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Biology-oriented synthesis of benzopyrano[3,4-*c*]pyrrolidines

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ABSTRACT

A natural product inspired synthesis of 6,6,5-tricyclic compounds via a silver(I)-catalyzed formal 1,3-dipolar cycloaddition of coumarins with α-iminoesters was developed. The reaction proceeds in a stepwise reaction course under formation of the *trans*-substituted diastereomer with respect to the 1,3-dipole and shows a broad substrate scope.

1. Introduction

The underlying scaffolds of natural products are biologically relevant because they define the areas of chemical space explored by nature during evolution.[1,2] In biology-oriented synthesis, (BIOS) biological relevance is employed as key criterion to choose compound classes for the synthesis of focused compound collections.[1,2] Compound libraries based on natural product scaffolds are commonly structurally complex. Therefore the development of efficient synthesis methods for such compound collections is highly important. In this regard, cycloaddition reactions are remarkable. The [3+2]-cycloaddition of iminoester-derived azomethine ylides with alkenes, for example, is a powerful method for the construction of substituted pyrrolidines, which can be found in several natural products and biological active compounds.[3–5]

There are more than 120 reported examples for natural products containing a 6,6,5-tricyclic scaffold with various biological activities (selected examples are presented in Fig. 1).[6]

Inspired by these natural products, we wanted to prepare a focused 6,6,5-tricyclic compound collection. 1,3-Dipolar cycloadditions with coumarin as dipolarophile have been investigated before in a few cases.[7] Therefore, we assumed that the 6,6,5-tricyclic scaffold **3** consisting of a fused lactone with a pyrrolidine, as found in some natural compounds, could be synthesized by 1,3-dipolar cycloaddition of coumarins **1** with iminoesters **2** (Scheme 1).

2. Results and discussion

To establish the proposed 1,3-dipolar cycloaddition, we investigated the reaction of coumarin **1** with the azomethine ylide precursor α-iminoester **2a** in the presence of silver(I) salts as catalysts and triethylamine as base. Fortunately, two diastereomers **3a** and **4a** of the desired cycloaddition product could be isolated in a 3:1 ratio with viable yield (Table 1, entry 1). Encouraged by these results, we optimized the reaction conditions using various metal salts as catalysts. In general, the reaction proceeded either with silver(I) or copper(I) salts (Table 1, entries 1–5). However, with copper(I) and copper(II) triflate no product formation was observed (Table 1, entries 6 and 7). The usage of other copper(I) salts resulted in the desired diastereomers **3a** and **4a** in a ratio of 3:1 with yields up to 50% for the major product **3a** after 24 h (Table 1, entries 4 and 5). The silver(I) catalyzed cycloadditions proceeded faster and resulted in similar diastereoselectivity, but with slightly higher yields of up to 69% (Table 1, entries 1–3). Nevertheless, silver(I) trifluoroacetate as catalyst leads to a higher diastereoselectivity of 5:1 and was therefore used for further optimization (Table 1, entry 2).

Investigation of various solvents revealed that in toluene and halogenated solvents only traces of the desired products **3a** and

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0968-0896/

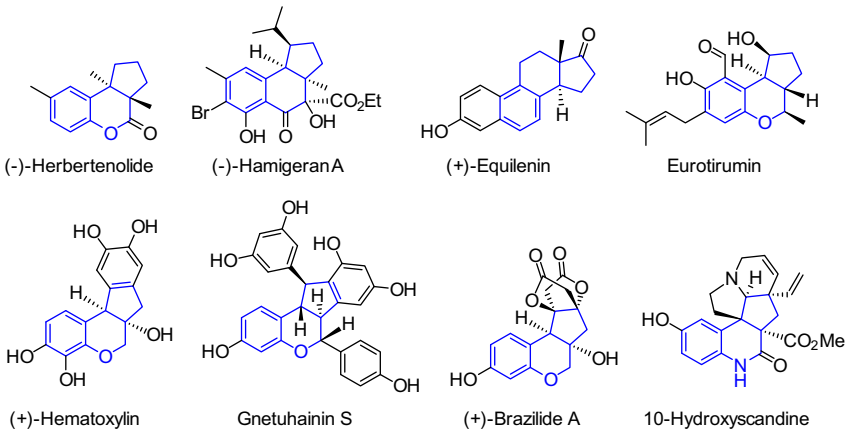
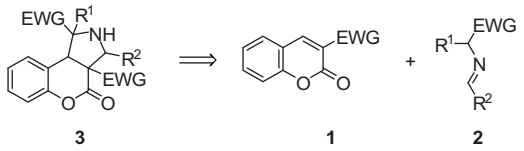


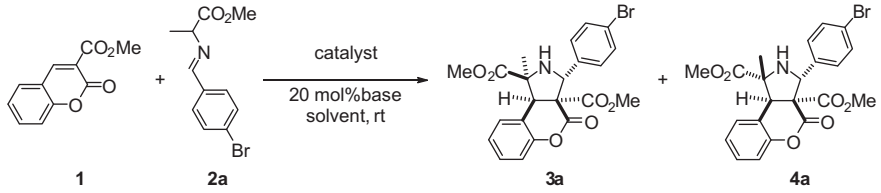
Figure 1. Selected examples for natural products containing a 6,6,5-tricyclic core structure.



Scheme 1. Retrosynthesis of the 6,6,5-tricyclic scaffold containing a fused lactone with a pyrrolidine.

4a were formed (Table 1, entries 8–11). Methanol, ethyl acetate, acetonitrile and 1,4-dioxane led to product formation, but with lower diastereoselectivity (up to 3:1), lower yields (up to 57% for the major product **3a**) and with a slower reaction rate compared to tetrahydrofuran (Table 1, entries 2, 12–15). Next we investigated the influence of the catalyst loading on the 1,3-dipolar cycloaddition of coumarin **1** and α-iminoester **2a** (Table 1, entries 16–19). The decrease of catalyst loading to 5 mol % had no major influence on the diastereoselectivity or yield (Table 1, entry 16).

