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Assembly of *N*-substituted pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones via copper catalyzed aryl amination

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ABSTRACT

Copper-catalyzed amination of *N*-heterocycle derived aryl iodides followed by intramolecular condensative cyclization afforded *N*-substituted pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-diones with good yields. By varying primary amines and substituents at aromatic ring of aryl iodides, a wide range of these heterocycles were assembled.

1. Introduction

In recent years, a considerable number of reports[1–7] have revealed that pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (PBD) is an important core structure for pharmaceutical design. The successful examples include compound **1** (Fig. 1) that has growth hormone releasing activity,[1] protein PLK1 inhibitor **2**,[2] ST2806 (**3**) that shows inhibitory activity to myeloid differentiation factor 88,[3] as well as protein thioesterase 1 (APT1) inhibitor **4**.[4] Additionally, PBDs have been used as the key intermediates for synthesis of several natural antibiotics and designed antitumor agents.[8]

Since N-functionalization of PBDs plays a key role to obtain diverse and bioactive derivatives, the development of powerful methods for preparing *N*-substituted PBDs (**A**, Fig. 2) is highly desired. Although direct alkylation of *N*-unsubstituted PBDs (**B**) is the most popular and widely used method for synthesizing *N*-substituted PBDs, it suffers from low yields when less reactive alkylating reagents are used.[3,4,9,10] In some cases special reactions have to be employed to achieve this transformation.[11] On the other hand, methods for elaboration of *N*-unsubstituted PBDs are limited. These tricyclic compounds have often been obtained via a condensation/cyclization process of isatoic anhydrides (**C**) with proline derivatives,[9,12] or a reduction/cyclization process of nitro or azido compounds **D**.[10,13] In these cases multi-step synthesis is generally

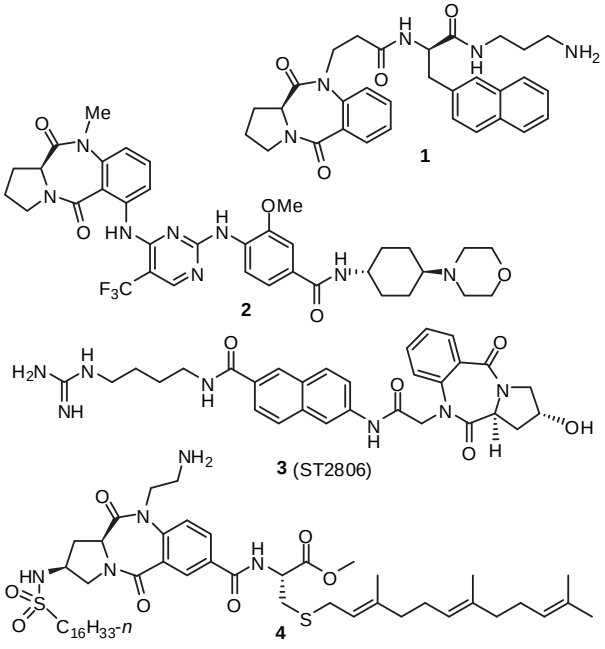

Figure 1. Some representative bioactive molecules with PBD core structure.

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required because some starting materials are not conveniently available (Fig. 2).

During the studies on the synthesis of heterocycles via copper-catalyzed cross-coupling reactions,[14,15] we became interested in aryl amination of aryl halides **E** that possess a proline core linked by an amide bond. We envisaged that after the amination took place, cyclization would occur via an intramolecular amide formation. This approach would offer a diverse and efficient method for assembling *N*-substituted PBDs using primary amines and aryl halides as the starting materials (Fig. 2).

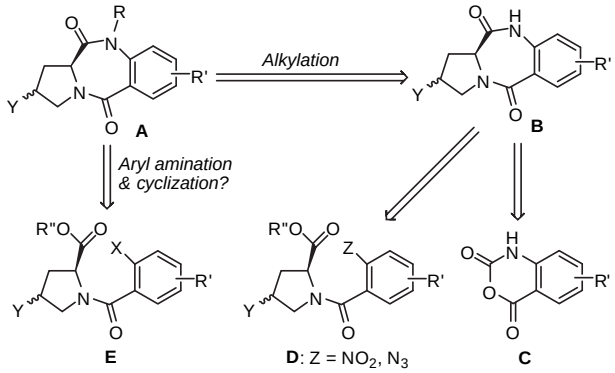
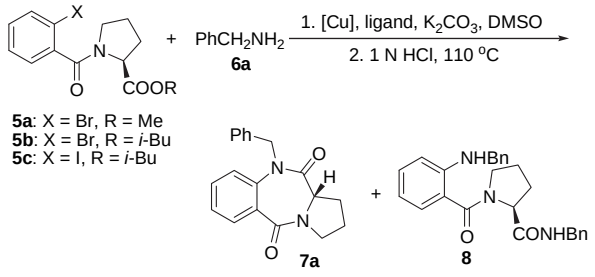


Figure 2. Possible approaches for assembling *N*-substituted PBDs.

