Application of Azomethine Ylides in the Synthesis of Carbohydrate-Derived Spiroheterocycles

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Abstract: A series of sugar-fused spiro-pyrrolidine, -pyrrolizidine, and -indolizidine heterocycles were synthesized through a unique application of a 1,3-dipolar cycloaddition reaction of an azomethine ylide with a carbohydrate-derived olefin. The 1,3-dipoles synthesized from secondary α-amino acids (sarcosine, proline, or pipecolinic acid) and 1,2-diketones (isatin or acenaphthoquinone), upon reaction with the olefin, gave the corresponding cycloaddition products in good-to-very good yields.

Key words: heterocycles, spiro compounds, carbohydrates, ylides, cycloadditions

Carbohydrate-based heterocycles have always attracted the attention of organic chemists and biologists[1] because of their promising bioactivities,[2] which include antiviral,[3] antimicrobial[4] and antitumor[5] activities. Such heterocycles have also been shown to be potentially useful as drugs for the treatment of several diseases, such as influenza H1N1,[6] HIV,[7] or cancer.[8] The synthesis of newer classes of carbohydrate-based heterocycles has therefore recently become an interesting field of research. Spiro-pyrrolidine-oxindole heterocycles are found in a range of bioactive entities of both synthetic and natural origin.[9] They occur as important motifs in a number of naturally occurring alkaloids, such as rhynchophylline,[10a] formosanine,[10b] horsfiline,[10c] elacomine,[10d] and spirotryprostatins A and B[10e,f] (Figure 1), which are known to possess moderate-to-high biological activities. In addition, some spiro-oxindole analogues are also known to display inhibitory activities against poliovirus, rhinovirus 3C-proteinase, and aldose reductase.[11] Although the synthesis of the spiro-oxindole core has been realized in a number of ways, the most notable advance was made by Grigg and his co-workers,[12] who were first to demonstrate a new approach to the synthesis of such spiro-pyrrolidine-oxindole skeletons by utilizing the well-known 1,3-dipolar azomethine ylide cycloaddition reaction. Since then, the azomethine ylide cycloaddition reaction has become one of the most popular approaches to the construction of the spiro-pyrrolidine-oxindole ring system, and a number of natural products such as (±)-horsfiline, (±)-coerulescine, and spirotryprostatin B, as well as some sugar-based spiro-oxindoles have been successfully synthesized by utilizing this key step.[13]

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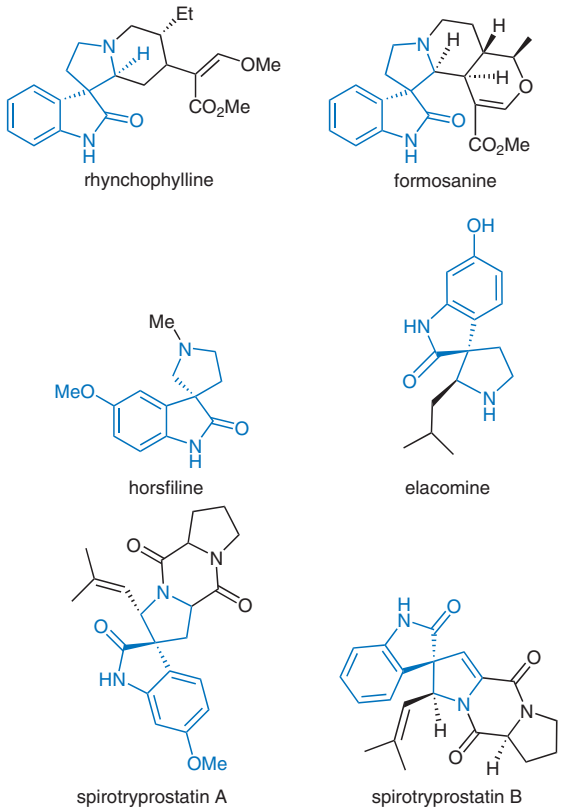
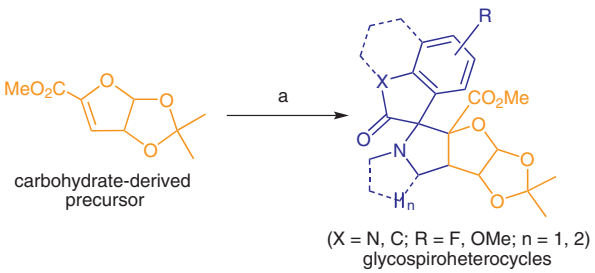


