DOI 10.1007/s10593-020-02702-8

Chemistry of Heterocyclic Compounds **2020**, *56*(5), 572–577

Synthetic studies toward novel pyrrolobenzodiazepine–coumarin hybrids

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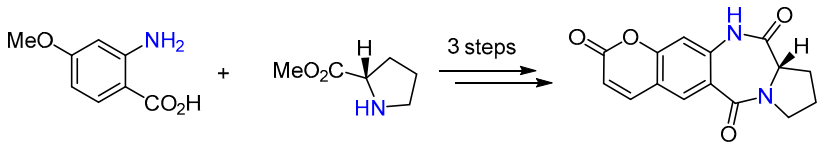
Published in Khimiya Geterotsiklicheskikh Soedinenii, 2020, *56*(5), 572–577

Submitted January 16, 2020
Accepted after revision May 11, 2020



New type of PBD–coumarin hybrids

A comprehensive screening of known methods for the synthesis of coumarins was performed in order to obtain a new type of pyrrolobenzodiazepine–coumarin hybrids. A Pechmann condensation turned out to be the method of choice for successful synthesis of the desired hybrid starting from the corresponding phenol derivative and malic acid. Overall, the desired pyrrolobenzodiazepine–coumarin hybrid was obtained in a 3 step sequence starting from readily available starting materials – L-proline methyl ester and 4-methoxyanthranilic acid.

Keywords: coumarin, pyrrolobenzodiazepines, pyrrolobenzodiazepine–coumarin hybrids, anticancer agents.

The pyrrolobenzodiazepines (PBDs) **1** are naturally occurring antitumor antibiotics typically possessing tricyclic right-handed twisted ring system due to an *S*-configuration of the chiral center at C(11a) atom (Fig. 1). This 3D setting allows the molecule perfectly fit within the minor groove of DNA and covalently bind to the guanine base with the electrophilic N(10)=C(11) moiety.[1–5] The first isolated member of PBD class was anthramycin **2** found in thermophilic actinomycete *Streptomyces refuineus* and published in 1965 by Leimgruber et al.[6] Since then a number of PBD monomers, dimers, and antibody-drug conjugates (ADC) **3** have been evaluated in clinical trials for cancer treatment.[7,8]

An important aspect of anticancer drug efficacy is their cellular localization. It was proposed that PBDs exhibit DNA sequence recognition properties, covalently binding purine–guanine–purine sites by their electrophilic N(10)=C(11) imine moiety.[1–5] A few attempts were made in the light of this theory to create PBD conjugates marked with fluorescent dye for the *in vitro* bioimaging studies. However, in general these compounds lack bioavailability, which can probably be explained by the fact that all conjugates made had a fluorescent dye connected to PBD through a linker.[9,10]

Herein we would like to report our attempts to elaborate synthetic method for the preparation of fused PDB–coumarins bearing imine moiety in position 7 of the

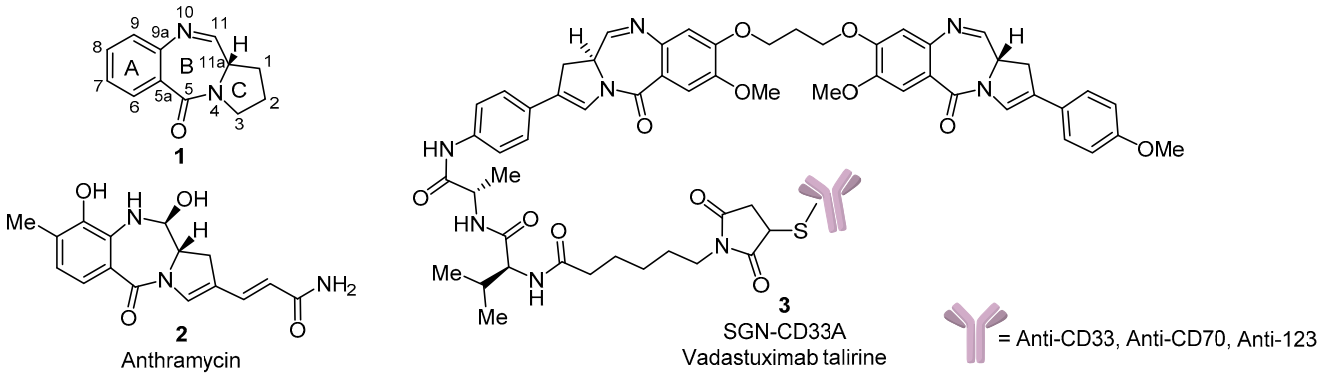
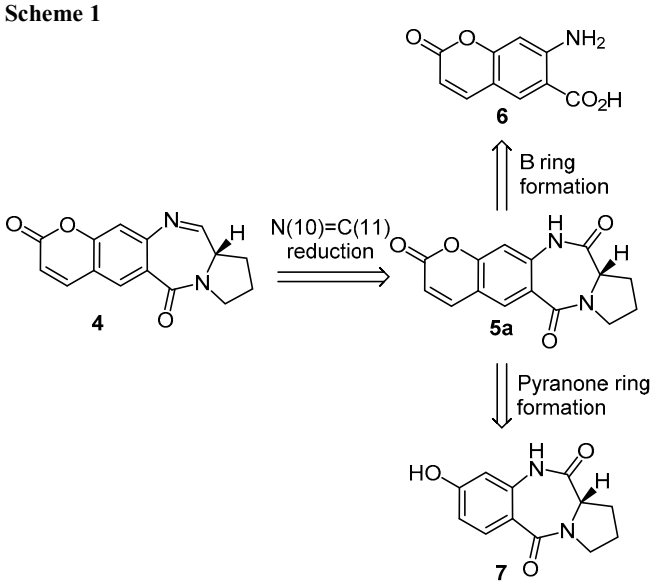