2. Results and discussion

With the above idea in mind, a coupling reaction between aryl bromide **5a** and benzylamine was conducted under our typical reaction conditions (10 mol % CuI, 20 mol % L-proline, K_2CO_3, DMSO, 90 °C).[16] It was found that after coupling the desired tricyclic product **7a** was isolated in 52% yield, together with amide **8** in 22% yield (Table 1, entry 1). The formation of **8** should be resulted from the simple condensation of methyl ester **5a** with benzylamine. After failed in inhibiting this side reaction by tuning the reaction conditions (using different bases and copper salts), we moved our attention to employing sterically hindered *i*-butyl ester **5b** as our substrate. This change could inhibit the direct intermolecular condensation with benzylamine. However, after coupling reaction condensative cyclization turned to be slow and the direct coupling product was isolated in 15% yield (entry 2). To solve this problem, we acidified the coupling reaction mixture with 1 N HCl and then heating the solution at 110 °C. In this case **7a** was isolated in 72%

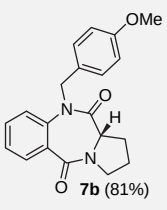
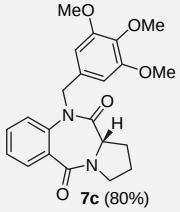
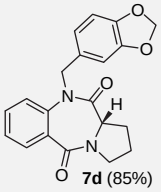
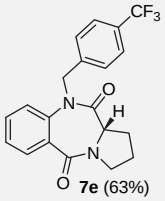
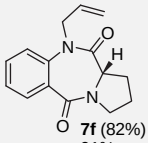
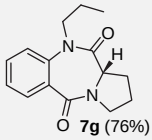
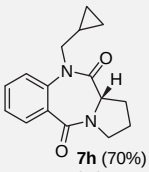
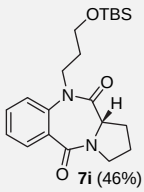
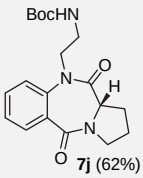
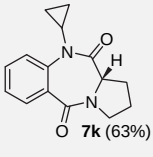
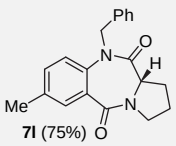
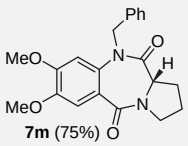
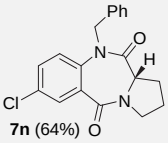
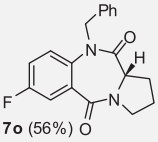
Table 1
Coupling of aryl halides **5** with benzylamine and subsequent cyclization under different conditions[a]



Entry	Substrate	Catalyst[b]	*T* (°C)	Yield of **7a**[c] (%)
1	**5a**	A	90	52[d]
2	**5b**	A	90	55[d]
3	**5b**	A	90	72
4	**5b**	B	90	74 (80% ee)
5	**5c**	B	80	78 (93% ee)

[a] Reaction conditions: aryl halide (1 mmol), benzylamine (2.5 mmol), catalyst (0.1 mmol), K_2CO_3 (2 mmol), DMSO (1 mL), 24 h; then 1 N HCl, 110 °C.
[b] A: CuI/L-proline; B: Pre-synthesized complex by heating a mixture of Cu_2O and L-proline in toluene.
[c] Isolated yield.
[d] The product was directly isolated from coupling reaction mixture, together with **8** in 22% yield (entry 1), or direct coupling product in 15% yield (entry 2).

Table 2
Synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones via coupling and subsequent condensation[a]

Entry	Product (yield)[b]	Entry	Product (yield)[b]
1	 **7b** (81%)	2	 **7c** (80%)
3	 **7d** (85%)	4	 **7e** (63%)
5	 **7f** (82%) 91% ee	6	 **7g** (76%) 95% ee
7	 **7h** (70%) 97% ee	8	 **7i** (46%)
9	 **7j** (62%)	10	 **7k** (63%)
11	 **7l** (75%)	12	 **7m** (75%)
13	 **7n** (64%)	14	 **7o** (56%)