Figure 1 Some spiro-oxindole-containing alkaloids

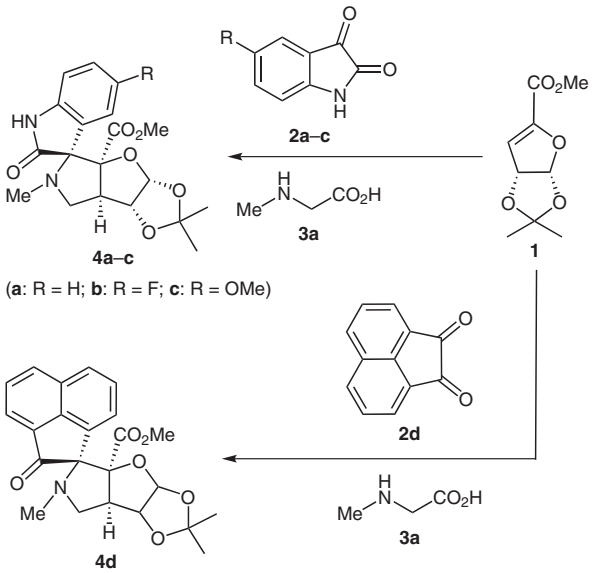
Prompted by reports on the structural features and biological activity of these molecules, we contemplated fusing structurally unique spiro-pyrrolidine-oxindole motifs with properly functionalized glycoside derivatives, on the assumption that fusion might lead to a new class of carbohydrate-based heterocycles with potential biological activities. Towards this end, we report, for the first time, a simple and short approach to a new series of sugar-fused spiro-oxindole and spiro-acenaphthylenone derivatives by using secondary α-amino acids (sarcosine, proline, or pipecolinic acid) and 1,2-diketones (isatin or acenaphthoquinone) to generate azomethine ylides that react with a sugar-derived precursor (Scheme 1).

To begin with, the α,β-unsaturated carbohydrate-derived ester **1**[14] was exposed to the azomethine ylide generated in situ from isatin (**2a**) and sarcosine (**3a**) to give the spiro heterocycle **4a** (Scheme 2). The effects of solvents on this particular [3+2] cycloaddition reaction were studied, taking ester **1**, isatin (**2a**), and sarcosine (**3a**) as the model

substrates. Whereas no reaction occurred in methanol or acetonitrile (Table 1, entries 4 and 5), the use of toluene as the solvent gave the corresponding cycloadduct **4a** in 83% yield (entry 1), compared with 30% in *N*,*N*-dimethylformamide and 51% in benzene (entries 2 and 3).



Scheme 1 *Reagents and conditions*: (a) *cis*-1,2-diketone **2a**, α-amino acid **3a**, toluene, reflux.



Scheme 2 Synthesis of glycospiro-pyrrolidine-oxindoles and a spiro-pyrrolidine-acenaphthylenone

Table 1 Effects of the Solvent on the Yield of the Cycloaddition Reaction

Entry	Solvent[a]	Temp (°C)	Time (h)	Yield (%)[b]
1	toluene	reflux	12	83
2	benzene	reflux	10	51
3	DMF	120	10	30
4	MeCN	reflux	12	nr[c]
5	MeOH	reflux	12	nr

[a] All the reactions were performed by using **1**, **2a**, and **3a**.
[b] Isolated yield.
[c] nr = No reaction.

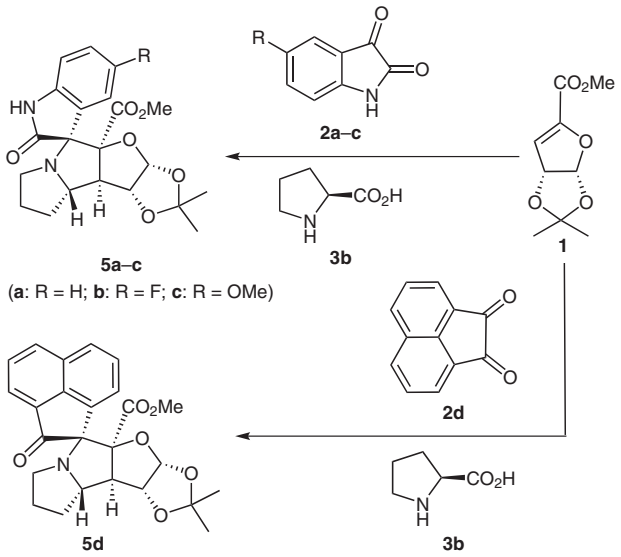
With this initial success, we decided to replace **2a** (R = H) with other derivatives **2b** (R = F) and **2c** (R = OMe) while keeping the amino acid unchanged. Upon reaction, the respective cycloaddition products **4b** and **4c** were isolated and characterized (Scheme 2). It was interesting to note that the presence of an electron-withdrawing substituent in the isatin moiety reduced the overall yield slightly, whereas an electron-donating substituent produced a marginal improvement in the yield of the glycospiro-pyrrolidine-oxindole adduct (Table 2, entries 1–3).