Figure 1. Structures of the representative PBDs.

coumarin ring. It was expected that planar iminocoumarin reacting with guanine residue would convert into a well-known fluorescent 7-aminocoumarin derivative suitable for bioimaging.

Retrosynthetically, we envisioned that the last step of PBD–coumarin hybrid **4** synthesis would be the introduction of the labile N(10)=C(11) imine moiety *via* reduction of the corresponding dilactam **5a** (Scheme 1). For the synthesis of the necessary dilactam **5a**, two different strategies could be employed. One possibility would be a formation of the B ring of PBD fragment starting from the functionalized coumarin **6**. Another option would be cyclization of the pyranone ring, starting from PBD derivative **7**. Both strategies were examined for the synthesis of intermediate **5a**.

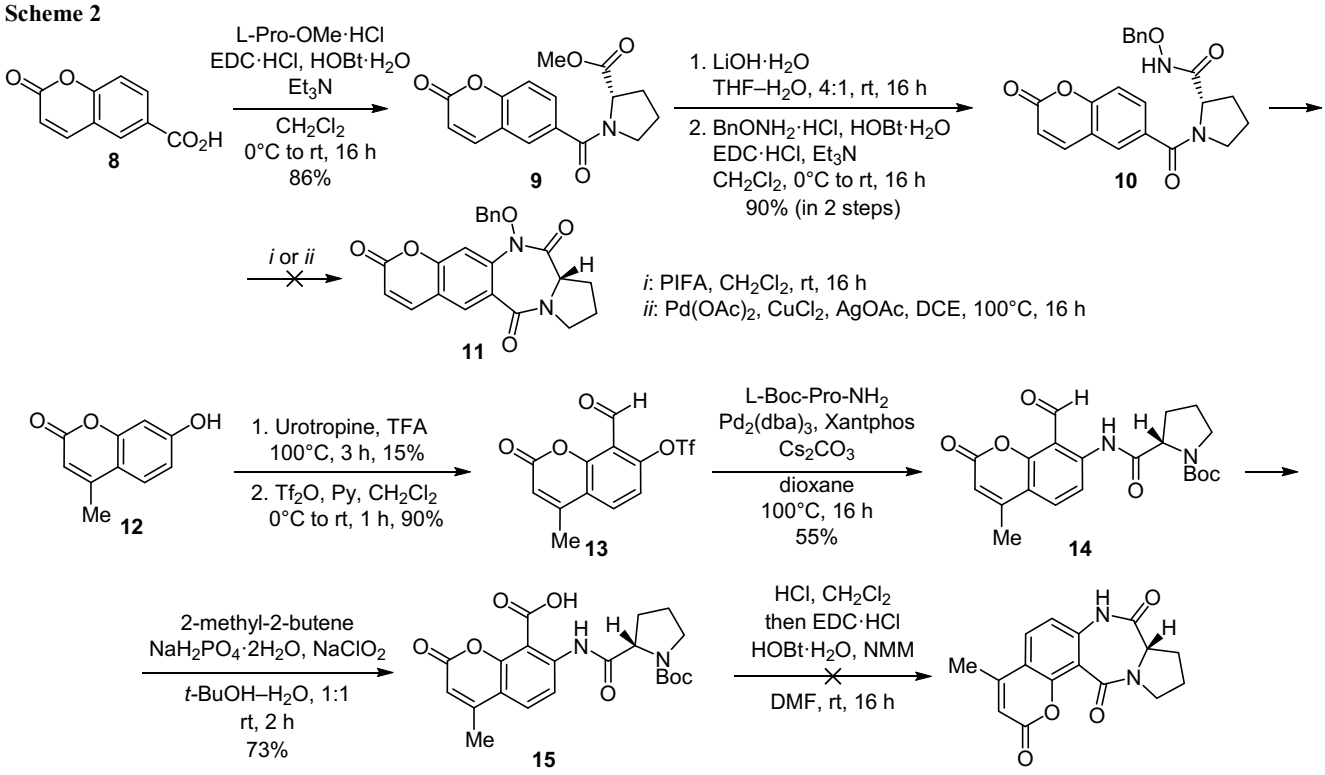
Scheme 1



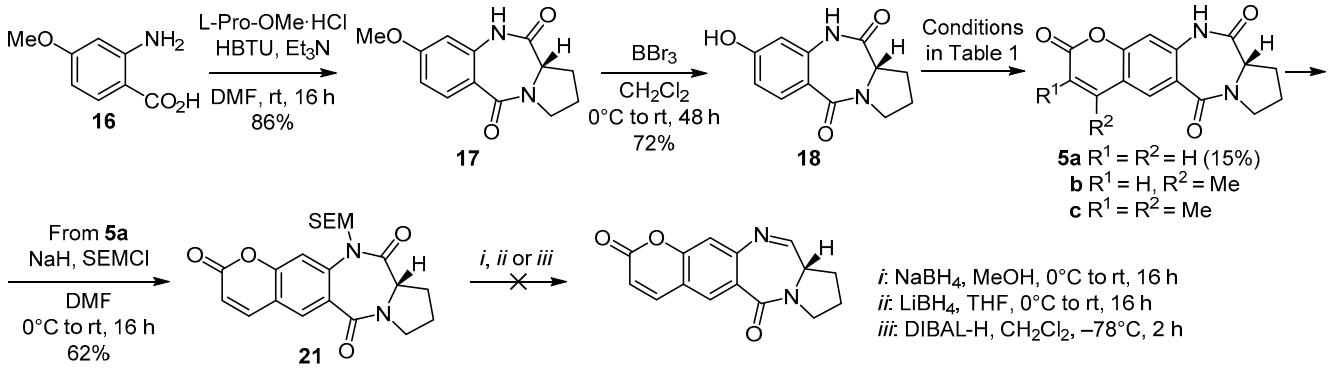
First, two different strategies for the formation of the B ring of PBD–coumarin hybrid **5a** were studied. The first approach was based on CH activation. The necessary cyclization precursor **10** was prepared in a three-step sequence starting from a commercially available 2-oxo-2*H*-chromene-6-carboxylic acid (**8**) (Scheme 2). Acid **8** was coupled to a proline ester, furnishing amide **9**. Hydrolysis of the ester fragment in intermediate **9**, followed by an amide coupling gave the desired precursor **10** for the B ring formation in a good overall yield. With intermediate **10** in hand, we turned our attention toward the CH activation-based cyclization step. Unfortunately, neither the hypervalent iodine approach[11] nor the Pd catalysis[12] gave the desired product **11**. In both cases, only the degradation of starting materials was observed.