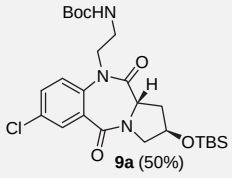
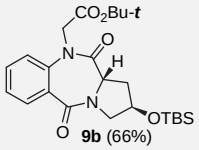
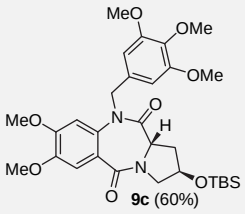
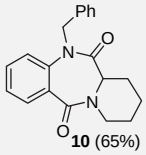
[a] Reaction conditions: 2-iodobenzamide (1 mmol), amine (2.5 mmol), catalyst (0.2 mmol, pre-synthesized complex by heating a mixture of Cu_2O and L-proline in toluene), K_2CO_3 (2 mmol), DMSO (1 mL), 80 °C, 24 h; then 1 N HCl, 110 °C for 5 h.
[b] Isolated yield.

yield (entry 3). Using a pre-synthesized complex by heating a mixture of Cu_2O and L-proline in toluene (its structure has not been fully established owing to technology issue) gave a similar result (entry 4). At this moment we determined the optical purity of our product, and were disappointedly found that the ee value of **7a** was only 80%. Since the coupling step might be responsible for the undesired racemization, we decided to utilize aryl iodide **5c** as the coupling partner, and hoped that this substrate could react with benzylamine at relatively low temperatures, thereby avoiding the possible racemization. To our delight, reaction of **5c** with benzylamine completed at 80 °C, affording **7a** with 78% yield and 93% ee, after cyclization at 110 °C (entry 5). Further reducing reaction temperatures led to low conversion at the coupling step.

The optimized reaction conditions were then tested by varying primary amines and substituted aryl iodides, and the results are summarized in Table 2. Four substituted benzyl amines bearing either electronic donating or withdrawing groups proceeded smoothly, giving the corresponding tricyclic products **7b**–**7e** in good yields (entries 1–4). Allylamine, simple and functionalized alkyl amines were compatible with these reaction conditions (entries 5–9). The additional functional groups in products **7f**, **7i**, and **7j** would allow further transformations to obtain other PBDs. Because cyclopropanyl halides could easily undergo ring-opening, introducing a *N*-cyclopropanyl group at PBDs is obviously forbidden, and therefore an alternative method was developed recently.[11] By using our procedure, the same type of compounds could be assembled from commercially available cyclopropan-amine (entry 10). The generality of our process was further demonstrated by formation of PBDs **7l**–**7o**, through coupling of benzylamine and substituted aryl iodides (entries 11–14). It is notable that products **7f**, **7g**, and **7h** showed ee values of 91%, 95%, and 97%, respectively, indicating that a slight racemization occurred in most cases.

Finally, we attempted to change the pyrrolidine unit of PBDs **7** via employing other cyclic amino acid derived aryl iodides. As indicated in Table 3, three 4-hydroxy-L-proline embodied tricyclic products were obtained with 50–66% yields (entries 1–3), while piperidine fused product **10** was produced in 65% yield (entry 4).

Table 3
Synthesis of other tricyclic compounds via coupling and subsequent condensation[a]

Entry	Product (yield)[b]	Entry	Product (yield)[b]
1	 **9a** (50%)	2	 **9b** (66%)
3	 **9c** (60%)	4	 **10** (65%)

[a] Reaction conditions: 2-iodobenzamide (1 mmol), amine (2.5 mmol), catalyst (0.2 mmol, pre-synthesized complex by heating a mixture of Cu_2O and L-proline in toluene), K_2CO_3 (2 mmol), DMSO (1 mL), 80 °C, 24 h; then 1 N HCl, 110 °C for 5 h.
[b] Isolated yield.

Noteworthy is that some of our products are potential building blocks for elaboration of the known bioactive compounds. For example, **7i** could be transferred to growth hormone releaser **1**;[1] **9a** could be converted into APT1 inhibitor **4**;[4] while **9b** could be used for assembling ST2806 (**3**) that inhibits myeloid differentiation factor 88.[3]

3. Conclusions

In summary, we have discovered that copper-catalyzed amination of *N*-heterocycle derived aryl iodides followed by intramolecular condensative cyclization could afford *N*-substituted pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-diones with good yields. A wide range of primary amines could be applied for this process, thereby giving a reliable method for diverse synthesis of these pharmaceutically important heterocycles.

4. Experimental

4.1. General remarks

All solvents were purified and dried prior to use. Optical rotations were measured by used a Perkin–Elmer 241MC polarimeter in the solvent indicated. ^{1}H NMR spectra were recorded at Bruker Avance 300 MHz, and ^{13}C NMR spectra were recorded at Bruker Avance 400 MHz, and assigned in parts per million (δ). ^{1}H NMR chemical shifts were given on the δ scale (ppm) and were referenced to internal TMS. Reference peaks for chloroform in ^{13}C NMR spectra were set at 77.0 ppm. Low-resolution mass spectra were recorded on a GILENT5973 instrument (EI) and a LCMS-2010EV instrument (ESI). High-resolution mass spectra were recorded on an IonSpec 4.7 Tesla FTMS instrument. Silica gel plate GF_{254} were used for thin layer chromatography (TLC) and silica gel H or 300–400 mesh were used for flash column chromatography. Enantiomeric excesses were determined by HPLC using a Daicel CH1RALPARK AD-H column (wavelength=254 or 214 nm) with hexane/*i*-PrOH as the eluent.