Table 1
Screening of reaction conditions[a]



Entry	mol %	Catalyst	Solvent	Base	*T* (h)	dr[b]	Yield[c] (%)	
							3a	**4a**
1	10	AgOAc	THF	Et_3N	8	3:1	61	20
2	10	AgTFA	THF	Et_3N	4	5:1	69	14
3	10	AgOTf	THF	Et_3N	2	3:1	53	17
4	10	$CuPF_6$	THF	Et_3N	24	3:1	50	15
5	10	$CuBF_4$	THF	Et_3N	24	3:1	48	16
6	10	CuOTf	THF	Et_3N	48	n.d.	Traces	
7	10	$CuOTf_2$	THF	Et_3N	48	n.d.	Traces	
8	10	AgTFA	Toluene	Et_3N	48	n.d.	Traces	
9	10	AgTFA	CH_2Cl_2	Et_3N	48	n.d.	Traces	
10	10	AgTFA	$CHCl_3$	Et_3N	48	n.d.	Traces	
11	10	AgTFA	DCE	Et_3N	48	n.d.	Traces	
12	10	AgTFA	MeOH	Et_3N	2	3:1	48	19
13	10	AgTFA	EtOAc	Et_3N	22	3:1	57	18
14	10	AgTFA	MeCN	Et_3N	22	2:1	46	19
15	10	AgTFA	1,4-Dioxane	Et_3N	22	2:1	40	24
16	5	AgTFA	THF	Et_3N	6	5:1	71	13
17	3	AgTFA	THF	Et_3N	20	3:1	59	20
18	1	AgTFA	THF	Et_3N	48	n.d.	Traces	
19	0.5	AgTFA	THF	Et_3N	48	n.d.	Traces	
20	5	AgTFA	THF	DIPEA	6	4:1	61	15
21	5	AgTFA	THF	Py	24	3:1	46	14
22	5	AgTFA	THF	Pyr	24	3:1	37	13
23	5	AgTFA	THF	DBU	48	n.d.	Traces	

n.d. = not determined; $CuBF_4 = Cu(CH_3CN)_4BF_4$; $CuPF_6 = Cu(CH_3CN)_4PF_6$, DCE = dichloroethane.

[a] Reaction conditions: catalyst (0.5–10 mol %), base (20 mol %), coumarin **1** (1 equiv, 0.15 mmol) and alanine ester imine **2a** (1.5 equiv, 0.225 mmol) in solvent (0.1 M) at 20 °C.

[b] Determined by ^1H NMR spectroscopy of crude reaction mixture.

[c] Yield of isolated pure product **3a** and **4a** after chromatography on silica gel.

Further decrease to 3 mol % reduced the diastereoselectivity to 3:1 and the yield for the major product**3a** to 59% (Table 1, entry 17). Lower catalyst loadings resulted in lower conversion and only traces of the desired diastereomers **3a** and **4a** (Table 1, entries 18 and 19). Lower diastereoselectivities and yields were also observed for various bases compared to triethylamine (Table 1, entries 20–23). Thus, the optimal reaction conditions for the 1,3-dipolar cycloaddition of coumarin **1** and α-iminoester **2a** are 5 mol % of AgTFA as catalyst in the presence of Et_3N as base in THF at 20 °C (Table 1, entry 16). The application of various chiral ligands with the intention to obtain an asymmetric version of the reaction resulted in low enantioselectivities of up to 24% (for details see Supplementary Table S1).

With the optimized reaction conditions in hand, we investigated the scope of the reaction. Therefore, coumarin **1** was reacted with various α-iminoesters **2** under the given conditions (Table 2). α-Iminoesters **2** based on glycine and alanine were tolerated in the formal 1,3-dipolar cycloaddition with coumarin **1** and resulted in equal diastereoselectivities (Table 2, entries 1–4). However, alanine ester imines **2** led to higher yields for the major diastereomer **3**. Also 1,3-dipoles **2** obtained from various arylaldehydes were investigated in the 1,3-dipolar cycloaddition with coumarin **1** (Table 2, entries 4–17). Regardless of the electronic properties of the aryl substitutions on α-iminoester **2,** the reactions proceeded with diastereoselectivity ratios of up to 9:1. However, unsubstituted α-iminoesters **2** (Table 2, entry 5) and imines having an electron-donating substituent, such as methyl or methoxy (Table 2, entries 9 and 10), gave the products with slightly higher diastereoselectivity and slightly higher yields than α-iminoesters **2** with aryl substituents having electron-withdrawing groups, such as fluorine or trifluoromethyl (Table 2, entries 4 and 6). The diastereoselectivity and the yield also depended on the position of the aromatic substituents. *para*-Substituents resulted in higher yields and diastereoselectivity than *meta*- or *ortho* substituents in the aromatic ring (Table 2, entries 6–8, 10–12). Further α-iminoesters with one or two substituents were used for the formal 1,3-dipolar cycloaddition and led to the desired products **3** in moderate yields and diastereoselectivity of up to 9:1 (Table 2, entries 13–17). Even the usage of α-iminoesters **2** containing heteroaryl and alkyl substituents yielded the desired products **3** and **4,** but with lower diastereoselectivity and yield (Table 2, entries 18–20). α-Iminoester **2**, prepared by condensation of aldehyde with valine ester hydrochloride and phenylglycine ester hydrochloride, did not lead to product formation (Table 2, entries 21 and 22).

The relative configurations of both diastereomers were determined by NOE experiments (Fig. 2A). The results showed that the major product is the unexpected *trans*-substituted diastereomer **3a** whereas the side product is the *exo* cycloaddition product **4a**. The configuration of the major product was further confirmed by crystal structure analysis of compound **3f** (Fig. 2B).

Since the W-shape for α-iminoester **2** is common under the tested reaction conditions, we proposed a stepwise mechanism for the reaction course (Scheme 2).[3–5] α-Iminoester **2** coordinates the silver(I) ion. Deprotonation with triethylamine results in the formation of an azomethine ylide, the active species, which undergoes nucleophilic attack on the coumarin **1** double bond in β-position of the lactone carbonyl group. The following ring closure results in the *trans*-substituted diastereomer with respect to the 1,3-dipole.

