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3-Nitro-2-phenyl-2-(trifluoromethyl)-2*H*-chromenes in reaction with *N*-methylazomethine ylide: stereoselective synthesis of 3a,4,4-trisubstituted chromeno[3,4-*c*]pyrrolidines

Vladislav Yu. Korotaev[1]*, Igor B. Kutyashev[1], Alexey Yu. Barkov[1], Vyacheslav Ya. Sosnovskikh[1]

[1] *Institute of Natural Sciences and Mathematics, Ural Federal University named after the First President of Russia B. N. Yeltsin, 71 Lenina Ave., Yekaterinburg 620000, Russia; e-mail: korotaev.vladislav@urfu.ru*

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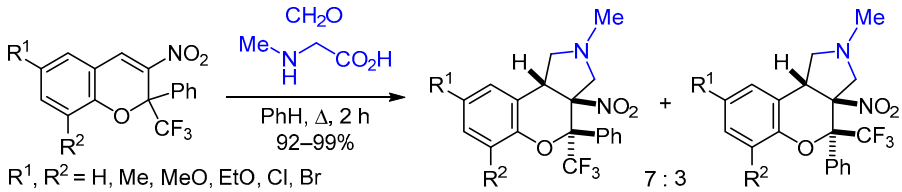


1,3-Dipolar cycloaddition of unstabilized azomethine ylide obtained *in situ* from sarcosine and paraform occurred stereoselectively at the double bond of 3-nitro-2-phenyl-2-(trifluoromethyl)-2*H*-chromenes activated by the presence of nitro group. The synthetic procedure required refluxing in benzene for 2 h and gave chromeno[3,4-*c*]pyrrolidines with *trans* configuration of trifluoromethyl group and nitro group as the major products. The structure of the obtained products was confirmed by X-ray structural analysis.

Keywords: chromeno[3,4-*c*]pyrrolidines, 3-nitro-2-phenyl-2-(trifluoromethyl)-2*H*-chromenes, unstabilized azomethine ylides, 1,3-dipolar cycloaddition.

The structural motif of pyrano[3,4-*c*]pyrrolidine represents a key feature of many biologically active molecules.[1] Of particular interest are derivatives of chromeno[3,4-*c*]-pyrrolidine, some of which have been recognized as promising pharmaceutical agents.[2] For example, fiduxosin shows α1A/α1B selectivity with respect to adrenoceptors and has been proposed as an improved analog of tamsulozine for the treatment of benign prostatic hyperplasia,[2a,b] while the investigational drug S33138 is able to block the dopamine receptor D_3 and can be used in the therapy of cognitive dysfunctions, schizophrenia, and Parkinson's disease (Fig. 1).[2c,d]

Despite the pronounced biological activity, chromeno-[3,4-*c*]pyrrolidines in general have not yet been thoroughly studied and there are relatively few methods available for their synthesis, which rely on stereoselective nucleophilic addition and cycloaddition reactions.[3] A simple and effective method for the synthesis of *cis*-fused chromeno-[3,4-*c*]pyrrolidines, which has recently attracted significant attention, is based on 1,3-dipolar cycloaddition of azomethine ylides at C=C bond of 3-nitro-2*H*-chromenes, which is activated by the presence of nitro group.[4] It should be noted that when the starting nitrochromene contains only one substituent at the position C-2, the 1,3-dipole preferentially attacks the double bond from the side of the less bulky 2-CH hydrogen atom. Thus, the addition of azomethine ylide generated *in situ* from paraformaldehyde and sarcosine to 2-aryl- and 2-trihalomethyl-substituted 3-nitro-2*H*-chromenes **1** resulted in the formation of chromeno[3,4-*c*]pyrrolidines **2** and **3** with *cis* configuration of the substituent R (R = Ar, CX_3) and nitro group in the pyran ring (Scheme 1).[5] In this context, we were interested in characterizing the reactivity of 2,2-disub-stituted 3-nitro-2*H*-chromenes bearing various substituents at the C-2 atom.

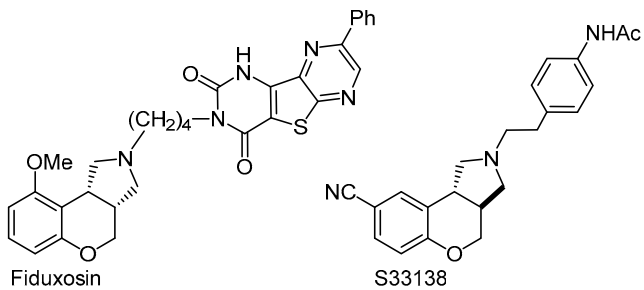
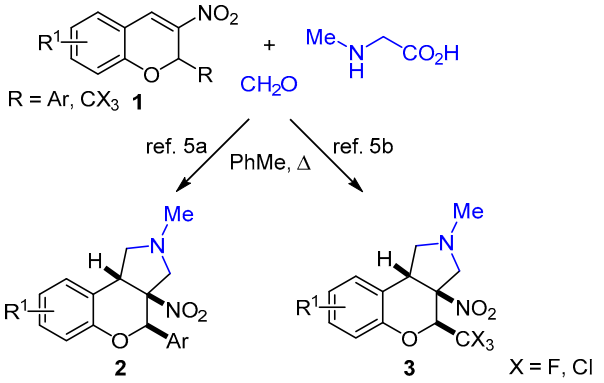


Figure 1. Biologically active *N*-alkylated derivatives of *cis*- and *trans*-chromeno[3,4-*c*]pyrrolidines.

Scheme 1



We recently reported the preparation of 2-phenyl-2-trifluoromethyl-2*H*-chromenes **4**[6a] that represent structural hybrids of 2-Ph- and 2-CF_3-2*H*-chromenes **1**, as well as studied their reactions with enamines[6a] and sodium azide.[6b] In a continuation of studies focused on the effects of 2-trihalomethyl group on the reactivity of 3-nitro-2*H*-chromenes and the stereoselectivity of processes involving such compounds,[7] in the currect work, we explored the [3+2] cycloaddition of azomethine ylides obtained from formaldehyde and sarcosine to 3-nitro-2*H*-chromenes **4** and developed a stereoselective method for the synthesis of 3a,4,4-trisubstituted chromeno[3,4-*c*]pyrrolidines.

Since the most stable configuration of chromenes **4** featured axial orientation of the phenyl substituent,[6a] it could be expected that the attack by azomethine ylide on the double bond from the side of equatorial CF_3 group would be more favorable. Indeed, the reaction of nitrochromenes **4a**–**f** with ylide derived from formaldehyde and sarcosine, performed by refluxing in benzene for 2 h, gave 92–99% yields of mixtures containing chromeno[3,4-*c*]-pyrrolidines *trans*-**5a**–**f** and *cis*-**5a**–**f**, with the major diastereomer having *trans* configuration of the nitro group and CF_3 group in the pyran ring (Scheme 2, Table 1).