Alternatively, attempts were made to cyclize B ring by lactonization reaction. The necessary intermediate for this strategy was prepared from commercially available 7-hydroxy-4-methyl-2*H*-chromen-2-one (**12**). First, aldehyde moiety was introduced using urotropine/TFA and the obtained intermediate was subsequently treated with Tf_2O to give triflate **13**. Although the structure of the final PBD–coumarin hybrid would be different we decided to continue the synthesis with triflate **13**, because regioisomer of the target compound would react with guanine residues in DNA in a similar manner forming fluorescent coumarin adduct with amino group in position 7. Palladium-catalyzed coupling[13] of intermediate **13** with a proline derivative gave the desired amide **14**, the aldehyde moiety of which was further oxidized giving the corresponding carboxylic acid **15**. Finally, the Boc protecting group was

Scheme 2



Scheme 3



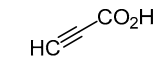
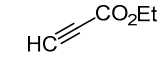
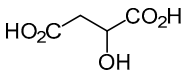
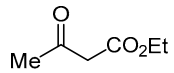
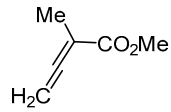
successfully cleaved under acidic conditions and the obtained intermediate was subjected to peptide coupling. Unfortunately, lactonization product was not observed by LC/MS even after adding of the additional amount of coupling reagents.

After unsuccessful attempts for the B ring cyclization, we turned our attention toward an alternative approach employing a pyranone ring formation in the last steps of the synthesis. The necessary building block **18** for this strategy was prepared in a two-step procedure from a commercially available 4-methoxyanthranilic acid (**16**) (Scheme 3). First, 4-methoxyanthranilic acid (**16**) and L-proline methyl ester were coupled together employing our previously developed methodology[14] furnishing dilactam **17** in 86% yield. Next, treatment of dilactam **17** with BBr_3 smoothly furnished phenol derivative **18** in 72% yield.