3. Conclusion

In conclusion, we developed a formal 1,3-dipolar cycloaddition of coumarin **1** with α-iminoesters **2** for the preparation of natural product inspired 6,6,5-tricyclic compounds. The reaction showed a broad substrate scope with respect to α-iminoester **2** and the *trans*-substituted diastereomer **3** was obtained as the major product with diastereoselectivities up to a ratio of 9:1.

4. Experimental section

4.1. General

Unless otherwise noted, all commercially available compounds were used as provided without further purifications. Dry solvents (THF, toluene, 1,4-dioxane) were used as commercially available; CH_2Cl_2 was purified by the Solvent Purification System *M-BRAUN Glovebox Technology SPS-800*. Solvents for chromatography were technical grade. Analytical thin-layer chromatography (TLC) was performed on *Merck silica gel aluminium plates* with F-254 indicator. Compounds were visualized by irradiation with UV light or potassium permanganate staining. Column chromatography was performed using *silica gel Merck 60* (particle size 0.040–0.063 mm). Solvent mixtures are understood as volume/volume.

^1H NMR and ^{13}C NMR were recorded on a *Bruker DRX300* (300 MHz), *Bruker DRX400* (400 MHz), *Bruker DRX500* (500 MHz) and *INOVA500* (500 MHz) using $CDCl_3$ or $(CD_3)_2SO$ as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: $\delta = 7.26$ ppm for ^1H, $\delta = 77.16$ ppm for ^{13}C; $(CD_3)_2SO$: $\delta = 2.50$ ppm for ^1H, $\delta = 39.52$ ppm for ^{13}C); multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet); coupling constants (J) are given in Hertz (Hz). High resolution mass spectra were recorded on a *LTQ Orbitrap* mass spectrometer coupled to an *Acceka HPLC*-System (HPLC column: *Hypersyl GOLD*, 50 mm × 1 mm, particle size 1.9 μm, ionization method: electron spray ionization). Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a *Bruker Tensor 27* spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1}).

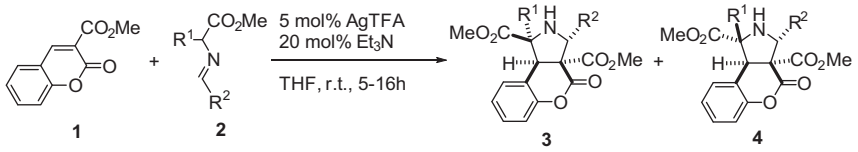
4.2. General procedure for silver-catalysed [3+2]-cycloaddition of azomethinylides with coumarins

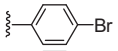
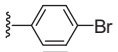
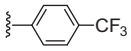
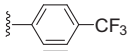
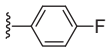
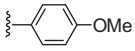
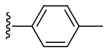
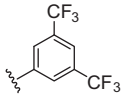
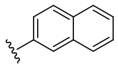
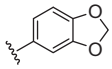
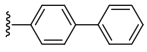
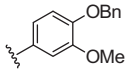
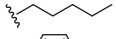
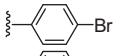
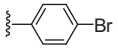
To a solution of coumarin **1** (1 equiv, 0.15 mmol) and α-iminoester **2** (1.5 equiv, 0.23 mmol) in THF (2 mL) silver(I)-trifluoroacetate (5 mol %, 7.5 μmol) and triethylamine (20 mol %, 30 μmol) were added. The resulting mixture was stirred for 5–16 h at 20 °C. Afterwards the solvent was removed under reduced pressure. The crude mixture was then directly charged onto silica gel and the product was purified using *n*-pentane/ethyl acetate as eluent. Yields, diastereoselectivity and regioselectivity are given in the tables.

4.2.1. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-bromophenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*] pyrrole-1,3a-dicarboxylate (3a)

71% yield; $R_f = 0.30$ (ethyl acetate/cyclohexane = 1:5); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.53$ (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.35–7.27 (m, 2H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.06 (d, $J = 8.2$ Hz, 1H), 5.50 (s, 1H), 4.06 (s, 1H), 3.50 (s, 3H), 3.15 (s, 3H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 173.74$, 167.42, 165.84, 150.84, 131.14, 129.86, 129.56, 129.01, 124.67, 122.14, 117.46, 117.13, 69.33, 66.35, 63.40, 53.28, 52.98, 52.18, 23.65 ppm; FT-IR: $\tilde{\nu} = 2924$, 2853, 1740, 1619, 1434, 1242, 1153, 1067, 1016 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}{}^{79}BrNO_6 = 474.05468$, found: 474.05550; calcd for $[M+H]^+$ $C_{22}H_{21}{}^{81}BrNO_6 = 476.05263$, found: 476.05243.

Table 2
Scope of the cycloaddition[a]



Entry	Product	R^1	R^2	dr[b]	Yield[c] (%)
1	**3a**	Me		5.5:1	71 (13)
2	**3b**	H		2:1	37 (17)
3	**3c**	H		3:1	46 (15)
4	**3d**	Me		3:1	64 (21)
5	**3e**	Me		8:1	72 (9)
6	**3f**	Me		4:1	67 (16)
7	**3g**	Me		3:1	57
8	**3h**	Me		2:1	50 (34)
9	**3i**	Me		9:1	69
10	**3j**	Me		5:1	71
11	**3k**	Me		5:1	68
12	**3l**	Me		4:1	52
13	**3m**	Me		2:1	65 (28)
14	**3n**	Me		9:1	68
15	**3o**	Me		9:1	63
16	**3p**	Me		3:1	48
17	**3q**	Me		2:1	43
18	**3r**	Me		2:1	53 (31)
19	**3s**	Me		1:1	48
20	**3t**	Me		1.5:1	54
21	**3u**	*i*Pr		n.r.	n.d.
22	**3v**	Ph		n.r.	n.d.

n.r. = no reaction.
[a] Reaction conditions: AgTFA (5 mol %), Et_3N (20 mol %), coumarin**1** (1 equiv, 0.15 mmol) and α-iminoester **2** (1.5 equiv, 0.225 mmol) in THF (0.1 M) at 20 °C.
[b] Determined by ^1H NMR spectroscopy of crude reaction mixture.
[c] Yield of isolated pure major product **3** after chromatography on silica gel, yield for the minor product **4** is given in brackets.