As shown in Table 1, the yields of products **5a**–**f** did not depend on the electron donor or acceptor properties of the substituents R^1 and R^2, but the fraction of the minor *cis*-isomer did not exceed 30–33%.

^{1}H NMR spectra of mixtures containing diastereomeric adducts **5a**–**f** were acquired in DMSO-d_6 solutions and showed the characteristic doublet signals of 3-CH_2 methylene protons in the range of 4.05−4.79 ppm with spin-spin coupling constants ^2J = 11.2–12.1 Hz and the triplet signal of 9b-CH benzyl proton was observed at 4.05–4.79 ppm with spin-spin coupling constant of ^2J = 6.7–7.9 Hz. ^{13}C NMR spectra of both the *trans*- and *cis*-isomers of compounds **5a**–**f** contained quartet signals of CF_3 group and C-4 atom in the ranges of 122.9–124.0 and 78.2–80.8 ppm, respectively, with spin-spin coupling constants $^1J_{CF}$ = 289.1–292.6 and $^2J_{CF}$ = 27.6–28.5 Hz. IR spectra of products **5a**–**f** featured characteristic nitro group vibration bands ν(NO_2) in the intervals of 1549−1557 and 1337−1342 cm^{-1}.

The reaction of pyrrolidines **5a**–**f** with oxalic acid in 8:3 hexane−Me_2CO mixture gave high yields (67–84%) of the respective oxalates **6a**–**f**. As a result of this treatment, the content of *cis*-isomers in oxalates **6c**,**d** dropped to 24 and 19%, respectively, while 6,8-dihalo-substituted derivatives **6e**,**f** were practically completely purified from the presence of *cis*-adduct (Scheme 3, Table 2).

Scheme 2

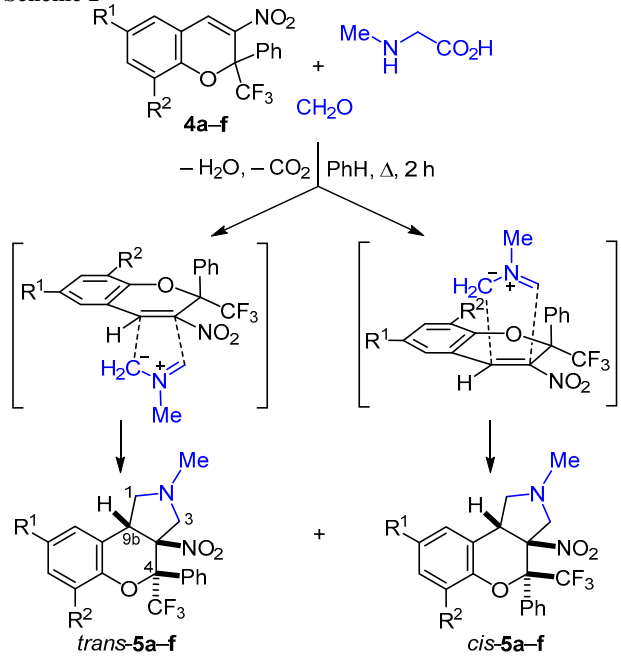


Table 1. Yields and isomer ratio of chromeno[3,4-*c*]pyrrolidines **5a**–**f**

Adduct	R^1	R^2	Yield, %	Ratio *trans*:*cis*
5a	H	H	95	67:33
5b	Me	H	98	68:32
5c	MeO	H	96	69:31
5d	H	EtO	99	70:30
5e	Cl	Cl	92	69:31
5f	Br	Br	93	69:31

Scheme 3

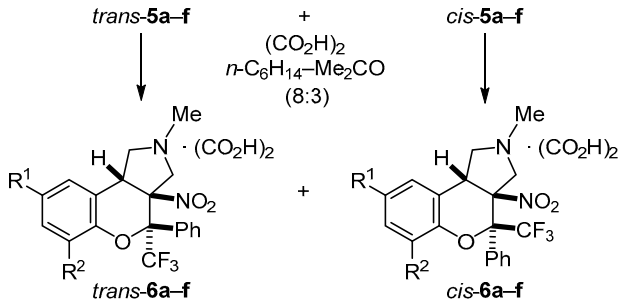


Table 2. Yields and isomer ratio of oxalates **6a**–**f**

Oxalate	R^1	R^2	Yield, %	Ratio *trans*:*cis*
6a	H	H	84	69:31
6b	Me	H	84	68:32
6c	MeO	H	79	76:24
6d	H	EtO	76	81:19
6e	Cl	Cl	68	96:4
6f	Br	Br	67	100:0

The individual *trans*-isomers **5a–f** were obtained by washing oxalates **6a–f** with acetone, suspending in CH_2Cl_2, and then adding aqueous NaOH solution (Scheme 4, Table 3).

Scheme 4

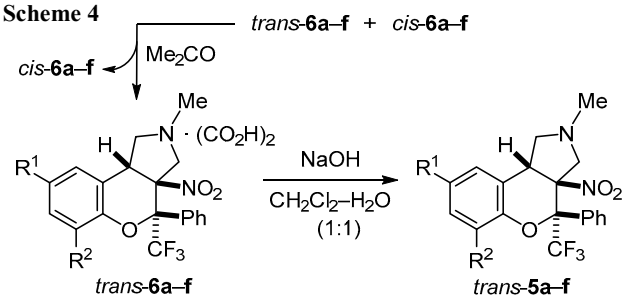


Table 3. Yields and melting points of *trans*-isomers **5a–f**

trans-Isomer	R^1	R^2	Yield, %	mp, °C
5a	H	H	62	101–102
5b	Me	H	64	114–115
5c	MeO	H	67	111–112
5d	H	EtO	60	152–153
5e	Cl	Cl	63	186–187
5f	Br	Br	67	184–185

The spatial structure of the major *trans*-isomers **5a–f** was confirmed by monocrystal X-ray diffraction analysis of compound *trans*-**5d** (Fig. 2). Cycloadduct *trans*-**5d** was indeed the isomer containing nitro group and trifluoromethyl group in a transoid relationship, with the latter occupying an axial position. The pyran and pyrrolidine rings were fused in a *cis*-3a,9b-equatorially-axial geometry and the rings had a distorted half chair and twist conformations, respectively.