4.2. General procedure for the synthesis of *N*-substituted pyrrolo[2,1-*c*][1,4]benzodiazepine- 5,11-diones

An oven-dried Schlenk tube was charged with an appropriate amine (2.5 mmol), aryl iodide (1 mmol), copper catalyst (34 mg, 0.2 mmol, pre-synthesized by heating a mixture of Cu_2O and L-proline in toluene), and K_2CO_3 (276 mg, 2 mmol). The tube was evacuated and backfilled with argon (three times), and then DMSO (1.0 mL) was added. The reaction mixture was stirred at 80 °C for 24 h. After cooling, 1 mL of 1 N HCl was added and then the mixture was stirred at 110 °C for 5 h. The mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to give the desired product.

*4.2.1. (S)-10-Benzyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7a**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J=7.8 Hz, 1H), 7.40 (t, J=7.8 Hz, 1H), 7.32–7.15 (m, 8H), 5.17 (d, J=15.6 Hz, 1H), 5.00 (d, J=15.9 Hz, 1H), 4.20–4.18 (m, 1H), 3.87–3.79 (m, 1H), 3.64–3.55 (m, 1H), 2.81–2.77 (m, 1H), 2.17–2.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 165.1, 139.8, 136.9, 131.9, 130.5, 130.3, 128.7 (2C), 127.3, 126.8 (2C), 125.9, 122.3, 57.2, 52.4, 46.6, 26.8, 23.8; EIMS m/z 306 (M^+); HRMS (EI) calcd for $C_{19}H_{18}N_2O_2$ (M^+) 306.1368, found 306.1365. HPLC: CH1RALPARK AD-H 0.46 cm×25 cm; detected at 214 nm; *n*-hexane/*i*-propanol: 80/20; flow: 0.7 mL/min; retention time: 17.5 min (minor), 25.6 min (major), ee=93%. $[\alpha]_D^{23.4}$ +366.8 (c 1.00, $CHCl_3$).

*4.2.2. (S)-10-(4-Methoxybenzyl)-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7b**).* ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.86 (d, *J*=7.8 Hz, 1H), 7.39 (t, *J*=6.0 Hz, 1H), 7.25–7.20 (m, 2H), 7.06 (d, *J*=8.7 Hz, 2H), 6.78 (d, *J*=9.0 Hz, 2H), 5.02 (s, 2H), 4.15–4.13 (m, 1H), 3.83–3.75 (m, 1H), 3.70 (s, 3H), 3.60–3.51 (m, 1H), 2.77–2.73 (m, 1H), 2.20–2.13 (m, 1H), 2.10–2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 164.9, 158.7, 139.6, 131.8, 130.5, 130.0, 128.9, 128.1 (2C), 125.7, 122.4, 113.9 (2C), 57.1, 55.0, 51.4, 46.5, 26.6, 23.7; EIMS *m*/*z* 336 (M^+); HRMS (EI) calcd for $C_{20}H_{20}N_2O_3$ (M^+) 336.1474, found 336.1464. $[\alpha]_D^{23.7}$ +245.8 (*c* 1.00, $CHCl_3$).

*4.2.3. (S)-10-(3,4,5-Trimethoxybenzyl)-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7c**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J*=6.3 Hz, 1H), 7.45 (t, *J*=8.1 Hz, 1H), 7.31–7.25 (m, 2H), 6.32 (s, 2H), 5.17 (d, *J*=15.9 Hz, 1H), 4.96 (d, *J*=15.6 Hz, 1H), 4.20–4.18 (m, 1H), 3.82–3.76 (m, 1H), 3.78 (s, 9H), 3.63–3.50 (m, 1H), 2.80–2.76 (m, 1H), 2.18–1.98 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 164.6, 152.9 (2C), 139.1, 136.5, 132.1, 131.6, 130.4, 129.7, 125.6, 122.0, 103.0 (2C), 60.3, 56.8, 55.6 (2C), 51.4, 46.1, 26.2, 23.3; ESI-MS *m*/*z* 397.3 $(M+H)^+$; HRMS (ESI) calcd for $C_{22}H_{24}N_2Na_1O_5$ $(M+Na)^+$ 419.1582, found 419.1577. $[\alpha]_D^{24.8}$ +279.2 (*c* 1.00, $CHCl_3$).

