Parallel Synthesis of a Novel C2-Aryl Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) Library

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A 66-member C2-aryl pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) library has been successfully synthesized in parallel via Suzuki coupling using PS-PPh_3Pd (catalyst) and PS-DEAM (scavenger) under microwave radiation. Library members were obtained in sufficient yield (up to 91%) and purity (85−98% crude) for biological evaluation.

Introduction

The pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a family of natural products that interact with DNA in a sequence-selective manner (Figure 1).[1−3] They bind in the minor groove of DNA, spanning three base pairs and forming a covalent bond between their electrophilic N10−C11 imine moiety and the N2 position of a guanine base. Both naturally occurring PBD monomers and the more recently introduced synthetic PBD dimers possess significant in vitro cytotoxicity and, in some cases, in vivo antitumor activity. One example, the PBD dimer SJG-136, is currently in Phase I evaluation in the clinic.[4−6] SAR studies have demonstrated that for both PBD monomers and dimers, C-ring 2,3-unsaturation and C2-substitution can enhance potency. For example, we have reported[7] the synthesis and preliminary biological evaluation of the first examples of C2-aryl-substituted PBDs which were found to be significantly more potent than their C-ring saturated/unsubstituted counterparts. Moreover, they were shown to be selectively cytotoxic toward melanoma and renal cell lines in vitro.

The SAR features of these novel compounds remained to be fully elucidated, and so the synthesis of further examples was necessary to optimize activity. This was considered to be best achieved through the generation of a comprehensive C2-aryl PBD library that maintained the obligatory PBD pharmacophore while generating molecular diversity at the C2-position. Such structural modifications are relatively easy to install, thus allowing straightforward sample generation for biological evaluation.

Solid-phase chemistry is a well-known method for the acceleration of library synthesis through facile purification and automation, and the solid-phase synthesis of saturated C-ring PBDs has already been reported.[8] Furthermore, PBD dilactam analogues (i.e., with a N10−C11 amide functionality) have been synthesized on a solid support by Kamal and co-workers.[9−11] However, difficulties in monitoring the formation of products and in obtaining them in sufficient quantities for biological evaluation have, to date, encouraged the development of alternative solution-phase approaches. In the work reported here, some of the major advantages of solid-phase methodologies such as employment of excess reagents, ease of purification, and automation have been retained by using immobilized reagents. In addition, the use of microwave radiation in conjunction with phase-separator cartridges has allowed a reduction in reaction and purification times, respectively.

The C2-aryl PBD subclass is accessible through Suzuki coupling chemistry via a key enol−triflate intermediate of type **11** (see Scheme 2). Previously, C2-aryl analogues had been obtained from PBD−5,10-dilactams which require reduction at the N10−C11 position to yield final products.[7,12] However, over-reduction of the N10−C11 imine functionality under these conditions can afford biologically inactive N10−C11 secondary amines as byproducts.[2] For similar reasons, this approach could not be used to efficiently install potentially reducible vinylic or alkynic substituents at the C2-position.[13] A further problem is that racemization at the critical C11a-position (*S* stereochemistry is important for maintaining DNA minor-groove shape complementarity)[1,14] has been observed in experiments where relatively strong base (e.g., Na_2CO_3) at reflux temperature has been used.[15] These issues prompted us to investigate the synthesis and use of the new C2-enol-triflate PBD intermediate **11** (Scheme 2). This key intermediate can be prepared on a multigram scale and then used as a substrate for the critical C2 cross-coupling reaction. We report here that the Suzuki coupling can be performed under microwave radiation with immobilized reagents to efficiently generate a N10−C11 imine-containing C2-aryl PBD library in a parallel manner.

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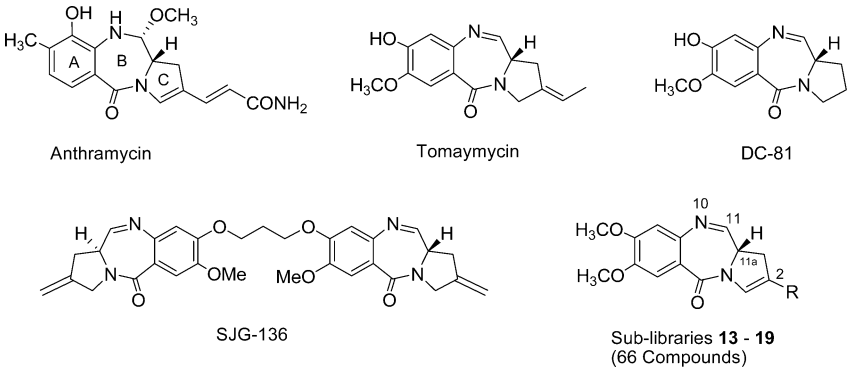
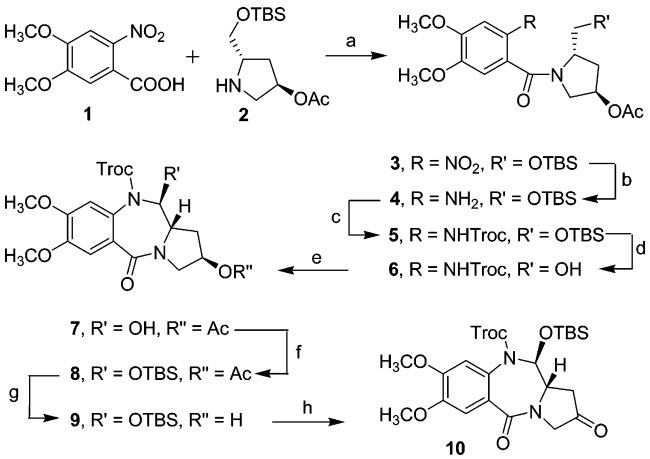


Figure 1. Structures of the naturally occurring PBD monomers anthramycin, tomaymycin, and DC-81, the synthetic PBD dimer SJG-136, and the C2-substituted PBD sub-libraries **13**−**19** (66 members, see Tables 1 and 2).

Scheme 1[a]