The same pyran ring conformation, but with *trans* configuration of CF_3 group relative to the pyrrolidine moiety apparently was present also in compounds *cis*-**5a–f** (Fig. 3). The axial orientation of trifluoromethyl substituent in both diastereomers was indicated by the close chemical shift values for the CF_3 groups in ^{19}F NMR spectra of *trans*- and *cis*-adducts **5a–f**, acquired in DMSO-d_6 solution

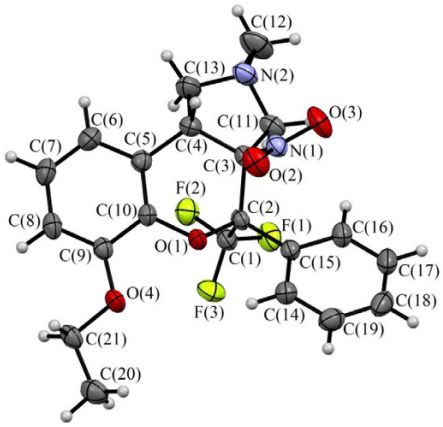


Figure 2. The molecular structure of compound *trans*-**5d** with atoms represented by thermal vibration ellipsoids of 30% probability.

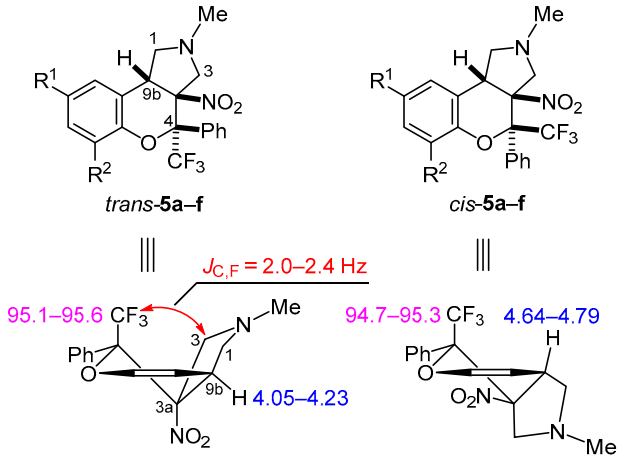


Figure 3. The signals of 9b-CH proton and CF_3 group in ^1H and ^{19}F NMR spectra of compounds **5a–f** acquired in DMSO-d_6 (δ, ppm).

(94.7–95.3 ppm and 95.1–95.6 ppm, respectively). The pseudoequatorial 9b-CH proton in the case of *trans*-isomers **5a–f** was observed as a triplet in the range of 4.05–4.23 ppm, while in *cis*-isomers **5a–f** this proton was in a pseudoaxial orientation and was shifted downfield due to the deshielding effect of the CF_3 group (4.64–4.79 ppm). The close proximity of CF_3 group and the C-3 atom of pyrrolidine ring in compounds *trans*-**5a–f** caused the latter ^{13}C NMR signal to appear as a quartet at 60.4–61.1 ppm with spin-spin coupling constant J_{CF} = 2.0–2.4 Hz. Such spin-spin coupling through space was absent in the *cis*-isomers. We should also note the greater chemical non-equivalence of 3-CH_2 methylene protons in the *trans*-isomers **5a–f** (Δδ 1.15–1.22 ppm) compared to the *cis*-isomers (Δδ 0.38–0.54 ppm). The same trends were observed in ^1H, ^{19}F, and ^{13}C NMR spectra of stereoisomeric oxalates **6a–f**.

Unfortunately, the reaction of nitrochromenes **4a–f** with ylide obtained from formaldehyde and proline proceeded nonselectively and led to the formation of mixtures containing approximately equal amounts of four regio- and stereoisomeric products, which we were unable to separate during this study.

Thus, the azomethine ylide obtained from formaldehyde and sarcosine was used in cycloaddition reactions with 3-nitro-2-phenyl-2-(trifluoromethyl)-2*H*-chromenes, which predominantly proceeded as an attack from the side of equatorial trifluoromethyl group and led to the formation of chromeno[3,4-*c*]pyrrolidines with a *trans* configuration of NO_2 and CF_3 groups as the major products. The different solubility of oxalates derived from stereoisomeric adducts in acetone allowed to purify the major isomer from the presence of the minor *cis*-isomer.

Experimental

IR spectra were recorded on a Bruker Alpha spectrometer equipped with an ATR accessory (ZnSe crystal). ^1H and ^{19}F NMR spectra were acquired on a Bruker DRX-400 spectrometer (400 and 376 MHz, respectively) in DMSO-d_6, using TMS and C_6F_6 as internal standards. ^{13}C NMR spectra were acquired on a Bruker Avance 500 spectrometer (126 MHz) in DMSO-d_6, using the solvent signal as internal standard (40.0 ppm). High-

resolution mass spectra (electrospray ionization) were recorded on a Waters Xevo Qtof instrument. Elemental analysis was performed on a PE 2400 automatic analyzer. Melting points were determined on an SMP40 apparatus.

The starting nitrochromenes **4a**–**f** were obtained according to a published procedure.[6a]

Synthesis of chromeno[3,4-*c*]pyrrolidines 5a–f (General method). A mixture of the appropriate nitrochromene **4a**–**f** (1.0 mmol), paraform (0.18 g, 6.0 mmol), and sarcosine (0.22 g, 2.5 mmol) in benzene (5 ml) was stirred and refluxed in a flask with Dean–Stark trap for 2 h. The reaction mixture was then cooled to room temperature, the unreacted residue of sarcosine was removed by filtration. Solvent was removed from the filtrate at reduced pressure and the residue containing a mixture of the product stereoisomers was washed with H_2O and dried at reduced pressure and room temperature. Chromenopyrrolidines **5a**–**f** were obtained as a mixture of *trans*- and *cis*-isomers.