Table 2 Synthesis of Sugar-Fused Spiro-Heterocycles through [3+2] Cycloaddition Reactions

Entry	1,2-Diketone	α-Amino acid[a]	Product	Time (h)	Yield (%)[b]
1	**2a** (X = H)	**3a**	**4a**	12	83
2	**2b** (X = F)	**3a**	**4b**	14	78
3	**2c** (X = OMe)	**3a**	**4c**	11	85
4	**2d**	**3a**	**4d**	11	82
5	**2a** (X = H)	**3b**	**5a**	11	81
6	**2b** (X = F)	**3b**	**5b**	12	75
7	**2c** (X = OMe)	**3b**	**5c**	11	83
8	**2d**	**3b**	**5d**	10	79
9	**2a** (X = H)	**3c**	**6a**	14	81
10	**2a** (X = H)	**3b**	**7a**	14	70

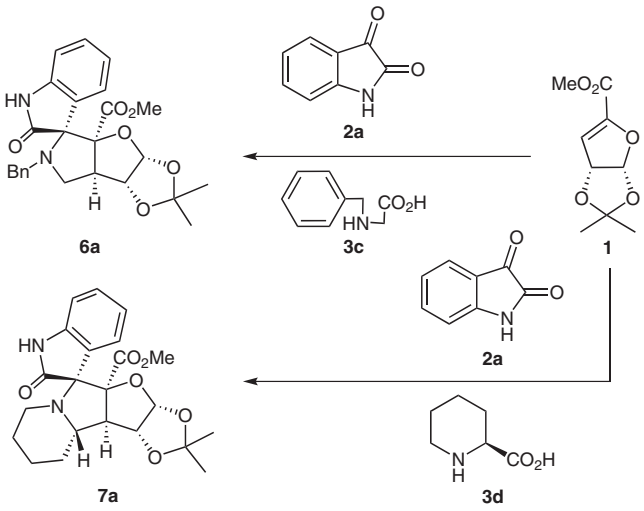
[a] All reactions were performed in refluxing toluene.
[b] Isolated yield.

Similar observations were made when sarcosine was replaced with L-proline **3b** (Scheme 3) and the reactions with **2a–c** were performed under optimal conditions to generate a series of glycospiro-pyrrolizidine-oxindoles **5a–c** (Table 2, entries 5–7) in reduced yields. We assume that an increase in steric crowding due to the presence of a five-membered ring is the yield-determining factor.



Scheme 3 Synthesis of glycospiro-pyrrolizidine-oxindoles and a spiro-pyrrolizidine-acenaphthylenone

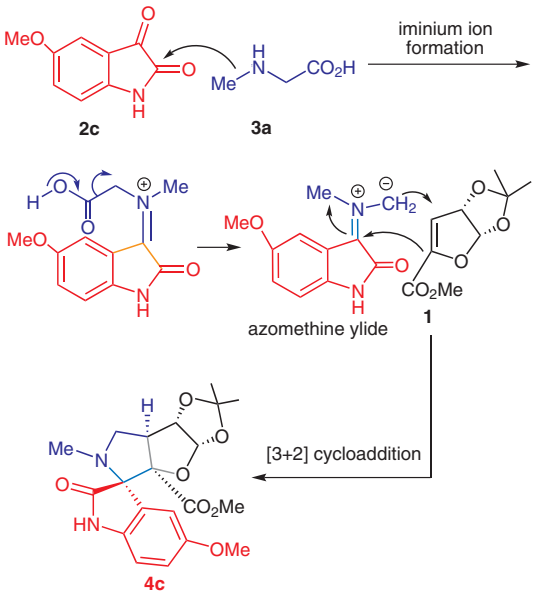
To establish the generality of the method, we replaced the isatin derivatives with acenaphthoquinone (**2d**); the products isolated were **4d** (82% with sarcosine) (Scheme 2) and **5d** (79% with proline) (Scheme 3) (Table 2, entries 4 and 8, respectively). When sarcosine and proline were replaced with *N*-benzylglycine (**3c**) or pipecolonic acid (**3d**), the cycloaddition products with isatin were identified as **6a** (81%) and **7a** (70%), respectively (Scheme 4; Table 2, entries 9 and 10).