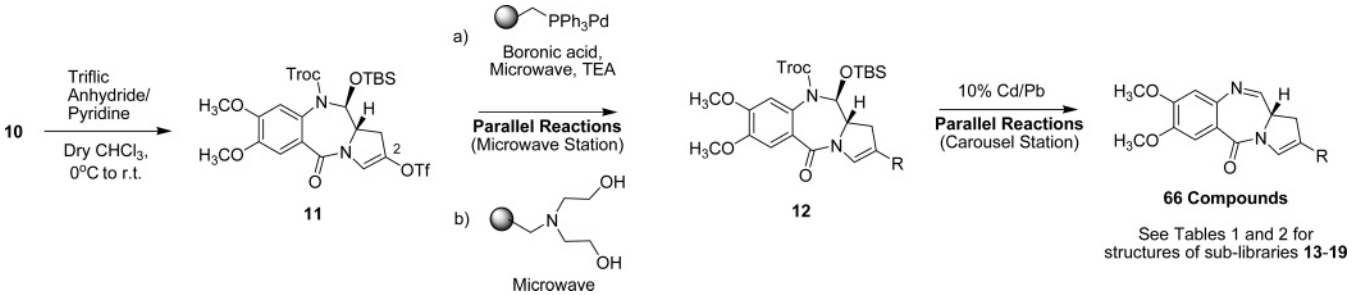
[a] Reagents and conditions: (a) 6-nitroveratric acid (1.2 equiv), EDCI (1.2 equiv), HOBt (1.2 equiv), DMF, DCM, 0 °C, 1 h, followed by **2** (1.0 equiv) in DCM, reflux, 3 h, 80%; (b) 10% Pd/C, EtOH, H_2 (45 psi), 3 h, 99%; (c) Troc-Cl (2.2 equiv), pyridine (4.0 equiv), DCM, −20° → room temp, 2.5 h, 99%; (d) THF, then AcOH/water 4.5:1, room temp, 48 h, 99%; (e) DAIB (1.78 equiv), TEMPO (0.2 equiv), DCM, room temp, 15 h, 77%; (f) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), DCM, room temp, 30 min, 99%; (g) K_2CO_3 0.35 M (1.0 equiv), MeOH, THF, room temp, 5 h, 92%; (h) DAIB (1.78 equiv), TEMPO (0.2 equiv), DCM, room temp, 18 h, 91%.

Results and Discussion

The TBS/acetyl-protected C-ring building block **2**[16] was coupled to commercially available 6-nitroveratric acid (**1**) in the presence of EDCI/HOBt to provide the amide **3** in 80% yield (Scheme 1). The nitro group was then hydrogenated to give amine **4** which was subsequently protected as the trichloroethyl carbamate (Troc) to give **5** (98% yield over two steps). The TBS protecting group was selectively removed in the presence of the C2-acetate using aqueous acetic acid in THF to give the primary alcohol **6**, which was oxidized with DAIB/TEMPO to afford the cyclized PBD system **7** in a 70% yield.[17] After TBS protection of the C11 OH group (**8**), the C2-acetate was removed under basic conditions (aq K_2CO_3) to give **9**. This was followed by a second DAIB/TEMPO oxidation to afford the required C2-ketone (**10**) in excellent yield (91%). This synthetic route allowed preparation of **10** on a large scale (i.e., 60 g), thus facilitating optimization of the subsequent triflation reaction (Scheme 2), which was previously known to provide disappointing yields of enol−triflate in PBD N10−C11 carbinolamine systems.[18] However, on this occasion, with the C11-hydroxy group protected with TBS, treatment with a large excess of triflic anhydride resulted in a much improved yield (55%) of the key PBD triflate **11**, along with 14% of unreacted ketone **10** which could be recycled.

Suzuki coupling (Scheme 2) was performed using **11** as a substrate to react with a diverse set of boronic acids and pinacol esters under microwave conditions (10 min, 100 °C). PS-PPh_3Pd was employed as a solid-supported palladium catalyst to facilitate workup, potentially allowing recycling of the catalyst. After complete consumption of triflate, *N*,*N*-diethanolaminomethyl polystyrene (PS-DEAM) was added to sequester any unreacted boronic acid/pinacol esters (microwave radiation, 10 min, 100 °C), and a phase separator cartridge then used to isolate the Suzuki products of type **12**. ^{1}H NMR and LC-MS analyses revealed that this workup procedure afforded relatively clean intermediates of type **12**

Scheme 2[a]



[a] The insertion of different substituents at the C2-position of the PBD triflate intermediate **11** to give intermediates of type **12** (for R, see Tables 1 and 2), followed by conversion to the PBD imine sub-libraries **13**−**19**. Purity analysis of the 66 PBD imine library members showed >85% AUC (area under the curve) by LC-MS in each case. Library members were further purified by preparative HPLC or flash chromatography to meet the more-stringent purity levels necessary for biophysical and biological evaluation (see Supporting Information).

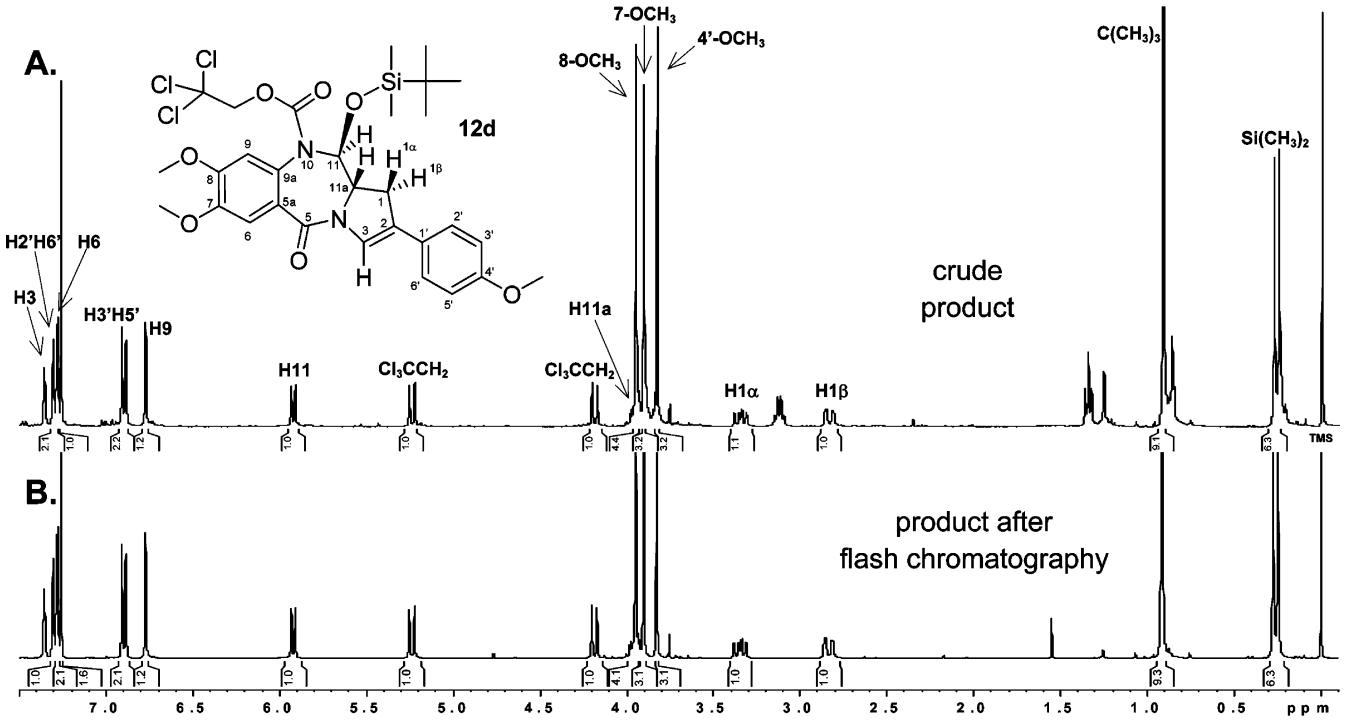
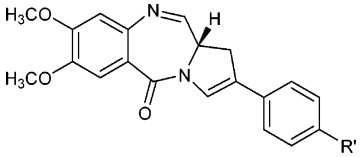
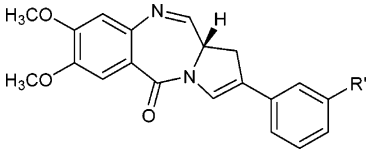
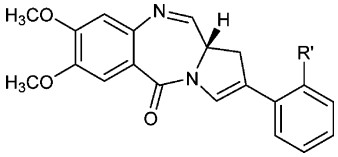
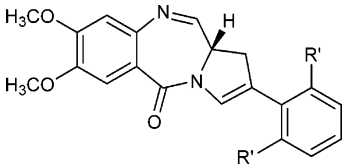


Figure 2. (A) ^{1}H NMR spectrum of crude **12d**, a product from the cross-coupling reaction of **11** catalyzed by PS-PPH$_3$Pd, followed by treatment with PS-DEAM and solution-phase extraction. (B) ^{1}H NMR spectrum of the same product after purification by flash chromatography, illustrating the acceptable level of purity of the crude product.

