolothiozoles through 1,3-dipolar cycloaddition methodology. Further work in this direction is in progress.

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17. *General procedure for synthesis cycloadducts* (**6**–**11**): A mixture of diketone (**4a**–**b**) (1 equiv), ethyl 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-6-eno-octopyranuronate (**3a**–**b**) (1 equiv), and a cyclic or acyclic secondary amino acid (**5a**–**c**) (1.2 equiv) was refluxed in dry toluene under N_2 for about 4–6 h under Dean–stark reaction condition to give cycloadduct (**6**–**11**). After the completion of reaction as indicated by TLC, the solvent was evaporated under reduced pressure. The residual mass was dissolved in chloroform (50 mL) and washed with water (50 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give a crude mass. The crude product was purified by column chromatography using hexane/EtOAc (8:2) as an eluent. *(a) Synthesis of trans-1,2:3,4-diisopropylidene-5-C[acenaphthene-1″-onespiro[2″.2′]-(3′-ethoxycarbonyl)-1′-N-methylpyrrolidine]-α-D-galactopyranose* (**6a**): isolated yield: 92% (0.440 g, 0.82 mmol) from 0.30 g of (*E*)-ethyl 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-6-eno-octopyranuronate (0.91 mmol). Yellow solid. Mp = 199 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.12 (t, *J* = 7.2 Hz, 3H); 1.25 (s, 3H); 1.26 (s, 3H); 1.40 (s, 3H); 1.40 (s, 3H); 1.91 (s, 3H); 3.15 (t, *J* = 9.3 Hz, 1H); 3.24–3.28 (m, 1H); 3.34 (q, *J* = 7.2 Hz, 2H); 3.60 (d, *J* = 9.6 Hz, 1H); 3.64–3.67 (m, 1H); 3.94–3.95 (m, 1H); 4.22 (dd, *J* = 1.5, 7.8 Hz, 1H); 4.24–4.27 (m, 1H); 4.56 (dd, *J* = 2.1, 7.8 Hz, 1H); 5.58 (d, *J* = 5.1 Hz, 1H); 7.43 (d, *J* = 6.9 Hz, 1H); 7.53 (t, *J* = 6.9 Hz, 1H); 7.65 (t, *J* = 7.2 Hz, 1H); 7.78 (d, *J* = 8.4 Hz, 1H); 7.89 (d, *J* = 7.2 Hz, 1H); 8.03 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.8, 23.3, 24.1, 24.8, 34.8, 39.4, 53.7, 54.3, 58.9, 66.4, 69.5, 70.1, 72.1, 75.5, 95.7, 107.5, 108.2, 120.1, 121.0, 123.9, 126.9, 127.2, 129.5, 130.5, 131.6, 135.4, 141.2, 169.8, 204.6. IR (KBr) ν_{max}: 1730, 1718 cm^{-1}. HRMS (EI) exact mass calcd for $C_{30}H_{35}NO_8$: 537.2363 (M^+), found 537.2364. Anal. Calcd for $C_{30}H_{35}NO_8$: C, 67.02; H, 6.56; N, 2.61. Found: C, 67.08; H, 6.65; N, 2.63. $[\alpha]_D^{25.8}$ +612.0 (*c* 0.2, $CHCl_3$).
(b) Synthesis of cis-1,2:3,4-diisopropylidene-5-C[acenaphthene-1″-onespiro[2″.2′]-(3′-ethoxycarbonyl)-1′-N-methylpyrrolidine]-α-D-galactopyranose (**6b**): isolated yield: 88% (0.430 g, 0.80 mmol) from 0.30 g of (*Z*)-ethyl 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-6-eno-octopyranuronate (0.91 mmol). Yellow solid. Mp = 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.86 (t, *J* = 7.2 Hz, 3H); 1.27 (s, 3H); 1.35 (s, 3H); 1.49 (s, 3H); 1.66 (s, 3H); 2.14 (s, 3H); 3.24 (d, *J* = 6.9 Hz, 1H); 3.49–3.55 (m, 1H); 3.58–3.62 (m, 2H); 3.75–3.86 (m, 1H); 3.93 (dd, *J* = 2.4, 7.5 Hz, 1H); 3.97–4.00 (m, 1H) 4.24–4.27 (m, 1H); 4.30–4.33 (m, 1H); 4.54 (dd, *J* = 2.4, 7.5 Hz, 1H); 5.55 (d, *J* = 5.1 Hz, 1H); 7.49 (d, *J* = 6.9 Hz,1H); 7.57–7.62 (m, 1H); 7.70–7.75 (m, 1H); 7.85–7.92 (m, 2H); 8.10 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.7, 23.5, 24.1, 25.0, 25.1, 34.8, 36.6, 51.8, 57.0, 59.2, 67.4, 69.4, 69.9, 70.6, 77.7, 95.5, 107.8, 108.4, 120.1, 120.8, 124.1, 127.0, 127.2, 129.5, 129.9, 130.7, 135.6, 141.1, 169.6, 205.8. IR (KBr) ν_{max}: 1730, 1716 cm^{-1}. HRMS (EI) exact mass calcd for $C_{30}H_{35}NO_8$ 537.2363 (M^+), found 537.2360. Anal. Calcd for $C_{30}H_{35}NO_8$: C, 67.02; H, 6.56; N, 2.61. Found: C, 67.10; H, 6.59; N, 2.60. $[\alpha]_D^{27.9}$ +537.6 (*c* 0.2, $CHCl_3$).