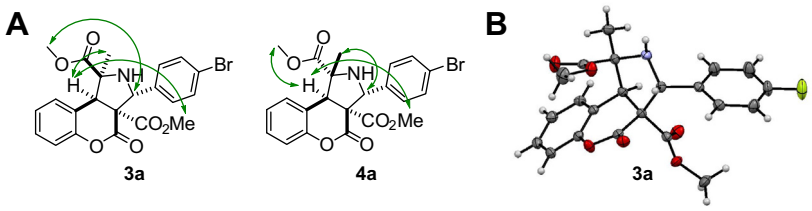


Figure 2. (A) Determination of the relative configuration of the diastereomers **3a** and **4a** by characteristic NOEs. (B) ORTEP plot of **3f** with the thermal ellipsoids at 50% probability.[8]

4.2.2. *rel*-(1*R*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-bromophenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*] pyrrole-1,3a-dicarboxylate (4a)

13% yield; R_f = 0.33 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.15 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 5.52 (s, 1H), 4.51 (s, 1H), 3.90 (s, 3H), 3.22 (s, 3H), 1.12 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.24, 166.38, 150.86, 138.12, 131.51, 130.14, 129.68, 129.32, 125.12, 122.36, 118.01, 117.03, 69.16, 66.90, 63.82, 53.37, 53.13, 50.90, 20.06 ppm; FT-IR: $\tilde{\nu}$ = 2926, 2848, 1739, 1617, 1488, 1436, 1242, 1151, 1065, 1016 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}{}^{79}BrNO_6$ = 474.05468, found: 474.05550; calcd for $[M+H]^+$ $C_{22}H_{21}{}^{81}BrNO_6$ = 476.05263, found: 476.05243.

4.2.3. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-bromophenyl)-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1, 3a-dicarboxy-late (3b)

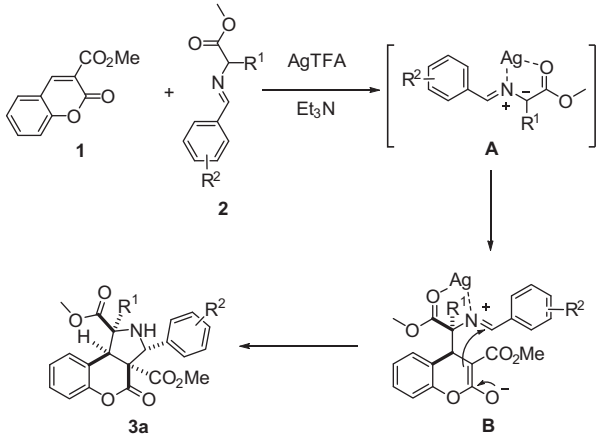
37% yield; R_f = 0.25 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.31–7.26 (m, 3H), 7.11 (d, J = 8.2 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 7.6 Hz, 1H), 5.10 (s, 1H), 3.95 (d, J = 10.9 Hz, 1H), 3.84–3.71 (m, 4H), 3.66 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.26, 166.99, 164.57, 150.03, 137.80, 132.04, 129.66, 129.45, 129.37, 125.01, 122.59, 118.10, 117.04, 67.82, 64.83, 62.93, 53.99, 53.45, 53.04 ppm; FT-IR: $\tilde{\nu}$ = 2925, 2849, 1734, 1489, 1435, 1244, 1153, 1073, 1010 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{19}{}^{79}BrNO_6$ = 460.03903, found: 460.04010; calcd for $[M+H]^+$ $C_{21}H_{19}{}^{81}BrNO_6$ = 462.03698, found: 462.03706.

4.2.4. *rel*-(1*R*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-bromophenyl)-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1, 3a-dicarboxy-late (4b)

17% yield; R_f = 0.31 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.31 (dd, J = 14.9, 7.3 Hz, 2H), 7.14 (t, J = 7.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 5.55 (s, 1H), 4.26 (d, J = 10.9 Hz, 1H), 3.83 (s, 3H), 3.78 (d, J = 10.9 Hz, 1H), 3.29 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.98, 165.34, 165.09, 150.14, 138.75, 131.60, 129.99, 129.81, 129.35, 125.17, 122.49, 118.61, 117.09, 66.69, 64.66, 64.41, 53.35, 52.78, 46.10 ppm; FT-IR: $\tilde{\nu}$ = 2925, 2850, 1738, 1488, 1456, 1221, 1145, 1072, 1009 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{19}{}^{79}BrNO_6$ = 460.03903, found: 460.04000; calcd for $[M+H]^+$ $C_{21}H_{19}{}^{81}BrNO_6$ = 462.03698, found: 462.03695.

4.2.5. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 4-oxo-3-(4-(trifluoromethyl) phenyl)-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1, 3a-dicarboxylate (3c)

46% yield; R_f = 0.19 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.34–7.27 (m, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.01–6.94 (m, 1H), 6.50 (d, J = 7.5 Hz, 1H), 5.13 (s, 1H), 4.07 (d, J = 10.8 Hz, 1H), 3.83–3.78 (m, 4H), 3.66 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.32, 166.77, 164.52, 150.09, 143.30, 130.75 (q, J = 32.4 Hz), 129.74, 129.43, 128.06, 125.79 (q, J = 3.8 Hz), 125.07, 124.14 (q, J = 272.1 Hz), 118.13, 117.11, 67.74, 64.83, 63.03, 53.99, 53.31, 52.98 ppm; FT-IR: $\tilde{\nu}$ = 2926, 2851, 1741, 1619, 1436, 1242, 1152, 1067, 1017 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{19}F_3NO_6$ = 450.11590, found: 450.11578.



Scheme 2. Proposed reaction course.