Table 1. Sub-libraries **13**−**16** of the C2-Aryl PBD Imine Library

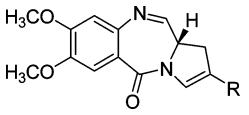
	sublibrary structures		general yields[a] (%)
13a−**w**[b]	para substituents (23 compounds)		18−47
14a−**k**[c]	meta substituents (11 compounds)		4−50
15a−**b**[d]	ortho substituents (2 compounds)		38−46
16a−**d**[e]	disubstituted (4 compounds)		14−41

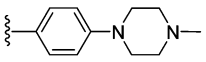
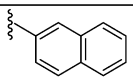
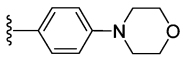
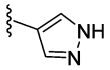
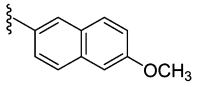
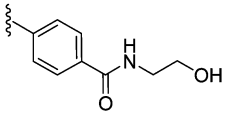
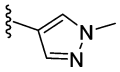
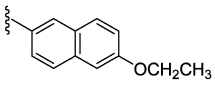
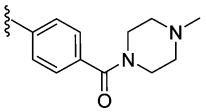
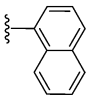
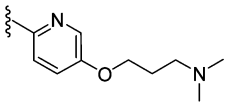
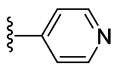
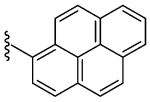
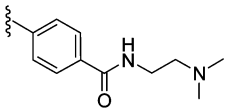
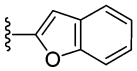
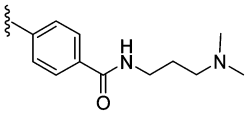
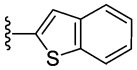
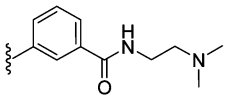
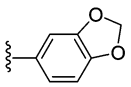
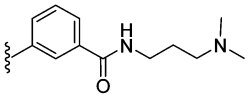
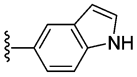
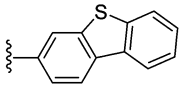
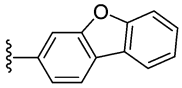
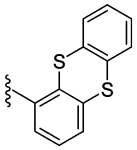
[a]See Supporting Information for individual yields and analytical data. [b] R′ = H, CH_3, CH_2CH_3, OCH_3, $C(CH_3)_3$, F, Cl, Br, $N(CH_3)_2$, SCH_3, $CHCH_2$, CN, CF_3, $CH(CH_3)_2$, NO_2, CHO, COOH, NH_2, OH, $NHCOCH_3$, $CONH_2$, Ph, OPh. [c] R′ = NH_2, NO_2, CF_3, Cl, CH_3, F, COOH, OCF_3, CN, $COOCH_3$, OCH_3. [d] R′ = CF_3, CH_3. [e] R′ = Cl, CH_3, OCH_3, F.

in excellent yield (e.g., 98% for **12d**) without the need for purification by flash column chromatography (see Figure 2). Finally, the N10-Troc group was cleaved under mild conditions using a 10% Cd/Pb couple leading to elimination of the C11−OTBS group to afford the target C2-substituted N10−C11 PBD imines (sub-libraries **13**−**19**, see Tables 1 and 2) in up to 91% isolated yield.

Compounds with nitro substituents (i.e., **13o** and **14b**, Scheme 3 and Table 1) had to be synthesized by a different procedure than that shown in Scheme 2 because the 10%

Table 2. Sub-libraries **17**−**19** of the C2-Aryl PBD Imine Library



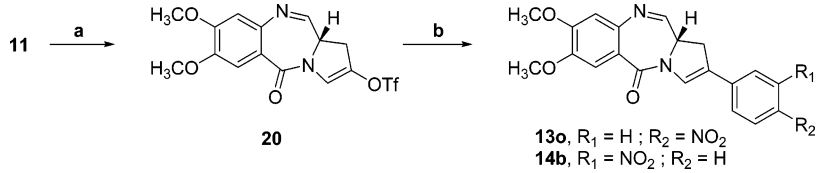
	Hydrophilic moieties		Heteroaryl		Naphthyl and Pyrenyl	
	Compounds **17**		Compounds **18**		Compounds **19**	
	R	**Yields**[a] **(%)**	**R**	**Yields**[a] **(%)**	**R**	**Yields**[a] **(%)**
a		45[b]		59[c]		47[c]
b		20[b]		20[b]		40[b]
c		21[b]		12[b]		22[b]
d		17[b]		14[c]		32[b]
e		19[b]		27[c]		39[b]
f		57[c]		33[b]	---	
g		50[c]		18[b]	---	
h		36[c]		33[c]	---	
i		36[c]		34[b]	---	
j	---			22[b]	---	
k	---			20[b]	---	
l	---			26[b]	---	

[a] See Supporting Information for analytical data. [b] Purified by preparative HPLC prior to biophysical and biological evaluation. [c] Purified by flash chromatography prior to biophysical and biological evaluation.

Cd/Pb couple would reduce them to the respective amines, **13r** and **14a**. Therefore, for these molecules, building block **11** was subjected to Troc-deprotection conditions to give the N10−C11 imine-containing PBD **20**, which was a suitable substrate for Suzuki-coupling to provide **13o** and **14b**.

Most importantly, representative library members displayed consistent optical rotation values (see Table S1 in Supporting Information), suggesting that the C11a-stereochemistry required for biological activity had been maintained throughout the synthetic pathway.[1,14] Although library members were obtained in a reasonable state of purity (i.e.,

Scheme 3[a]



[a] Reagents and conditions: (a) 10% Cd/Pb, THF, ammonium acetate solution, room temp, 2 h, 94%; (b) 3- or 4-nitrophenyl boronic acids, PS-PPh_3Pd, TEA, toluene/EtOH/water, 100 °C, microwave, 15 min, 31 and 34%, respectively, isolated yields.

>85%; see LC-MS data in Supporting Information), they were further purified by preparative HPLC (for small scale, <10 mg) or flash chromatography (for larger scale, 10−50 mg) to meet the more-stringent purity levels required for biophysical and biological evaluation.