With building block **18** in hand, we further screened the known methods for coumarin cyclization from the corresponding phenols (Table 1). By using propiolic acid for cyclization under Brønsted acid[15] (entry 1), Lewis acid (entry 2),[16] or transition metal catalysis[17] (entry 3), only degradation of substrate **18** was observed. Also, a condensation/cyclization sequence with ethyl propiolate promoted either by Lewis acid[18] (entry 4) or palladium catalysis[19] (entry 5) failed in our hands. To our delight, employing the Pechmann[20] condensation protocol, the desired PDB–coumarin hybrid **5a** was isolated as a mixture of regioisomers, however only in 15% yield (entry 6). Our further attempts in synthesizing substituted coumarins, unfortunately, were also unsuccessful. Treatment of a mixture containing phenol building block **18** and ethyl acetoacetate with H_2SO_4 (entry 7) or $AlCl_3$ (entry 8) caused only degradation of the starting phenol **18**. Also, the protocol described by Kwon's group[21] (entry 9) was not successful for this particular substrate. Despite the low isolated yield, the concise synthesis of PDB–coumarin hybrid **5a** employing a combination of malic and sulfuric acid (entry 6) allowed to easily obtain gram quantities of this crucial building block. With sufficient quantities of compound **5a** in hand, we further studied the C(11) amide group reduction step.

As it is known from the literature,[22] for the selective reduction of C(11) carbonyl group in PBD–dilactams, the neighboring N(10) nitrogen atom has to be appropriately functionalized. For this purpose, protected derivative of

Table 1. Reagents and conditions for the cyclization of compound **18**

Entry	Reagent	Conditions	Product	Yield, %
1		TfOH, chlorobenzene, 100°C, 1 h	**5a**	<5
2		$Yb(OTf)_3$, dioxane, MW, 90°C, 10 min		<5
3		TFA, K_2PtCl_4, AgOTf, rt, 24 h		<5
4		$ZnCl_2$, dioxane, 110°C, 1 h		<5
5		$Pd(dba)_3·CHCl_3$, NaOAc, HCO_2H		<5
6		H_2SO_4, rt, 0.5 h, then 120°C, 18 h		15
7		70% H_2SO_4 in EtOH, rt, 16 h	**5b**	<5
8		$AlCl_3$, nitrobenzene, 130°C, 3 h		<5
9		PPh_3, PhH, 80°C, 24 h, then diethylaniline, 200°C, 24 h	**5c**	<5

dilactam **5a** was synthesized (Scheme 3). By the treatment of dilactam **5a** with NaH, followed by 2-(trimethylsilyl)-ethoxymethyl chloride (SEMCl), the corresponding intermediate **21** was obtained in 62% yield. A further reduction of compound **21** employing three different conditions failed in our hands. In all cases unidentified side reactions took place, resulting in a cleavage of the pyranone ring.

In summary, a number of the literature-known methods were tested for the synthesis of a new type of PBD–coumarin hybrids. It was found that only employing Pechmann condensation the desired hybrids can be obtained in significant quantities. The newly developed methodology allowed synthesis of the desired PBD–coumarin hybrid in only 3 steps from commercially available starting materials.

Experimental

IR spectra were recorded on a Shimadzu Prestige-21 FTIR spectrometer in the 4000–600 cm^{-1} range in thin films. ^1H NMR spectra were recorded on a Varian Mercury (400 MHz) spectrometer in $CDCl_3$ (compounds **9**, **10**, **13**–**15**,

21a) and a Bruker (300 MHz) spectrometer in $CDCl_3$ (compound **17**) or MeOH-d_4 (compound **18**). ^{13}C NMR spectra were recorded on a Varian Mercury (100 MHz) spectrometer in $CDCl_3$ (compounds **9**, **10**, **13**–**15**, **21a**) or MeOH-d_4 (compounds **17**, **18**). Chemical shift values are referenced against residual protons in the deuterated solvents ($CDCl_3$: 7.26 ppm for ^1H nuclei, 77.2 ppm for ^{13}C nuclei; MeOH-d_4: 3.31 ppm for ^1H nuclei, 49.0 ppm for ^{13}C nuclei). HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer (ESI). Optical rotations were measured using a PerkinElmer 141 polarimeter. Melting points were determined using a Stanford Research System MPA100 automated melting point apparatus and are uncorrected.

All reactions were performed under an atmosphere of argon unless indicated otherwise. Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. Flash chromatography was carried out using Merck Kieselgel (230–400 mesh).