(3a*S,4*R**,9b*R**)-2-Methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*trans*-5a) and (3a*S**,4*S**,9b*R**)-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*cis*-5a)**, 67:33 mixture of *trans*:*cis* isomers. Yield 0.36 g (95%), light-yellow oil. IR spectrum, ν, cm^{-1}: 1557, 1494, 1455, 1365, 1342. ^1H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.29 (1H, t, *J* = 8.1, 1-CHH); 2.34 (3H, s, NCH_3); 3.09 (1H, d, *J* = 12.0, 3-CHH); 3.67 (1H, t, *J* = 8.7, 1-CHH); 4.10 (1H, t, *J* = 7.5, 9b-CH); 4.27 (1H, d, *J* = 12.0, 3-CHH); 7.11−7.27 (4H, m, H Ar); 7.39−7.51 (5H, m, H Ph); *cis*-isomer: 2.09 (3H, s, NCH_3); 2.27 (1H, dd, *J* = 9.2, *J* = 5.3, 1-CHH); 2.66 (1H, d, *J* = 11.2, 3-CHH); 3.04 (1H, d, *J* = 11.2, 3-CHH); 4.71 (1H, t, *J* = 6.7, 9b-CH); 7.27−7.37 (4H, m, H Ar); 7.52−7.69 (5H, m, H Ph); the signal of 1-CHH proton overlapped with the signal of 1-CHH proton in the *trans*-isomer. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 40.8 (NCH_3); 43.2 (C-9b); 60.5 (q, *J* = 2.3, C-3); 60.6 (C-1); 79.7 (q, *J* = 27.8, C-4); 98.4; 116.9; 123.2 (q, *J* = 289.8, CF_3); 123.7; 126.9 (2C Ph); 127.7; 128.2; 128.3 (2C Ph); 128.4; 129.9; 131.2; 148.6; *cis*-isomer: 40.4 (NCH_3); 41.2 (C-9b); 62.0; 63.2; 78.2 (q, *J* = 27.7, C-4); 97.4; 116.5; 123.5 (q, *J* = 292.3, CF_3); 123.5; 126.7 (q, *J* = 2.0, 2C Ph); 127.8; 128.1; 128.2; 128.3 (2C Ph); 130.0; 132.2; 148.4. ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.1 (s, CF_3); *cis*-isomer: 95.0 (s, CF_3). Found, *m*/*z*: 379.1263 $[M+H]^+$. $C_{19}H_{18}F_3N_2O_3$. Calculated, *m*/*z*: 379.1264.

(3a*S,4*R**,9b*R**)-2,8-Dimethyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*trans*-5b) and (3a*S**,4*S**,9b*R**)-2,8-dimethyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*cis*-5b)**, 68:32 mixture of *trans*- and *cis*-isomers. Yield 0.38 g (98%), light-yellow oil. IR spectrum, ν, cm^{-1}: 1555, 1499, 1454, 1338. ^1H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.26 (3H, s, CH_3); 2.34 (3H, s, NCH_3); 2.28 (1H, t, *J* = 8.2, 1-CHH); 3.07 (1H, d, *J* = 12.0, 3-CHH); 3.64 (1H, t, *J* = 8.5, 1-CHH); 4.05 (1H, t, *J* = 7.5, 9b-CH); 4.25 (1H, d, *J* = 12.0, 3-CHH); 7.01−7.16 (3H, m, H-6,7,9); 7.38−7.49 (5H, m, H Ph); *cis*-isomer: 2.09 (3H, s, NCH_3); 2.29 (3H, s, CH_3); 2.26 (1H, dd, *J* = 9.2, *J* = 5.3, 1-CHH); 2.62 (1H, d, *J* = 11.2, 3-CHH); 3.04 (1H, d, *J* = 11.2, 3-CHH); 4.64 (1H, t, *J* = 6.7, 9b-CH); 7.01−7.16 (3H, m, H-6,7,9); 7.51−7.66 (5H, m, H Ph); the signal of 1-CHH proton overlapped with the signal of 1-CHH proton in the *trans*-isomer. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 20.2 (CH_3); 40.8 (NCH_3); 43.2 (C-9b); 60.5 (q, *J* = 2.2, C-3); 60.6 (C-1); 79.7 (q, *J* = 27.8, C-4); 98.5; 116.7; 123.2 (q, *J* = 289.8, CF_3); 123.3; 126.9 (2C Ph); 127.8; 128.2; 128.3 (2C Ph); 129.0; 129.8; 132.7; 146.5; *cis*-isomer: 20.2 (CH_3); 40.4 (NCH_3); 41.3 (C-9b); 62.0; 63.2; 78.2 (q, *J* = 27.7, C-4); 97.6; 116.2; 123.5 (q, *J* = 292.3, CF_3); 126.7 (q, *J* = 1.9, 2C Ph); 127.9; 128.2; 128.3 (2C Ph); 129.9; 131.2; 132.3; 132.7; 146.3. ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.1 (s, CF_3); *cis*-isomer: 95.2 (s, CF_3). Found, *m*/*z*: 393.1419 $[M+H]^+$. $C_{20}H_{20}F_3N_2O_3$. Calculated, *m*/*z*: 393.1421.

(3a*S,4*R**,9b*R**)-8-Methoxy-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*trans*-5c) and (3a*S**,4*S**,9b*R**)-8-methoxy-2-methyl-3a-nitro-4-(trifluoromethyl)-4-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*cis*-5c)**, 69:31 mixture of *trans*- and *cis*-isomers. Yield 0.39 g (96%), light-yellow oil. IR spectrum, ν, cm^{-1}: 1555, 1499, 1450, 1341. ^1H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.34 (3H, s, NCH_3); 2.29 (1H, t, *J* = 8.1, 1-CHH); 3.06 (1H, d, *J* = 11.8, 3-CHH); 3.67 (1H, t, *J* = 8.5, 1-CHH); 4.07 (1H, t, *J* = 7.5, 9b-CH); 4.26 (1H, d, *J* = 11.8, 3-CHH); 6.78 (1H, d, *J* = 3.0, H-9); 6.89 (1H, dd, *J* = 8.9, *J* = 3.0, H-7); 7.12 (1H, d, *J* = 8.9, H-6); 7.38−7.50 (5H, m, H Ph); *cis*-isomer: 2.09 (3H, s, NCH_3); 2.23 (1H, dd, *J* = 9.2, *J* = 5.8, 1-CHH); 2.59 (1H, d, *J* = 11.2, 3-CHH); 3.63 (1H, dd, *J* = 9.2, *J* = 8.1, 1-CHH); 4.66 (1H, t, *J* = 7.0, 9b-CH); 6.85 (1H, dd, *J* = 8.9, *J* = 3.0, H-7); 6.94 (1H, d, *J* = 3.0, H-9); 7.08 (1H, d, *J* = 8.9, H-6); 7.51−7.67 (5H, m, H Ph); the signal of 3-CHH proton overlapped with the signal of 3-CHH proton in the *trans*-isomer. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 41.3 (NCH_3); 44.2 (C-9b); 55.8 (CH_3O); 61.0 (C-1); 61.1 (q, *J* = 2.3, C-3); 80.3 (q, *J* = 27.6, C-4); 99.0; 112.5; 114.8; 118.3; 123.7 (q, *J* = 290.0, CF_3); 127.5 (2C Ph); 128.7 (2C Ph); 128.8; 130.3; 131.8; 142.8; 155.7; *cis*-isomer: 40.9 (NCH_3); 42.4 (C-9b); 55.9 (CH_3O); 62.7; 63.8; 78.8 (q, *J* = 27.7, C-4); 98.3; 112.6; 114.5; 117.9; 124.0 (q, *J* = 292.6, CF_3); 127.2 (q, *J* = 1.6, 2C Ph); 128.7 (2C Ph); 128.8, 130.4; 132.8; 142.6; 155.8. ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.2 (s, CF_3); *cis*-isomer: 95.3 (s, CF_3). Found, *m*/*z*: 409.1370 $[M+H]^+$. $C_{20}H_{20}F_3N_2O_4$. Calculated, *m*/*z*: 409.1370.