Scheme 4 Synthesis of glycospiro-pyrrolidine-oxindole and spiro-indolizidine-oxindole

From mechanistic considerations, it is accepted that an intermediate imminium ion[12] is formed by the reaction of **2c** with **3a** (Scheme 5); this is followed by rapid decarboxylation to form the azomethine ylide, which undergoes cycloaddition reaction with dipolarophile **1** to give the cycloadduct **4c**. The azomethine ylide probably attacks **1** from the face opposite to that of the acetal linkage to avoid steric crowding, thereby projecting the ester group and H_a on the α-face. Furthermore, to avoid dipolar repulsion between the amide carbonyl and the ester carbonyl in **4c**, the amide keto group will go to the β-face, and the product is expected to have the structure shown in Figure 2.

The absence of a signal for an olefinic proton and the presence of two triplet signals at δ = 3.42 and 3.51 ppm for the *N*-methylene protons of the pyrrolidine moiety and another triplet signal at δ = 3.83 ppm for the adjacent methine proton (ring-juncture) in the ^{1}H NMR spectrum of **4c** proved that a cyclization involving the olefin and the azomethine ylide had indeed taken place. This was confirmed by the presence of two other singlets at δ = 2.20 and 3.46 ppm for the *N*-methyl and methoxycarbonyl groups, respectively, of the fused pyrrolidine moiety. The peaks at δ = 50.7, 54.5, and 79.2 ppm in the ^{13}C NMR spectrum of **4c** were characteristic of methylene, methane, and spiro carbons, respectively; sharp and intense peaks at δ = 52.4 and 35.4 ppm were allocated to the methoxycarbonyl and *N*-methyl carbons, respectively. ^{1}H–^{1}H correlation spectroscopy (COSY), ^{1}H–^{13}C heteronuclear single



Scheme 5 Probable mechanistic pathway

quantum coherence spectroscopy (HSQC), and ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC) permitted the clear identification of most of the signals, thereby establishing the disposition of the atoms in the pentacyclic framework in **4c**. The spiro carbon (δ = 79.2 ppm) showed an HMBC correlation with H_b (δ = 3.42 ppm), H_c (δ = 3.51 ppm), *N*-methyl protons (δ = 2.20 ppm), and methoxycarbonyl protons (δ = 3.46 ppm). Furthermore, a similar correlation of H_a (δ = 3.83 ppm) with methylene carbon (δ = 54.5 ppm) and ester carbonyl (δ = 170.3 ppm) confirmed the structure of the product. Crucial evidence for the stereochemistry was obtained by nuclear Overhauser effect spectroscopy (NOESY). The aromatic H_f (δ = 6.70 ppm) showed a NOESY relationship with the methoxycarbonyl protons (δ = 3.46 ppm) (Figure 2), indicating that the aromatic moiety and the ester group are disposed in the same plane. A few more characteristic NOESY correlations of H_a with H_b, of H_c with H_d, and of H_d with H_c are clearly visible, indicating the close proximity of these atoms in space.

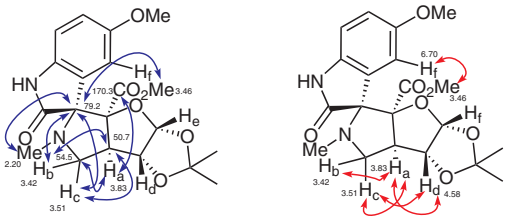


Figure 2 Characteristic HMBC (blue) and NOESY (red) correlations of **4c**

In conclusion, we have developed a simple synthesis of glycospiro-pyrrolidines, -pyrrolizidines, and -indolizidines from a carbohydrate-derived precursor by a 1,3-dipolar cycloaddition reaction of a series of azomethine ylides generated in situ in a one-pot sequence. The struc-

tural resemblance of the products to a number of naturally occurring bioactive alkaloids may lead to the identification of newer structural motifs with potential biological activities. To the best of our knowledge, this is the first report of the synthesis of sugar-fused spiroheterocycles with an attached oxindole/acenaphthylenone core by means of 1,3-dipolar azomethine ylide cycloaddition reactions.