In summary, this approach has allowed the rapid synthesis of a set of 66 N10−C11 imine-containing C2-aryl-substituted PBDs with stereochemical integrity at the C11a-position. Furthermore, the use of scavengers, immobilized catalyst, and phase-separator cartridges allowed the simultaneous workup of multiple reactions in parallel. Library members were obtained in sufficiently good yield and purity (>85%) to allow both DNA-binding affinity and in vitro cytotoxicity to be evaluated, the results of which will be reported elsewhere.

Experimental Section

Optical rotations were measured on an ADP 220 polarimeter (Bellingham Stanley Ltd., Tunbridge Wells, Kent, U.K.) and concentrations (*c*) are given in g/100 mL. Melting points were measured using a digital melting point apparatus (Electrothermal, Dubuque, IA). IR spectra were recorded on a Perkin-Elmer Spectrum 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were acquired at 300 K using a Bruker Avance NMR spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported relative to TMS (δ = 0.0 ppm), and signals are designated as s (singlet), d (doublet), t (triplet), dt (double triplet), dd (doublet of doublets), ddd (double doublet of doublets), or m (multiplet), with coupling constants given in hertz. A pro-PBD numbering system is used for carbon and proton assignments for intermediates **2**−**6** (i.e., based on the final tricyclic PBD ring system). Mass spectroscopy data were collected using a Waters Micromass ZQ instrument coupled to a Waters 2695 HPLC with a Waters 2996 PDA. The following Waters Micromass ZQ parameters were used: capillary (kV), 3.38; cone (V), 35; extractor (V), 3.0; source temperature (°C), 100; desolvation temperature (°C), 200; cone flow rate (L/h), 50; desolvation flow rate (L/h), 250. High-resolution mass spectroscopy data were recorded on a Waters Micromass QTOF Global in positive W-mode using metal-coated borosilicate glass tips to introduce the samples into the instrument. Thin layer chromatography (TLC) was performed on silica gel aluminum plates (Merck 60, F_{254}), and flash chromatography utilized silica gel (Merck 60, 230−400 mesh ASTM). Except for the HOBt (NovaBiochem) and solid-supported reagents (Argonaut), all other chemicals and solvents were purchased from Sigma-Aldrich.

(3*R*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(4,5-dimethoxy-2-nitrobenzoyl)pyrrolidin-3-yl Acetate (3). *N*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide hydrochloride (EDCI) (1.26 g, 6.6 mmol, 1.2 Equiv.) was added to a cold (ice bath), magnetically stirred solution of 6-nitroveratric acid (1.49 g, 6.6 mmol, 1.2 equiv) in dry DMF (2 mL) and DCM (80 mL). Subsequently, 1-hydroxybenzotriazole hydrate (HOBt) (1.03 g, 6.6 mmol, 1.2 equiv) was added to the mixture which was stirred under a nitrogen atmosphere for 1 h. At this point, a solution of **2** (1.5 g, 5.5 mmol, 1.0 equiv) in DCM (80 mL) was added dropwise into the reaction flask over 1 h, and the mixture was magnetically stirred at room temperature for 15 h. It was then heated at reflux for 3 h when TLC indicated complete consumption of starting material. The reaction mixture was washed with NH_4Cl (60 mL), $NaHCO_3$ (60 mL), and brine (60 mL) and was dried over $MgSO_4$, and the excess solvent was removed under reduced pressure. Flash chromatography purification (EtOAc/hexane 4:6) afforded product **3** as a colorless solid (2.11 g, 80%). R_f: 0.35 (EtOAc/Hexane 6:4). $[\alpha]_D^{19}$: −91.9° (*c* = 0.41, $CHCl_3$). mp: 133−135 °C. IR (film, ν_{max}, cm^{-1}): 2953, 2856, 1740 (OC═O), 1648 (NC═O), 1579, 1525, 1463, 1427, 1338, 1278, 1243, 1225, 1115, 1070, 1028, 1004, 837, 780. ^{1}H NMR ($CDCl_3$, 400 MHz) rotamers: δ 0.12 (s, 6 H, $Si(CH_3)_2$), 0.93 (s, 9 H, $C(CH_3)_3$), 2.04 (s, 3 H, $OCOCH_3$), 2.20 − 2.28 (m, 1 H, H1α), 2.39 − 2.45 (m, 1 H, H1β), 3.22 (d, 1 H, *J* = 11.7 Hz, H3α), 3.47 (dd, 1 H, *J* = 11.9, 4.7 Hz, H3β), 3.75 (d, 1 H, *J* = 8.4 Hz, H11), 3.94 (s, 3 H, 7-OCH_3), 3.98 (s, 3 H, 8-OCH_3), 4.21 (d, 1 H, *J* = 9.8 Hz, H11), 4.56 (m, 1 H, H11a), 5.19 (m, 1 H, H2β), 6.73 (s, 1 H, H6), 7.68 (s, 1 H, H9). ^{13}C NMR ($CDCl_3$, 100 MHz) rotamers: δ 171.0 (OC═O), 166.3 (C5), 154.0 (C7), 149.1 (C8), 137.6 (C5a), 127.8 (C9a), 109.1 (C6), 107.3 (C9), 72.9 (*C*2), 62.6 (C11), 57.4 (C11a), 56.5, 56.6 (7-OCH_3 and 8-OCH_3), 52.0 (C3), 33.0 (C1), 25.7 ($C(CH_3)_3$), 21.2 ($OCOCH_3$), 18.1 (Cquat), −5.5 ($SiCH_3)_2$). MS (ESI^+) *m*/*z* (relative intensity): 483.0 ($[M + H]^{+}$, 100%). Anal. Calcd for $C_{22}H_{34}N_2O_8Si$: C, 54.75; H, 7.10; N, 5.80%. Found: C, 54.50; H, 7.08; N, 5.79%. See Supporting Information for synthesis of building block **2**.

(3*R*,5*S*)-1-(2-Amino-4,5-dimethoxybenzoyl)-5-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidin-3-yl Acetate (4). Palladium on charcoal catalyst (6.17 g, 10% w/w) was added as a slurry in EtOAc (***CAUTION:*** *pyrophoric*) to a solution of **3** (61.75 g, 127.9 mmol, 1 equiv) in ethanol (400 mL). The reaction mixture was agitated under an atmosphere of hydrogen (45 psi) in a Parr apparatus for 3 h. The mixture was filtered through celite, and the solvent was removed