Methyl (2*S*)-1-[(2-oxo-2*H*-chromen-6-yl)carbonyl]-pyrrolidine-2-carboxylate (9). Et_3N (0.88 ml, 6.311 mmol, 3.00 equiv) was added to a mixture of 2-oxo-2*H*-chromene-6-carboxylic acid (**8**) (400 mg, 2.104 mmol, 1.00 equiv), L-Pro-OMe·HCl (418 mg, 2.524 mmol, 1.20 equiv), EDC·HCl (605 mg, 3.155 mmol, 1.50 equiv), and HOBt·H_2O (483 mg, 3.155 mmol, 1.50 equiv) in CH_2Cl_2 (10 ml) at 0°C. The resulting mixture was allowed to warm up to room temperature and stirred overnight, then H_2O and CH_2Cl_2 were added. The organic phase was separated, and the H_2O phase was extracted with CH_2Cl_2 (2×50 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent petroleum ether – EtOAc, gradient from 2:1 to 0:1). Yield 544 mg (86%), beige solid, mp 130–133°C, $[\alpha]_D^{20}$ –73.20° (*c* 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1746, 1622, 1448, 1175. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.80–7.62 (3H, m, H Ar); 7.34 (1H, d, *J* = 9.0, H Ar); 6.46 (1H, d, *J* = 9.6, H Ar); 4.67 (1H, dd, *J* = 8.4, *J* = 4.9, CH); 3.77 (3H, s, OCH_3); 3.73–3.62 (1H, m, CH_2); 3.61–3.50 (1H, m, CH_2); 2.39–2.28 (1H, m, CH_2); 2.11–1.85 (3H, m, CH_2). ^{13}C NMR spectrum, δ, ppm: 172.6; 168.0; 160.2; 155.1; 143.1; 132.6; 130.9; 127.6; 118.7; 117.7; 117.0; 59.4; 52.5; 50.2; 29.4; 25.5. Found, *m*/*z*: 302.1036 $[M+H]^+$. $C_{16}H_{16}NO_5$. Calculated, *m*/*z*: 302.1028.

(2*S*)-*N*-(Benzoxy)-1-[(2-oxo-2*H*-chromen-6-yl)carbonyl]-pyrrolidine-2-carboxamide (10). LiOH·H_2O (76 mg, 3.156 mmol, 3.00 equiv) was added to a solution of compound **9** (317 mg, 1.052 mmol, 1.00 equiv) in THF (8 ml) and H_2O (2 ml), and the resulting mixture was stirred overnight at room temperature. THF was partly evaporated, the residue was acidified with 5% HCl to pH 1, then brine and EtOAc were added. The organic layer was separated, and the H_2O phase was extracted with EtOAc (8×20 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. *O*-Benzylhydroxylamine hydrochloride (336 mg, 2.103 mmol, 2.00 equiv), HOBt·H_2O (402 mg, 2.628 mmol, 2.50 equiv), EDC·HCl (605 mg, 3.154 mmol, 3.00 equiv), and CH_2Cl_2 (7 ml) were added to the crude product. The resulting mixture was cooled to 0°C, and Et_3N (0.88 ml, 6.308 mmol, 6.00 equiv) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred overnight, then H_2O and CH_2Cl_2 were added. The organic phase was separated, and the H_2O phase was extracted with CH_2Cl_2 (2×50 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent $CHCl_3$–EtOAc, gradient from 100:0 to 100:5). Yield 370 mg (90%), light-brown solid, mp 160–163°C, $[\alpha]_D^{20}$ –59.00° (*c* 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1739, 1622, 1449, 1415, 1179. ^1H NMR spectrum, δ, ppm (*J*, Hz): 9.61 (1H, br. s, NH); 7.69 (1H, d, *J* = 9.6, H Ar); 7.66–7.55 (2H, m, H Ar); 7.47–7.27 (6H, m, H Ar); 6.48 (1H, d, *J* = 9.6, H Ar); 4.94 (2H, m, AB system, $PhCH_2O$); 4.58 (1H, br. s, CH); 3.64–3.41 (2H, m, CH_2); 2.62–2.39 (1H, m, CH_2); 2.20–1.96 (2H, m, CH_2); 1.94–1.78 (1H, m, CH_2). ^{13}C NMR spectrum, δ, ppm: 169.4; 169.0; 160.1; 155.2; 142.9; 135.4; 132.2; 130.8; 129.2; 128.8; 128.7; 127.5; 118.8; 117.9; 117.1; 78.3; 57.8; 50.7; 27.0; 25.8. Found, *m*/*z*: 415.1280 $[M+Na]^+$. $C_{22}H_{20}NaN_2O_5$. Calculated, *m*/*z*: 415.1270.