(3a*S,4*R**,9b*R**)-6-Ethoxy-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*trans*-5d) and (3a*S**,4*S**,9b*R**)-6-ethoxy-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*cis*-5d)**, 70:30 mixture of *trans*- and *cis*-isomers. Yield 0.42 g (99%), colorless prisms, mp 135–136°C. IR spectrum, ν, cm^{-1}: 1549, 1474, 1337. ^1H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 1.39 (3H, t, *J* = 7.0, OCH_2CH_3); 2.29 (1H, t, *J* = 8.0, 1-CHH); 2.32 (3H, s, NCH_3); 3.08 (1H, d, *J* = 11.8, 3-CHH); 3.65 (1H, t, *J* = 8.4, 1-CHH); 4.16 (1H, t, *J* = 7.4, 9b-CH); 4.16 (1H, dq, *J* = 9.9, *J* = 7.0, OCHHCH$_3$); 4.18 (1H, dq,

J = 9.9, *J* = 7.0, OCHHCH$_3$); 4.23 (1H, d, *J* = 11.8, 3-CHH); 6.72−6.76 (1H, m, H-7); 6.98−7.04 (2H, m, H-8,9); 7.37−7.45 (5H, m, H Ph); *cis*-isomer: 1.31 (3H, t, *J* = 6.9, CH$_3$); 2.19 (1H, dd, *J* = 9.2, *J* = 5.9, 1-CHH); 2.09 (3H, s, NCH$_3$); 2.57 (1H, d, *J* = 11.3, 3-CHH); 3.11 (1H, d, *J* = 11.3, 3-CHH); 3.61 (1H, t, *J* = 8.6, 1-CHH); 4.09 (1H, dq, *J* = 10.0, *J* = 7.0, OCHHCH$_3$); 4.14 (1H, dq, *J* = 10.0, *J* = 7.0, OCHHCH$_3$); 4.66 (1H, t, *J* = 6.8, 9b-CH); 6.87−6.90 (1H, m, H-7); 6.96−7.08 (2H, m, H-8,9); 7.52−7.70 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 14.6 (CH$_3$); 40.8 (NCH$_3$); 43.1 (C-9b); 60.7 (C-1); 60.9 (q, *J* = 2.4, C-3); 64.1 (OCH$_2$); 79.8 (q, *J* = 28.1, C-4); 98.3; 112.1; 118.8; 123.2 (q, *J* = 289.1, CF$_3$); 123.6; 125.0; 126.8 (2C Ph); 128.3 (2C Ph); 129.8; 131.3; 138.0; 147.4; *cis*-isomer: 14.6 (CH$_3$); 40.4 (NCH$_3$); 41.8 (C-9b); 62.2; 63.3; 64.3 (OCH$_2$); 78.2 (q, *J* = 28.0, C-4); 97.8; 112.5; 118.9; 123.4 (q, *J* = 292.2, CF$_3$); 123.5; 126.0; 126.7 (q, *J* = 1.5, 2C Ph); 128.2 (2C Ph); 129.9; 132.4; 138.0; 147.3. ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 94.5 (s, CF$_3$); *cis*-isomer: 95.0 (s, CF$_3$). Found, *m*/*z*: 423.1523 [M+H]$^+$. $C_{21}H_{22}F_3N_2O_4$. Calculated, *m*/*z*: 423.1526.

(3a*S,4*R**,9b*R**)-6,8-Dichloro-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]-pyrrole (*trans*-5e) and (3a*S**,4*S**,9b*R**)-6,8-dichloro-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*cis*-5e)**, 69:31 mixture of *trans*- and *cis*-isomers. Yield 0.41 g (92%), white powder, mp 161–162°C. IR spectrum, ν, cm^{-1}: 1550, 1454, 1340. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.30 (1H, t, *J* = 8.5, 1-CHH); 2.37 (3H, s, NCH$_3$); 3.13 (1H, d, *J* = 12.1, 3-CHH); 3.70 (1H, t, *J* = 8.4, 1-CHH); 4.22 (1H, t, *J* = 7.9, 9b-CH); 4.33 (1H, d, *J* = 12.1, 3-CHH); 7.40 (1H, dd, *J* = 2.3, *J* = 1.0, H-9); 7.45−7.56 (5H, m, H Ph); 7.71 (1H, d, *J* = 2.3, H-6); *cis*-isomer: 2.10 (3H, s, NCH$_3$); 2.22 (1H, dd, *J* = 9.2, *J* = 6.1, 1-CHH); 2.64 (1H, d, *J* = 11.4, 3-CHH); 3.12 (1H, d, *J* = 11.4, 3-CHH); 3.62 (1H, t, *J* = 8.7, 1-CHH); 4.78 (1H, t, *J* = 7.0, 9b-CH); 7.53−7.70 (9H, m, H-6,9, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 40.6 (NCH$_3$); 44.0 (C-9b); 60.2 (C-1); 60.4 (q, *J* = 2.0, C-3); 80.6 (q, *J* = 28.1, C-4); 98.0; 122.5; 122.9 (q, *J* = 290.0, CF$_3$); 126.3; 126.6 (2C Ph); 127.6; 128.2; 128.5; 128.6 (2C Ph); 130.3; 130.5; 143.7; *cis*-isomer: 40.1 (NCH$_3$); 41.9 (C-9b); 62.2; 63.0; 79.1 (q, *J* = 28.5, C-4); 97.4; 122.1; 123.2 (q, *J* = 291.9, CF$_3$); 126.4; 126.6 (2C Ph); 127.1; 128.0, 128.2; 128.6 (2C Ph); 130.3; 131.4; 143.4. ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.4 (s, CF$_3$); *cis*-isomer: 94.7 (s, CF$_3$). Found, *m*/*z*: 447.0483 [M+H]$^+$. $C_{19}H_{16}Cl_2F_3N_2O_3$. Calculated, *m*/*z*: 447.0485.