*4.2.4. (S)-10-(Benzo[d][1,3]dioxol-5-ylmethyl)-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7d**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J*=7.8, 1.2 Hz, 1H), 7.42 (td, *J*=8.1, 1.8 Hz, 1H), 7.29–7.22(m, 2H), 6.71–6.59 (m, 3H), 5.98 (s, 2H), 5.04 (d, *J*=15.6 Hz, 1H), 4.92 (*J*=15.6 Hz, 1H), 4.16–4.14 (m, 1H), 3.85–3.78 (m, 1H), 3.62–3.53 (m, 1H), 2.78–2.73 (m, 1H), 2.19–1.99 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.0, 147.9, 146.8, 139.6, 131.9, 130.8, 130.5, 130.2, 125.9, 122.3, 120.2, 108.3, 107.5, 101.0, 57.2, 52.0, 46.6, 26.7, 23.8; EIMS *m*/*z* 350 (M^+); HRMS (EI) calcd for $C_{20}H_{18}N_2O_4$ (M^+) 350.1267, found 350.1270. $[\alpha]_D^{24.0}$ +339.4 (*c* 1.00, $CHCl_3$).

*4.2.5. (S)-10-(4-(Trifluoromethyl)benzyl)-2,3-dihydro-1H-benzo[e]-pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7e**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J*=6.3 Hz, 1H), 7.55 (d, *J*=8.4 Hz, 2H), 7.43 (t, *J*=8.1 Hz, 1H), 7.31–7.26 (m, 3H), 7.18 (d, *J*=8.1 Hz, 1H), 5.21 (d, *J*=15.9 Hz, 1H), 5.08 (d, *J*=16.2 Hz, 1H), 4.22 (d, *J*=5.7 Hz, 1H), 3.85–3.79 (m, 1H), 3.64–3.55 (m, 1H), 2.78–2.70 (m, 1H), 2.77–1.99 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 164.9, 141.1 (q, *J*=1.3 Hz, 1C), 139.4, 132.1, 130.4 (*J*=7.4 Hz, 2C), 129.4 (q, *J*=32.4 Hz, 1C), 126.9 (2C), 126.1, 125.6 (q, *J*=3.7 Hz, 2C), 123.9 (q, *J*=271 Hz, 1C), 121.9; 57.1, 51.9, 46.6, 26.7, 23.7; EIMS *m*/*z* 374 (M^+); HRMS (EI) calcd for $C_{20}H_{17}F_3N_2O_2$ (M^+) 374.1242, found 350.1245. $[\alpha]_D^{24.2}$ +260.1 (*c* 1.00, $CHCl_3$).

*4.2.6. (S)-10-Allyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7f**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J*=8.1, 1.5 Hz, 1H), 7.49 (t, *J*=6.0 Hz, 1H), 7.37–7.27 (m, 2H), 5.97–5.87 (m, 1H), 5.22–5.16 (m, 2H), 4.59 (dd, *J*=16.2, 5.1 Hz, 1H), 4.35 (dd, *J*=16.2, 5.4 Hz, 1H), 4.12–4.09 (m, 1H), 3.86–3.78 (m, 1H), 3.62–3.53 (m, 1H), 2.77–2.72 (m, 1H), 2.18–1.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 165.1, 139.9, 133.3, 132.0, 130.3, 130.2, 125.8, 122.1, 117.3, 57.2, 51.7, 46.7, 26.7, 23.8; EIMS *m*/*z* 256 (M^+); HRMS (EI) calcd for $C_{15}H_{16}N_2O_2$ (M^+) 256.1212, found 256.1218; HPLC: CH1RALPARK AD-H 0.46 cm×25 cm; detected at 214 nm; *n*-hexane/*i*-propanol: 80/20; flow: 0.7 mL/min; retention time: 10.9 min (minor), 15.6 min (major), ee=91%. $[\alpha]_D^{24.8}$ +465.1 (*c* 1.00, $CHCl_3$).

*4.2.7. (S)-10-Propyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7g**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.5 Hz, 1H), 7.52 (t, *J*=7.8 Hz, 1H), 7.33–7.27 (m, 2H), 4.25–4.15 (m, 1H), 4.05–4.02 (m, 1H), 3.85–3.77(m, 1H), 3.66–3.51 (m, 2H), 2.75–2.70 (m, 1H), 2.18–2.08 (m, 1H), 2.04–1.92 (m, 2H), 1.67–1.41 (m, 2H), 0.82 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 165.1, 139.4, 131.9, 131.2, 130.2, 125.8, 122.6, 57.4, 49.8, 46.5, 26.7, 23.9, 21.2, 11.1; EIMS *m*/*z* 258 (M^+); HRMS (EI) calcd for $C_{15}H_{18}N_2O_2$ (M^+) 258.1368, found 258.1364; HPLC: CH1RALPARK AD-H 0.46 cm×25 cm; detected at 214 nm; *n*-hexane/*i*-propanol: 80/20; flow: 0.7 mL/min; retention time: 10.1 min (minor), 14.5 min (major), ee=95%. $[\alpha]_D^{24.7}$ +529.1 (*c* 1.00, $CHCl_3$).