Melting points were recorded in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as the internal standard. Mass spectra were recorded in ESI mode. Optical rotations were measured at 589 nm. TLC was performed on precoated plates (0.2 mm, silica gel 60 F_{254}). All solvents were distilled and purified as necessary.

Glyco Spiro Heterocycles 4–7; General Procedure

A mixture of diketone **2a–d** (0.275 mmol, 1.1 equiv), α-amino acid **3a–d** (0.275 mmol, 1.1 equiv), and the carbohydrate-derived olefin **1** (0.25 mmol, 1.0 equiv) in toluene (10 mL) was refluxed under N_2 for 12 h. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography [silica gel (100–200 mesh), EtOAc–PE (1:4)].

Methyl (3a*S*,4a*R*,6*S*,7a*S*,7b*S*)-2,2,7-Trimethyl-2′-oxo-1′,2′,3a,7,7a,7b-hexahydrospiro[1,3-dioxolo[4,5]furo[3,2-*b*]pyrrole-6,3′-indole]-4a(5*H*)-carboxylate (4a)

Yellow gum; yield: 83%; $[\alpha]_D^{25}$ –73.8 (*c* 0.6, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.37 (s, 3 H), 2.19 (s, 3 H), 3.40 (s, 3 H), 3.43 (t, *J* = 9.0 Hz, 1 H), 3.49 (t, *J* = 9.0 Hz, 1 H), 3.84 (t, *J* = 9.0 Hz, 1 H), 4.58 (d, *J* = 3.6 Hz, 1 H), 6.12 (d, *J* = 3.0 Hz, 1 H), 6.75 (d, *J* = 7.8 Hz, 1 H), 6.98 (br t-like, *J* = 7.8 Hz, 1 H), 7.08 (br d, *J* = 7.2 Hz, 1 H), 7.21 (dt, *J* = 1.2, 7.8 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.9 (CH_3), 27.3 (CH_3), 35.3 (CH_3), 50.6 (CH), 52.3 (CH_3), 54.5 (CH_2), 78.8 (C), 83.4 (CH), 100.2 (C), 109.4 (CH), 109.4 (C), 109.7 (CH), 113.5 (C), 122.3 (CH), 125.3 (CH), 129.7 (CH), 141.7 (C), 170.2 (C), 176.0 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{22}N_2NaO_6$: 397.1376; found: 397.1362.

Methyl (3a*S*,4a*R*,6*S*,7a*S*,7b*S*)-5′-Fluoro-2,2,7-trimethyl-2′-oxo-1′,2′,3a,7,7a,7b-hexahydrospiro[1,3-dioxolo[4,5]furo[3,2-*b*]pyrrole-6,3′-indole]-4a(5*H*)-carboxylate (4b)

Light brown gum; yield: 78%; $[\alpha]_D^{25}$ –94.0 (*c* 0.13, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.38 (s, 3 H), 2.19 (s, 3 H), 3.41(t, *J* = 9.0 Hz, 1 H), 3.48 (m, 4 H), 3.82 (t-like, *J* = 8.4, 9.6 Hz, 1 H), 4.57 (d, *J* = 3.0 Hz, 1 H), 6.11 (d, *J* = 3.6 Hz, 1 H), 6.69 (dd, *J* = 4.2, 8.4 Hz, 1 H), 6.85 (dd, *J* = 2.4, 7.8 Hz, 1 H), 6.92 (dt, *J* = 2.4, 8.4 Hz, 1 H), 7.34 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.8 (CH_3), 27.3 (CH_3), 35.3 (CH_3), 50.7 (CH), 52.4 (CH_3), 54.4 (CH_2), 79.1 (C), 83.2 (CH), 100.1 (C), 109.5 (CH), 110.2 (CH), 113.3 (CH), 113.6 (C), 116.2 (CH), 127.4 (C), 137.7 (C), 158.0 (C), 170.1 (C), 176.1 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{21}FN_2NaO_6$: 415.1281; found: 415.1269.