8-Formyl-4-methyl-2-oxo-2*H*-chromen-7-yl trifluoromethanesulfonate (13). A mixture of 7-hydroxy-4-methyl-2*H*-chromen-2-one (**12**) (1.00 g, 5.676 mmol, 1.00 equiv), urotropine (1.19 g, 8.514 mmol, 1.50 equiv), and TFA (15 ml) was stirred at 100°C for 3 h, then cooled to room temperature, poured into H_2O, and extracted with Et_2O. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent petroleum ether – EtOAc, gradient from 9:1 to 0:1). 7-Hydroxy-4-methyl-2-oxo-2*H*-chromene-6-carbaldehyde was isolated as a pale-yellow solid in 174 mg (15%) yield.

Pyridine (0.15 ml, 1.910 mmol, 3.00 equiv) and Tf_2O (0.16 ml, 0.955 mmol, 1.50 equiv) were added to a solution of 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-6-carbaldehyde (130 mg, 0.637 mmol, 1.00 equiv) in CH_2Cl_2 (10 ml) at 0°C, and the resulting mixture was stirred for 1 h at room temperature, then saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the H_2O layer was extracted with CH_2Cl_2 (2×20 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent petroleum ether – EtOAc, gradient from 3:1 to 1:2). Yield 193 mg (90%), pale-yellow solid, mp 162–165°C. IR spectrum, ν, cm^{-1}: 1745, 1704, 1427, 1207. ^1H NMR spectrum, δ, ppm (*J*, Hz): 10.71 (1H, s, COH); 7.89 (1H, d, *J* = 8.8, H Ar); 7.28 (1H, d, *J* = 8.8, H Ar); 6.44 (1H, s, CH); 2.50 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 185.1; 157.8; 155.9; 151.1; 148.7; 130.7; 120.8; 118.8 (q, *J* = 320.7); 118.5; 117.1; 116.4; 19.1. Found, *m*/*z*: 336.9999 $[M+H]^+$. $C_{12}H_8F_3O_6S$. Calculated, *m*/*z*: 336.9994.

***tert*-Butyl (2*S*)-2-[(8-formyl-4-methyl-2-oxo-2*H*-chromen-7-yl)carbamoyl]pyrrolidine-1-carboxylate (14)**. Compound **13** (227 mg, 0.675 mmol, 1.00 equiv), L-Boc-Pro-NH_2

(174 mg, 0.810 mmol, 1.20 equiv), $Pd_2(dba)_3$ (7.9 mg, 0.034 mmol, 0.05 equiv), Xantphos (58 mg, 0.101 mmol, 0.15 equiv), and Cs_2CO_3 (308 mg, 0.945 mmol, 1.40 equiv) were placed in a pressure tube, evacuated and backfilled with Ar twice, then dioxane (2 ml) was added. The resulting mixture was stirred overnight at 100°C, then cooled to room temperature. CH_2Cl_2 was added, and the mixture was filtered through syringe filter, filtrate was evaporated, and the residue was purified by flash column chromatography (eluent petroleum ether – EtOAc, gradient from 9:1 to 3:7). Yield 149 mg (55%), white solid, mp 165–168°C, $[\alpha]_D^{20}$ –140.20° (*c* 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1739, 1699, 1596, 1515, 1387. ^1H NMR spectrum (rotamers), δ, ppm (*J*, Hz): 12.22 (1H, s, NH); 10.76 (1H, s, COH); 8.75 (1H, d, *J* = 7.8, H Ar), 7.86–7.72 (1H, m, H Ar); 6.25 (1H, s, H Ar); 4.49–4.25 (1H, m, CH); 3.87–3.73 (1H, m, CH_2), 3.70–3.47 (1H, m, CH_2); 2.45 (3H, s, CH_3); 2.39–2.22 (1H, m, CH_2); 2.20–2.07 (1H, m, CH_2); 2.02–1.88 (2H, m, CH_2); 1.48 and 1.31 (9H, both s, $C(CH_3)_3$). ^{13}C NMR spectrum (rotamers), δ, ppm: 191.8; 173.9; 173.5; 159.0; 156.8; 155.2; 154.1; 152.5; 143.8; 132.4; 132.2; 115.6; 115.3; 114.8; 113.4; 109.0; 80.8; 62.8; 62.4; 47.4; 47.0; 31.7; 31.0; 30.8; 28.4; 24.6; 24.0; 19.1. Found, *m*/*z*: 423.1522 $[M+Na]^+$. $C_{21}H_{24}NaN_2O_6$. Calculated, *m*/*z*: 423.1532.