*4.2.8. (S)-10-(Cyclopropylmethyl)-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7h**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J*=7.8,1.5 Hz, 1H), 7.52 (t, *J*=7.9 Hz, 1H), 7.36–7.29 (m, 2H), 4.07 (d, *J*=7.5 Hz, 1H), 4.03 (d, *J*=7.5 Hz, 1H), 3.86–3.78 (m, 1H), 3.64–3.52 (m, 2H), 2.75–2.69 (m, 1H), 2.19–2.09 (m, 1H), 2.06–1.95 (m, 2H), 1.01–0.82 (m, 1H), 0.47–0.38 (m, 2H), 0.23–0.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 165.0, 139.5, 131.7, 131.2, 130.0, 125.8, 123.1, 57.2, 52.6, 46.4, 26.5, 23.8, 10.0, 4.3, 3.5; EIMS *m*/*z* 270 (M^+); HRMS (EI) calcd for $C_{16}H_{18}N_2O_2$ (M^+) 270.1368, found 270.1370; HPLC: CH1RALPARK AD-H 0.46 cm×25 cm; detected at 214 nm; *n*-hexane/*i*-propanol: 80/20; flow: 0.7 mL/min; retention time: 10.3 min (minor), 15.9 min (major), ee=97%. $[\alpha]_D^{24.4}$ +431.9 (*c* 1.00, $CHCl_3$).

*4.2.9. (S)-10-(3-(tert-Butyldimethylsilyloxy)propyl)-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7i**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.5 Hz, 1H), 7.54 (t, *J*=7.5 Hz, 1H), 7.40–7.30 (m, 2H), 4.35–4.25 (m, 1H), 4.07 (d, *J*=5.7 Hz, 1H), 3.86–3.81 (m, 2H), 3.63–3.55 (m, 3H), 2.78–2.73 (m, 1H), 2.20–2.10 (m, 1H), 2.08–1.98 (m, 2H), 1.95–1.86 (m, 1H), 1.84–1.73 (m, 1H), 0.89 (s, 9H), 0.045 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 165.0, 139.7, 131.9, 130.7, 130.1, 126.0, 122.6, 59.9, 57.3, 46.5, 45.3, 31.0, 26.6, 25.7 (3C), 23.8, 18.1, −5.6 (2C). ESI-MS *m*/*z* 389.2 $(M+H)^+$; HRMS (EI) calcd for $C_{21}H_{32}N_2O_3Si$ (M^+) 388.2182, found 388.2177. $[\alpha]_D^{24.8}$ +284.5 (*c* 1.00, $CHCl_3$).

*4.2.10. (S)-tert-Butyl-2-(5,11-dioxo-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(5H,11H,11aH)-yl)ethylcarbamate (**7j**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J*=7.8, 1.5 Hz, 1H), 7.54 (t, *J*=7.6 Hz, 1H), 7.39–7.27 (m, 2H), 4.81 (br s, 1H), 4.13–3.95 (m, 2H), 3.93–3.78 (m, 2H), 3.60–3.51 (m, 1H), 3.37 (m, 2H), 2.73–2.68 (m, 1H), 2.18–2.10 (m, 1H), 2.08–1.93 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 164.5, 155.4, 139.2, 131.8, 130.0, 129.8, 125.5, 122.0, 78.9, 56.7, 48.2, 46.1, 38.8, 27.8 (3C), 26.1, 23.3; EIMS *m*/*z* 359 (M^+); HRMS (EI) calcd for $C_{19}H_{25}N_3O_4$ (M^+) 359.1845, found 359.1848. $[\alpha]_D^{24.8}$ +332.8 (*c* 1.00, $CHCl_3$).

*4.2.11. (S)-10-Cyclopropyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a]-[1,4]diazepine-5,11(10H,11aH)-dione (**7k**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J*=7.6, 1.5 Hz, 1H), 7.53 (t, *J*=7.8 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 1H), 7.27 (m, 1H), 4.03–4.01 (m, 1H), 3.79–3.73 (m, 1H), 3.60–3.50 (m, 1H), 3.18–3.11 (m, 1H), 2.79–2.74 (m, 1H), 2.09–1.92 (m, 3H), 1.33–1.14 (m, 1H), 0.88–0.65 (m, 2H), 0.23–0.14 (m., 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 165.4, 140.1, 131.6, 129.8, 129.7, 125.2, 122.9, 58.0, 46.6, 30.3, 26.5, 23.6, 11.5, 7.4; ESI-MS *m*/*z* 257.2 $(M+H)^+$; HRMS (EI) calcd for $C_{15}H_{16}N_2O_2$ (M^+) 256.1212, found 256.1212. $[\alpha]_D^{24.8}$ +362.2 (*c* 1.00, $CHCl_3$).