under reduced pressure (120 mbar, 40 °C) to afford **4** as brown-yellow oil (57.5 g, 99%). R_f: 0.16 (EtOAc/hexane 6:4). $[\alpha]_D^{19}$: −105.1° (c = 0.49, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 3455, 3355 (NH_2), 2931, 2857, 1740 (OC═O), 1628 (NC═O), 1594, 1516, 1401, 1238, 1165, 1120, 1006, 837, 778, 668. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 6 H, Si-$(CH_3)_2$), 0.88 (s, 9 H, C$(CH_3)_3$), 1.98 (s, 3 H, OCOCH_3), 2.09−2.15 (m, 1 H, H1α), 2.32−2.39 (m, 1 H, H1β), 3.57−3.64 (m, 2 H, H3α and H11), 3.73−3.77 (m, 4 H, H3β and 8-OCH_3), 3.82 (s, 3 H, 7-OCH_3), 4.00−4.11 (m (br), 1 H, H11), 4.40−4.60 (m, 1 H, H11a), 5.21−5.27 (m, 1 H, H2β), 6.21 (s, 1 H, H9), 6.69 (s, 1 H, H6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6 (OC═O), 170.0 (C5), 151.9 (C7), 141.7 (C9a), 140.9 (C8), 112.2 (C6), 110.9 (C5a), 100.6 (C9), 73.5 (C2), 62.6 (C11), 57.0 (C11a), 55.8, (7-OCH_3), 56.6 (8-OCH_3), 56.3 (C3), 32.9 (C1), 25.8 (C$(CH_3)_3$), 21.1 (OCOCH_3), 18.1 (Cquat), −5.5 (Si$CH_3)_2$). MS (ESI^+) m/z (relative intensity): 453.1 ($[M + H]^{\cdot+}$, 100%).

(3*R*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(4,5-dimethoxy-2-((2,2,2-trichloroethoxy)carbonylamino)-benzoyl)pyrrolidin-3-yl Acetate (5). 2,2,2-Trichloroethyl chloroformate (1.6 mL, 11.7 mmol, 2.2 equiv) was added to a cooled (−20 °C), stirred solution of **4** (2.40 g, 5.3 mmol, 1.0 equiv) and pyridine (1.7 mL, 21.2 mmol, 4.0 equiv) in dry DCM (70 mL). The mixture was allowed to warm to room temperature over a period of 2.5 h. The initial workup involved washing with NH_4Cl (60 mL), $CuSO_4$ (60 mL), water (60 mL), and brine (60 mL). The organic layer was dried over $MgSO_4$, and the excess solvent was removed under reduced pressure to afford **5** as a colorless oil (3.32 g, 99%). R_f: 0.59 (EtOAc/hexane 6:4). $[\alpha]_D^{20}$: − 43.4° (c = 0.98, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 3318, 2954, 2858, 1774, 1743 (OC═O and OC═ON), 1601 (NC═O), 1525, 1464, 1422, 1398, 1230, 1200, 1125, 1004, 836, 777, 720. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.28 (s, 6 H, Si$(CH_3)_2$), 0.87 (s, 9 H, C$(CH_3)_3$), 1.96 (s, 3 H, OCOCH_3), 2.10−2.16 (m, 1 H, H1α), 2.35−2.41 (m, 1 H, H1β), 3.55−3.65 (br m, 1 H, H3α), 3.68−3.74 (m, 2 H, H11 and H3β), 3.78 (s, 3 H, 7-OCH_3), 3.91 (s, 3 H, 8-OCH_3), 4.06−4.10 (m, 2 H, Cl_3CCH_2 rotamers and H11), 4.55−4.65 (m, 1 H, H11a), 4.74−4.82 (m, 1 H, Cl_3CCH_2, rotamers), 5.20−5.25 (m, 1 H, H2β), 6.75 (s, 1 H, H6), 7.82 (br s, 1 H, H9), 9.38 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5 (OC═O), 169.2 (C5), 153.1 and 151.4 (OC═ONH, rotamers), 151.9 (C8), 144.1 (C7), 132.2 (C5a), 114.8 (C9a), 111.1 (C6), 104.3 (C9), 95.3 and 93.9 (Cl_3C, rotamers), 77.3 and 76.3 (Cl_3CCH_2, rotamers), 73.4 (C2), 62.3 (C11), 57.3 (C11a), 57.2 (C3), 56.1, 56.2 (7-OCH_3 and 7-OCH_3), 32.5 (C1), 25.8 (C$(CH_3)_3$), 21.1 (OCOCH_3), 18.1 (Cquat), −5.5 (Si$CH_3)_2$). MS (ESI^+) m/z (relative intensity): 629.0 ($[M + H]^{\cdot+}$, 100%).

(3*R*,5*S*)-1-(4,5-Dimethoxy-2-((2,2,2-trichloroethoxy)carbonylamino)benzoyl)-5-(hydroxymethyl)pyrrolidin-3-yl Acetate (6). Aqueous acetic acid (AcOH 81 mL, water 18 mL) was added to a solution of **5** (5.10 g, 8.1 mmol, 1.0 equiv) in THF (45 mL). The resulting solution was stirred at room temperature for over 48 h. The excess THF was then removed under reduced pressure, and the resulting mixture was neutralized with saturated $NaHCO_3$ to pH 7.0 (***CAUTION:*** *vigorous effervescence*). The resulting aqueous layer was extracted with DCM (5 × 150 mL), which was then dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/petroleum ether 6:4) to give **6** as a colorless oil (4.16 g, 99%). R_f: 0.02 (EtOAc/hexane 6:4). $[\alpha]_D^{18}$: − 65.0° (c = 0.50, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 3358 (br NH and OH), 3015, 2941, 1740 (OC═O and OC═ON), 1602 (NC═O), 1525, 1463, 1433, 1398, 1231, 1174, 1125, 1037, 969, 817, 756. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.01 (s, 3 H, OCOCH_3), 2.05−2.13 (m, 1 H, H1β), 2.27 (dd, 1 H, J = 14.2, 7.6 Hz, H1α), 3.62 (d, 1 H, J = 12.4 Hz, H3α), 3.65−3.74 (m, 1 H, H11), 3.76 (dd, 1 H, J = 12.6, 3.8 Hz, H3β), 3.85 (s, 3 H, 7-OCH_3), 3.93 (s, 3 H, 8-OCH_3), 3.98−4.08 (m, 1 H, H11), 4.55−4.65 (m, 1 H, H11a), 4.79 (d, 1 H, J = 12.1 Hz, Cl_3-CCH_2), 4.84 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.18−5.25 (m, 1 H, H2β), 6.80 (s, 1 H, H6), 7.73 (br s, 1 H, H9), 9.03 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6 (OC═O), 170.4 (C5), 152.1 (OC═ONH), 151.5 (C8), 144.6 (C7), 131.2 (C5a), 115.5 (C9a), 110.8 (C6), 104.8 (C9), 95.3 (Cl_3C), 74.4 (Cl_3CCH_2), 72.5 (C2), 64.5 (C11), 58.8 (C11a), 56.6 (C3), 56.5 (7-OCH_3), 56.1 (8-OCH_3), 33.7 (C1), 21.1 (OCOCH_3). MS (ESI^+) m/z (relative intensity): 363.1 ($[M - Cl_3CCH_2O + H]^{\cdot+}$, 100%), 513.1 ($[M + H]^{\cdot+}$, 95%).