7-({[(2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-carbonyl}amino)-4-methyl-2-oxo-2*H*-chromene-8-carboxylic acid (15). 2-Methyl-2-butene (1.3 ml), followed by solution of $NaH_2PO_4 \cdot 2H_2O$ (195 mg, 1.249 mmol, 5.00 equiv) in H_2O (2.7 ml), and solution of $NaClO_2$ (80% purity, 110 mg, 0.974 mmol, 3.90 equiv) in H_2O (0.7 ml) was added to a solution of compound **14** (100 mg, 0.250 mmol, 1.00 equiv) in *t*-BuOH (2.7 ml) and THF (2.7 ml). The resulting mixture was stirred for 2 h at room temperature, then diluted with saturated aqueous $Na_2S_2O_3$, acidified with 10% HCl, and extracted with EtOAc (3×20 ml). The organic phase was washed with H_2O and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reversed-phase flash column chromatography, eluent (H_2O + 0.1% AcOH)–MeOH. Yield 76 mg (73%), colorless wax, $[\alpha]_D^{20}$ –143.50° (*c* 0.2, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1703, 1596, 1519, 1396. ^1H NMR spectrum (rotamers), δ, ppm: 11.52 and 11.35 (1H, both s, NH); 8.81–8.67 (1H, m, H Ar); 8.31 (1H, br. s, COOH); 7.80–7.67 (1H, m, H Ar); 6.30 (1H, s, H Ar); 4.49–4.25 (1H, m, CH); 3.72 (1H, br. s, CH_2); 3.65–3.42 (1H, m, CH_2); 2.48 (3H, s, CH_3); 2.38–2.11 (2H, m, CH_2); 2.05–1.87 (2H, m, CH_2); 1.49 and 1.34 (9H, both s, $C(CH_3)_3$). ^{13}C NMR spectrum (rotamers), δ, ppm: 173.0; 167.7; 161.0; 155.3; 154.4; 154.0; 153.6; 153.1; 144.2; 143.6; 129.3; 117.0; 116.5; 115.7; 115.4; 113.0; 112.6; 106.9; 106.3; 81.0; 62.9; 62.3; 47.3; 47.0; 31.6; 30.6; 28.4; 24.6; 24.0; 19.3. Found, *m*/*z*: 439.1485 $[M+Na]^+$. $C_{21}H_{24}NaN_2O_7$. Calculated, *m*/*z*: 439.1481.

(11a*S*)-8-Methoxy-2,3-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11(10*H*,11a*H*)-dione (17). Et_3N (42.0 ml, 299.107 mmol, 10.00 equiv) was added to a stirred solution of 4-methoxyanthranilic acid (**16**) (5.00 g, 29.911 mmol, 1.00 equiv) and HBTU (17.01 g, 44.866 mmol, 1.5 equiv) in DMF (150 ml), and the resulting slurry was stirred for 15 min at room temperature, then L-Pro-OMe·HCl (9.91 g, 59.821 mmol, 2.00 equiv) was added and stirring was continued for 16 h. The volatiles were removed *in vacuo*, and brine and CH_2Cl_2 were added to the residue. The organic phase was separated, and the H_2O phase was extracted with CH_2Cl_2 (2×100 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. THF–H_2O–HCl (50:350:1 ml) solution was added to the obtained material, and the resulting mixture was stirred overnight at room temperature and then evaporated. The residue was purified by flash column chromatography (eluent petroleum ether – EtOAc, gradient from 9:1 to 0:1), then reversed-phase column chromatography (eluent H_2O–MeOH, gradient from 90:10 to 5:95). Yield 6.33 g (86%), light-yellow solid, mp 164–167°C, $[\alpha]_D^{20}$ 426.50° (*c* 1.0, MeOH). IR spectrum, ν, cm^{-1}: 1694, 1622, 1440, 850. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.21 (1H, br. s, NH); 7.96 (1H, d, *J* = 8.8, H Ar); 6.81 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 6.46 (1H, d, *J* = 2.4, H Ar); 4.11–4.05 (1H, m, CH); 3.84 (3H, s, OCH_3); 3.82–3.73 (1H, m, CH_2); 3.66–3.54 (1H, m, CH_2); 2.80–2.67 (1H, m, CH_2); 2.10–1.95 (3H, m, CH_2). ^{13}C NMR spectrum, δ, ppm: 172.5; 167.8; 164.6; 139.5; 133.2; 120.4; 112.5; 106.4; 58.4; 56.1; 48.3; 27.1; 24.5. Found, *m*/*z*: 247.1084 $[M+H]^+$. $C_{13}H_{15}N_2O_3$. Calculated, *m*/*z*: 247.1083.