Methyl (3a*S*,4a*R*,6*S*,7a*S*,7b*S*)-5′-Methoxy-2,2,7-trimethyl-2′-oxo-1′,2′,3a,7,7a,7b-hexahydrospiro[1,3-dioxolo[4,5]furo[3,2-*b*]pyrrole-6,3′-indole]-4a(5*H*)-carboxylate (4c)

Light brown gum; yield: 85%; $[\alpha]_D^{25}$ –65.1 (*c* 0.42, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.37 (s, 3 H), 2.20 (s, 3 H), 3.42(t, *J* = 9.0 Hz, 1 H), 3.46 (s, 3 H), 3.51 (t, *J* = 9.0 Hz, 1 H), 3.76 (s, 3 H), 3.83 (t, *J* = 9.0 Hz, 1 H), 4.58 (d, *J* = 3.6 Hz, 1 H), 6.13 (d, *J* = 3.0 Hz, 1 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 6.70 (d, *J* = 2.4 Hz, 1 H), 6.75 (dd, *J* = 3.0, 8.4 Hz, 1 H), 7.35 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.9 (CH_3), 27.3 (CH_3), 35.4 (CH_3), 50.7 (CH), 52.4 (CH_3), 54.5 (CH_2), 55.8 (CH_3), 79.2 (C), 83.4 (CH), 100.2 (C), 109.5 (CH), 110.3 (CH), 111.5 (CH), 113.5 (C), 115.1 (CH), 126.7(C), 135.1 (C), 155.6 (C), 170.3 (C), 176.2 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{24}N_2NaO_7$: 427.1481; found: 427.1465.

Methyl (1*S*,3a′*S*,4a′*R*,7a′*S*,7b′*S*)-2′,2′,7′-Trimethyl-2-oxo-3a′,7′,7a′,7b′-tetrahydro-2*H*-spiro[acenaphthylene-1,6′-[1,3]dioxolo[4,5]furo[3,2-*b*]pyrrole]-4a′(5′*H*)-carboxylate (4d)

Yellow gum; yield: 82%; $[\alpha]_D^{25}$ –130.7 (*c* 0.14, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.33 (s, 6 H), 2.17 (s, 3 H), 3.20 (s, 3 H), 3.53 (t, *J* = 9.6 Hz, 1 H), 3.62 (t, *J* = 9.6 Hz, 1 H), 3.94 (t, *J* = 9.0 Hz, 1 H), 4.65 (d, *J* = 2.4 Hz, 1 H), 6.07 (d, *J* = 3.0 Hz, 1 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 7.71 (t, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.87 (d, *J* = 7.2 Hz, 1 H), 8.07 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.8 (CH_3), 27.3 (CH_3), 35.2 (CH_3), 50.8 (CH), 52.0 (CH_3), 55.0 (CH_2), 81.9 (C), 83.5 (CH), 100.6 (C), 108.8 (CH), 113.5 (C), 121.2 (CH), 121.5 (CH), 125.4 (CH), 128.1 (CH), 128.3 (CH), 130.4 (C), 131.4 (CH), 132.3 (C), 135.4 (C), 142.7 (C), 170.4 (C), 204.2 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{23}NaNO_6$: 432.1423; found: 432.1409.

Methyl (3a*R*,4a*S*,5*R*,9a*S*,9b*R*,9c*R*)-2,2-Dimethyl-2′-oxo-1′,2′,7,8,9,9a,9b,9c-octahydrospiro[1,3-dioxolo[4,5]furo[3,2-*a*]pyrrolizine-5,3′-indole]-4a(3a*H*)-carboxylate (5a)

Yellow gum; yield: 81%; $[\alpha]_D^{25}$ –85.3 (*c* 0.53, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.35 (s, 3 H), 1.78–1.84 (m, 1 H), 1.86–1.94 (m, 1 H), 2.03–2.08 (m, 1 H), 2.19–2.24 (m, 1 H), 2.73 (dt, *J* = 3.0, 7.8 Hz, 1 H), 3.03 (q, *J* = 8.4 Hz, 1 H), 3.37 (s, 3 H), 3.46 (d, *J* = 8.4 Hz, 1 H), 4.14 (m, 1 H), 4.61 (d, *J* = 3.0 Hz, 1 H), 6.16 (d, *J* = 3.6 Hz, 1 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 6.96 (t, *J* = 7.8 Hz, 1 H), 7.17 (d, *J* = 7.2 Hz, 1 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 7.94 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.1 (CH_2), 26.5 (CH_3), 26.8 (CH_3), 29.8 (CH_2), 46.9 (CH_2), 52.2 (CH_3), 58.2 (CH), 66.0 (CH), 77.3 (C), 82.9 (CH), 103.3 (C), 108.9 (CH), 110.0 (CH), 113.0 (C), 121.7 (CH), 124.9 (C), 126.6 (CH), 129.7 (CH), 141.8 (C), 170.9 (C), 177.0 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{24}N_2NaO_6$: 423.1532; found: 423.1548.