2*R*-Acetoxy-11*S*-hydroxy-7,8-dimethoxy-5-oxo-1,2,3,10,11,11a-hexahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10-carboxylic Acid 2,2,2-Trichloro-ethyl Ester (7). Diodobenzene diacetate (83.7 g, 259.8 mmol, 1.78 equiv) and 2,2,6,6-tetramethylpiperidine nitroxyl (TEMPO) (4.50 g, 28.8 mmol, 0.2 equiv) were added to solution of **6** (74.7 g, 145.4 mmol, 1.0 equiv) in dry DCM (1.5 L), and the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with DCM (500 mL) and washed with a saturated solution of sodium bisulphite (700 mL). The aqueous layer was back-extracted with DCM (3 × 400 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (EtOAc/petroleum ether 7:3) afforded **7** as a colorless solid (57.65 g, 77%). R_f: 0.34 (EtOAc). $[\alpha]_D^{18}$: + 99.4° (c = 0.48, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 3421 (br OH), 3008, 2946, 1719 (OC═O and OC═ON), 1623 (NC═O), 1603, 1515, 1429, 1374, 1304, 1238, 1212, 1057, 870, 819, 758, 711, 644. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.04 (s, 3 H, OCOCH_3), 2.34−2.46 (m, 2 H, H1β and H1α), 3.69−3.77 (m, 2 H, H3β and 11a), 3.92 (s, 3 H, 8-OCH_3), 3.95 (s, 3 H, 7-OCH_3), 4.05 (dd, 1 H, J = 13.1, 2.4 Hz, H3α), 4.23 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.25 (d, 1 H, J = 12.0 Hz, Cl_3-CCH_2), 5.38 (p, 1 H, J = 4.1 Hz, H2β), 5.70 (dd, 1 H, J = 9.7, 3.8 Hz, H11), 6.81 (s, 1 H, H9), 7.27 (s, 1 H, H6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3 (OC═O), 167.4 (C5), 154.4 (OC═ONH), 151.1 (C8), 148.8 (C7), 127.5 (C9a), 124.7 (C5a), 112.7 (C9), 110.7 (C6), 95.0 (Cl_3C), 87.6 (C11), 75.0 (Cl_3CCH_2), 71.4 (C2), 58.3 (C11a), 56.19 and 56.13 (8-OCH_3 and 7-OCH_3), 51.1 (C3), 35.9 (C1), 21.0 (OCOCH_3). MS (ESI^+) m/z (relative intensity): 510.8 ($[M - H]^{\cdot+}$, 100%), 512.5 ($[M + H]^{\cdot+}$, 99%). HRMS: theoretical mass [M + $H]^{\cdot+}$, 511.0442; measured mass [M + $H]^{\cdot+}$, 511.0426 (δ 3 ppm).

2*R*-Acetoxy-11*S*-(*tert*-butyl-dimethyl-silanyloxy)-7,8-dimethoxy-5-oxo-1,2,3,10,11,11a-hexahydro-1*H*,5*H*-pyr-

rolo[2,1-*c*][1,4]benzodiazepine-10-carboxylic Acid 2,2,2-Trichloro-ethyl Ester (8). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.6 mL, 2.4 mmol, 1.5 equiv) was added to a stirred solution of **7** (834 mg, 1.6 mmol, 1.0 equiv) and 2,6-lutidine (0.4 mL, 3.3 mmol, 2.0 equiv) in dry DCM (5 mL), and the stirring was continued for 30 min at room temperature. The reaction mixture was then diluted with DCM (20 mL), and the organic layer was washed with saturated $CuSO_4$ (2 × 20 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo to afford **8** as a colorless solid (1.01 g, 99%). R_f: 0.35 (EtOAc/hexane 6:4). $[\alpha]_D^{18}$: + 52.7° (c = 0.237, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 3023, 2956, 1738 (OC═O), 1718 (OC═ON), 1644 (NC═O), 1605, 1518, 1466, 1428, 1411, 1376, 1301, 1245, 1214, 1116, 1075, 1041, 1023, 842, 784, 756, 730, 712. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.23 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $C(CH_3)_3$), 2.03 (s, 3 H, $OCOCH_3$), 2.18−2.25 (m, 1 H, H1β), 2.30−2.40 (m, 1 H, H1α), 3.66−3.72 (m, 2 H, H3β and 11a), 3.89 (s, 3 H, 8-OCH_3), 3.95 (s, 3 H, 7-OCH_3), 4.13 (d, 1 H, J = 13.4 Hz, H3α), 4.18 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.23 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.37 (p, 1 H, J = 2.6 Hz, H2β), 5.77 (d, 1 H, J = 8.9 Hz, H11), 6.74 (s, 1 H, H9), 7.28 (s, 1 H, H6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3 (OC═O), 167.9 (C5), 153.5 (OC═ONH), 151.0 (C8), 148.9 (C7), 128.0 (C9a), 125.4 (C5a), 112.9 (C9), 110.6 (C6), 95.2 (Cl_3C), 88.2 (C11), 74.7 (Cl_3CCH_2), 71.7 (C2), 60.5 (C11a), 56.1 (7-OCH_3), 56.9 (8-OCH_3), 51.2 (C3), 36.2 (C1), 25.5 ($C(CH_3)_3$) 21.0 ($OCOCH_3$), 17.8 (Cquat), − 4.3 and −5.3 ($Si(CH_3)_2$). MS (ESI^+) m/z (relative intensity): 627.1 ($[M + H]^{\cdot+}$, 100%). HRMS: theoretical mass $[M + H]^{\cdot+}$, 625.1307; measured mass $[M + H]^{\cdot+}$, 625.1277 (δ 5 ppm).

11*S*-(*tert*-Butyl-dimethyl-silanyloxy)-2*R*-hydroxy-7,8-dimethoxy-5-oxo-1,2,3,10,11,11a-hexahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10-carboxylic Acid 2,2,2-Trichloro-ethyl Ester (9). An aqueous solution of K_2CO_3 (732 mg, 5.3 mmol, 1.0 equiv) in water (15 mL) was added to a stirred solution of **8** (3.32 g, 5.3 mmol, 1.0 equiv) in MeOH (15 mL) and THF (5 mL). The reaction mixture was stirred at room temperature for a minimum of 5 h. Excess solvent was removed by rotary evaporation under reduced pressure, and the remaining aqueous solution was neutralized to pH 7.0 with 1 N HCl. The aqueous layer was extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was subjected to flash chromatography (EtOAc) to afford **9** as a colorless solid (2.84 g, 92%). R_f: 0.24 (EtOAc). $[\alpha]_D^{22}$: +58.3° (c = 0.59, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 3400 (br OH), 2932, 1721 (OC═ON), 1629 (NC═O), 1604, 1515, 1456, 1430, 1407, 1302, 1273, 1214, 1117, 1075, 987, 837, 754, 712, 638. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.22 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $C(CH_3)_3$), 2.06−2.11 (m, 1 H, H1β), 2.28−2.33 (m, 1 H, H1α), 3.60 (dd, 1 H, J = 4.3, 12.7 Hz, H3β), 3.71 (q, 1 H, J = 7.4, 8.3 Hz, H11a), 3.88 (s, 6 H, 8-OCH_3 and 7-OCH_3), 4.01 (d, 1 H, J = 12.9 Hz, H3α), 4.17 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 4.58 (br s, 1 H, H2β), 5.23 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.54 (d, 1 H, J = 9.0 Hz, H11), 6.73 (s, 1 H, H9), 7.21 (s, 1 H, H6). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.4 (C5), 153.6 (OC═ONH), 151.9 (C8), 148.8 (C7), 128.0 (C9a), 125.5 (C5a), 112.8 (C9), 110.5 (C6), 95.2 (Cl_3C), 88.2 (C11), 74.7 (Cl_3CCH_2), 69.5 (C2), 60.8 (C11a), 56.0, 55.9 (7-OCH_3 and 8-OCH_3), 54.0 (C3), 38.8 (C1), 25.6 ($C(CH_3)_3$), 17.8 (Cquat), − 4.2 and −5.2 ($Si(CH_3)_2$). MS (ESI^+) m/z (relative intensity): 585.1 ($[M + H]^{\cdot+}$, 100%).