4.2.6. *rel*-(1*R*,3*R*,3a*S*,9b*R*)-Dimethyl 4-oxo-3-(4-(trifluoro-methyl)phenyl)-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*] pyrrole-1,3a-dicarboxylate (4c)

15% yield; R_f = 0.21 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.36–7.27 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 5.65 (s, 1H), 4.29 (d, J = 10.9 Hz, 1H), 3.86–3.78 (m, 4H), 3.25 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.94, 165.30, 165.05, 150.15, 143.93, 130.71, 129.99, 129.88, 128.09, 126.02, 125.38 (q, J = 3.8 Hz), 125.24, 118.53, 117.13, 117.08, 66.56, 64.82, 64.40, 53.32, 52.79, 46.02 ppm; FT-IR: $\tilde{\nu}$ = 2924, 2850, 1739, 1619, 1491, 1436, 1242, 1151, 1066, 1016 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{19}F_3NO_6$ = 450.11590, found: 450.11569.

4.2.7. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-(4-(tri-fluoromethyl)phenyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*] pyrrole-1,3a-dicarboxylate (3d)

64% yield; R_f = 0.28 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.79 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.37–3.28 (m, 2H), 7.15 (t, J = 7.0 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 5.61 (s, 1H), 4.08 (s, 1H), 3.51 (s, 3H), 3.10 (s, 3H), 1.81 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.77, 167.36, 165.74, 150.87, 130.37 (q, J = 32.7 Hz), 129.63, 129.03, 128.57, 128.06, 124.92 (q, J = 3.7 Hz), 124.73, 124.24 (q, J = 272.1 Hz), 117.40, 117.17, 69.43, 66.35, 63.60, 53.18, 53.09, 52.20, 23.70 ppm; FT-IR: $\tilde{\nu}$ = 2954, 1765, 1724, 1614, 1418, 1355, 1252, 1229, 1112, 1064, 1016 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}F_3NO_6$ = 464.13155, found: 464.13170.

4.2.8. *rel*-(1*R*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-(4-(tri-fluoromethyl)phenyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (4d)

21% yield; R_f = 0.36 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67–7.58 (m, 4H), 7.36–7.29 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 5.63 (s, 1H), 4.55 (s, 1H), 3.91 (s, 3H), 3.18 (s, 3H), 1.14 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.16, 166.33, 166.30, 150.85, 143.27, 130.50 (q, J = 32.3 Hz), 130.16, 129.76, 128.04, 125.31 (q, J = 3.7 Hz), 125.20, 117.88, 117.07, 69.18, 66.74, 63.94, 53.33, 53.17, 50.76, 20.15 ppm; FT-IR: $\tilde{\nu}$ = 2957, 1738, 1618, 1493, 1434, 1323, 1251, 1155, 1106, 1063, 1016 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}F_3NO_6$ = 464.13155, found: 464.13139.

4.2.9. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-phenyl-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-dicarboxy-late (3e)

72% yield; R_f = 0.28 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, J = 7.4 Hz, 2H), 7.37–7.30 (m, 3H), 7.30–7.24 (m, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 5.56 (s, 1H), 4.10 (s, 1H), 3.51 (s, 3H), 3.08 (s, 3H), 1.81 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.80, 167.49, 165.87, 150.88, 139.22, 129.44, 129.01, 128.20, 128.07, 124.58, 117.72, 117.07, 69.48, 67.27, 63.77, 53.12, 53.08, 52.10, 23.72 ppm; FT-IR: $\tilde{\nu}$ = 2949, 1770, 1722, 1490, 1452, 1238, 1149, 1079, 1029 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{22}NO_6$ = 396.14416, found: 396.14317.

4.2.10. *rel*-(1*R*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-phenyl-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-dicarboxy-late (4e)

9% yield; R_f = 0.31 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (d, J = 7.3 Hz, 2H), 7.38–7.32 (m, 3H), 7.32–7.28 (m, 3H), 7.18–7.12 (m, 1H), 7.08 (d, J = 8.3 Hz, 1H), 5.56 (s, 1H), 4.51 (s, 1H), 3.91 (s, 3H), 3.15 (s, 3H), 1.12 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.43, 166.48, 138.85, 130.13, 129.57, 128.45, 128.42, 127.56, 125.02, 118.27, 116.99, 69.30, 67.89, 64.13, 53.18, 53.11, 51.20, 20.08 ppm; FT-IR: $\tilde{\nu}$ = 2951, 1722, 1488, 1454, 1242, 1149, 1081, 1017 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{22}NO_6$ = 396.14416, found: 396.14284.

4.2.11. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-fluorophenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3f)

67% yield; R_f = 0.30 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (dd, J = 8.4, 5.5 Hz, 2H), 7.35–7.27 (m, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 8.7 Hz, 2H), 5.52 (s, 1H), 4.08 (s, 1H), 3.50 (s, 3H), 3.13 (s, 3H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.82, 167.50, 165.91, 162.61 (d, J = 246.4 Hz), 150.86, 135.00 (d, J = 3.0 Hz), 129.83 (d, J = 8.1 Hz), 129.49, 129.00, 124.62, 117.59, 117.10, 114.87 (d, J = 21.3 Hz), 69.27, 66.38, 63.44, 53.19, 52.93, 52.13, 23.69 ppm; FT-IR: $\tilde{\nu}$ = 2952, 2849, 1768, 1728, 1507, 1454, 1214, 1140, 1113, 1095, 1015 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}FNO_6$ = 414.13474, found: 414.13488.

4.2.12. *rel*-(1*R*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-fluorophenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (4f)

16% yield; R_f = 0.33 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (dd, J = 8.5, 5.4 Hz, 2H), 7.35–7.28 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.04 (t, J = 8.5 Hz, 2H), 5.55 (s, 1H), 4.52 (s, 1H), 3.90 (s, 3H), 3.20 (s, 3H), 1.59 (s, 1H), 1.12 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.30, 166.46, 166.45, 162.67 (d, J = 247.2 Hz), 150.88, 134.74 (d, J = 3.2 Hz), 130.13, 129.65, 129.38 (d, J = 8.1 Hz), 125.09, 118.08, 117.02, 115.31 (d, J = 21.5 Hz), 69.18, 66.99, 63.88, 53.28, 53.13, 50.97, 19.98 ppm; FT-IR: $\tilde{\nu}$ = 2918, 1770, 1728, 1503, 1458, 1246, 1142, 1115, 1003 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}FNO_6$ = 414.13474, found: 414.13490.