Methyl (3a*R*,4a*S*,5*R*,9a*S*,9b*R*,9c*R*)-5′-Fluoro-2,2-dimethyl-2′-oxo-1′,2′,7,8,9,9a,9b,9c-octahydrospiro[1,3-dioxolo[4,5]furo[3,2-*a*]pyrrolizine-5,3′-indole]-4a(3a*H*)-carboxylate (5b)

Light brown gum; yield: 75%; $[\alpha]_D^{25}$ –59.1 (*c* 0.12, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.35 (s, 3 H), 1.78–1.82 (m, 1 H), 1.92–1.95 (m, 1 H), 2.08–2.10 (m, 1 H), 2.19–2.21 (m, 1 H), 2.72 (br t, *J* = 5.4, 7.8 Hz, 1 H), 3.03(q, *J* = 8.4 Hz, 1 H), 3.43 (d, *J* = 9.0 Hz, 1 H), 3.46 (s, 3 H), 4.15 (q, *J* = 7.2 Hz, 1 H), 4.59 (d, *J* = 3.0 Hz, 1 H), 6.13 (d, *J* = 3.0 Hz, 1 H), 6.73 (m, 1 H), 6.95 (m, 2 H), 7.43 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.9 (CH_2), 26.5 (CH_3), 26.9 (CH_3), 29.7 (CH_2), 46.4 (CH_2), 52.4 (CH_3), 58.3 (CH), 65.8 (CH), 77.2 (C), 82.6 (CH), 103.5 (C), 109.2 (CH), 110.3 (CH), 113.3 (C), 114.5 (CH), 116.2 (CH), 127.8 (C), 137.6 (C), 157.6 (C), 170.9 (C), 176.8 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{23}FN_2NaO_6$: 441.1438; found: 441.1456.

Methyl (3a*R*,4a*S*,5*R*,9a*S*,9b*R*,9c*R*)-5′-Methoxy-2,2-dimethyl-2′-oxo-1′,2′,7,8,9,9a,9b,9c-octahydrospiro[1,3-dioxolo[4,5]furo[3,2-*a*]pyrrolizine-5,3′-indole]-4a(3a*H*)-carboxylate (5c)
Light brown gum; yield: 83%; $[\alpha]_D^{25}$ –29.5 (*c* 0.12, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.35 (s, 3 H), 1.76–1.82 (m, 1 H), 1.88–1.93 (m, 1 H), 2.04–2.09 (m, 1 H), 2.17–2.22 (m, 1 H), 2.72 (dt, *J* = 3.0, 8.4 Hz, 1 H), 2.99 (q, *J* = 8.4 Hz, 1 H), 3.42 (s, 3 H), 3.45 (d, *J* = 9.0 Hz, 1 H), 3.76 (s, 3 H), 4.12 (q-like, *J* = 6.6, 8.4 Hz, 1 H), 4.61 (d, *J* = 3.0 Hz, 1 H), 6.16 (d, *J* = 3.0 Hz, 1 H), 6.72–6.81 (m, 3 H), 7.94 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.2 (CH_2), 26.5 (CH_3), 26.8 (CH_3), 29.8 (CH_2), 46.5 (CH_2), 52.2 (CH_3), 55.9 (CH_3), 57.9 (CH), 66.0 (CH), 77.4 (C), 82.9 (CH), 103.4 (C), 109.0 (CH), 110.3 (CH), 113.0 (C), 113.8 (CH), 114.4 (CH), 126.2 (C), 135.1 (C), 155.1 (C), 170.8 (C), 177.1 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{26}N_2NaO_7$: 453.1638; found: 453.1619.