(3a*S,4*R**,9b*R**)-6,8-Dibromo-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*trans*-5f) and (3a*S**,4*S**,9b*R**)-6,8-dibromo-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole (*cis*-5f)**, 69:31 mixture of *trans*- and *cis*-isomers. Yield 0.50 g (93%), white powder, mp 151–152°C. IR spectrum, ν, cm^{-1}: 1553, 1448, 1341. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.29 (1H, t, *J* = 8.5, 1-CHH); 2.37 (3H, s, NCH$_3$); 3.12 (1H, d, *J* = 12.1, 3-CHH); 3.71 (1H, t, *J* = 8.4, 1-CHH); 4.23 (1H, t, *J* = 7.9, 9b-CH); 4.34 (1H, d, *J* = 12.2, 3-CHH); 7.45−7.60 (6H, m, H Ph, H-9); 7.91 (1H, d, *J* = 2.3, H-6); *cis*-isomer: 2.10 (3H, s, NCH$_3$); 2.20 (1H, dd, *J* = 9.3, *J* = 6.1, 1-CHH); 2.62 (1H, d, *J* = 11.5, 3-CHH); 3.13 (1H, d, *J* = 11.5, 3-CHH); 3.61 (1H, t, *J* = 8.7, 1-CHH); 4.79 (1H, t, *J* = 7.1, 9b-CH); 7.55−7.72 (9H, m, H-9, H Ph); 7.87 (1H, d, *J* = 2.2, H-6). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 40.6 (NCH$_3$); 44.0 (C-9b); 60.2 (C-1); 60.4 (q, *J* = 2.0); 80.8 (q, *J* = 28.1, C-4); 98.1; 111.9; 115.6; 122.9 (q, *J* = 290.3, CF$_3$); 126.7 (2C); 127.3; 128.6 (2C); 129.7; 130.3; 130.6; 133.5; 145.1; *cis*-isomer: 40.1 (NCH$_3$); 42.0 (C-9b); 62.2; 63.1; 79.2 (q, *J* = 28.1, C-4); 97.5; 111.4; 115.6; 123.1 (q, *J* = 291.8, CF$_3$); 126.6 (q, *J* = 1.5, 2C Ph); 128.2; 128.5 (2C Ph); 129.8; 130.2; 131.4; 133.3; 144.8. ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.6 (s, CF$_3$); *cis*-isomer: 94.8 (s, CF$_3$). Found, *m*/*z*: 534.9471 [M+H]$^+$. $C_{19}H_{16}Br_2F_3N_2O_3$. Calculated, *m*/*z*: 534.9474.

Synthesis of chromeno[3,4-*c*]pyrrolidine oxalates 6a–f. The appropriate mixture of diastereomeric chromeno[3,4-*c*]-pyrrolidines **5a**–**f** was dissolved in an 8:3 mixture of hexane and acetone (9 ml). The obtained solution was stirred and treated by dropwise addition of oxalic acid (0.11 g, 1.2 mmol) solution in anhydrous acetone (2 ml). The reaction mixture was maintained for 30 min. The obtained precipitate was filtered off, washed with H$_2$O (5×1 ml), and dried at 100°C. Products **6a**–**f** were isolated as white powders.

(3a*S,4*R**,9b*R**)-2-Methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]-pyrrole oxalate (*trans*-6a) and (3a*S**,4*S**,9b*R**)-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno-[3,4-*c*]pyrrole oxalate (*cis*-6a)**, 69:31 mixture of *trans*- and *cis*-isomers. Yield 0.39 g (84%), mp 209−210°C (decomp.). IR spectrum, ν, cm^{-1}: 1751, 1651, 1560, 1492, 1455, 1361, 1336. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.35 (1H, t, *J* = 8.0, 1-CHH); 2.37 (3H, s, NCH$_3$); 3.14 (1H, d, *J* = 12.0, 3-CHH); 3.68 (1H, t, *J* = 8.4, 1-CHH); 4.12 (1H, t, *J* = 7.4, 9b-CH); 4.30 (1H, d, *J* = 12.0, 3-CHH); 7.10−7.36 (4H, m, H Ar); 7.38−7.51 (5H, m, H Ph); *cis*-isomer: 2.13 (3H, s, NCH$_3$); 2.73 (1H, d, *J* = 11.4, 3-CHH); 3.10 (1H, d, *J* = 11.4, 3-CHH); 3.65 (1H, t, *J* = 8.6, 1-CHH); 4.72 (1H, t, *J* = 6.7, 9b-CH); 7.10−7.69 (9H, m, H Ar, H Ph); the signal of 1-CHH proton in the *cis*-isomer overlapped with the signal of NCH$_3$ protons in the *trans*-isomer. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 40.9 (NCH$_3$); 43.3 (C-9b); 60.4 (q, *J* = 2.4, C-3); 60.5 (C-1); 79.7 (q, *J* = 27.9, C-4); 98.3; 117.0; 123.2 (q, *J* = 289.7, CF$_3$); 123.8; 127.0 (2C Ph); 127.8; 128.3; 128.4 (2C Ph); 128.5; 130.0; 131.2; 148.7; 161.2 (2C CO$_2$H); *cis*-isomer: 40.6 (NCH$_3$); 41.3 (C-9b); 61.9; 63.1; 78.2 (q, *J* = 27.6, C-4); 97.4; 116.6; 123.4 (q, *J* = 292.2, CF$_3$); 123.4; 124.7; 126.8 (q, *J* = 1.8, 2C Ph); 127.9; 128.2; 128.4 (2C Ph); 130.1; 132.1; 148.5; 161.2 (2C CO$_2$H). ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.1 (s, CF$_3$); *cis*-isomer: 95.0 (s, CF$_3$). Found, %: C 53.77; H 4.24; N 6.05. $C_{19}H_{17}F_3N_2O_3\cdot(CO_2H)_2$. Calculated, %: C 53.85; H 4.09; N 5.98.

(3a*S,4*R**,9b*R**)-2,8-Dimethyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]-pyrrole oxalate (*trans*-6b) and (3a*S**,4*S**,9b*R**)-2,8-dimethyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole oxalate (*cis*-6b)**, 68:32