4.2.13. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(3-fluorophenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3g)

57% yield; R_f = 0.30 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40 (t, J = 9.8 Hz, 2H), 7.35–7.27 (m, 3H), 7.14 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.00–6.92 (m, 1H), 5.55 (s, 1H), 4.06 (s, 1H), 3.50 (s, 3H), 3.15 (s, 3H), 1.79 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.90, 167.37, 165.78, 162.77 (d, J = 245.7 Hz), 150.89, 142.36 (d, J = 7.0 Hz), 129.54, 129.47 (d, J = 8.0 Hz), 129.03, 124.66, 123.72 (d, J = 2.9 Hz), 117.58, 117.11, 115.08 (d, J = 4.0 Hz), 114.90 (d, J = 2.8 Hz), 69.32, 66.29 (d, J = 1.9 Hz), 63.62, 53.17, 53.05, 52.12, 23.79 ppm; FT-IR: $\tilde{\nu}$ = 2918, 1763, 1722, 1487, 1453, 1355, 1231, 1113, 1021 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}FNO_6$ = 414.13474, found: 414.134973.

4.2.14. *rel*-(1*S*,3*S*,3a*S*,9b*R*)-Dimethyl 3-(2-fluorophenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3h)

50% yield; R_f = 0.22 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.32–7.26 (m, 2H), 7.15 (t, J = 7.6 Hz, 2H), 7.07–6.99 (m, 2H), 5.91 (s, 1H), 4.13 (s, 1H), 3.48 (s, 3H), 3.16 (s, 3H), 1.79 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.79, 167.09, 164.73, 160.96 (d, J = 249.0 Hz), 150.84, 130.86 (d, J = 3.7 Hz), 129.99 (d, J = 8.5 Hz), 129.51, 129.11, 126.79 (d, J = 11.4 Hz), 124.70, 124.08 (d, J = 3.4 Hz), 117.89, 116.99, 115.58 (d, J = 22.2 Hz), 69.98, 64.23, 62.66 (d, J = 2.0 Hz), 53.45, 53.23, 52.14, 24.14 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1774, 1739, 1488, 1454, 1241, 1177, 1115, 1001 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}FNO_6$ = 414.13474, found: 414.13457.

4.2.15. *rel*-(1*R*,3*S*,3a*S*,9b*R*)-Dimethyl 3-(2-fluorophenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (4h)

34% yield; R_f = 0.28 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.57–7.51 (m, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.33–7.28 (m, 2H), 7.19–713 (m, 2H), 7.08 (d, J = 7.7 Hz, 1H), 7.06–6.99 (m, 1H), 5.90 (s, 1H), 4.59 (s, 1H), 3.96 (s, 1H), 3.89 (s, 3H), 3.27 (s, 3H), 1.12 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$ δ = 174.72, 166.27, 165.90, 160.62 (d, J = 248.1 Hz), 151.09, 149.27, 134.61, 130.29, 130.06 (d, J = 8.5 Hz), 129.94 (d, J = 3.6 Hz), 129.60, 126.61 (d, J = 11.8 Hz), 125.05, 124.42 (d, J = 3.4 Hz), 118.50, 116.94, 115.54 (d, J = 22.2 Hz), 69.02, 63.89, 61.77 (d, J = 3.7 Hz), 53.30, 53.04, 50.44, 21.23 ppm; FT-IR: $\tilde{\nu}$ = 2918, 1768, 1723, 1486, 1457, 1245, 1114, 1095, 1009 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}FNO_6$ = 414.13474, found: 414.13465.

4.2.16. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-methoxyphenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3i)

69% yield; R_f = 0.19 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, J = 8.7 Hz, 2H), 7.38–7.27 (m, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 5.50 (s, 1H), 4.09 (s, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 3.13 (s, 3H), 1.80 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.77, 167.60, 165.95, 159.47, 150.89, 131.11, 129.39, 129.27, 129.00, 124.54, 117.80, 117.06, 113.37, 69.39, 67.00, 63.61, 55.38, 53.17, 53.07, 52.06, 23.71 ppm; FT-IR: $\tilde{\nu}$ = 2927, 1766, 1730, 1610, 1587, 1454, 1239, 1163, 1113, 1030 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{24}NO_7$ = 426.15473, found: 426.15489.

4.2.17. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-(*p*-tolyl)-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3j)

71% yield; R_f = 0.31 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.49 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.31–7.26 (m, 1H), 7.16–7.11 (m, 3H), 7.05 (d, J = 8.2 Hz, 1H), 5.52 (s, 1H), 4.08 (s, 1H), 3.50 (s, 3H), 3.10 (s, 3H), 2.32 (s, 3H), 1.80 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.82, 167.58, 165.88, 150.93, 137.83, 136.23, 129.38, 129.02, 128.75, 127.93, 124.53, 117.88, 117.05, 69.52, 67.27, 63.82, 53.27, 53.05, 52.02, 23.79, 21.28 ppm; FT-IR: $\tilde{\nu}$ = 2925, 1766, 1735, 1492, 1454, 1350, 1234, 1165, 1115, 1021 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{24}NO_6$ = 410.15981, found: 410.15974.

4.2.18. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-(*m*-tolyl)-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3k)

68% yield; R_f = 0.30 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.32–7.26 (m, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.16–7.11 (m, 1H), 7.10–7.03 (m, 2H), 5.53 (s, 1H), 4.09 (s, 1H), 3.50 (s, 3H), 3.10 (s, 3H), 2.36 (s, 3H), 1.81 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.78, 167.46, 165.83, 150.93, 139.19, 137.67, 129.42, 129.02, 128.91, 128.66, 127.99, 125.09, 124.56, 117.83, 117.06, 69.55, 67.34, 63.86, 53.24, 53.02, 52.05, 23.76, 21.54 ppm; FT-IR: $\tilde{\nu}$ = 2950, 1764, 1734, 1491, 1454, 1367, 1215, 1197, 1143, 1112, 1070 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{24}NO_6$ = 410.15981, found: 410.15977.