11*S*-(*tert*-Butyl-dimethyl-silanyloxy)-7,8-dimethoxy-2,5-dioxo-1,2,3,10,11,11a-hexahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-10-carboxylic Acid 2,2,2-Trichloro-ethyl Ester (10). Diodobenzene diacetate (2.44 g, 7.6 mmol, 1.78 equiv) and 2,2,6,6-tetramethylpiperidine nitroxyl (TEMPO) (133 mg, 0.9 mmol, 0.2 equiv) were added to a solution of **9** (2.49 g, 4.3 mmol, 1.0 equiv) in dry DCM (40 mL). The mixture was stirred at room temperature for 18 h. It was then diluted with DCM (50 mL), washed with a saturated solution of sodium bisulphite (2 × 25 mL) and brine (40 mL), and dried over $MgSO_4$, and the excess solvent was removed under reduced pressure. Flash chromatography (EtOAc/hexane 6:4) afforded **10** as a colorless solid (2.26 g, 91%). R_f: 0.62 (EtOAc). $[\alpha]_D^{22}$: +95.0° (c = 0.80, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 2934, 1763 (C2═O), 1720 (OC═ON), 1649 (NC═O), 1604, 1515, 1402, 1274, 1217, 1120, 1075, 1002, 866, 834, 756, 712. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.22, 0.23 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $C(CH_3)_3$), 2.56 (dd, 1 H, J = 3.1, 19.6, H1β), 2.96 (dd, 1 H, J = 10.3, 18.9, H1α), 3.90 (s, 3 H, 8-OCH_3), 3.95−3.99 (m, 5 H, H3β, H11a and 7-OCH_3), 4.21 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 4.32 (d, 1 H, J = 20.9 Hz, H3α), 5.24 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.83 (d, 1 H, J = 9.3 Hz, H11), 6.77 (s, 1 H, H9), 7.25 (s, 1 H, H6). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.8 (C2), 168.0 (C5), 153.7 (OC═ONH), 151.4 (C8), 149.2 (C7), 128.0 (C9a), 124.5 (C5a), 113.0 (C9), 110.4 (C6), 95.1 (Cl_3C), 87.4 (C11), 74.8 (Cl_3CCH_2), 58.9 (C11a), 56.2 (7-OCH_3), 56.0 (8-OCH_3), 52.8 (C3), 40.3 (C1), 25.5 ($C(CH_3)_3$), 17.8 (Cquat), − 4.2 and −5.3 ($Si(CH_3)_2$). MS (ESI^+) m/z (relative intensity): 615.1 ($[M + MeOH + H]^{\cdot+}$, 100%). HRMS: theoretical mass $[M + H]^{\cdot+}$, 581.1044; measured mass $[M + H]^{\cdot+}$, 581.1057 (δ 2 ppm).

11*S*-(*tert*-Butyl-dimethyl-silanyloxy)-7,8-dimethoxy-5-oxo-2-trifluoromethanesulfonyloxy-1,10,11,11a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10-carboxylic Acid 2,2,2-Trichloro-ethyl Ester (11). Anhydrous pyridine (4.37 mL, 54.1 mmol, 9.0 equiv) and triflic anhydride (sealed ampule, 8.90 mL, 52.9 mmol, 8.8 equiv) were added to a cold (ice bath), vigorously stirred solution of **10** (3.5 g, 6.0 mmol, 1.0 equiv) in dry chloroform (100 mL). The ice bath was removed, and the reaction mixture was allowed to stir at room temperature for a minimum of 3 h. At this point, TLC analysis still showed the presence of starting material. An additional equivalent of pyridine and Tf_2O were added (0.48 and 1.0 mL, respectively), and the reaction was continued for a further hour. The reaction mixture was then diluted with chloroform (100 mL) and washed with water (100 mL), saturated $CuSO_4$ (100 mL), and saturated $NaHCO_3$ (100 mL). The organic layer was dried over $MgSO_4$, and the solution was concentrated in vacuo. The residue was subjected to purification by flash chromatography (EtOAc/petroleum ether 2:8) to give **11** as a light yellow solid (2.33 g, 55%) and remaining starting material **10** (240 mg, 14%).

R_f: 0.53 (EtOAc/hexane 4:6). $[\alpha]_D^{22}$: +56.2° (c = 0.59, $CHCl_3$). IR (film, ν_{max}, cm^{-1}): 3008, 2930, 2858, 1725 (OC═ON), 1651 (NC═O), 1516, 1423, 1214, 1136, 1078, 897, 835, 783, 760, 713, 642. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.25, 0.27 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $C(CH_3)_3$), 2.82 (dd, 1 H, J = 2.8, 16.7 Hz, H1β), 3.33 (ddd, 1 H, J = 2.0, 10.7, 16.6 Hz, H1α), 3.90 (s, 3 H, 8-OCH_3), 3.94 (s, 3 H, 7-OCH_3), 3.88−3.96 (m, 1 H, H11a), 4.20 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.23 (d, 1 H, J = 12.0 Hz, Cl_3CCH_2), 5.93 (d, 1 H, J = 9.3 Hz, H11), 6.74 (s, 1 H, H9), 7.17 (s, 1 H, H3), 7.23 (s, 1 H, H6). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.9 (C5), 153.6 (OC═ONH), 151.8 (C8), 149.3 (C7), 136.0 (C2), 127.9 (C9a), 123.8 (C5a), 121.0 (C3), 118.5 (q, J = 256 Hz from $^{13}C^{19}F_3$ coupling, CF_3), 113.2 (C9), 110.7 (C6), 95.1 (Cl_3C), 86.4 (C11), 74.9 (Cl_3CCH_2), 60.6 (C11a), 56.2 (7-OCH_3), 56.0 (8-OCH_3), 34.4 (C1), 25.5 ($C(CH_3)_3$), 17.8 (Cquat), − 4.2 and −5.4 ($Si(CH_3)_2$). MS (ESI^+) m/z (relative intensity): 715.0 ($[M + H]^{\bullet+}$, 100%). HRMS: theoretical mass $[M + H]^{\bullet+}$, 713.0537; measured mass $[M + H]^{\bullet+}$, 713.0519 (δ 3 ppm).