mixture of *trans*- and *cis*-isomers. Yield 0.40 g (84%), mp 214–215°C (decomp.). IR spectrum, ν, cm^{-1}: 1730, 1634, 1563, 1502, 1451, 1365, 1328. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.26 (3H, s, CH_3); 2.33 (1H, t, *J* = 7.9, 1-CHH); 2.35 (3H, s, NCH_3); 3.11 (1H, d, *J* = 11.8, 3-CHH); 3.66 (1H, t, *J* = 8.6, 1-CHH); 4.06 (1H, t, *J* = 7.4, 9b-CH); 4.28 (1H, d, *J* = 11.8, 3-CHH); 7.00−7.17 (3H, m, H-6,7,9); 7.38−7.49 (5H, m, H Ph); *cis*-isomer: 2.12 (3H, s, CH_3); 2.29 (3H, s, NCH_3); 2.67 (1H, d, *J* = 11.4, 3-CHH); 3.08 (1H, d, *J* = 11.4, 3-CHH); 3.62 (1H, t, *J* = 9.2, 1-CHH); 4.65 (1H, t, *J* = 6.7, 9b-CH); 7.00−7.17 (3H, m, H-6,7,9); 7.51−7.67 (5H, m, H Ph); the signal of 1-CHH proton of the *cis*-isomer overlapped with the signals of *trans*-isomer. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 20.2 (8-CH_3); 41.0 (NCH_3); 43.2 (C-9b); 60.3 (q, *J* = 2.3, C-3); 60.4 (C-1); 79.7 (q, *J* = 27.8, C-4); 98.2; 116.4; 122.8; 123.2 (q, *J* = 289.5, CF_3); 127.0 (2C Ph); 127.9; 128.4 (2C Ph); 129.2; 130.0; 131.1; 132.8; 146.5; 161.2 (2C CO_2H); *cis*-isomer: 20.3 (8-CH_3); 40.7 (NCH_3); 41.5 (C-9b); 61.6; 62.9; 78.1 (q, *J* = 28.2, C-4); 97.5; 116.8; 123.5 (q, *J* = 292.4, CF_3); 123.9; 126.7 (q, *J* = 1.6, 2C Ph); 128.0; 128.4 (2C Ph); 129.0; 130.1; 131.1; 132.0; 146.4; 161.2 (2C CO_2H). ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.0 (s, CF_3); *cis*-isomer: 95.1 (s, CF_3). Found, %: C 54.57; H 4.44; N 5.84. $C_{20}H_{19}F_3N_2O_3\cdot(CO_2H)_2$. Calculated, %: C 54.78; H 4.39; N 5.81.

(3a*S,4*R**,9b*R**)-8-Methoxy-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno-[3,4-*c*]pyrrole oxalate (*trans*-6c) and (3a*S**,4*S**,9b*R**)-8-methoxy-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole oxalate (*cis*-6c)**, 76:24 mixture of *trans*- and *cis*-isomers. Yield 0.39 g (79%), mp 213–214°C (decomp.). IR spectrum, ν, cm^{-1}: 1727, 1615, 1563, 1500, 1462, 1428, 1365, 1328. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.33 (1H, t, *J* = 8.2, 1-CHH); 2.36 (3H, s, NCH_3); 3.11 (1H, d, *J* = 11.9, 3-CHH); 3.69 (1H, t, *J* = 8.6, 1-CHH); 3.73 (3H, s, CH_3O); 4.08 (1H, t, *J* = 7.3, 9b-CH); 4.29 (1H, d, *J* = 11.9, 3-CHH); 6.79 (1H, d, *J* = 2.8, H-9); 6.90 (1H, dd, *J* = 8.9, *J* = 2.8, H-7); 7.19 (1H, d, *J* = 8.9, H-6); 7.37−7.57 (5H, m, H Ph); *cis*-isomer: 2.12 (3H, s, NCH_3); 2.30 (1H, d, *J* = 11.5, 3-CHH); 3.76 (3H, s, CH_3O); 3.65 (1H, t, *J* = 8.8, 1-CHH); 4.68 (1H, t, *J* = 7.0, 9b-CH); 6.86 (1H, dd, *J* = 8.9, *J* = 2.8, H-7); 6.95 (1H, d, *J* = 2.8, H-9); 7.09 (1H, d, *J* = 8.9, H-6); 7.52−7.67 (5H, m, H Ph); the signals of 1-CHH and 3-CHH protons of the *cis*-isomer overlapped with the signals of *trans*-isomer. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 41.0 (NCH_3); 43.6 (C-9b); 55.4 (CH_3O); 60.3 (C-1); 60.4 (q, *J* = 2.4, C-3); 79.8 (q, *J* = 27.6, C-4); 98.2; 112.0; 114.6; 118.0; 123.2 (q, *J* = 289.6, CF_3); 123.9; 127.1 (2C Ph); 128.4 (2C Ph); 130.0; 131.1; 142.4; 155.3; 161.1 (2C CO_2H); *cis*-isomer: 40.7 (NCH_3); 42.0 (C-9b); 55.5 (CH_3O); 61.7; 62.9; 78.2 (q, *J* = 28.4, C-4); 97.6; 112.1; 114.3; 117.6; 123.5 (q, *J* = 292.7, CF_3); 123.8; 126.8 (q, *J* = 1.6, 2C Ph); 128.4 (2C Ph); 130.1; 132.1; 142.3; 145.4; 161.1 (2C CO_2H). ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.1 (s, CF_3); *cis*-isomer: 95.3 (s, CF_3). Found, %: C 52.92; H 4.29; N 5.73. $C_{20}H_{19}F_3N_2O_4\cdot(CO_2H)_2$. Calculated, %: C 53.02; H 4.25; N 5.62.

(3a*S,4*R**,9b*R**)-6-Ethoxy-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]-pyrrole oxalate (*trans*-6d) and (3a*S**,4*S**,9b*R**)-6-ethoxy-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole oxalate (*cis*-6d)**, 81:19 mixture of *trans*- and *cis*-isomers. Yield 0.39 g (76%), mp 206–207°C (decomp.). IR spectrum, ν, cm^{-1}: 1726, 1614, 1563, 1492, 1475, 1361, 1326. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 1.39 (3H, t, *J* = 7.0, OCH_2CH_3); 2.29 (1H, t, *J* = 7.8, 1-CHH); 2.34 (3H, s, NCH_3); 3.12 (1H, d, *J* = 11.8, 3-CHH); 3.66 (1H, t, *J* = 8.6, 1-CHH); 4.12 (1H, t, *J* = 7.4, 9b-CH); 4.15 (1H, dq, *J* = 10.2, *J* = 7.0, OCHHCH$_3$); 4.18 (1H, dq, *J* = 10.2, *J* = 7.0, OCHHCH$_3$); 4.25 (1H, d, *J* = 11.8, 3-CHH); 6.74 (1H, dd, *J* = 6.8, *J* = 1.6, H-7); 6.96−7.05 (2H, m, H-8,9); 7.36−7.46 (5H, m, H Ph); *cis*-isomer: 1.31 (3H, t, *J* = 6.9, OCH_2CH_3); 2.11 (3H, s, NCH_3); 2.62 (1H, d, *J* = 11.3, 3-CHH); 3.62 (1H, t, *J* = 9.2, 1-CHH); 4.11 (1H, dq, *J* = 10.2, *J* = 7.0, OCHHCH$_3$); 4.14 (1H, dq, *J* = 10.2, *J* = 7.0, OCHHCH$_3$); 4.67 (1H, t, *J* = 6.8, 9b-CH); 6.89 (1H, dd, *J* = 6.8, *J* = 1.6, H-7); 6.96−7.09 (2H, m, H-8,9); 7.53−7.58 (5H, m, H Ph); the signals of 1-CHH and 3-CHH protons of the *cis*-isomer overlapped with the signals of the *trans*-isomer. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 14.6 (CH_3); 40.8 (NCH_3); 43.1 (C-9b); 60.6 (C-1); 60.9 (q, *J* = 2.2, C-3); 64.2 (OCH_2); 79.9 (q, *J* = 28.1, C-4); 98.2; 112.2; 118.8; 123.2 (q, *J* = 289.5, CF_3); 123.7; 124.8; 126.8 (2C Ph); 128.4 (2C Ph); 129.9; 131.2; 138.1; 147.5; 161.1 (2C CO_2H); *cis*-isomer: 14.6 (CH_3); 40.5 (NCH_3); 41.8 (C-9b); 62.0; 63.2; 64.3 (OCH_2); 78.2 (q, *J* = 28.2, C-4); 97.8; 112.6; 118.9; 124.6 (q, *J* = 292.8, CF_3); 123.6; 124.8; 126.7 (q, *J* = 1.6, 2C Ph); 128.3 (2C Ph); 130.0; 132.3; 138.1; 147.3; 161.1 (2C CO_2H). ^{19}F NMR spectrum, δ, ppm: *trans*--isomer: 94.5 (s, CF_3); *cis*-isomer: 95.1 (s, CF_3). Found, %: C 54.28; H 4.26; N 5.47. $C_{21}H_{21}F_3N_2O_4\cdot(CO_2H)_2$. Calculated, %: C 53.91; H 4.52; N 5.47.