4.2.19. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-(*o*-tolyl)-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3l)

52% yield; R_f = 0.31 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.32–7.27 (m, 1H), 7.23–7.18 (m, 1H), 7.18–7.10 (m, 3H), 7.03 (d, J = 7.9 Hz, 1H), 5.91 (s, 1H), 4.16 (s, 1H), 3.49 (s, 3H), 3.03 (s, 3H), 2.63 (s, 3H), 1.80 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 174.33, 166.64, 165.13, 150.91, 138.44, 137.63, 130.33, 129.45, 129.17, 128.19, 127.99, 125.73, 124.67, 118.10, 116.87, 69.45, 64.43, 63.17, 52.92, 52.86, 52.09, 24.27, 20.09 ppm; FT-IR: $\tilde{\nu}$ = 2928, 1764, 1731, 1489, 1452, 1375, 1247, 1213, 1146, 1118, 1058 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{24}NO_6$ = 410.15981, found: 410.15986.

4.2.20. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(3,5-bis(trifluoro-methyl)phenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochrom-eno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3m)

65% yield; R_f = 0.35 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 2H), 7.80 (s, 1H), 7.38–7.28 (m, 2H), 7.21–7.13 (m, 1H), 7.08 (d, J = 7.9 Hz, 1H), 5.69 (s, 1H), 4.06 (s, 1H), 3.50 (s, 3H), 3.14 (s, 3H), 1.82 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.87, 167.10, 165.65, 150.75, 142.74, 131.34 (q, J = 33.2 Hz), 129.78, 129.08, 128.35 (q, J = 2.7 Hz), 124.88, 123.45 (q, J = 272.9 Hz), 121.90 (q, J = 3.9 Hz), 117.21, 117.08, 69.34, 65.45, 63.40, 53.31, 52.80, 52.34, 23.68 ppm; FT-IR: $\tilde{\nu}$ = 2927, 1763, 1739, 1493, 1455, 1350, 1276, 1172, 1121, 1014 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{24}H_{20}F_6NO_6$ = 532.11893, found: 532.11851.

4.2.21. *rel*-(1*R*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(3,5-bis(trifluoro-methyl)phenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochrom-eno[3,4-*c*]pyrrole-1,3a-dicarboxylate (4m)

28% yield; R_f = 0.44 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (s, 2H), 7.81 (s, 1H), 7.41–7.37 (m, 1H), 7.36–7.30 (m, 1H), 720–7.14 (m, 1H), 7.10 (d, J = 8.2 Hz, 1H), 5.75 (s, 1H), 4.62 (s, 1H), 3.94 (s, 3H), 3.29 (s, 3H), 1.16 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.15, 166.02, 165.82, 150.88, 142.89, 131.64 (q, J = 33.3 Hz), 130.28, 129.90, 127.84 (q, J = 3.4 Hz), 126.69 (d, J = 272.1 Hz), 125.41, 124.73, 122.05 (q, J = 4.9 Hz), 117.74, 117.09, 68.82, 65.33, 63.87, 53.48, 53.19, 49.29, 21.20 ppm; FT-IR: $\tilde{\nu}$ = 2959, 1734, 1622, 1456, 1360, 1255, 1226, 1166, 1109, 1013 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{24}H_{20}F_6NO_6$ = 532.11893, found: 532.11934.

4.2.22. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-3-(naphthalen-2-yl)-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3n)

68% yield; R_f = 0.27 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (s, 1H), 7.91–7.84 (m, 1H), 7.84–7.78 (m, 2H), 7.78–7.73 (m, 1H), 7.51–7.43 (m, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.33–7.27 (m, 1H), 7.20–7.11 (m, 1H), 7.08 (d, J = 8.2 Hz, 1H), 5.73 (s, 1H), 4.17 (s, 1H), 3.53 (s, 3H), 2.95 (s, 3H), 1.86 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.90, 167.50, 166.01, 150.89, 136.80, 133.25, 133.08, 129.46, 129.03, 128.30, 127.71, 127.57, 126.99, 126.14, 125.98, 124.60, 117.71, 117.09, 69.47, 67.24, 63.74, 53.23, 53.10, 52.13, 23.77 ppm; FT-IR: $\tilde{\nu}$ = 2922, 1770, 1723, 1588, 1490, 1454, 1251, 1184, 1117, 1003 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{26}H_{24}NO_6$ = 446.15981, found: 446.15994.

4.2.23. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3o)

63% yield; R_f = 0.18 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7-26 (m, 2H), 7.18–7.08 (m, 3H), 7.05 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.94 (s, 2H), 5.48 (s, 1H), 4.06 (s, 1H), 3.49 (s, 3H), 3.22 (s, 3H), 1.78 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.85, 167.44, 165.90, 150.87, 147.43, 147.31, 133.21, 129.45, 129.03, 124.59, 121.58, 117.70, 117.06, 108.63, 107.81, 101.14, 69.21, 66.82, 63.47, 53.26, 52.91, 52.10, 23.76 ppm; FT-IR: $\tilde{\nu}$ = 2926, 1768, 1731, 1611, 1486, 1443, 1236, 1152, 1114, 1034 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{22}NO_8$ = 440.13399, found: 440.13399.

4.2.24. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-([1,1′-biphenyl]-4-yl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexa-hydrochromeno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3p)

48% yield; R_f = 0.27 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.3 Hz, 2H), 7.65–7.54 (m, 4H), 7.48–7.41 (m, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.33–7.27 (m, 1H), 7.21–7.11 (m, 1H), 7.08 (d, J = 8.3 Hz, 1H), 5.61 (s, 1H), 4.13 (s, 1H), 3.52 (s, 3H), 3.11 (s, 3H), 1.83 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.77, 167.53, 165.88, 150.88, 140.91, 140.74, 138.25, 129.47, 129.02, 128.92, 128.54, 127.51, 127.13, 126.68, 124.61, 117.68, 117.10, 69.51, 67.05, 63.76, 53.18, 53.13, 52.14, 23.71 ppm; FT-IR: $\tilde{\nu}$ = 2952, 1766, 1733, 1587, 1487, 1453, 1247, 1228, 1115, 1003 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{28}H_{26}NO_6$ = 472.17546, found: 472.17530.