Methyl (1*R*,3a′*R*,4a′*S*,9a′*S*,9b′*R*,9c′*R*)-2′,2′-Dimethyl-2-oxo-7′,8′,9′,9a′,9b′,9c′-hexahydro-2*H*-spiro[acenaphthylene-1,5′-[1,3]dioxolo[4,5]furo[3,2-*a*]pyrrolizine]-4a′(3a′*H*)-carboxylate (5d)
Yellow gum; yield: 79%; $[\alpha]_D^{25}$ –169.6 (*c* 0.57, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.31 (s, 3 H), 1.86–1.96 (m, 2 H), 2.05–2.11 (m, 1 H), 2.23–2.29 (m, 1 H), 2.78 (br t-like, *J* = 6.6 Hz, 1 H), 3.19 (s, 3 H), 3.24 (m, 1 H), 3.54 (d, *J* = 9.0 Hz, 1 H), 4.26–4.33 (m, 1 H), 4.67 (d, *J* = 3.0 Hz, 1 H), 6.11 (d, *J* = 3.0 Hz, 1 H), 7.49 (d, *J* = 6.9 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.71 (t, *J* = 7.5 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 8.05 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9 (CH_2), 26.5 (CH_3), 26.8 (CH_3), 29.8 (CH_2), 47.6 (CH_2), 51.9 (CH_3), 59.1 (CH), 66.1 (CH), 80.7 (C), 82.9 (CH), 103.7 (C), 108.6 (CH), 113.0 (C), 122.1 (CH), 123.1 (CH), 125.6 (CH), 127.6 (CH), 128.3 (CH), 130.6 (C), 131.2 (CH), 132.0 (C), 135.0 (C), 142.3 (C), 171.5 (C), 202.4 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{25}H_{25}NO_6Na$: 458.1580; found: 458.1570.

Methyl (3a*R*,4a*S*,5*R*,7a*R*,7b*R*)-6-Benzyl-2,2-dimethyl-2′-oxo-1′,2′,6,7,7a,7b-hexahydrospiro[1,3-dioxolo[4,5]furo[2,3-*c*]pyrrole-5,3′-indole]-4a(3a*H*)-carboxylate (6a)
Yellow gum; yield: 71%; $[\alpha]_D^{25}$ –40.4 (*c* 0.22, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.37 (s, 3 H), 3.25–3.31 (m, 2 H), 3.38 (s, 3 H), 3.42 (d, *J* = 13.2 Hz, 1 H), 3.48 (d, *J* = 13.2 Hz, 1 H), 3.78 (t, *J* = 9.6 Hz, 1 H), 4.48 (d, *J* = 2.4 Hz, 1 H), 6.14 (d, *J* = 3.0 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 6.99 (dt, *J* = 0.6, 7.2 Hz, 1 H), 7.19–7.33 (m, 7 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.8 (CH_3), 27.3 (CH_3), 50.2 (CH), 50.9 (CH_2), 52.2 (CH_3), 52.9 (CH_2), 78.8 (C), 83.2 (CH), 99.9 (C), 109.3 (CH), 109.6 (CH), 113.6 (C), 122.3 (CH), 125.4 (CH), 126.2 (C), 127.2 (CH), 128.3 (4 × CH), 129.7 (CH), 138.2 (C), 141.9 (C), 170.1 (C), 176.3 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{25}H_{26}N_2NaO_6$: 473.1689; found: 473.1675.

Methyl (3a*R*,4a*S*,5*R*,10a*S*,10b*R*,10c*R*)-2,2-Dimethyl-2′-oxo-1′,2′,3a,7,8,9,10,10a,10b,10c-decahydro-4a*H*-spiro[1,3-dioxolo[4,5]furo[3,2-*a*]indolizine-5,3′-indole]-4a-carboxylate (7a)
White solid; yield: 80%; mp: 244–246 °C; $[\alpha]_D^{25}$ –150.9 (*c* 0.14, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.36 (s, 3 H), 1.40–1.56 (m, 4 H), 1.78–1.83 (m, 1 H), 2.01 (br d, *J* = 10.8 Hz, 1 H), 2.34–2.38 (m, 2 H), 3.34 (s, 3 H), 3.39 (m, 2 H.), 4.51 (d, *J* = 3.0 Hz, 1 H), 6.08 (d, *J* = 3.0 Hz, 1 H), 6.72 (d, *J* = 7.5 Hz, 1 H), 6.95 (t, *J* = 7.5 Hz, 1 H), 7.06 (d, *J* = 7.2 Hz, 1 H), 7.18 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.23 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7 (CH_2), 25.2 (CH_2), 26.7 (CH_3), 27.3 (CH_3), 31.5 (CH_2), 45.9 (CH_2), 52.0 (CH_3), 57.1 (CH), 60.3 (CH), 78.9 (C), 82.0 (CH), 98.7 (C), 109.4 (CH), 109.5 (CH), 113.4 (C), 122.0 (CH), 125.1 (CH), 126.3 (C), 129.4 (CH), 142.0 (C), 170.3 (C), 176.5 (C).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{26}N_2O_6Na$: 437.1689; found: 437.1699.

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