(11a*S*)-8-Hydroxy-2,3-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11(10*H*,11a*H*)-dione (18). BBr_3 (1 M in CH_2Cl_2, 50.8 ml, 50.758 mmol, 5.00 equiv) was added dropwise to a solution of compound **17** (2.50 g, 10.152 mmol, 1.00 equiv) in CH_2Cl_2 (150 ml) at 0°C. The resulting mixture was allowed to warm up to room temperature and stirred overnight, then cooled with an ice-water bath and additional BBr_3 (1 M in CH_2Cl_2, 101.5 ml, 101.516 mmol, 10 equiv) was added dropwise. After stirring overnight at room temperature, the reaction mixture was cooled to 0°C and cold H_2O was carefully added, followed by CH_2Cl_2. CH_2Cl_2 layer was separated and extracted with H_2O (2×100 ml). The combined H_2O layer was evaporated and purified by reversed-phase column chromatography (eluent H_2O–MeOH, gradient from 90:10 to 5:95). Yield 1.70 g (72%), white solid, mp 239–242°C, $[\alpha]_D^{20}$ 443.00° (*c* 0.1, MeOH). IR spectrum, ν, cm^{-1}: 1681, 1600, 1439, 746. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.73 (1H, d, *J* = 8.7, H Ar); 6.70 (1H, dd, *J* = 8.7, *J* = 2.4, H Ar); 6.51 (1H, d, *J* = 2.4, H Ar); 4.18–4.12 (1H, m, CH); 3.76–3.65 (1H, m, CH_2); 3.60–3.49 (1H, m, CH_2); 2.70–2.61 (1H, m, CH_2); 2.12–1.89 (3H, m, CH_2). ^{13}C NMR spectrum, δ, ppm: 172.5; 168.0; 162.9; 139.6; 133.3; 119.3; 113.6; 108.0; 58.4; 48.2; 27.0; 24.6. Found, *m*/*z*: 233.0931 $[M+H]^+$. $C_{12}H_{13}N_2O_3$. Calculated, *m*/*z*: 233.0926.

(11a*S*)-12-{[2-(Trimethylsilyl)ethoxy]methyl}-8,9,10,10a-tetrahydro-2*H*,6*H*-chromeno[7,6-*e*]pyrrolo[1,2-*a*][1,4]-diazepine-2,6,11(12*H*)-trione (21). A mixture of compound **18** (1.60 g, 6.900 mmol, 1.00 equiv), 2-hydroxysuccinic acid (1.85 g, 13.779 mmol, 2.00 equiv), and H_2SO_4 (2.9 ml) was stirred for 30 min at room temperature and then overnight at 120°C. After cooling to room temperature, ice water was added and the resulting mixture was stirred for

30 min, then CH_2Cl_2 was added. The organic phase was separated, and the H_2O phase was extracted with CH_2Cl_2 (2×50 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent $CHCl_3$–MeOH, gradient from 1:0 to 10:1). Compound **5a** was isolated as a light-yellow solid in 15% yield (295 mg) and used in the next step.

NaH (60% in mineral oil, 15 mg, 0.366 mmol, 1.30 equiv) was added to a solution of compound **5a** (80 mg, 0.281 mmol, 1.00 equiv) in DMF (1 ml) at 0°C, and the resulting mixture was stirred for 20 min at this temperature, then SEMCl (0.075 ml, 0.422 mmol, 1.50 equiv) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred overnight, then brine and CH_2Cl_2 were added. The organic phase was separated, and the H_2O phase was extracted with CH_2Cl_2 (2×50 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent petroleum ether – EtOAc, gradient from 1:0 to 0:1). Yield 72 mg (62%), light-yellow oil, $[\alpha]_D^{20}$ 342.20° (*c* 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2953, 1746, 1699, 1645, 1454, 1250, 836. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.09 (1H, s, H Ar); 7.73 (1H, d, *J* = 9.3, H Ar); 7.72 (1H, s, H Ar); 6.45 (1H, d, *J* = 9.6, H Ar); 5.58 (1H, d, *J* = 9.8, NCH_2O); 4.66 (1H, d, *J* = 9.8, NCH_2O); 4.14–4.11 (1H, m, CH); 3.84–3.64 (3H, m, NCH_2, OCH_2); 3.61–3.53 (1H, m, NCH_2); 2.79–2.72 (1H, m, CH_2); 2.15–1.99 (3H, m, CH_2); 1.05–0.98 (2H, m, CH_2Si); 0.04 (9H, s, $Si(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 169.7; 164.1; 159.8; 156.0; 42.8; 142.5; 130.4; 126.6; 117.4; 116.8; 110.6; 78.2; 67.3; 57.6; 47.1; 26.9; 23.8; 18.4; –1.3. Found, *m*/*z*: 415.1690 $[M+H]^+$. $C_{21}H_{27}N_2O_5Si$. Calculated, *m*/*z*: 415.1689.

Supplementary information file containing ^1H and ^{13}C NMR spectra of all synthesized compounds, as well as COSY and ^1H–^{13}C HMBC spectra of compounds **10**, **13** and ^1H–^{13}C HSQC spectra of compounds **10**, **13**–**15** is available at the journal website at http://link.springer.com/journal/10593.

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