*4.2.12. (S)-10-Benzyl-7-methyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7l**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.29–7.07 (m, 7H), 5.11 (d, *J*=15.6 Hz, 1H), 5.01 (d, *J*=15.9 Hz, 1H), 4.17 (d, *J*=5.4 Hz, 1H), 3.81 (t, *J*=9.3 Hz, 1H), 3.62–3.53 (m, 1H), 2.78–2.74 (m, 1H), 2.33 (s, 3H), 2.18–2.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 164.8, 136.9, 136.6, 135.4, 132.3, 129.9, 129.8, 128.2 (2C), 126.8, 126.3 (2C), 121.7, 56.8, 51.8, 46.1, 26.3, 23.4, 20.2; EIMS *m*/*z* 320 (M^+); HRMS (EI) calcd for $C_{20}H_{20}N_2O_2$ (M^+) 320.1525, found 320.1523. $[\alpha]_D^{25.0}$ +336.8 (*c* 1.00, $CHCl_3$).

*4.2.13. (S)-10-Benzyl-7,8-dimethoxy-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7m**).* ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.34–7.21 (m, 6H), 6.60 (s, 1H), 5.26 (d, J=15.6 Hz, 1H), 4.80 (J=15.3 Hz, 1H), 4.20–4.27 (m, 1H), 3.90 (s, 3H), 3.83–3.76 (m, 1H), 3.64 (s, 3H), 3.62–3.55 (m, 1H), 2.81–2.77 (m, 1H), 2.20–1.99 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 165.0, 151.4, 146.6, 137.5, 133.9, 128.8 (2C), 127.5, 127.0 (2C), 122.8, 111.2, 105.2, 57.4, 56.0, 55.8, 52.6, 46.6, 26.7, 23.8; ESI-MS m/z 367.3 $(M+H)^+$; HRMS (ESI) calcd for $C_{21}H_{22}N_2NaO_4$ $(M+Na)^+$ 389.1478, found 389.1472. $[\alpha]_D^{24.9}$ +231.4 (c 1.00, $CHCl_3$).

*4.2.14. (S)-10-Benzyl-7-chloro-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7n**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J=2.4 Hz, 1H), 7.36–7.24 (m, 4H), 7.13 (m, 3H), 5.14 (d, J=15.9 Hz, 1H), 4.99 (d, J=15.6 Hz, 1H), 4.18 (m, 1H), 3.82–3.79 (m, 1H), 3.61–3.57 (m, 1H), 2.80–2.73 (m, 1H), 2.15–2.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 163.3, 137.8, 136.1, 131.5, 131.4, 131.1, 129.6 (2C), 128.4, 127.0 (2C), 126.3, 123.2, 56.7, 51.8, 46.3, 26.3, 23.3; EIMS m/z 340 (M^+); HRMS (EI) calcd for $C_{19}H_{17}ClN_2O_2$ (M^+) 340.0979, found 340.0981. $[\alpha]_D^{25.0}$ +192.7 (c 1.00, $CHCl_3$).

*4.2.15. (S)-10-Benzyl-7-fluoro-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**7o**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J=9.0, 2.8 Hz, 1H), 7.32–7.06 (m, 7H), 5.13 (d, J=15.9 Hz, 1H), 4.98 (d, J=15.9 Hz, 1H), 4.18 (m, 1H), 3.85–3.78 (m, 1H), 3.63–3.53 (m, 1H), 2.80–2.69 (m, 1H), 2.17–2.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.3, 159.2 (d, J=247.1 Hz, 1C), 136.2, 135.5 (d, J=2.9 Hz, 1C), 131.9 (d, J=7.5 Hz, 1C), 128.3 (2C), 127.0, 126.3 (2C), 123.8 (d, J=8.2 Hz, 1C), 118.7 (d, J=23.1 Hz, 1C), 116.1 (d, J=24.0 Hz, 1C), 56.8, 52.0, 46.3, 26.3, 23.3; EIMS m/z 324 (M^+); HRMS (EI) calcd for $C_{19}H_{17}FN_2O_2$ (M^+) 324.1274, found 324.1273. $[\alpha]_D^{25.0}$ +181.9 (c 1.00, $CHCl_3$).