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19. *Synthesis of trans-1,2:3,4-diisopropylidene-5-C[acenaphthene-1″-onespiro[2″.2′]-(3′-ethoxycarbonyl)-pyrrolizidine]-α-D-galactopyranose* (**7a**): isolated yield: 86% (0.440 g, 0.78 mmol) from 0.30 g of (*E*)-ethyl 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-6-eno-octopyranuronate (0.91 mmol). Yellow solid. Mp = 174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.03 (t, *J* = 7.2 Hz, 3H); 1.29 (s, 3H); 1.35 (s, 3H); 1.37 (s, 3H); 1.47 (s, 3H); 1.72–1.85 (m, 3H); 2.28–2.38 (m, 2H); 2.52–2.59 (m, 1H); 2.93–3.00 (m, 1H); 3.28 (q, *J* = 7.2 Hz, 2H); 4.01–4.06 (m, 1H); 4.07 (d, *J* = 11.4 Hz, 1H); 4.23–4.33 (m, 3H); 4.61 (dd, *J* = 2.1, 8.1 Hz, 1H); 5.61 (d, *J* = 5.1 Hz, 1H); 7.50 (d, *J* = 6.9 Hz, 1H); 7.62 (t, *J* = 8.1 Hz, 1H); 7.73 (t, *J* = 8.1 Hz, 1H); 7.85 (d, *J* = 8.4 Hz, 1H); 8.01 (d, *J* = 6.9 Hz, 1H); 8.09 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.9, 22.8, 23.3, 23.9, 24.1, 26.5, 32.0, 45.8, 45.9, 55.6, 58.0, 64.2, 64.5, 64.6, 69.0, 69.6, 71.6, 95.0, 106.6, 107.4, 119.8, 121.1, 123.3, 126.2, 126.3, 126.4, 128.8, 129.6, 130.7, 135.2, 169.0, 204.8. HRMS (EI) exact mass calcd for $C_{32}H_{37}NO_8$ 564.2597 $(M+H)^+$, found 564.2594. IR (KBr) ν_{max}: 1730, 1716 cm^{-1}. Anal. Calcd for $C_{32}H_{37}NO_8$: C, 68.19; H, 6.62; N, 2.49. Found: C, 68.21; H, 6.69; N, 2.40. $[\alpha]_D^{27.7}$ +277.8 (*c* 0.2, $CHCl_3$).
20. *Synthesis of trans-1,2:3,4-diisopropylidene-5-C[spiro[2′.3″]oxindolo-3′-ethoxycarbonyl-1′-N-methylpyrrolidine]-α-D-galactopyranose* (**9a**): isolated yield: 84% (0.380 g, 0.76 mmol) from 0.30 g of (*E*)-ethyl 6,7 dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-6-eno-octopyranuronate (0.91 mmol). Colorless solid. Mp = 130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.79 (t, *J* = 7.2, 3H); 1.31 (s, 3H); 1.32 (s, 3H); 1.45 (s, 3H); 1.47 (s, 3H); 2.07 (s, 3H); 3.15 (t, *J* = 9 Hz, 1H); 3.21–3.31 (m, 1H); 3.57 (d, *J* = 9.0 Hz, 1H); 3.60–3.63 (m, 1H); 3.70–3.81 (m, 2H); 3.96 (d, *J* = 3.9 Hz, 1H); 4.25–4.28 (m, 1H); 4.31 (dd, *J* = 1.8, 5.1, 1H); 4.61 (dd, *J* = 1.5, 7.8 Hz, 1H); 5.61 (d, *J* = 5.1 Hz, 1H); 6.88 (d, *J* = 7.5 Hz, 1H); 6.98 (t, *J* = 7.5 Hz, 1H); 7.17–7.24 (m, 2H); 8.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.5, 24.4, 25.1, 25.8, 35.4, 40.4, 54.3, 54.9, 60.4, 67.6, 70.6, 71.1, 72.9, 73.0, 96.7, 108.5, 109.2, 109.9, 122.3, 125.6, 126.8, 129.1, 141.3, 170.7, 179.1. IR (KBr) ν_{max}: 3296, 1730, 1710 cm^{-1}. HRMS (EI) exact mass calcd for $C_{26}H_{34}N_2O_8$: 503.2393 $(M+H)^+$ found 503.2399. Anal. Calcd for $C_{26}H_{34}N_2O_8$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.19; H, 6.94; N, 5.65. $[\alpha]_D^{28.4}$ −34.2 (*c* 0.2, $CHCl_3$).
21. The detailed X-ray crystallographic data (CCDC numbers for **9a** and **10b** are 763779 and 763778, respectively) are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.