(3a*S,4*R**,9b*R**)-6,8-Dichloro-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]-pyrrole oxalate (*trans*-6e) and (3a*S**,4*S**,9b*R**)-6,8-dichloro-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrrole oxalate (*cis*-6e)**, 96:4 mixture of *trans*- and *cis*-isomers. Yield 0.30 g (68%), mp 231–232°C (decomp.). IR spectrum, ν, cm^{-1}: 1730, 1649, 1569, 1492, 1464, 1416, 1369, 1330. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 2.32 (1H, t, *J* = 8.3, 1-CHH); 2.38 (3H, s, NCH_3); 3.15 (1H, d, *J* = 12.1, 3-CHH); 3.71 (1H, t, *J* = 8.4, 1-CHH); 4.23 (1H, t, *J* = 7.7, 9b-CH); 4.35 (1H, d, *J* = 12.1, 3-CHH); 7.40 (1H, d, *J* = 2.1, H-7(9)); 7.45−7.57 (5H, m, H Ph); 7.71 (1H, d, *J* = 2.1, H-9(7)); *cis*-isomer: 2.14 (3H, s, NCH_3); 2.31 (1H, dd, *J* = 9.4, *J* = 5.8, 1-CHH); 2.72 (1H, d, *J* = 11.6, 3-CHH); 3.17 (1H, d, *J* = 11.6, 3-CHH); 3.64 (1H, t, *J* = 8.8, 1-CHH); 4.79 (1H, t, *J* = 6.9, 9b-CH); 7.56 (1H, d, *J* = 2.5, H-6); 7.57−7.70 (7H, m, H-7,9, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer: 40.7 (NCH_3); 43.9 (C-9b); 60.0 (C-1); 60.2 (q, *J* = 2.1, C-3); 80.6 (q, *J* = 28.0, C-4); 97.8; 122.6; 122.9 (q, *J* = 289.5, CF_3); 126.4; 126.6 (3C); 127.7; 128.4; 128.7 (2C Ph); 130.4 (2C); 143.7; 161.0 (2C CO_2H). ^{19}F NMR spectrum, δ, ppm: *trans*-isomer: 95.4 (s, CF_3); *cis*-isomer: 94.7 (s,

CF_3). Found, %: C 46.83; H 3.13; N 5.28. $C_{19}H_{15}Cl_2F_3N_2O_3 \cdot (CO_2H)_2$. Calculated, %: C 46.95; H 3.19; N 5.21.

(3a*S,4*R**,9b*R**)-6,8-Dibromo-2-methyl-3a-nitro-4-phenyl-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno-[3,4-*c*]pyrrole oxalate (*trans*-6f)**. Yield 0.42 g (67%), mp 231–232°C (decomp.). IR spectrum, ν, cm^{-1}: 1720, 1652, 1567, 1497, 1455, 1367, 1327. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (1H, t, *J* = 8.2, 1-CHH); 2.38 (3H, s, NCH_3); 3.13 (1H, d, *J* = 12.1, 3-CHH); 3.71 (1H, t, *J* = 8.5, 1-CHH); 4.23 (1H, t, *J* = 7.9, 9b-CH); 4.35 (1H, d, *J* = 12.1, 3-CHH); 7.44−7.60 (6H, m, H-7(9), H Ph); 7.91 (1H, d, *J* = 1.6, H-9(7)). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 40.7 (NCH_3); 43.9 (C-9b); 60.0 (C-1); 60.1 (q, *J* = 2.1, C-3); 80.8 (q, *J* = 28.3, C-4); 97.7; 112.0; 115.7; 122.8 (q, *J* = 290.1, CF_3); 126.7 (3C); 128.7 (2C Ph); 129.8; 130.3; 130.4; 133.8; 145.2; 161.0 (2C CO_2H). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 95.6 (s, CF_3). Found, %: C 40.24; H 2.51; N 4.54. $C_{19}H_{15}Br_2F_3N_2O_3 \cdot (CO_2H)_2$. Calculated, %: C 40.28; H 2.74; N 4.57.

Purification of *trans*-isomers of chromeno[3,4-*c*]-pyrrolidines 5a–f from *cis*-isomers. The appropriate mixture containing diastereomeric chromeno[3,4-*c*]pyrrolidine oxalates **6a**–**f** (1.0 mmol) was washed with Me_2CO (5×1 ml), dissolved in CH_2Cl_2 (3 ml), and treated with NaOH (0.05 g, 1.3 mmol) as solution in H_2O (3 ml). The obtained mixture was stirred for 1 h at room temperature, the organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure and the solid residue was recrystallized from hexane. Chromeno[3,4-*c*]pyrrolidines *trans*-**5a**−**f** were isolated as white powders. The yields and melting points of individual *trans*-isomers **5a**−**f** are presented in Table 3.

X-ray structural analysis of compound *trans*-**5d** was performed at 22°C on an Xcalibur 3 diffractometer with CCD detector according to the standard procedure (CuKα radiation, graphite monochromator, ω-scanning). Crystals suitable for X-ray structural analysis were obtained by slow evaporation of a solution of compound *trans*-**5d** in CH_2Cl_2. The structure of compound *trans*-**5d** was solved by direct method using the SHELX97 software suite.[8] The positions of all non-hydrogen atoms were independently refined in anisotropic approximation, the hydrogen atom positions were calculated geometrically and refined according to the "rider" method with dependent temperature parameters. The complete X-ray diffraction dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1862682).

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