*4.2.16. tert-Butyl-2-((2R,11aS)-2-(tert-butyldimethylsilyloxy)-7-chloro-5,11-dioxo-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(5H,11H,11aH)-yl)ethylcarbamate (**9a**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.38 (d, J=8.4 Hz, 1H), 4.81–4.78 (m, 1H), 4.62–4.55 (m, 1H), 4.19–4.15 (m, 1H), 4.06–3.86 (m, 2H), 3.78–3.72 (dd, J=12.0, 5.4 Hz 1H), 3.60–3.54 (dd, J=12.6, 5.1 Hz, 1H), 3.39–3.33 (m, 2H), 2.88–2.81 (m, 1H), 2.07–1.98 (m, 1H), 1.39 (s, 9H), 0.87 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 163.7, 155.4, 137.7, 131.9, 131.3, 130.5, 129.6, 123.6, 79.1, 69.1, 55.6, 53.3, 48.4, 38.6, 35.1, 27.8 (3C), 25.2 (3C), 17.5, −5.3 (2C); ESI-MS m/z 546 $(M+Na)^+$; HRMS (ESI) calcd for $C_{25}H_{38}ClN_3O_5SiNa$ $(M+Na)^+$ 546.2167, found 546.2162. $[\alpha]_D^{25.0}$ +174.2 (c 1.00, $CHCl_3$).

*4.2.17. tert-Butyl2-((2R,11aS)-2-(tert-butyldimethylsilyloxy)-5,11-dioxo-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(5H,11H,11aH)-yl)acetate (**9b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J=7.8, 1.5 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 7.34 (t, J=7.5 Hz, 1H), 7.19 (d, J=8.1 Hz, 1H), 4.61–4.55 (m, 2H), 4.27 (dd, J=8.1, 3.6 Hz, 1H), 4.15–4.10 (m, 1H), 3.80 (dd, J=12.0, 5.4 Hz, 1H), 3.56 (dd, J=12.0, 5.4 Hz, 1H), 2.90–2.83 (m, 1H), 2.09–2.00 (m, 1H), 1.48 (s, 9H), 0.87 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.7, 165.5, 139.6, 132.3, 130.3, 129.3, 126.1, 121.7, 82.4, 69.4, 55.8, 53.6, 52.0, 35.5, 27.9 (3C), 25.6 (3C), 17.9, −4.8 (2C); ESI-MS m/z 461.1 $(M+H)^+$; HRMS (EI) calcd for $C_{24}H_{36}N_2O_5Si$ $(M)^+$ 460.2393, found 460.2393. $[\alpha]_D^{23.7}$ +400.7 (c 1.00, $CHCl_3$).

*4.2.18. (2R,11aS)-2-(tert-Butyldimethylsilyloxy)-7,8-dimethoxy-10-(3,4,5-trimethoxybenzyl)-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**9c**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.66 (s, 1H), 6.38 (s, 2H), 5.07 (d, J=15.6 Hz, 1H), 4.90 (d, J=15.6 Hz, 1H), 4.63–4.58 (m, 1H), 4.33–4.29 (m, 1H), 3.82 (s, 3H), 3.69 (s, 9H), 3.76–3.61 (m, 1H), 3.63 (s, 3H), 3.64–3.59 (m, 1H), 2.94–2.87 (m, 1H), 2.11–2.02 (m, 1H), 0.87 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 165.0, 153.0, 151.1, 146.5, 136.6, 133.1, 132.5, 122.0, 110.8, 105.0, 103.2 (2C), 69.2, 60.3, 55.9, 55.7 (2C), 55.6 (2C), 55.5, 53.2, 52.0, 35.2, 25.2 (3C), 17.5, −5.3 (2C); ESI-MS m/z 587.2 $(M+H)^+$; HRMS (EI) calcd for $C_{30}H_{42}N_2O_8Si$ (M^+) 586.2710, found 587.2783. $[\alpha]_D^{23.7}$ +133.8 (c 1.00, $CHCl_3$).

*4.2.19. 5-Benzyl-7,8,9,10-tetrahydrobenzo[e]pyrido[1,2-a][1,4]diazepine-6,12(5H,6aH)-dione (**10**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, J=7.5, 1.5 Hz, 1H), 7.39 (td, J=7.6, 1.5 Hz, 1H), 7.31–7.11 (m, 7H), 5.07 (s, 2H), 4.54 (dt, J=13.5, 3.6 Hz, 1H), 4.31(dd, J=6.6, 2.7 Hz, 1H), 2.91 (td, J=13.2, 3.6 Hz, 1H), 2.28–2.21 (m, 1H), 2.10–1.96 (m, 1H), 1.87–1.81 (m, 1H), 1.73–1.66 (m, 2H), 1.62–1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.5, 140.0, 137.0, 131.7, 130.2, 130.1, 128.7 (2C), 127.3, 126.7 (2C), 125.9, 121.2, 51.2 (2C), 40.3, 23.6, 23.2, 19.2; EIMS m/z 320 (M^+); HRMS (EI) calcd for $C_{20}H_{20}N_2O_2$ (M^+) 320.1525, found 320.1521.

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