Trifluoro-methanesulfonic Acid 7,8-dimethoxy-5-oxo-1,11a*S*-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-2-yl Ester (20). A freshly prepared aqueous solution of ammonium acetate (1.3 mL) was poured into a solution of **11** (166 mg, 0.23 mmol, 1.0 equiv) in THF (2 mL). While the mixture was vigorously stirred, 10% Cd/Pb (232 mg, 5.60 mmol, 8.0 equiv) was added to the reaction mixture. After the mixture was stirred 2 h at room temperature, TLC analysis showed no starting material. $CHCl_3$ (8 mL) and water (4 mL) were added to the mixture, followed by extraction in a separating funnel. The organic layer was dried over $MgSO_4$, filtered, and evaporated under vacuum. The resulting oil was purified by flash chromatography (EtOAc/hexane 5:5) to give **20** as a yellow solid (88 mg, 94%). IR (ATR, ν_{max}, cm^{-1}): 3008, 2934, 1627, 1604, 1512, 1421, 1329, 1249, 1207, 1136, 1069, 907, 830, 787, 765. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.38 (ddd, 1 H, J = 1.84, 5.64, 16.54 Hz, H1β), 3.55 (ddd, 1 H, J = 2.04, 11.90, 16.41 Hz, H1α), 3.94 (s, 3 H, 8-OCH_3), 3.95 (s, 3 H, 7-OCH_3), 4.43 (ddd, 1 H, J = 4.02, 5.52, 11.88 Hz, H11a), 6.82 (s, 1 H, H9), 7.21 (t, 1 H, J = 1.94 Hz, H3), 7.46 (s, 1 H, H6), 7.87 (d, 1 H, J = 3.92 Hz, H11). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (C5), 160.8 (C11), 152.4 (C8), 148.1 (C7), 140.3 (C9a), 136.0 (C2), 120.9 (C3), 117.7 (C5a), 113.8 (CF_3), 111.6 (C6), 110.0 (C9), 56.2 (7-OCH_3 and 8-OCH_3), 53.1 (C11a), 34.5 (C1). MS (ESI^+) m/z (relative intensity): 291.92 ($[M - SO_2CF_3 + H_2O + H]^{\bullet+}$ 100%), 407.0 ($[M + H]^{\bullet+}$ 50%), 424.90 ($[M + H_2O + H]^{\bullet+}$ 20%). HRMS: theoretical mass $[M + H]^{\bullet+}$, 407.0525; measured mass $[M + H]^{\bullet+}$, 407.0529 (δ 1 ppm).

General Procedure for Parallel Synthesis of C2-Aryl PBD Imines (13−19) using Building Block 11. The synthesis of **13g** is described below as an example. The other library members were synthesized using the same method, and their spectroscopic and analytical data are provided in Supporting Information.

Polystyrene-supported triphenylphosphine palladium(0) ($PS\text{-}PPh_3Pd$, loading 0.1 mmol/g) (15 mg, 1.4 μmol, 0.01 equiv) was added to a solution of **11** (100 mg, 0.14 mmol, 1.0 equiv), 4-chlorophenylboronic acid (23.5 mg, 0.15 mmol, 1.1 equiv), and triethylamine (0.12 mL, 6.0 equiv) in toluene (1.0 mL), ethanol (1.0 mL), and water (0.2 mL) in an Emrys process vial which was sealed with a Reseal septum. The reaction mixture was subjected to microwave irradiation at 100 °C for 10 min (Optimizer Microwave Station, Personal Chemistry, Cambridge, U.K.). *N*,*N*-Diethanolaminomethyl polystyrene (PS-DEAM, loading 1.8 mmol/g) [87.5 mg, 0.14 mmol, 1.0 equiv (13 equiv on boronic acid excess)] was then added to the reaction mixture to sequester excess boronic acid, and irradiation was continued for a further 10 min at 100 °C. Water (3 mL) was then added into the vial, and the mixture was transferred to a phase-separator (PS) cartridge fitted with a selectively permeable frit and coupled to a Na_2SO_4 drying cartridge that had been pre-conditioned with DCM (3 mL). Extraction with DCM (2 × 5 mL), followed by parallel rotary evaporation under reduced pressure (ACTEvap Parallel Evaporation Unit, Advanced ChemTech, Louisville, KY) yielded the cross-coupled product (**13g** precursor) as an oil. Subsequently, 10% Cd/Pb couple[19] (140 mg, 1.12 mmol, 8.0 equiv) was added to a vigorously stirred solution of the Suzuki product (**13g** precursor) in THF (1.5 mL) and 1 N ammonium acetate (1.0 mL), and the reaction mixture was stirred at room temperature for 1 h. (Note: the time required may vary between 0.5 and 2.5 h according to the substrate.) The reaction mixture was then poured into an identical PS cartridge pre-conditioned with DCM and coupled to a Na_2SO_4 cartridge. After extraction with DCM (2 × 5 mL), the combined organic phase was concentrated with an ACTEvap to yield the crude PBD−imine **13g** as an oil. The crude material was subjected to preparative HPLC purification, followed by lyophilysation to produce 95.5% pure **13g** as a yellow solid (34.5 mg, 67%). $[\alpha]_D^{25}$: + 796° (c = 0.34, $CHCl_3$). IR (ATR, ν_{max}, cm^{-1}): 2934, 1623 (NC═O), 1598, 1507, 1449, 1424, 1382, 1263, 1213, 1092, 1008, 874, 819, 748, 666. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.38 (dd, 1 H, J = 5.1, 16.2 Hz, H1β), 3.58 (dd, 1 H, J = 11.6, 16.0 Hz, H1α), 3.95 (s, 3 H, 8-OCH_3), 3.97 (s, 3 H, 7-OCH_3), 4.44 (dt, 1 H, J = 4.6, 11.5 Hz, H11a), 6.84 (s, 1 H, H9), 7.27 (s, 2 H, H3′ and H5′), 7.32 (s, 2 H, H2′ and H6′), 7.50 (s, 1 H, H3), 7.52 (s, 1 H, H6), 7.90 (d, 1 H, J = 3.7 Hz, H11). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (C11), 161.6 (C5), 152.1 (C8), 147.8 (C7), 140.4 (C9a), 133.1 (C4′), 131.8 (C1′), 128.9 (C3′ and C5′), 126.0 (C2′ and C6′), 124.1 (C3), 122.1 (C2), 118.8 (C5a), 111.5 (C6), 109.8 (C9), 56.3 (7-OCH_3), 56.2 (8-OCH_3), 53.9 (C11a), 35.4 (C1). MS (ESI^+) m/z (relative intensity): 368.95 ($[M + H]^{\bullet+}$, 20%), 386.96 ($[M + H_2O + H]^{\bullet+}$, 100%). HRMS: theoretical mass $[M + H]^{\bullet+}$, 369.1000; measured mass $[M + H]^{\bullet+}$, 369.0993 (δ 2 ppm).

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Supporting Information Available. Structures, yields, optical rotations (selected entries), purity data (LC-MS), and

analytical data (selected FT-IR, one- and two-dimensional ^{1}H NMR, ^{13}C NMR, MS, and HRMS) are provided for all library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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