4.2.25. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochrom-eno[3,4-*c*]pyrrole-1,3a-dicarboxylate (3q)

43% yield; R_f = 0.12 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 7.3 Hz, 2H), 7.36–7.31 (m, 3H), 7.30–7.25 (m, 2H), 7.20 (d, J = 1.6 Hz, 1H), 7.16–7.11 (m, 1H), 7.11–7.02 (m, 2H), 6.84 (d, J = 8.4 Hz, 1H), 5.45 (s, 1H), 5.16 (s, 2H), 4.07 (s, 1H), 3.92 (s, 3H), 3.50 (s, 3H), 3.06 (s, 3H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.69, 167.53, 165.97, 150.88, 149.25, 147.67, 137.16, 129.41, 128.97, 128.61, 127.92, 127.40, 124.55, 120.09, 117.71, 117.08, 113.54, 111.85, 70.96,

69.32, 67.06, 63.51, 56.20, 53.17, 52.98, 52.09, 23.64 ppm; FT-IR: $\tilde{\nu}$ = 2923, 1769, 1734, 1507, 1489, 1453, 1264, 1180, 1115, 1004 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{30}H_{30}NO_8$ = 532.19659, found: 532.19649.

4.2.26. *rel*-(1*S*,3*S*,3a*S*,9b*R*)-Dimethyl 3-(furan-2-yl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-di-carboxylate (3r)

53% yield; R_f = 0.12 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.36 (m, 1H), 7.36–7.30 (m, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.18–7.12 (m, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.44 (d, J = 3.2 Hz, 1H), 6.35 (dd, J = 3.2, 1.4 Hz, 1H), 5.65 (s, 1H), 4.15 (s, 1H), 3.41 (s, 6H), 1.82 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.32, 166.97, 164.74, 151.82, 150.51, 142.80, 129.55, 129.16, 124.83, 117.75, 117.07, 110.76, 108.88, 70.57, 63.48, 63.13, 54.11, 53.71, 52.18, 24.16 ppm; FT-IR: $\tilde{\nu}$ = 2922, 1771, 1729, 1491, 1439, 1242, 1183, 1114, 1001 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{20}H_{20}NO_7$ = 386.12343, found: 386.12581.

4.2.27. *rel*-(1*R*,3*S*,3a*S*,9b*R*)-Dimethyl 3-(furan-2-yl)-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-di-carboxylate (4r)

31% yield; R_f = 0.18 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.47 (m, 1H), 7.37–7.28 (m, 2H), 7.22–7.15 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.37–6.24 (m, 2H), 5.47 (s, 1H), 4.79 (s, 1H), 3.85 (s, 3H), 3.48 (s, 3H), 3.10 (s, 1H), 1.01 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.19, 165.73, 164.94, 152.42, 151.10, 142.79, 130.48, 129.47, 125.23, 119.35, 116.79, 110.59, 108.58, 67.92, 62.79, 61.02, 53.60, 53.08, 47.78, 24.58 ppm; FT-IR: $\tilde{\nu}$ = 2922, 1769, 1735, 1491, 1459, 1352, 1245, 1161, 1115, 1012 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{20}H_{20}NO_7$ = 386.12343, found: 386.12492.

4.2.28. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 3-isobutyl-1-methyl-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-di-carboxylate (3s)

48% yield; R_f = 0.18 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31–7.23 (m, 2H), 7.15–7.08 (m, 1H), 7.05 (d, J = 8.2 Hz, 1H), 4.39–4.32 (m, 1H), 3.81 (s, 1H), 3.70 (s, 3H), 3.40 (s, 3H), 1.82–1.73 (m, 1H), 1.70 (s, 3H), 1.51–1.34 (m, 2H), 0.98 ppm (t, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.81, 169.20, 166.05, 150.53, 129.33, 128.92, 124.50, 117.85, 117.09, 71.09, 64.26, 62.48, 56.34, 53.58, 52.08, 41.75, 25.65, 24.30, 23.90, 21.64 ppm; FT-IR: $\tilde{\nu}$ = 2954, 2922, 1753, 1724, 1490, 1452, 1379, 1227, 1167, 1114, 1009 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{20}H_{26}NO_6$ = 376.17546, found: 376.17647.

4.2.29. *rel*-(1*S*,3*R*,3a*S*,9b*R*)-Dimethyl 1-methyl-4-oxo-3-pentyl-1,2,3,3a,4,9b-hexahydro-chromeno[3,4-*c*]pyrrole-1,3a-dicarboxy-late (3t)

54% yield; R_f = 0.27 (ethyl acetate/cyclohexane = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29–7.23 (m, 2), 7.15–7.08 (m, 1H), 7.05 (d, J = 8.2 Hz, 1H), 4.25 (dd, J = 9.3, 4.2 Hz, 1H), 3.81 (s, 1H), 3.70 (s, 3H), 3.40 (s, 3H), 1.70 (s, 3H), 1.64–1.39 (m, 4H), 1.36–1.28 (m, 4H), 0.89 ppm (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.83, 169.16, 166.08, 150.55, 129.33, 128.91, 124.50, 117.78, 117.08, 70.93, 66.18, 62.36, 56.20, 53.57, 52.05, 33.15, 31.98, 27.08, 24.20, 22.69, 14.17 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1768, 1729, 1491, 1454, 1226, 1166, 1115, 1032 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{28}NO_6$ = 390.19111, found: 390.19142.

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Supplementary data

Supplementary data (copies of ^{1}H NMR- and ^{13}C NMR-spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2015.02.044.

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8. CCDC 1036882 (**3f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif