Cyclopropyl Building Blocks in Organic Synthesis, 50[+]

An Easy Access to Bicyclic Peptides with an Octahydro[2*H*]pyrazino[1,2-*a*]pyrazine Skeleton

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Dedicated to Professor Kurt Heyns on the occasion of his 90th birthday

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A new route to octahydrospiro(cyclopropane-1,1′-[2*H*]-pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones **12**–**15** has been developed. Michael additions of primary amines onto methyl **2-Me** or *tert*-butyl **2-*t*Bu** 2-chloro-2-cyclopropylideneacetates, followed by DCC- or EDC-induced coupling with Boc- or FmocGlyOH, deprotection and cyclization led to α-amino esters **4a**–**c** and chlorohexahydrodiazepinediones **5a**–**c**, or in the case of **2-*t*Bu** to the α-amino ester **7** exclusively. This reaction sequence with (*S*)-BocPheOH and (*S*)-BocTrpOH diastereoselectively gave (3′*R*,5′*S*)-**9a,b** and (2′*S*,6′*R*)-**11a,b** as the main products. Further peptide coupling, deprotection and cyclization with **4a**–**c** yielded octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones (7′*S*,9a′*S*)-**12a**–**d**, (6a′*S*,11a′*S*)-**12e**, (7′*S*,9a′*R*)-**13a**–**d** and (6a′*S*,11a′*R*)-**13e** which were easily separated. The α-amino esters **9a,b** yielded (4′*S*,9a′*R*)-**14a** (≡**15a**) and (4′*S*,9a′*R*)-**14b** (≡**15b**), (4′*S*,7′*S*,9a′*R*)-**14c** and (4′*R**,7′*S**,9a′*S**)-**15c**. The formation of compounds with three stereogenic centers **14c** and **15c** was accompanied by partial racemization. The versatility of the reported reaction sequence is limited by the steric availability of the secondary amino group in the intermediates **4**, **9** and **10**, as well as in the Michael adducts formed from primary amines and **2-Me**.

Introduction

Multifunctional small molecules are versatile and often even essential building blocks for short and elegant routes in organic synthesis. In this respect the readily available methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**)[1a] is an outstanding example.[1] It was our aim to investigate the utility of this compound for the parallel automated synthesis of perhydrospiro(cyclopropane-1,1′-[2*H*]pyrazino-[1,2-*a*]pyrazine)-3′,6′,9′-triones (**1**), a potentially useful class of geometrically defined peptidomimetics[2] (Figure 1).

These bicyclic tripeptides have an octahydro[2*H*]pyrazino[1,2-*a*]pyrazine skeleton, and thereby constitute a structurally interesting class of compounds which has previously been noted only in three publications,[3] whereas perhydro-

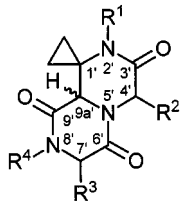

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Figure 1

pyrazino[2,3-*b*]pyrazines are well documented throughout the literature.[4] In the most recent work,[3c] octahydro-[2*H*]pyrazino[1,2-*a*]pyrazines were especially prepared in the search for improved antibacterial agents, but the flexibility of the reaction sequence reported by these authors is somewhat limited, and the authors also mention that previously published procedures[3a,b] could not be reproduced.

Results and Discussion

The Michael additions of primary amines onto methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**) yield adducts which can be coupled with BocGlyOH to give dipeptides **3a**−**c** (Scheme 1). Compared with the primary amino group in natural amino acids, the amino group in the Michael adducts of **2-Me** is considerably more sterically encumbered. To increase the yield in the peptide coupling, a three-

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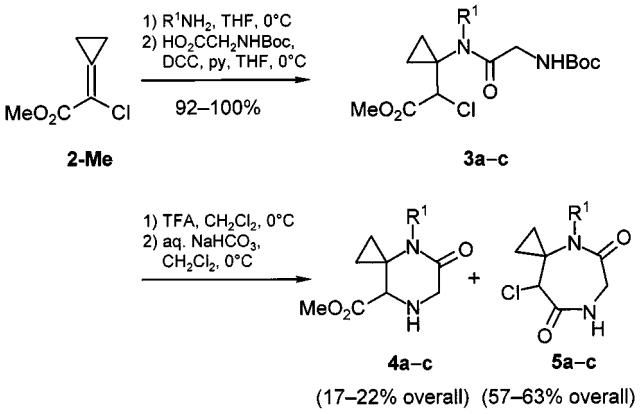
fold excess of BocGlyOH and DCC in the presence of pyridine was used to accelerate the acylation. However, the benzylamine adduct of **2-Me** failed to react with (*S*)-BocProOH or even (*S*)-BocAlaOH under the conditions which were appropriate for couplings. Unlike ordinary peptide couplings, a lack of reactivity for the benzylamine adduct was even observed towards activated esters like *N*-carboxyanhydrides (NCA′s) and $FmocGlyOC_6F_5$ in the presence of pyridine or NEt_3. Deprotection of **3a**−**c** with trifluoroacetic acid (TFA) and basic workup were accompanied by cyclization and gave separable mixtures of the hexahydropyrazinone-type α-amino esters **4a**−**c** and the chlorohexahydrodiazepinediones **5a**−**c**. The skeleton of the α-amino esters **4** has previously been found in the hydrolysis product of the naturally occurring lycomarasmine.[5]



Scheme 1. For details see Table 1

Table 1. α-Amino esters **4a**−**c** and the chlorohexahydrodiazepinediones **5a**−**c** from methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**)

	R^1	**4** (%)[a]	**5** (%)[a]
a	*n*-pentyl	22	60
b	Bzl	18	60
c	$PhCH_2CH_2$	18	63

[a] Overall yields.

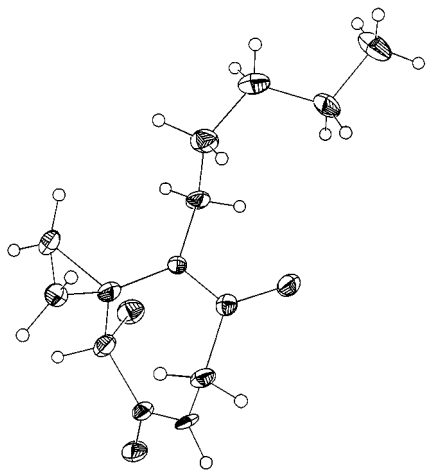
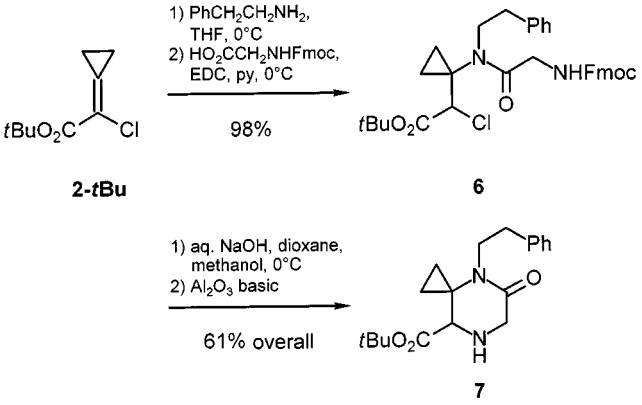


Figure 2. Structure of the chlorohexahydrodiazepinedione **5a** in the crystal

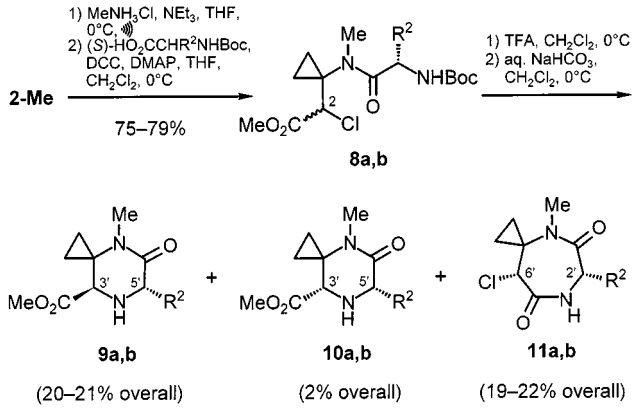
The constitution of the chlorohexahydrodiazepinedione **5a** was proved by an X-ray crystal structure analysis[6] (Figure 2).

In order to favor the formation of the six-membered ring α-amino esters **4** over that of the seven-membered ring lactams **5** from the amine adducts of 2-chloroacrylates **2** the *tert*-butyl ester **2-*t*Bu**[7] was applied, and appropriate modifications of several steps in the reaction sequence were introduced. Thus, addition of 2-phenylethylamine to **2-*t*Bu**, subsequent coupling with a twofold excess of FmocGlyOH in the presence of pyridine, deprotection with aqueous NaOH and cyclization by treatment with basic Al_2O_3 gave **7** in 61% overall yield (Scheme 2).

An interesting kinetic resolution was observed when chiral nonracemic amino acids were used in this coupling-



Scheme 2



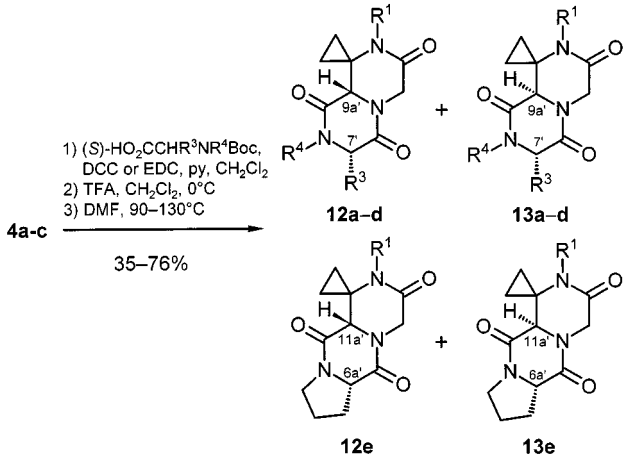
Scheme 3. For details see Table 2

Table 2. Six-membered ring amino esters (3′*R*,5′*S*)-**9a,b**, (3′*S*,5′*S*)-**10a,b** and seven-membered ring lactams (2′*S*,6′*R*)-**11a,b** obtained from **2-Me**

	R^2	**9** (%)[a]	**10** (%)[a]	**11** (%)[a]
a	Bzl	20	2	19
b	(indol-3′′-yl)CH_2	21	2	22

[a] Overall yields.

cyclization sequence (Scheme 3). In this case the methylamine Michael adduct of **2-Me** with the least sterically encumbered secondary amino group was used, and it was successfully coupled with (*S*)-BocPheOH and (*S*)-BocTrpOH to yield **8a,b**. The (2*S*)-isomers of **8a,b**, after deprotection and cyclization, reacted almost exclusively to the α-amino esters (3′*R*,5′*S*)-**9a,b**, whereas the (2*R*) isomers formed single diastereomers of the chlorolactams (2′*S*,6′*R*)-**11a,b** and only traces of the α-amino esters (3′*S*,5′*S*)-**10a,b**. The structure including the absolute configurations of the α-amino ester (3′*R*,5′*S*)-**9a** was established by X-ray crystal structure analyses of several bicyclic tripeptides obtained after incorporation of another amino acid residue (see below), while the configurations of the asymmetric centers in the chlorolactams (2′*S*,6′*R*)-**11a,b** were assigned on the basis of 2D-NOESY NMR experiments showing cross-peaks between H-2′ and H-6′.



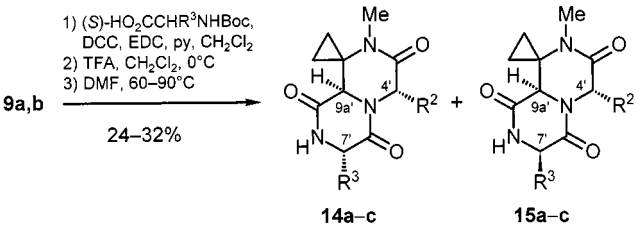
Scheme 4. For details see Table 3

By repeating the sequence of coupling with Boc-protected amino acids, deprotection and cyclization as described above for adducts of **2-Me**, but with the α-amino esters **4** and **9**, bicyclic tripeptides **12**−**15** were obtained (Schemes 4 and 5). The amino group of **4** was found to be more easily sterically accessible than those in the analogous α-amino esters **9** and **10** with their additional α-alkyl groups. Thus, **4a** smoothly coupled with (*S*)-BocPheOH, **4b** with (*S*)-BocMetOH, (*S*)-BocPheOH and (*S*)-BocProOH and **4c** with (*S*)-BocTrpOH to give tricyclic peptides each as separable pairs of diastereomers **12a**−**e** and **13a**−**e**, respectively. Their configurations were determined by X-ray crystal structure analyses and/or by 2D-NOESY NMR experiments. Based on the assumption that the (*S*) configurations of the incorporated amino acids were retained at C-7′ or C-6a′, respectively, the configurations at C-9a′ for **12a**−**d** and at C-11a′ for **12e** can be assigned as (*S*) and (*R*) for **13**. Interestingly, all 9a′*S*-isomers **12a**−**d** and the 11a′*S*-isomer **12e** had a negative sign for the optical rotations, while all 9a′*R*-isomers **13a**−**d** and the 11a′*R*-isomer **13e** had positive rotations (Table 3).

Table 3. Transformations of **4** to the octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones (7′*S*,9a′*S*)-**12a**−**d**, (6a′*S*,11a′*S*)-**12e**, (7′*S*,9a′*R*)-**13a** and (6a′*S*,11a′*R*)-**13e**

	R^1	R^3	R^4	$[\alpha]_D^{20}$ of **12**[a]	$[\alpha]_D^{20}$ of **13**[a]	yields (**12** + **13**) (%)
a	*n*-pentyl	Bzl	H	−47.2 (0.70)	+ 7.5 (0.32)	50[b]
b	Bzl	CH_2CH_2SMe	H	−59.7 (0.14)	+28.8 (0.17)	16 and 19[c]
c	Bzl	Bzl	H	−93.6 (0.22)	+31.1 (0.17)	59[b]
d	$PhCH_2CH_2$	(indol-3′′-yl)CH_2	H	−84.9 (1.39)	+60.3 (0.63)	56[b]
e	Bzl	$R^3 = R^4 = (CH_2)_3$		−42.1 (0.21)	+41.4 (0.29)	76[b]

[a] Optical rotations in methanol. − [b] Yields of the diastereomeric mixtures resulting from **4a**−**c**. − [c] Yields of separated diastereomers from **4b**.



Scheme 5. For details see Table 4

Table 4. Transformations of the α-amino esters **8** to the octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones **14** and **15**

	R^2	R^3	**14** (%)	**15** (%)
a	Bzl	H	26[a]	
b	(indol-3′′-yl)CH_2	H	32[a]	
c	Bzl	CH_2CH_2SMe	16	8

[a] **14a** and **15a** as well as **14b** and **15b** are identical for R^3 = H.

The relative configurations of **12c** and **12d** were determined by X-ray crystal structure analysis (Figure 3).

The acylation of the cyclic peptide **9** with Boc-protected amino acids was found to be more difficult which must be due to the sterical shielding of the secondary amino group by the substituent at C-4′. Even BocGlyOH formed the corresponding **14a** (identical with **15a**) and **14b** (identical with **15b**) only in low yields (26 and 32%, respectively), and the DCC-induced coupling with (*S*)-BocMetOH proceeded even less efficiently. To improve the yield a sixfold excess of (*S*)-BocMetOH and a threefold excess of DCC as well as prolonged reaction times were required. The more drastic reaction conditions must be responsible for partial racemization at the stereogenic center of the newly attached (*S*)-BocMetOH leading to two diastereomers **14c** and **15c** which could be separated by chromatography.

The structure of the main diastereomer **14c** with the absolute configurations at C-4′, C-7′ and C-9a′ was confirmed by X-ray crystal structure analysis due to the presence of sulfur as a heavy atom (Figure 4). For the bicyclic tripeptides **14a** (≡**15a**) and **14b** (≡**15b**) only the relative configurations at C-4′ and C-9a′ have been proved rigorously, but **14a** (≡**15a**) and **14b** (≡**15b**) were not accompanied by any other diastereomer, and therefore, based on the reasonable assumption that no racemization occurred during their formations, *R* configuration at C-3′ in compounds **9a,b** and thus *R* configuration at C-9a′ in **14a,b** can be attributed.

The minor diastereomer **15c** displayed strong cross-peaks between the signals of 9a′-H and CH_2Ph and strong cross-peaks between 9a′-H and 7′-H in the 2D-NOESY NMR spectrum. Therefore, the relative (4′*R**,7′*S**,9a′*S**) configuration was assigned to this compound.

In conclusion, a new approach to a novel class of geometrically defined tripeptides **12**−**15** with an octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-trione skeleton starting from the easily accessible building block **2-Me** has been developed. This methodology can be adapted to a combinational automated parallel synthesis in solution phase. Further work along these lines is currently in progress.

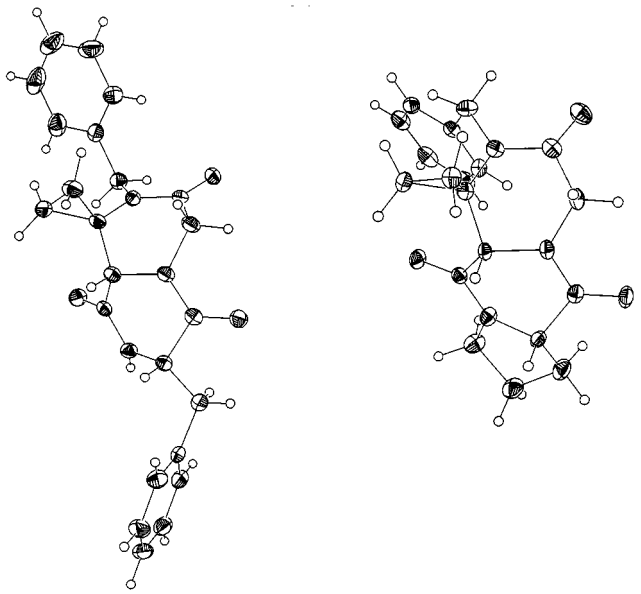


Figure. 3. Structures of octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones **12c** and **12e** in the crystal

Experimental Section

General: ^{1}H- and ^{13}C-NMR spectra: Bruker AW 250 at 250 MHz and 62.9 MHz, respectively. NOESY spectra: Bruker AMX 300 at 300 MHz. Chemical shifts in $CDCl_3$ or CD_3OD are reported in δ values relative to tetramethylsilane (δ = 0.00); for ^{1}H NMR chloroform (δ = 7.26) or methanol (δ = 3.30) and for ^{13}C NMR chloroform (δ = 77.00) or methanol (δ = 49.30) were used as internal standards unless otherwise stated. The DEPT-135 pulse sequence was used for the determination of signal types: + = primary or tertiary carbon, − = secondary carbon, C_{quat} = quaternary carbon. − IR spectra: Bruker IFS 66. − Low-resolution EI mass spectra: Varian CH-7 with Varian Aerograph 1740 spectrometer with an ionizing voltage of 70 eV. − High-resolution mass spectra: VG-70-250S instrument. − Elemental analyses were performed by the Mikroanalytisches Laboratorium im Institut für Organische Chemie, Universität Göttingen. − Melting points are uncorrected. − Preparative column chromatography: Merck silica gel 60 (63−200 μm), ICN neutral alumina (50−200 μm) or Fluka basic alumina type 5016A. − All reactions were carried out under dry nitrogen or argon in oven- and/or flame-dried glassware. Unless otherwise specified, aqueous solutions of $NaHCO_3$, Na_2CO_3 and $KHSO_4$ were used. Solvents were dried according to commonly used procedures.

General Procedure for Michael Addition and DCC-Coupling to 3 and 8 (GP 1): To a solution of primary amine (7.67−15.0 mmol) or to a mixture of methylamine hydrochloride (20.5−36.2 mmol) and NEt_3 (25.7−45.2 mmol) in THF (10−30 mL) at 0 °C was ad-

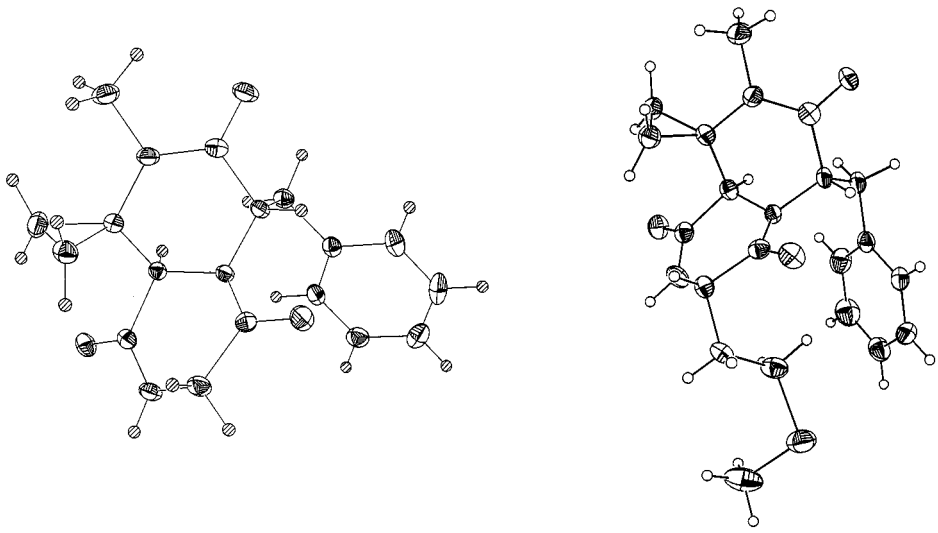


Figure. 4. Structures of octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones **14a** (≡**15a**) and **14c** in the crystal

ded dropwise a solution of methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**)[1a] (13.4−30.0 mmol) in THF (10−30 mL) and stirring was continued for 4−5 h. In the case of methylamine addition to **2-Me** an ultrasonic bath was applied every hour for 5 min, and when the reaction was complete, the solid was filtered off. The filtrate was treated with the Boc-protected amino acid (15.3−45.0 mmol) in THF (20−75 mL), pyridine (15.3−279 mmol) or DMAP (1.80−3.27 mmol) and DCC (15.3−45.0 mmol) in THF (20−30 mL) or CH_2Cl_2 (20 mL) at 0 °C. After stirring overnight the precipitated DCU was removed by filtration and the solution was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (10−30 mL), and the solution was washed with 15% $KHSO_4$ solution, H_2O, three times with saturated $NaHCO_3$ solution and dried ($MgSO_4$ or Na_2SO_4). After concentration in vacuo purification of the residue was performed by column chromatography on silica gel.

General Procedure for Deprotection and Cyclization to 4 and 5 or 9, 10 and 11 (GP 2): To a stirred solution of **3** or **8** (4.31−14.3 mmol) in CH_2Cl_2 (10−30 mL) was added dropwise trifluoroacetic acid (TFA, 29.5−98.2 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature with stirring overnight and was poured into a well stirred mixture of Na_2CO_3 or $NaHCO_3$ solutions (pH = 9−10) and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (100−300 mL). Combined organic solutions were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was treated with diethyl ether and the precipitate was filtered off to give pure **5** or **11** after recrystallization from the appropriate solvent. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel to yield **4** or **9** and **10**. Purification and separation could also be achieved by column chromatography on basic alumina.

General Procedure for Peptide Coupling, Deprotection and Cyclization to 12 and 13 or 14 and 15 (GP 3): A stirred solution of **4** or **9** (0.69−1.41 mmol), Boc-protected amino acid (0.75−2.80 mmol) and pyridine (0.89−3.10 mmol) in CH_2Cl_2 (3−10 mL) was treated with EDC (0.75−0.89 mmol) or a solution of DCC (1.29−2.74 mmol) in CH_2Cl_2 (3−10 mL) at 0 °C. After stirring overnight at the same temp. the precipitated DCU was filtered off and washed with CH_2Cl_2. The filtrate was shaken with 15% solutions of $KHSO_4$ or HCl (1 M), H_2O and saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4 or $MgSO_4$), concentrated in vacuo, and the residue was purified by column chromatography on silica gel. The crude product was dissolved in CH_2Cl_2 (3−4 mL) and treated with TFA (9.82−13.2 mmol) at 0 °C. The stirred reaction mixture was allowed to warm to room temperature overnight and poured into a well stirred mixture of Na_2CO_3 and $NaHCO_3$ solutions (pH = 9−10) and CH_2Cl_2. The aqueous layer was extracted two times with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvent the residue was dissolved in DMF (2.5−4 mL) and heated up to 60−130 °C until the cyclization reaction was complete (TLC). Isolation of the products was achieved by crystallization from the appropriate solvent or/and separation by column chromatography on silica gel or neutral alumina.

Methyl Hexahydro-6′-oxo-1′-pentylspiro(cyclopropane-1,2′-pyrazine)-3′-carboxylate (4a) and 6′-Chlorohexahydro-4′-pentylspiro-(cyclopropane-1,5′-[1*H*][1,4]diazepine)-3′,7′-dione (5a): Pentylamine (668 mg, 7.67 mmol) in THF (10 mL) was treated with a solution of methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**, 1.12 g, 7.64 mmol) in THF (10 mL), BocGlyOH (2.68 g, 15.3 mmol) in THF (20 mL), pyridine (1.21 g, 15.3 mmol) and DCC (3.16 g, 15.3 mmol) in THF (20 mL) according to GP 1. After workup and column chromatography on silica gel (150 g, petroleum ether/diethyl ether, 1 : 1), 2.85 g (95%) of **3a** (R_f = 0.26) was obtained as a yellow oil. Deprotection of **3a** in CH_2Cl_2 (10 mL) with TFA (6.00 g, 52.6 mmol) and basic workup according to GP 2 afforded a semisolid which was purified on basic alumina (100 g, CH_2Cl_2/MeOH, 100 : 2). − Fraction I (R_f = 0.48): 429 mg (22% overall) of **4a** as a colorless oil. − IR (film): $\tilde{\nu}$ = 3321 (NH) cm^{-1}, 3091, 2953, 2869, 1737 (C=O), 1666 (C=O), 1433, 1342, 1202, 1024, 971, 881, 789, 730. − ^1H NMR ($CDCl_3$): δ = 0.71−0.79 (m, 1 H, cpr-H), 0.83 (t, *J* = 7.1 Hz, 3 H, CH_3), 0.92−1.00 (m, 1 H, cpr-H), 1.15−1.33 (m, 8 H, cpr-H and pent-H), 2.49 (br. s, 1 H, NH), 2.60−2.70 (m, 1 H), 3.06 (s, 1 H, 3′-H), 3.44−3.54 (m, 1 H), AB system (δ_A = 3.49, δ_B = 3.56, *J* = 16.1 Hz, 2 H), 3.72 (s, 3 H, CH_3O). − ^{13}C NMR ($CDCl_3$): δ = 8.90 (−, cpr-C), 13.67 (+, CH_3), 15.64 (−, cpr-C), 22.33 (−), 28.44 (−), 28.75 (−), 39.78 (C_{quat}, cpr-C), 41.23 (−), 48.06 (−), 52.45 (+, CH_3O), 63.08 (+, C-3′), 172.51 (C_{quat}, C=O), 172.92 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 254 (47) [M^+], 239 (2) [$M^+ - CH_3$], 226 (18) [$M^+ - C_2H_4$], 212 (31), 195 (100) [$M^+ - C_2H_3O_2$], 167 (54), 155 (97), 123 (34), 96 (32). − $C_{13}H_{22}N_2O_3$ (254.3): calcd. C 61.39, H 8.72, N 11.01; found C 61.11, H 9.00, N 10.93. − Fraction II (R_f = 0.42): 1.19 g (60% overall) of **5a** as colorless crystals, m.p. 139 °C (ethyl acetate/petroleum ether). − IR (KBr): $\tilde{\nu}$ = 3264 (NH) cm^{-1}, 2957, 2929, 2870, 1676 (C=O), 1641 (C=O), 1460, 1423, 1326, 1235, 1042, 938, 795, 720, 607. − ^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.14−1.38 (m, 7 H, cpr-H and pent-H), 1.41−1.49 (m, 2 H, cpr-H), 1.70−1.73 (m, 1 H, cpr-H), 3.07−3.19 (m_c, 1 H, 2′-H), 3.68−3.81 (m, 2 H, CH_2N), 3.83 (s, 1 H, 6′-H), 4.42 (dd, *J* = 1.9, *J* = 14.5 Hz, 1 H, 2′-H), 7.34 (d, *J* = 6.3 Hz, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 13.69 (+, CH_3), 14.96 (−, cpr-C), 19.88 (−, cpr-C), 22.31 (−), 29.07 (−), 29.18 (−), 41.79 (C_{quat}, cpr-C), 47.42 (−), 50.20 (−), 64.68 (+, C-6′), 168.37 (C_{quat}, C=O), 169.84 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 260/258 (0.1/0.1) [M^+], 223 (76) [M^+ − Cl], 166 (100) [M^+ − Cl − C_4H_9]. − $C_{12}H_{19}ClN_2O_2$ (258.8): calcd. C 55.70, H 7.40, Cl 13.70, N 10.83; found C 55.96, H 7.63, Cl 13.78, N 10.91.

X-Ray Crystal Structure Analysis of 5a:[6] Single crystal from ethylacetate/petroleum ether, 0.80 × 1.00 × 1.00 mm, *T* = 150 K, Stoe-Siemens-AED four-circle diffractometer, Mo-K_α (graphite monochromator); λ = 71.073 pm, empirical formula $C_{12}H_{19}ClN_2O_2$, space group $P2_1/c$; unit cell dimensions: *a* = 1548.9 pm; *b* = 657.7 pm; *c* = 1325.0 pm; α = 90°; β = 107.56°; γ = 90°; d_{calcd} = 1.336 g/cm³, *V* = 1.2868 nm³, *Z* = 4, μ(Mo-K_α) = 0.290 mm^{-1}; range for data collection: 3.56 ≤ θ ≤ 22.50°; index ranges: −11 ≤ *h* ≤ 16, −1 ≤ *k* ≤ 7, −14 ≤ *l* ≤ 14; 1660 independent reflections [*R*(int) = 0.1506]. Structure solutions: Direct methods (SHELXS-97[8]) and structure refinement (SHELXL-97[9]): Full-matrix least-squares on F^2, *R* values: *R*1 = 0.0701, *wR*2 = 0.2001 (for all data with 186 parameters and 60 restraints); goodness-of-fit on F^2 = 1.121. Extinction coefficient = 0.041; largest diff. peak and hole 645 and −718 e nm^{-3}.

Methyl 1′-Benzylhexahydro-6′-oxospiro(cyclopropane-1,2′-pyrazine)-3′-carboxylate (4b) and 4′-Benzyl-6′-chlorohexahydrospiro-(cyclopropane-1,5′-[1*H*][1,4]diazepine)-3′,7′-dione (5b): From benzylamine (1.61 g, 15.0 mmol) in THF (30 mL), methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**, 2.20 g, 15.0 mmol) in THF (30 mL), BocGlyOH (7.88 g, 45.0 mmol) in THF (75 mL), pyridine (22.1 g, 279 mmol) and DCC (9.27 g, 45.0 mmol) in THF (30 mL) according to GP 1 was obtained after separation on silica gel (600 g, hexane/diethyl ether, 3 : 2) 6.16 g (100%) of **3b** (R_f = 0.2, hexane/diethyl ether, 1 : 1). **3b** in CH_2Cl_2 (20 mL) was deprotected with TFA (11.2 g, 98.2 mmol) according to GP 2. Two products were obtained after usual workup and purification of the oily resi-

due by column chromatography on silica gel (75 g, CH_2Cl_2/MeOH, 100 : 5). − Product I (R_f = 0.23): 760 mg (18% overall) of **4b** as a colorless oil which crystallized slowly to a white solid, m.p. 45−47 °C. − IR (KBr): $\tilde{\nu}$ = 3426 (NH) cm^{-1}, 3297 (NH), 2952, 1734 (C=O), 1662 (C=O), 1496, 1419, 1343, 1212, 1147, 1032, 730, 704. − ^1H NMR ($CDCl_3$): δ = 0.77 (ddd, *J* = 5.0, *J* = 7.3, *J* = 10.6 Hz, 1 H, cpr-H), 0.93 (ddd, *J* = 5.1, *J* = 6.5, *J* = 10.6 Hz, 1 H, cpr-H), 1.12 (dt, *J* = 6.9, *J* = 11 Hz, 1 H, cpr-H), 1.34 (dt, *J* = 6.9, *J* = 11 Hz, 1 H, cpr-H), 2.58 (br. s, 1 H, NH), 3.03 (s, 1 H, 3′-H), 3.45 (s, 3 H, CH_3O), AB system (δ_A = 3.71, δ_B = 3.73, J_{AB} = 16.0 Hz, 2 H, 5′-H), 4.20 (d, *J* = 15.6 Hz, 1 H, C*H*HPh), 4.55 (d, *J* = 15.6 Hz, 1 H, CH*H*Ph), 7.09−7.13 (m, 2 H, Ar-H), 7.16−7.28 (m, 3 H, Ar-H). − Addition of an excess of TFA shifts the following signals: 3.03 → 3.45, 3.79 → 3.92, 2.58 → 5.55. − ^{13}C NMR ($CDCl_3$): δ = 8.81 (−, cpr-C), 15.04 (−, cpr-C), 40.80 (C_{quat}, cpr-C), 45.61 (−), 48.00 (−), 52.34 (+, CH_3O), 65.82 (+, C-3′), 127.10 (+, C-*para*), 127.25 (+, 2 C), 128.38 (+, 2 C), 137.70 (C_{quat}, C-*ipso*), 172.65 (C_{quat}, C=O), 173.06 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 274 (12) [M^+], 246 (12) [$M^+ - C_2H_4$], 218 (16), 215 (22) [$M^+ - C_2H_3O_2$], 202 (36), 187 (28) [$M^+ - C_2H_3O_2 - C_2H_4$], 186 (19), 142 (24), 104 (45) [$C_7H_4O^+$], 91 (100) [$C_7H_7^+$]. − $C_{15}H_{18}N_2O_3$: calcd. 274.1317; found 274.1317 (MS). − Product II: 2.50 g (60% overall) of **5b** as colorless crystals, m.p. 175 °C (ethanol/heptane). − IR (KBr): $\tilde{\nu}$ = 3417 (NH) cm^{-1}, 3204 (NH), 3087, 2955, 1674 (C=O), 1658 (C=O), 1496, 1464, 1419, 1350, 1329, 1235, 1047, 963, 802, 721. − ^1H NMR (CD_3OD): δ = 1.03−1.17 (m, 1 H, cpr-H), 1.20−1.30 (m, 1 H, cpr-H), 1.40−1.55 (m, 2 H, cpr-H), 3.71 (d, *J* = 14.7 Hz, 1 H), 4.12 (s, 1 H, 6′-H), 4.45 (d, *J* = 15.8 Hz, 1 H), 4.68 (d, *J* = 14.7 Hz, 1 H), 5.24 (d, *J* = 15.8 Hz, 1 H), 7.10−7.18 (m, 2 H, Ar-H), 7.20−7.34 (m, 3 H, Ar-H). − ^{13}C NMR (CD_3OD): δ = 15.12 (−, cpr-C), 20.27 (−, cpr-C), 43.44 (C_{quat}, cpr-C), 47.98 (−, C-2′), 53.97 (−, CH_2Ph), 66.59 (+, C-6′), 127.32 (+, 2 C), 128.47 (+, C-*para*), 130.00 (+, 2 C), 139.84 (C_{quat}, C-*ipso*), 170.52 (C_{quat}, C=O), 173.53 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 278 (0.5) [M^+], 250 (1) [$M^+ - C_2H_4$], 243 (100) [M^+ − Cl], 215 (5) [$M^+ - Cl - C_2H_4$], 186 (83) [$M^+ - C_7H_8$], 104 (5) [$C_7H_4O^+$], 91 (100) [$C_7H_7^+$]. − $C_{14}H_{15}ClN_2O_2$ (278.7): calcd. C 60.33, H 5.42, N 10.05; found: C 60.45, H 5.34, N 9.73.

Methyl Hexahydro-6′-oxo-1′-(2-phenylethyl)spiro(cyclopropane-1,2′-pyrazine)-3′-carboxylate (4c) and 6′-Chlorohexahydro-4′-(2-phenylethyl)spiro(cyclopropane-1,5′-[1*H*][1,4]diazepine)-3′,7′-dione (5c): 2-Phenylethylamine (1.62 g, 13.4 mmol) in THF (20 mL) was treated with a solution of methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**, 1.96 g, 13.4 mmol) in THF (20 mL), BocGlyOH (4.69 g, 26.8 mmol), pyridine (2.12 g, 26.8 mmol) and DCC (5.53 g, 26.8 mmol) in THF (30 mL) according to GP 1. After workup and column chromatography on silica gel (200 g, petroleum ether/diethyl ether, 1 : 1), 5.21 g (92%) of **3c** (R_f = 0.31) was obtained as a yellow oil. Deprotection of **3c** in CH_2Cl_2 (30 mL) with TFA (11.2 g, 98.2 mmol) and basic workup according to GP 2 afforded a semi-solid which gave two products after usual workup and purification of the oily residue on silica gel (75 g, CH_2Cl_2/MeOH, 100 : 5). − Product I: 695 mg (18% overall) of **4c** (R_f = 0.33) as a pale yellow oil. − IR (film): $\tilde{\nu}$ = 3327 (NH) cm^{-1}, 3026, 2950, 2857, 1734 (C=O), 1706 (C=O), 1652 (C=O), 1456, 1419, 1272, 1207, 1143, 1029, 735, 701. − ^1H NMR ($CDCl_3$): δ = 0.64−0.73 (m, 1 H, cpr-H), 0.91−1.00 (m, 1 H, cpr-H), 1.19−1.32 (m, 2 H, cpr-H), 2.50 (br. s, 1 H, NH), 2.55−2.67 (m, 2 H), 3.04−3.16 (m, 1 H), 3.10 (s, 1 H, 3′-H), 3.51−3.66 (m, 1 H), AB system (δ_A = 3.54, δ_B = 3.63, J_{AB} = 15.9 Hz, 2 H), 3.74 (s, 3 H, CH_3O), 7.14−7.31 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 8.94 (−, cpr-C), 15.67 (−, cpr-C), 34.90 (−), 40.46 (C_{quat}, cpr-C), 44.10 (−), 48.15 (−), 52.55 (+, CH_3O), 62.96 (+, C-3′), 126.43 (+, C-*para*), 128.42 (+, 2 C), 128.57 (+, 2 C), 138.43 (C_{quat}, C-*ipso*), 172.54 (C_{quat}, C=O), 172.91 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 288 (39) [M^+], 260 (21) [$M^+ - C_2H_4$], 229 (59) [$M^+ - C_2H_3O_2$], 201 (32) [$M^+ - C_4H_7O_2$], 169 (44), 140 (100), 105 (44) [$C_8H_9^+$]. − $C_{16}H_{20}N_2O_3$ (288.4): calcd. C 66.65, H 6.99, N 9.72; found C 66.37, H 7.07, N 9.90. − Product II: 2.47 g (63%) of **5c** (R_f = 0.27) as colorless crystals, m.p. 174 °C (ethyl acetate/petroleum ether). − IR (KBr): $\tilde{\nu}$ = 3433 (NH) cm^{-1}, 3269 (NH), 3027, 2973, 1675 (C=O), 1641 (C=O), 1444, 1422, 1326, 1040, 755, 699, 612. − ^1H NMR ($CDCl_3$): δ = 0.79−1.10 (m, 3 H, cpr-H), 1.24−1.33 (m, 1 H, cpr-H), 1.72 (br. s, 1 H, NH), 2.79−2.92 (m, 2 H, CH_2Ph), 3.28−3.40 (m, 1 H), 3.73 (s, 1 H, 6′-H), 3.80 (dd, *J* = 7.7, *J* = 14.4 Hz, 1 H), 4.06−4.17 (m, 1 H), 4.46 (dd, *J* = 1.7, *J* = 14.4 Hz, 1 H), 7.14−7.34 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 15.30 (−, cpr-C), 19.87 (−, cpr-C), 34.75 (−), 41.98 (C_{quat}, cpr-C), 47.51 (−), 52.84 (−), 64.63 (+, C-6′), 126.70 (+, C-*para*), 128.59 (+, 2 C), 128.89 (+, 2 C), 139.18 (C_{quat}, C-*ipso*), 168.23 (C_{quat}, C=O), 170.05 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 292 (1) [M^+], 257 (100) [M^+ − Cl], 229 (2) [$M^+ - Cl - C_2H_4$], 200 (21), 173 (10), 144 (11), 104 (29) [$C_8H_8^+$], 91 (5) [$C_7H_7^+$]. − $C_{15}H_{17}ClN_2O_2$ (292.8): calcd. C 61.54, H 5.85, Cl 12.10, N 9.57; found C 61.77, H 5.84, Cl 11.89, N 9.28.

***tert*-Butyl Hexahydro-6′-oxo-1′-(2-phenylethyl)spiro(cyclopropane-1,2′-pyrazine)-3′-carboxylate (7):** To a solution of 2-phenylethylamine (121 mg, 1.00 mmol) in THF (10 mL) was added dropwise a solution of *tert*-butyl 2-chloro-2-cyclopropylideneacetate (**2-*t*Bu**, 189 mg, 1.00 mmol)[7] in THF (10 mL) at 0 °C. After additional stirring for 4 h at the same temp. the solution was treated with FmocGlyOH (601 mg, 2.02 mmol), EDC (383 mg, 2.00 mmol) and pyridine (158 mg, 2.00 mmol). The reaction mixture was allowed to warm to room temp. during 24 h, washed with aqueous HCl (2 M, 20 mL), H_2O (20 mL), saturated $NaHCO_3$ (20 mL) and dried ($MgSO_4$). Evaporation of the solvent gave 580 mg (98%) of the crude product **6** (R_f = 0.38, petroleum ether/diethyl ether, 7 : 1). This product was dissolved in a mixture of dioxane (15 mL) and MeOH (4 mL) and treated with aqueous NaOH (4 M, 1 mL) at 0 °C. After 5 min aqueous HCl (2 M) was added until pH = 8−9 and the mixture was dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography on basic alumina (120 g, CH_2Cl_2/MeOH, 100 : 1) to yield 204 mg (61% overall) of **7** as an amorphous solid (R_f = 0.30, CH_2Cl_2/MeOH, 100 : 5). − IR (film): $\tilde{\nu}$ = 3323 (NH) cm^{-1}, 2977, 2923, 1726 (C=O), 1670 (C=O), 1454, 1407, 1369, 1347, 1233, 1154, 843, 748, 701. − ^1H NMR ($CDCl_3$): δ = 0.59−0.68 (m, 1 H, cpr-H), 0.89−0.98 (m, 1 H, cpr-H), 1.13−1.28 (m, 2 H, cpr-H), 1.47 (s, 9 H, *t*Bu-H), 2.57 (br. s, 1 H, NH), 2.66−2.76 (m, 2 H, CH_2Ph), 3.00 (s, 1 H, 3′-H), 3.24−3.33 (m, 1 H, 5′-H), 3.40−3.48 (m, 1 H, 5′-H), AB system (δ_A = 3.64, δ_B = 3.56, J_{AB} = 15.9 Hz, 2 H, CH_2N), 7.16−7.32 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 8.73 (−, cpr-C), 15.91 (−, cpr-C), 28.07 (+, *t*Bu-C), 35.29 (−), 40.86 (C_{quat}, cpr-C), 44.98 (−), 48.10 (−), 63.45 (+, C-3′), 82.64 (C_{quat}, *t*Bu-C), 126.52 (+), 128.53 (+, 2 C), 128.67 (+, 2 C), 138.63 (C_{quat}, C-*ipso*), 171.19 (C_{quat}, C=O), 172.68 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 330 (8) [M^+], 302 (4) [$M^+ - C_2H_4$], 274 (23) [$M^+ - C_4H_8$], 246 (15) [$M^+ - C_2H_4 - C_4H_8$], 229 (100), 201 (60), 155 (25), 142 (13), 126 (21), 105 (34) [$C_8H_9^+$]. − $C_{19}H_{26}N_2O_3$: calcd. 330.1943; found 330.1943 (HRMS).

Methyl (3′*R*,5′*S*)- and (3′*S*,5′*S*)-5′-Benzylhexahydro-1′-methyl-6′-oxospiro(cyclopropane-1,2′-pyrazine)-3′-carboxylates (9a) and (10a) and (2′*S*,6′*R*)-2′-Benzyl-6′-chlorohexahydro-4′-methylspiro(cyclopropane-1,5′-[1*H*][1,4]diazepine-3′,7′-dione (11a): From methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**, 4.41 g, 30.1 mmol), meth-

ylamine hydrochloride (2.45 g, 36.3 mmol), Et_3N (4.58 g, 45.2 mmol) in THF (30 mL), (*S*)-BocPheOH (9.12 g, 34.4 mmol) and DMAP (400 mg, 3.27 mmol) in CH_2Cl_2 (50 mL), DCC (7.00 g, 33.9 mmol) in CH_2Cl_2 (20 mL) according to GP 1. The residue was separated by column chromatography on silica gel (250 g, hexane/diethyl ether, 1 : 1) to give 10.1 g (79%) of **8a** (R_f = 0.21). This product **8a** (1.83 g, 4.31 mmol) in CH_2Cl_2 (9 mL) was deprotected with TFA (3.36 g, 29.5 mmol) according to GP 2. Three products were obtained after usual workup and purification of the oily residue by column chromatography on silica gel (100 g, $CHCl_3$/MeOH, 100 : 8). − Product I (R_f = 0.20): 27 mg (2% overall) of **10a** as a colorless oil. − $[\alpha]_D^{20}$ = −28.2 (*c* = 0.21 in MeOH). − IR (film): $\tilde{\nu}$ = 3301 cm^{-1}, 2950, 1738 (C=O), 1672 (C=O), 1496, 1436, 1393, 1354, 1217, 1172, 1031, 754, 703. − ^1H NMR ($CDCl_3$): δ = 0.80 (m_c, 1 H, cpr-H), 0.96 (m_c, 1 H, cpr-H), 1.22 (m_c, 2 H, cpr-H), 2.12 (br. s, 1 H, NH), 2.77 (s, 3 H, CH_3N), 2.85 (dd, *J* = 8.6, *J* = 14.6 Hz, 1 H, C*H*HPh), 3.13 (s, 1 H, 3′-H), 3.42 (dd, *J* = 4.8, *J* = 14.6 Hz, 1 H, CH*H*Ph), 3.73 (s, 3 H, CH_3O), 3.83 (dd, *J* = 4.8, *J* = 8.6 Hz, 1 H, 5′-H), 7.23−7.37 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 8.45 (−, cpr-C), 15.96 (−, cpr-C), 30.01 (+, CH_3N), 36.25 (−, CH_2Ph), 40.92 (C_{quat}, cpr-C), 52.56 (+, CH_3O), 57.05 (+, C-5′), 62.44 (+, C-3′), 126.34 (+, C-*para*), 128.29 (+, 2 C), 129.31 (+, 2 C), 138.73 (C_{quat}, C-*ipso*), 173.09 (C_{quat}, C=O), 174.35 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 288 (7) [M^+], 229 (12) [$M^+ - C_2H_3O_2$], 197 (100) [$M^+ - C_7H_7$], 169 (28) [$M^+ - C_7H_7 - C_2H_4$], 165 (12), 137 (14), 120 (8), 109 (16), 91 (14) [$C_7H_7^+$], 83 (8), 68 (8). − $C_{16}H_{20}N_2O_3$: calcd. 288.1473; found 288.1473 (HRMS). − Product II (R_f = 0.23): 320 mg (20% overall) of **9a** as a colorless oil. − $[\alpha]_D^{20}$ = −44.9 (*c* = 0.20 in MeOH). − IR (film): $\tilde{\nu}$ = 3326 (NH) cm^{-1}, 3026, 2952, 1738 (C=O), 1644 (C=O), 1496, 1454, 1431, 1399, 1342, 1295, 1175, 1028, 1003, 753, 701, 666. − ^1H NMR ($CDCl_3$): δ = 0.52−0.65 (m, 2 H, cpr-H), 0.93 (dt, *J* = 7.6, *J* = 10.2 Hz, 1 H, cpr-H), 1.32 (dt, *J* = 6.9, *J* = 10.2 Hz, 1 H, cpr-H), 2.00 (br. s, 1 H, NH), 2.72 (s, 3 H, CH_3N), 3.00 (s, 1 H, 3′-H), 3.06 (dd, *J* = 8.2, *J* = 13.6 Hz, 1 H, C*H*HPh), 3.24 (dd, *J* = 3.8, *J* = 13.6 Hz, 1 H, CH*H*Ph), 3.71 (s, 3 H, CH_3O), 4.14 (dd, *J* = 3.8, *J* = 8.1 Hz, 1 H, 5′-H), 7.23−7.33 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 9.39 (−, cpr-C), 9.70 (−, cpr-C), 28.00 (+, CH_3N), 39.64 (−, CH_2Ph), 41.23 (C_{quat}, cpr-C), 52.28 (+, CH_3O), 57.20 (+, C-5′), 61.95 (+, C-3′), 126.60 (+, C-*para*), 128.38 (+, 2 C), 129.62 (+, 2 C), 137.88 (C_{quat}, C-*ipso*), 170.95 (C_{quat}, C=O), 171.93 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 288 (5) [M^+], 229 (12) [$M^+ - C_2H_3O_2$], 197 (100) [$M^+ - C_7H_7$], 169 (36) [$M^+ - C_7H_7 - C_2H_4$], 165 (12), 137 (15), 120 (8), 109 (20), 91 (10), 81 (8), 68 (7). − $C_{16}H_{20}N_2O_3$: calcd. 288.1473; found 288.1473 (MS). − Product III: 310 mg (19% overall) of **11a** as fine needles, m.p. 199−200 °C (ethanol/H_2O). − IR (KBr): $\tilde{\nu}$ = 3454 (NH) cm^{-1}, 3244 (NH), 3079, 2972, 1678 (C=O), 1659 (C=O), 1496, 1455, 1434, 1399, 1047, 754, 722, 700, 636, 571, 526. − ^1H NMR ($CDCl_3$ + traces of CD_3OD): δ = 1.11−1.21 (m, 1 H, cpr-H), 1.23−1.32 (m, 1 H, cpr-H), 1.37−1.49 (m, 2 H, cpr-H), 2.66 (br. s, 1 H, NH), 2.88 (dd, *J* = 9.0, *J* = 14.6 Hz, 1 H, C*H*HPh), 3.35 (dd, *J* = 5.6, *J* = 14.6 Hz, 1 H, CH*H*Ph), 3.09 (s, 3 H, CH_3N), 3.77 (s, 1 H, 6′-H), 4.80 (dd, *J* = 5.6, *J* = 9.0 Hz, 1 H, 2′-H), 7.21−7.34 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$ + traces of CD_3OD): δ = 15.45 (−, cpr-C), 21.38 (−, cpr-C), 35.60 (+, CH_3N), 36.23 (−, CH_2Ph), 40.67 (C_{quat}, cpr-C), 54.31 (+, C-2′), 65.16 (+, C-6′), 127.30 (+, C-*para*), 129.03 (+, 2 C), 129.10 (+, 2 C), 135.77 (C_{quat}, C-*ipso*), 167.75 (C_{quat}, C=O), 170.93 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 294/292 (12/37) [M^+], 257 (52) [$M^+ - Cl$], 229 (56) [$M^+ - Cl - C_2H_4$], 201 (29) [$M^+ - C_7H_7$], 173 (26) [$M^+ - C_7H_7 - C_2H_4$], 146 (16), 120 (28), 110 (100), 82 (27), 68 (16). − $C_{15}H_{17}ClN_2O_2$ (292.8): calcd. C 61.54, H 5.85, N 9.57; found C 61.86, H 6.01, N 9.80. − 2D-NOESY NMR experiment showed cross-peaks between 2′-H and 6′-H and no cross-peaks between 6′-H and CH_2Ph.

Methyl (3′*R*,5′*S*)- and (3′*S*,5′*S*)-Hexahydro-5′-[(indol-3′′-yl)-methyl]-1′-methyl-6′-oxospiro(cyclopropane-1,2′-pyrazine)-3′-carboxylate (9b and 10b) and (2′*S*,6′*R*)-6′-Chlorohexahydro-2′-[(indol-3′′-yl)methyl]-4′-methylspiro(cyclopropane-1,5′-[1*H*]-[1,4]diazepine)-3′,7′-dione (11b): A suspension of methylamine hydrochloride (1.38 g, 20.5 mmol) and Et_3N (2.60 g, 25.7 mmol) in THF (30 mL) was treated with a solution of methyl 2-chloro-2-cyclopropylideneacetate (**2-Me**, 2.51 g, 17.1 mmol) in THF (20 mL), (*S*)-BocTrpOH (10.4 g, 34.2 mmol), DMAP (220 mg, 1.80 mmol) and DCC (7.06 g, 34.2 mmol) in THF (30 mL) according to GP 1. After workup and column chromatography on silica gel (180 g, petroleum ether/ethyl acetate, 1 : 1), 5.95 g (75%) of **8b** (R_f = 0.22) was obtained as a yellow oil. Deprotection of **8b** (3.74 g, 8.06 mmol) in CH_2Cl_2 (20 mL) with TFA (7.07 g, 62.0 mmol), usual workup and column chromatography of the oily residue on silica gel (150 g, CH_2Cl_2/MeOH, 100 : 5) according to GP 2 afforded three products. − Product I (R_f = 0.35): 81 mg (2% overall) of **10b** as an amorphous solid. − $[\alpha]_D^{20}$ = −70.7 (*c* = 0.91 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3303 (NH) cm^{-1}, 3054, 2950, 2924, 1738 (C=O), 1659 (C=O), 1457, 1432, 1400, 1216, 1171, 744. − ^1H NMR ($CDCl_3$): δ = 0.77−1.03 (m, 2 H, cpr-H), 1.06−1.26 (m, 2 H, cpr-H), 2.78 (s, 3 H, CH_3N), 3.14 (dd, *J* = 7.3, *J* = 15.3 Hz, 1 H, C*H*HC$_8$H$_6$N), 3.18 (s, 1 H, 3′-H), 3.53 (dd, *J* = 4.8, *J* = 15.1 Hz, 1 H, CH*H*C$_8$H$_6$N), 3.70 (s, 3 H, CH_3O), 3.95 (t, *J* = 6.2 Hz, 1 H, 5′-H), 7.08−7.20 (m, 3 H, Ar-H), 7.33 (d, *J* = 7.4 Hz, 1 H, Ar-H), 7.67 (d, *J* = 7.3 Hz, 1 H, Ar-H), 8.37 (br. s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 8.28 (−, cpr-C), 15.38 (−, cpr-C), 25.73 (−), 29.91 (+, CH_3N), 41.03 (C_{quat}, cpr-C), 52.52 (+, CH_3O), 56.15 (+, C-5′), 62.32 (+, C-3′), 111.14 (+, C-7′′), 111.80 (C_{quat}, C-2′′), 118.79 (+, C-4′′ or C-6′′), 119.18 (+, C-6′′ or C-4′′), 121.71 (+, C-5′′), 123.65 (+, C-2′′), 127.72 (C_{quat}, C-3a′′), 136.10 (C_{quat}, C-7a′′), 173.03 (C_{quat}, C=O), 174.51 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 327 (11) [M^+], 268 (2) [$M^+ - C_2H_3O_2$], 198 (100) [$M^+ - C_9H_7N$], 169 (4), 151 (3), 139 (21), 130 (40) [$C_9H_8N^+$]. − $C_{18}H_{21}N_3O_3$ (327.4): calcd. C 66.04, H 6.47, N 12.84; found C 66.08, H 6.51, N 12.61. − Product II (R_f = 0.25): 819 mg (21% overall) of **9b** as an amorphous solid. − $[\alpha]_D^{20}$ = −51.3 (*c* = 0.94 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3292 (NH) cm^{-1}, 3056, 2951, 1737 (C=O), 1628 (C=O), 1458, 1433, 1400, 1342, 1202, 1173, 745. − ^1H NMR ($CDCl_3$): δ = 0.12−0.32 (m, 2 H, cpr-H), 0.78−0.88 (m, 1 H, cpr-H), 1.18−1.28 (m, 1 H, cpr-H), 2.29 (br. s, 1 H, NH), 2.69 (s, 3 H, CH_3N), 2.91 (s, 1 H, 3′-H), 3.35 (d, *J* = 4.7 Hz, 2 H, CH_2C$_8$H$_6$N), 3.67 (s, 3 H, CH_3O), 4.17 (t, *J* = 5.7 Hz, 1 H, 5′-H), 7.03−7.18 (m, 3 H, Ar-H), 7.35 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.65 (d, *J* = 7.8 Hz, 1 H, Ar-H), 8.60 (br. s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 9.00 (−, cpr-C), 9.19 (−, cpr-C), 27.99 (+, CH_3N), 29.27 (−), 41.51 (C_{quat}, cpr-C), 52.19 (+, CH_3O), 56.41 (+, C-5′), 61.97 (+, C-3′), 111.07 (C_{quat}, C-3′′), 111.25 (+, C-7′′), 119.21 (+, C-4′′ or C-6′′), 119.34 (+, C-6′′ or C-4′′), 121.94 (+, C-5′′), 123.36 (+, C-2′′), 127.59 (C_{quat}, C-3a′′), 136.38 (C_{quat}, C-7a′′), 171.58 (C_{quat}, C=O), 176.51 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 327 (7) [M^+], 268 (3) [$M^+ - C_2H_3O_2$], 198 (100) [$M^+ - C_9H_7N$], 169 (3), 151 (3), 139 (17), 130 (29) [$C_9H_8N^+$]. − $C_{18}H_{21}N_3O_3$ (327.4): calcd. C 66.04, H 6.47, N 12.84; found C 65.85, H 6.66, N 12.68. − Product III: 861 mg (22% overall) of **11b** as colorless crystals, m.p. 202 °C (ethyl acetate/petroleum ether). − $[\alpha]_D^{20}$ = −60.3 (*c* = 0.38 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3320 (NH) cm^{-1}, 3060, 2939, 1660 (C=O), 1457, 1431, 1340, 1303, 1098, 1044, 804, 750. − ^1H NMR (CD_3OD): δ = 1.17−1.31 (m, 2 H, cpr-H), 1.48−1.56 (m, 2 H, cpr-H), 3.03−3.12 (m, 1 H, C*H*HC$_8$H$_6$N), 3.09 (s, 3 H, CH_3N), 3.43 (dd, *J* = 6.6, *J* = 14.7 Hz, 1 H, CH*H*C$_8$H$_6$N),

4.12 (s, 1 H, 6′-H), 5.13 (t, J = 7.3 Hz, 1 H, 2′-H), 7.01−7.14 (m, 2 H, Ar-H), 7.21 (s, 1 H, Ar-H), 7.35 (d, J = 7.7 Hz, 1 H, Ar-H), 7.60 (d, J = 7.9 Hz, 1 H, Ar-H). − ^{13}C NMR (CD_3OD): δ = 16.39 (−, cpr-C), 22.57 (−, cpr-C), 27.19 (−), 36.12 (+, CH_3N), 42.72 (C_{quat}, cpr-C), 54.28 (+, C-2′), 67.36 (+, C-6′), 110.73 (+, C-7′′), 112.82 (C_{quat}, C-3′′), 119.21 (+, C-6′′), 120.80 (+, C-4′′), 122.94 (+, C-5′′), 125.58 (+, C-2′′), 128.58 (C_{quat}, C-3a′′), 138.56 (C_{quat}, C-7a′′), 170.28 (C_{quat}, C=O), 174.12 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 333/331 (2/8) [M^+], 295 (4) [M^+ − HCl], 202 (1) [M^+ − C_9H_7N], 130 (100) [$C_9H_8N^+$]. − $C_{17}H_{18}ClN_3O_2$ (331.8): calcd. C 61.54, H 5.47, Cl 10.69, N 12.66; found C 61.31, H 5.67, Cl 10.58, N 12.44. − 2D-NOESY NMR experiment showed cross-peaks between 2′-H and 6′-H.

(7′*S*,9a′*S*)- and (7′*S*,9a′*R*)-7′-Benzyloctahydro-2′-pentylspiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones (12a and 13a): A solution of the α-amino ester **4a** (177 mg, 696 μmol) in CH_2Cl_2 (10 mL) was treated with (*S*)-BocPheOH (240 mg, 905 μmol) in CH_2Cl_2 (10 mL), EDC (173 mg, 902 μmol) and pyridine (71.6 mg, 905 μmol) according to GP 3. Workup without further purification afforded 297 mg (85%) of the crude coupled products (R_f = 0.36, CH_2Cl_2/MeOH, 100 : 2) which were deprotected in CH_2Cl_2 (3 mL) with TFA (1.50 g, 13.2 mmol). Workup, cyclization in DMF (1 mL) at 110 °C for 15 h and crystallization of the residue from ethyl acetate/petroleum ether gave 129 mg (50% from **4a**) of **12a** and **13a** as a 1 : 1 mixture. Separation on silica gel (75 g, ethyl acetate) gave two fractions. − Fraction I (R_f = 0.38): 52 mg of **13a** as colorless crystals, m.p. 128−129 °C (ethyl acetate/petroleum ether). − $[\alpha]_D^{20}$ = +7.5 (c = 0.32 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3235 (NH) cm^{-1}, 2956, 2930, 2870, 1686 (C=O), 1440, 1408, 1347, 1280, 1209, 754, 702. − ^{1}H NMR ($CDCl_3$): δ = 0.82−0.92 (m, 2 H, cpr-H), 0.86 (t, J = 7.2 Hz, 3 H, CH_3), 1.19−1.49 (m, 7 H, cpr-H and pent-H), 1.51−1.83 (m, 1 H, cpr-H), 2.85 (dd, J = 9.8, J = 14.4 Hz, 1 H), 3.09−3.13 (m, 1 H), 3.34−3.44 (m, 1 H), 3.50 (dd, J = 3.8, J = 14.5 Hz, 1 H), 3.76 (s, 1 H, 9a′-H), 3.95 (d, J = 16.3 Hz, 1 H), 4.18 (dd, J = 3.5, J = 9.7 Hz, 1 H, 7′-H), 4.85 (d, J = 16.3 Hz, 1 H), 6.01 (s, 1 H, NH), 7.18−7.36 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 9.25 (−, cpr-C), 13.27 (−, cpr-C), 13.96 (+, CH_3), 22.26 (−), 28.51 (−), 28.96 (−), 36.88 (−), 38.86 (C_{quat}, cpr-C), 43.49 (−), 45.93 (−), 55.28 (+, C-7′), 62.14 (+, C-9a′), 127.56 (+), 129.13 (+, 2 C), 129.19 (+, 2 C), 135.41 (C_{quat}, C-*ipso*), 165.30 (C_{quat}, C=O), 165.39 (C_{quat}, C=O), 168.38 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 369 (100) [M^+], 354 (7) [M^+ − CH_3], 340 (39) [M^+ − C_2H_5], 326 (31) [M^+ − C_3H_7], 278 (56) [M^+ − C_7H_7], 91 (35) [$C_7H_7^+$]. − $C_{21}H_{27}N_3O_3$ (369.5): calcd. C 68.27, H 7.37, N 11.37; found C 68.57, H 7.30, N 11.24. − Fraction II (R_f = 0.23): 55 mg of **12a** as colorless crystals, m.p. 139 °C (ethyl acetate/petroleum ether). − $[\alpha]_D^{20}$ = −47.2 (c = 0.70 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3236 (NH) cm^{-1}, 2957, 2931, 2870, 2846, 1693 (C=O), 1665 (C=O), 1644 (C=O), 1454, 1433, 1411, 1320, 1208, 1030, 759, 705. − ^{1}H NMR ($CDCl_3$): δ = 0.81−0.97 (m, 2 H, cpr-H), 0.84 (t, J = 7.2 Hz, 3 H, CH_3), 1.04−1.33 (m, 7 H, cpr-H and pent-H), 1.34−1.52 (m, 1 H, cpr-H), 2.73 (s, 1 H, 9a′-H), 3.01−3.07 (m, 1 H), 3.12 (d, J = 5.3 Hz, 2 H), 3.24−3.29 (m, 1 H), 3.82 (d, J = 16.5 Hz, 1 H), 4.26 (dd, J = 5.0, J = 8.3 Hz, 1 H, 7′-H), 4.79 (d, J = 16.5 Hz, 1 H), 6.63 (s, 1 H, NH), 7.17−7.30 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 9.50 (−, cpr-C), 12.93 (−, cpr-C), 13.92 (+, CH_3), 22.21 (−), 28.25 (−), 28.83 (−), 39.03 (C_{quat}, cpr-C), 40.02 (−), 42.75 (−), 45.92 (−), 57.30 (+, C-7′), 60.51 (+, C-9a′), 127.59 (+), 128.81 (+, 2 C), 129.80 (+, 2 C), 135.06 (C_{quat}, C-*ipso*), 165.02 (C_{quat}, C=O), 165.09 (C_{quat}, C=O), 168.12 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 369 (91) [M^+], 354 (11) [M^+ − CH_3], 340 (76) [M^+ − C_2H_5], 326 (35) [M^+ − C_3H_7], 278 (86) [M^+ − C_7H_7], 91 (100) [$C_7H_7^+$]. − $C_{21}H_{27}N_3O_3$ (369.5): calcd. C 68.27, H 7.37, N 11.37; found C 68.01, H 7.16, N 11.31. − 2D-NOESY NMR spectrum of **12a** displayed cross-peaks between 7′-H and 9a′-H, but no cross-peaks between 9a′-H and CH_2(C-7′).

(7′*S*,9a′*S*)- and (7′*S*,9a′*R*)-2′-Benzyl-7′-[2-(methylthio)ethyl]octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones (12b and 13b): From α-amino ester **4b** (386 mg, 1.41 mmol), (*S*)-BocMetOH (697 mg, 2.80 mmol) in CH_2Cl_2 (20 mL), pyridine (245 mg, 3.10 mmol) and DCC (577 mg, 2.80 mmol) in CH_2Cl_2 (10 mL) according to GP 3. Column chromatography of the residue on silica gel (75 g, CH_2Cl_2/MeOH, 100 : 2) afforded 550 mg (77%) of the coupled products (R_f = 0.4). Trituration with diethyl ether gave a solid (278 mg, mixture of two diastereomers) and an oil (250 mg, only one diastereomer). The oily fraction was dissolved in CH_2Cl_2 (3 mL) and deprotected with TFA (1.12 g, 9.82 mmol) for 24 h. Standard workup afforded an oil which solidified within 24 h due to spontaneous cyclization at room temp. Recrystallization from aqueous MeOH gave 85 mg of **12b** (16% from **4b**) as colorless crystals, m.p. 152−153 °C (MeOH/H_2O). − $[\alpha]_D^{20}$ = −59.7 (c = 0.14 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3454 (NH) cm^{-1}, 2919, 1691 (C=O), 1668 (C=O), 1496, 1456, 1405, 1346, 1240, 1168, 985, 737. − ^{1}H NMR ($CDCl_3$ + traces of CD_3OD): δ = 0.70−0.85 (m, 1 H, cpr-H), 0.97−1.11 (m, 2 H, cpr-H), 1.40−1.49 (m, 1 H, cpr-H), 1.97 (m_c, 1 H, 7′-CH_2), 2.10 (s, 3 H, CH_3S), 2.37 (m_c, 1 H, 7′-CH_2), 2.70 (m_c, 2 H, CH_2S), 3.43 (s, 1 H, NH), 3.66 (s, 1 H, 9a′-H), 4.03 (d, J = 15.7 Hz, 1 H), 4.12 (dd, J = 7.4, J = 4.9 Hz, 1 H, 7′-H), 4.21 (d, J = 15.8 Hz, 1 H), 4.95 (d, J = 15.8 Hz, 1 H), 5.09 (d, J = 15.7 Hz, 1 H), 7.15−7.31 (m, 5 H, Ar-H). − 2D-NOESY NMR spectrum of **12b** displayed cross-peaks between 7′-H and 9a′-H, but no cross-peaks between 9a′-H and CH_2(C-7′). − ^{13}C NMR ($CDCl_3$): δ = 8.76 (−, cpr-C), 13.73 (−, cpr-C), 15.01 (+, CH_3S), 28.56 (−), 29.89 (−), 39.29 (C_{quat}, cpr-C), 45.77 (−), 48.40 (−), 53.01 (+, C-7′), 62.83 (+, C-9a′), 126.54 (+, 2 C), 127.26 (+, C-*para*), 128.61 (+, 2 C), 137.67 (C_{quat}, C-*ipso*), 166.59 (C_{quat}, C=O), 167.32 (C_{quat}, C=O), 169.85 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 375/374/373 (4/12/49) [M^+], 312 (8) [M^+ − C_2H_5S], 299 (21) [M^+ − C_3H_6S], 254 (4), 215 (6), 208 (9) [M^+ − C_7H_7 − C_3H_6S], 187 (16), 158 (6), 123 (5), 123 (10), 104 (70), 91 (100) [$C_7H_7^+$], 61 (22) [$C_2H_5S^+$]. − $C_{19}H_{23}N_3O_3S$: calcd. 373.1460; found 373.1460 (HRMS). − The crystalline fraction was deprotected with TFA (1.12 g, 9.82 mmol). After usual workup, this substance was dissolved in DMF (4 mL) and heated to 90−100 °C overnight. Crystallization from DMF/H_2O yielded 100 mg (19%) of **13b** as small needles, m.p. 187−188 °C (MeOH/H_2O). − $[\alpha]_D^{20}$ = +28.8 (c = 0.17 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3450 (NH) cm^{-1}, 3222 (NH), 2930, 1691 (C=O), 1675 (C=O), 1643 (C=O), 1496, 1416, 1329, 1288, 1246, 1186, 729. − ^{1}H NMR ($CDCl_3$ + traces of CD_3OD): δ = 0.81−0.90 (m, 1 H, cpr-H), 0.98−1.18 (m, 2 H, cpr-H), 1.25−1.34 (m, 1 H, cpr-H), 1.90−2.16 (m, 2 H, 7′-CH_2), 2.08 (s, 3 H, CH_3S), 2.43−2.54 (m, 2 H, CH_2S), 2.57 (s, 1 H, NH), 3.89 (s, 1 H, 9a′-H), 4.04 (d, J = 16.2 Hz, 1 H), 4.10 (dd, J = 8.6, J = 5.1 Hz, 1 H, 7′-H), 4.21 (d, J = 15.8 Hz, 1 H), 4.98 (d, J = 15.7 Hz, 1 H), 4.99 (d, J = 16.2 Hz, 1 H), 7.13−7.31 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$ + CD_3OD): δ = 9.47 (−, cpr-C), 14.29 (−, cpr-C), 15.48 (+, CH_3S), 30.28 (−), 31.97 (−), 40.94 (C_{quat}, cpr-C), 46.66 (−), 48.74 (−), 55.75 (+, C-7′), 62.27 (+, C-9a′), 127.27 (+, 2 C), 128.14 (+, C-*para*), 129.43 (+, 2 C), 138.20 (C_{quat}, C-*ipso*), 166.61 (C_{quat}, C=O), 167.96 (C_{quat}, C=O), 171.01 (C_{quat}, C=O). − MS (70 eV); *m/z* (%): 375/374/373 (10/32/60) [M^+], 312 (12) [M^+ − C_2H_5S], 299 (22) [M^+ − C_3H_6S], 282 (7) [M^+ − C_7H_7], 254 (5), 234 (6), 208 (10) [M^+ − C_7H_7 − C_3H_6S], 187 (18), 104 (25), 91 (100) [$C_7H_7^+$], 85 (32). − $C_{19}H_{23}N_3O_3S$: calcd. 373.1460; found 373.1460 (HRMS).

(7′*S*,9a′*S*)- and (7′*S*,9a′*R*)-2′,7′-Dibenzyloctahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones (12c and 13c): α-Amino ester **4b** (342 mg, 1.25 mmol) in CH_2Cl_2 (6 mL) was treated with (*S*)-BocPheOH (398 mg, 1.50 mmol), DCC (309 mg, 1.50 mmol) and pyridine (160 mg, 2.02 mmol) in CH_2Cl_2 (3 mL) according to GP 3. Workup and column chromatography on silica gel (50 g, CH_2Cl_2/MeOH, 100 : 5) yielded 543 mg (83%) of the coupled products as a glass-like solid ($R_f \approx 0.25$). Deprotection of these products in CH_2Cl_2 (3 mL) with TFA (1.68 g, 14.7 mmol), standard workup, cyclization in DMF (2.5 mL) at 100 °C for 19 h and crystallization from DMF/H_2O gave 288 mg (59% from **4b**) of **12c** and **13c** as a 1 : 1 mixture. Separation was achieved by column chromatography on neutral alumina (act. III, 70 g, CH_2Cl_2/MeOH, 100 : 1). − Fraction I ($R_f = 0.33$): 116 mg of **12c** as cubes or prisms, m.p. 149−151 °C (MeOH/H_2O, dec.). − $[\alpha]_D^{20} = -93.6$ ($c = 0.22$ in MeOH). − IR (KBr): $\tilde{\nu}$ = 3433 (NH) cm^{-1}, 3252 (NH), 3027, 1686 (C=O), 1653 (C=O), 1496, 1417, 1348, 697. − ^1H NMR ($CDCl_3$): δ = 0.82 (m_c, 1 H, cpr-H), 0.93 (m_c, 1 H, cpr-H), 1.05 (m_c, 1 H, cpr-H), 1.35 (dt, J = 6.3, J = 10.4 Hz, 1 H, cpr-H), 2.82 (dd, J = 10.5, J = 14.6 Hz, 1 H, 7′-CH_2), 3.53 (dd, J = 3.5, J = 14.5 Hz, 1 H, 7′-CH_2), 3.70 (s, 1 H, 9a′-H), 4.10 (d, J = 15.6 Hz, 1 H), 4.19 (dd, J = 3.7, J = 10.3 Hz, 1 H, 7′-H), 4.22 (d, J = 15.8 Hz, 1 H), 5.02 (d, J = 16.1 Hz, 1 H), 5.09 (d, J = 16.1 Hz, 1 H), 5.70 (br. s, 1 H, NH), 7.17−7.39 (m, 10 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 8.88 (−, cpr-C), 13.65 (−, cpr-C), 36.59 (−), 39.65 (C_{quat}, cpr-C), 46.06 (−), 48.27 (−), 55.28 (+, C-7′), 62.76 (+, C-9a′), 126.68 (+, 2 C), 127.33 (+), 127.70 (+), 128.68 (+, 2 C), 129.04 (+, 2 C), 129.36 (+, 2 C), 135.33 (C_{quat}, C-*ipso*), 137.74 (C_{quat}, C-*ipso*), 165.82 (C_{quat}, C=O), 169.53 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 389 (40) [M^+], 361 (3) [$M^+ - C_2H_4$], 306 (4), 298 (20) [$M^+ - C_7H_7$], 270 (8), 245 (4), 215 (9), 201 (12), 186 (30), 146 (12), 104 (41), 91 (100) [$C_7H_7^+$]. − $C_{23}H_{23}N_3O_3 \cdot 0.75H_2O$ (389.5): calcd. C 68.55, H 6.13, N 10.43; found 68.45, H 6.24, N 9.94. − Fraction II ($R_f = 0.24$): 53 mg of **13c** as colorless crystals, m.p. 175−182 °C (ethanol/hexane). − $[\alpha]_D^{20} = +31.1$ ($c = 0.17$ in MeOH). − IR (KBr): $\tilde{\nu}$ = 3437 (NH) cm^{-1}, 3250 (NH), 3029, 2927, 1685 (C=O), 1664 (C=O), 1496, 1454, 1414, 1346, 1316, 753, 732, 702. − ^1H NMR ($CDCl_3$): δ = 0.77−0.87 (m, 1 H, cpr-H), 0.94−0.99 (m, 1 H, cpr-H), 1.07−1.27 (m, 2 H, cpr-H), 2.97 (s, 1 H, 9a′-H), 3.07 (dd, J = 7.6, J = 13.8 Hz, 1 H, 7′-CH_2), 3.20 (dd, J = 4.1, J = 13.9 Hz, 1 H, 7′-CH_2), 3.97 (d, J = 16.5 Hz, 1 H), 4.21 (d, J = 15.6 Hz, 1 H), 4.27 (dd, J = 3.7, J = 7.3 Hz, 1 H, 7′-H), 4.88 (d, J = 15.8 Hz, 1 H), 4.99 (d, J = 16.5 Hz, 1 H), 5.85 (br. s, 1 H, NH), 7.12−7.35 (m, 10 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 8.94 (−, cpr-C), 12.89 (−, cpr-C), 39.99 (−), 40.39 (C_{quat}, cpr-C), 46.15 (−), 47.52 (−), 57.60 (+, C-7′), 60.96 (+, C-9a′), 126.69 (+, 2 C), 127.36 (+), 127.73 (+), 128.69 (+, 2 C), 129.02 (+, 2 C), 129.70 (+, 2 C), 135.07 (C_{quat}, C-*ipso*), 137.47 (C_{quat}, C-*ipso*), 164.58 (C_{quat}, C=O), 165.25 (C_{quat}, C=O), 168.84 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 389 (46) [M^+], 345 (5), 298 (25) [$M^+ - C_7H_7$], 270 (10) [$M^+ - C_2H_4 - C_7H_7$], 215 (8), 201 (11), 186 (22), 146 (7), 120 (7), 104 (30), 91 (100) [$C_7H_7^+$]. − $C_{23}H_{23}N_3O_3$: calcd. 389.1739; found 389.1739 (HRMS).

X-Ray Crystal Structure Analysis of 12c:[6] Single crystal from MeOH/H_2O, 0.50 × 0.50 × 0.40 mm, T = 133 K, Stoe-Siemens-Huber four-circle diffractometer, Mo-K_α (graphite monochromator); λ = 71.073 pm, empirical formula $C_{23}H_{23}N_3O_3 \times 0.75\ H_2O$, space group $P2_12_12_1$; unit cell dimensions: a = 697.2 pm; b = 951.9 pm; c = 2965.5 pm; α = 90°; β = 90°; γ = 90°; d_{calcd} = 1.376 g/cm^3, V = 1.9669 nm^3, Z = 4, μ(Mo-K_α) = 0.095 mm^{-1}; range for data collection: $2.54 \le \theta \le 27.91°$; index ranges: $-9 \le h \le 6$, $-12 \le k \le 12$, $-38 \le l \le 38$; 4379 independent reflections [R(int) = 0.0454]. Structure solutions: Direct methods (SHELXS-97[8]) and structure refinement (SHELXL-97[9]): Full-matrix least-squares on F^2, R values: $R1$ = 0.0550, $wR2$ = 0.1052 (for all data with 284 parameters and 3 restraints); goodness-of-fit on F^2 = 1.059. Flack-x-parameter = −0.4(12); largest diff. peak and hole 288 and −254 e nm^{-3}.

(7′*S*,9a′*S*)- and (7′*S*,9a′*R*)-7′-[(Indol-3′′-yl)methyl]octahydro-2′-(2-phenylethyl)spiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-triones (12d and 13d): A solution of **4c** (166 mg, 576 μmol) in CH_2Cl_2 (10 mL) was treated with (*S*)-BocTrpOH (227 mg, 746 μmol) in CH_2Cl_2 (5 mL), EDC (143 mg, 746 μmol) and pyridine (59.1 mg, 746 μmol) according to GP 3. Workup without further purification afforded 268 mg (81%) of the crude coupled products which were deprotected in CH_2Cl_2 (3 mL) with TFA (1.50 g, 13.2 mmol). Workup, cyclization in DMF (2 mL) at 110 °C for 48 h and crystallization of the residue from CH_2Cl_2/petroleum ether yielded 142 mg (56% from **4c**) of a mixture of **12d** and **13d**. Separation on silica gel (60 g, CH_2Cl_2/MeOH, 100 : 5) gave two fractions. − Fraction I ($R_f = 0.34$): 51 mg of **12d** as colorless crystals, m.p. 120−121 °C (CH_2Cl_2/petroleum ether). − $[\alpha]_D^{20} = -84.9$ ($c = 1.39$ in MeOH). − IR (KBr): $\tilde{\nu}$ = 3304 (NH) cm^{-1}, 3058, 2927, 1681 (C=O), 1457, 1411, 1346, 1264, 1203, 1106, 743, 701. − ^1H NMR ($CDCl_3$): δ = 0.72−0.76 (m, 1 H, cpr-H), 0.98−1.25 (m, 3 H, cpr-H), 2.68−2.73 (m, 1 H, C*H*HC_8H_6N), 2.86−3.02 (m, 2 H, CH_2Ph), 3.37−3.41 (m, 1 H, CH*H*C_8H_6N), 3.59 (s, 1 H, 9a′-H), 3.61−3.71 (m, 2 H, 4′-H), 3.98 (d, J = 15.9 Hz, 1 H, C*H*HN), 4.19 (dd, J = 3.5, J = 10.4 Hz, 1 H, 7′-H), 4.91 (d, J = 15.9 Hz, 1 H, CH*H*N), 5.80 (s, 1 H, NH), 7.07−7.32 (m, 8 H, Ar-H), 7.38 (d, J = 8.0 Hz, 1 H, Ar-H), 7.54 (d, J = 7.9 Hz, 1 H), 8.33 (s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 9.62 (−, cpr-C), 13.58 (−, cpr-C), 26.73 (−), 34.83 (−), 38.87 (C_{quat}, cpr-C), 45.93 (−), 46.00 (−), 53.60 (+, C-7′), 62.44 (+, C-9a′), 109.28 (C_{quat}, C-3′′), 111.60 (+, C-7′′), 118.29 (+, C-4′′ or C-6′′), 119.97 (+, C-6′′ or C-4′′), 122.74 (+, C-5′′), 123.51 (+, C-2′′), 126.56 (C_{quat}, C-3a′′), 126.56 (+), 128.51 (+, 2 C), 128.82 (+, 2 C), 136.57 (C_{quat}, C-7a′′), 138.58 (C_{quat}, C-*ipso*), 165.71 (C_{quat}, C=O), 166.22 (C_{quat}, C=O), 169.25 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 442 (13) [M^+], 412 (2) [$M^+ - CH_4N$], 335 (2) [$M^+ - CH_4N - C_6H_5$], 313 (2) [$M^+ - C_9H_7N$], 262 (8), 197 (8), 137 (10), 130 (100) [$C_9H_8N^+$], 105 (6) [$C_8H_9^+$], 91 (5) [$C_7H_7^+$]. − $C_{26}H_{26}N_4O_3$: calcd. 442.2005; found 442.2004 (HRMS). − 2D-NOESY NMR spectrum of **12d** displayed cross-peaks between 7′-H and 9a′-H, but no cross-peaks between 9a′-H and CH_2(C-7′). − Fraction II ($R_f = 0.29$): 42 mg of **13d** as a pale yellow solid, m.p. 115−117 °C (CH_2Cl_2/petroleum ether). − $[\alpha]_D^{20} = +60.3$ ($c = 0.63$ in MeOH). − IR (KBr): $\tilde{\nu}$ = 3307 (NH) cm^{-1}, 2923, 1674 (C=O), 1496, 1456, 1418, 1344, 1197, 1103, 745, 701. − ^1H NMR ($CDCl_3$): δ = 0.66−0.89 (m, 3 H, cpr-H), 0.94−1.05 (m, 1 H, cpr-H), 2.57−2.66 (m, 1 H), 2.71−2.82 (m, 1 H), 2.86 (s, 1 H, 9a′-H), 3.13−3.23 (m, 1 H), 3.29 (d, J = 5.5 Hz, 2 H), 3.49−3.61 (m, 1 H), 3.69 (d, J = 16.5 Hz, 1 H), 4.24 (d, J = 3.0 Hz, 1 H, 7′-H), 4.82 (d, J = 16.5 Hz, 1 H), 6.29 (d, J = 2.4 Hz, 1 H, NH), 7.00 (s, 1 H, 2′′-H), 7.12−7.29 (m, 7 H, Ar-H), 7.35 (d, J = 7.8 Hz, 1 H, 7′′-H), 7.57 (d, J = 7.7 Hz, 1 H, 4′′-H), 8.49 (s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 9.50 (−, cpr-C), 12.93 (−, cpr-C), 30.06 (−), 34.54 (−), 39.21 (C_{quat}, cpr-C), 44.72 (−), 45.91 (−), 56.57 (+, C-7′), 60.65 (+, C-9a′), 109.03 (C_{quat}, C-3′′), 111.32 (+, C-7′′), 118.65 (+, C-4′′ or C-6′′), 119.95 (+, C-6′′ or C-4′′), 122.58 (+, C-5′′), 124.24 (+, C-2′′), 126.52 (C_{quat}, C-3a′′), 126.63 (+), 128.47 (+, 2 C), 128.66 (+, 2 C), 136.16 (C_{quat}, C-7a′′), 138.26 (C_{quat}, C-*ipso*), 165.04 (C_{quat}, C=O), 166.09 (C_{quat}, C=O), 168.52 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 442 (8) [M^+], 313 (4) [$M^+ - C_9H_7N$], 130 (100) [$C_9H_8N^+$], 105 (6) [$C_8H_9^+$]. − $C_{26}H_{26}N_4O_3$: calcd. 442.2005; found 442.2004 (MS).

(6a′*S*,11a′*S*)- and (6a′*S*,11a′*R*)-2′-Benzyldecahydrospiro(cyclopropane-1,1′-[6*H*]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine)-3′,6′,11′-triones (12e and 13e): From α-amino ester **4b** (361 mg, 1.32 mmol), (*S*)-BocProOH (323 mg, 1.50 mmol), pyridine (160 mg, 2.02 mmol) in CH_2Cl_2 (6 mL) and DCC (309 mg, 1.50 mmol) in CH_2Cl_2 (3 mL) according to GP 3. After workup and column chromatography on silica gel (50 g, CH_2Cl_2/MeOH, 100 : 2.5) 570 mg (92%) of coupled products (R_f = 0.27) were obtained. These products were deprotected in CH_2Cl_2 (2 mL) with TFA (1.12 g, 9.82 mmol). Further workup, heating in DMF (3 mL) at 120−130 °C for 3 h and evaporation of the solvent gave 340 mg (76% from **4b**) of the two diastereomers **12e** and **13e** as an oil. Separation was achieved by column chromatography on silica gel (50 g, CH_2Cl_2/MeOH, 100 : 2). − Fraction I (R_f = 0.33): 120 mg of **12e** as colorless crystals, m.p. 254−256 °C. − $[\alpha]_D^{20}$ = −42.1 (*c* = 0.21 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3425 (NH) cm^{-1}, 2952, 1684 (C=O), 1674 (C=O), 1495, 1419, 1351, 1291, 1258, 1244, 1176, 1159, 986, 742, 697. − ^{1}H NMR ($CDCl_3$): δ = 0.66 (ddd, *J* = 10.6, *J* = 7.5, *J* = 4.8 Hz, 1 H, cpr-H), 0.88 (ddd, *J* = 10.6, *J* = 6.8, *J* = 4.8 Hz, 1 H, cpr-H), 1.14 (dt, *J* = 10.1, *J* = 7.5 Hz, 1 H, cpr-H), 1.59 (dt, *J* = 10.1, *J* = 7.2 Hz, 1 H, cpr-H), 1.85−1.97 (m, 1 H, 8′-H), 2.00−2.09 (m, 1 H, 8′-H), 2.28−2.37 (m, 2 H, 7′-H), 3.49 (s, 1 H, 11a′-H), 3.52 (m_c, 2 H, 9′-H), 4.06 (d, *J* = 15.1 Hz, 1 H), 4.88 (t, *J* = 8.1 Hz, 6a′-H, 1 H), 4.27 (d, *J* = 15.8 Hz, 1 H), 4.94 (d, *J* = 15.2 Hz, 1 H), 5.18 (d, *J* = 15.8 Hz, 1 H), 7.16−7.31 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 8.85 (−, cpr-C), 14.77 (−, cpr-C), 23.40 (−, C-7′ or C-8′), 27.33 (−, C-8′ or C-7′), 39.85 (C_{quat}, cpr-C), 45.30 (−), 45.70 (−), 49.20 (−), 59.40 (+, C-6a′), 64.59 (+, C-11a′), 126.59 (+, 2 C), 127.18 (+, C-*para*), 128.60 (+, 2 C), 138.11 (C_{quat}, C-*ipso*), 163.97 (C_{quat}, C=O), 167.50 (C_{quat}, C=O), 170.60 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 339 (30) [M^+], 311 (2) [$M^+ - C_2H_4$], 257 (10), 248 (13) [$M^+ - C_7H_7$], 224 (100), 220 (18) [$M^+ - C_2H_4 - C_7H_7$], 214 (10), 166 (3), 143 (9), 99 (13), 91 (19) [$C_7H_7^+$], 83 (9), 69 (12), 56 (40), 44 (100). − Fraction II (R_f = 0.26): **13e** as colorless crystals, m.p. 193−198 °C (MeOH/H_2O). − $[\alpha]_D^{20}$ = +41.4 (*c* = 0.29 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3431 (NH) cm^{-1}, 2950, 1668 (C=O), 1656 (C=O), 1497, 1453, 1408, 1299, 723. − ^{1}H NMR ($CDCl_3$): δ = 0.60 (dt, *J* = 11.0, *J* = 6.5 Hz, 1 H, cpr-H), 0.82 (m_c, 1 H, cpr-H), 1.17−1.45 (m, 2 H, cpr-H), 1.87 (m_c, 2 H, 8′-H), 2.00 (m_c, 1 H, 7′-H), 2.48 (m_c, 1 H, 7′-H), 3.48 (m_c, 1 H, 9′-H), 3.68 (m_c, 1 H, 9′-H), 3.78 (d, *J* = 18.4 Hz, 1 H), 4.05 (d, *J* = 16.0 Hz, 1 H), 4.11 (m_c, 1 H, 6a′-H), 4.67 (s, 1 H, 11a′-H) 4.85 (d, *J* = 16.2 Hz, 1 H), 5.33 (d, *J* = 18.4 Hz, 1 H), 7.11−7.32 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 7.35 (−, cpr-C), 7.79 (−, cpr-C), 21.72 (−, C-7′ or C-8′), 29.97 (−, C-8′ or C-7′), 41.84 (C_{quat}, cpr-C), 44.27 (−), 45.63 (−), 46.01 (−), 58.58 (+, C-6a′), 62.85 (+, C-11a′), 126.22 (+, 2 C), 127.24 (+, C-*para*), 128.70 (+, 2 C), 136.90 (C-*ipso*), 159.24 (C_{quat}, C=O), 164.54 (C_{quat}, C=O), 165.50 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 339 (81) [M^+], 311 (8) [$M^+ - C_2H_4$], 296 (5), 256 (12), 248 (10) [$M^+ - C_7H_7$], 220 (12) [$M^+ - C_2H_4 - C_7H_7$], 214 (10), 186 (50), 149 (12), 146 (10), 123 (10), 104 (70), 91 (100) [$C_7H_7^+$], 70 (21). − $C_{19}H_{21}N_3O_3$: calcd. 339.1582; found 339.1582 (HRMS).

X-Ray Crystal Structure Analysis of 12e:[6] Single crystal from MeOH/H_2O, 0.70 × 0.70 × 0.60 mm, *T* = 133 K, Stoe-Siemens-Huber four-circle diffractometer, Mo-K_α (graphite monochromator); λ = 71.073 pm, empirical formula $C_{19}H_{21}N_3O_3$, space group $P2_12_12_1$; unit cell dimensions: *a* = 955.9 pm; *b* = 1076.8 pm; *c* = 1544.3 pm; α = 90°; β = 90°; γ = 90°; d_{calcd} = 1.418 g/cm^3, *V* = 1.5896 nm^3, *Z* = 4, μ(Mo-K_α) = 0.098 mm^{-1}; range for data collection: 2.31 ≤θ ≤ 28.39°; index ranges: −12 ≤ *h* ≤ 12, −14 ≤ *k* ≤ 14, −20 ≤ *l* ≤ 20; 3983 independent reflections [*R*(int) = 0.0345]. Structure solutions: direct methods (SHELXS-97[8]) and structure refinement (SHELXL-97[9]); full-matrix least-squares on F^2, *R* values: *R*1 = 0.0463, *wR*2 = 0.1013 (for all data with 227 parameters and no restraints); goodness-of-fit on F^2 = 1.284. Flack-x-parameter = 0.8(11); extinction coefficient = 0.0087; largest diff. peak and hole 279 and −251 e nm^{-3}.

(4′*S*,9a′*R*)-4-Benzyl-2′-methyloctahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine-3′,6′,9′-trione [14a (≡15a)]: The α-amino ester **9a** (320 mg, 1.11 mmol), BocGlyOH (226 mg, 1.29 mmol), pyridine (118 mg, 1.49 mmol) in CH_2Cl_2 (7 mL) was coupled with DCC (266 mg, 1.29 mmol) in CH_2Cl_2 (7 mL) according to GP 3. Workup and column chromatography of the residue on silica gel (60 g, CH_2Cl_2/MeOH, 100 : 4) afforded 256 mg (52%) of the coupled product (R_f = 0.24). This product (179 mg, 402 μmol) was deprotected in CH_2Cl_2 (3 mL) with TFA (1.12 g, 9.82 mmol) and, after workup, cyclized in DMF (2.5 mL) at 60 °C overnight. After cooling down to room temp. the reaction mixture was diluted with H_2O, kept overnight at +5 °C, and crystals were filtered off. A further amount of product was received after extraction with $CHCl_3$ (3 × 10 mL), washing of the organic layers with H_2O (3 × 4 mL) and drying (Na_2SO_4). The solvent was evaporated in vacuo, and an oily residue was purified on silica gel (10 g, CH_2Cl_2/MeOH, 15 : 1). After recrystallization from MeOH, 63 mg of **14a** (26% from **9a**) as colorless crystals were isolated, m.p. >250 °C. − $[\alpha]_D^{20}$ = +45.6 (*c* = 0.17 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3447 (NH) cm^{-1}, 3254 (NH), 2926, 1695 (C=O), 1684 (C=O), 1646 (C=O), 1458, 1427, 1396, 1323, 1286, 1224, 1156, 1104, 799, 766, 709, 674, 606, 501. − ^{1}H NMR (CD_3OD): δ = 0.86−0.95 (m, 1 H, cpr-H), 1.18−1.34 (m, 3 H, cpr-H), 2.82 (s, 3 H, CH_3N), 3.26 (dd, *J* = 5.8, *J* = 13.7 Hz, 1 H, CH_2Ph), 3.35 (dd, *J* = 7.7, *J* = 13.8 Hz, 1 H, CH_2Ph), AB system (δ_A = 3.87, δ_B = 3.90, *J* = 17.9 Hz, 2 H, 7′-H), 4.11 (s, 1 H, 9a′-H), 5.22 (dd, *J* = 5.9, *J* = 7.5 Hz, 1 H, 4′-H), 7.19−7.31 (m, 5 H, Ar-H). − ^{13}C NMR (CD_3OD): δ = 7.81 (−, cpr-C), 9.98 (−, cpr-C), 28.99 (+, CH_3N), 37.53 (−, *C*H_2Ph), 42.11 (C_{quat}, cpr-C), 45.04 (−, C-7′), 57.74 (+, C-4′ or C-9a′), 59.81 (+, C-9a′ or C-4′), 128.09 (+, C-*para*), 129.53 (+, 2 C), 130.24 (+, 2 C), 137.21 (C_{quat}, C-*ipso*), 164.59 (C_{quat}, C=O), 164.94 (C_{quat}, C=O), 169.68 (C_{quat}, C=O). − MS (70 eV); *m*/*z* (%): 313 (80) [M^+], 270 (6), 255 (12) [$M^+ - C_2H_4NO$], 222 (55) [$M^+ - C_7H_7$], 199 (38), 194 (100) [$M^+ - C_7H_7 - C_2H_4$], 166 (80) [$M^+ - C_7H_7 - CO - C_2H_4$], 137 (38) [166 − CH_2NH], 109 (46) [137 − C_2H_4], 91 (60) [$C_7H_7^+$], 68 (30).

X-Ray Crystal Structure Analysis of 14a (≡15a):[6] Single crystal from MeOH/H_2O, 0.60 × 0.60 × 0.50 mm, *T* = 133 K, Stoe-Siemens-Huber four-circle diffractometer, Mo-K_α (graphite monochromator); λ = 71.073 pm, empirical formula $C_{17}H_{19}N_3O_3$, space group $P2_1$; unit cell dimensions: *a* = 865.7 pm; *b* = 1039.4 pm; *c* = 868.8 pm; α = 90°; β = 102.71°; γ = 90°; d_{calcd} = 1.365 g/cm^3, *V* = 0.7626 nm^3, *Z* = 2, μ(Mo-K_α) = 0.095 mm^{-1}; range for data collection: 2.40 ≤ θ ≤ 29.12°; index ranges: −11 ≤ *h* ≤ 11, −14 ≤ *k* ≤ 14, −11 ≤ *l* ≤ 11; 4032 independent reflections [*R*(int) = 0.0213]. Structure solutions: Direct methods (SHELXS-97[8]) and structure refinement (SHELXL-97[9]); full-matrix least-squares on F^2, *R* values: *R*1 = 0.0332, *wR*2 = 0.0824 (for all data with 212 parameters and 2 restrains); goodness-of-fit on F^2 = 1.052. Flack-x-parameter = 0.5(6); largest diff. peak and hole 238 and −266 e nm^{-3}.

(4′*S*,9a′*R*)-4′-[(Indol-3′′-yl)methyl]-2′-methyloctahydrospiro-(cyclopropane-1,1′-[2*H*]pyrazino[1,2-*a*]pyrazine)-3′,6′,9′-trione [14b (≡15b)]: A solution of α-amino ester **9b** (225 mg, 687 μmol) in CH_2Cl_2 (6 mL) was treated with BocGlyOH (156 mg, 890 μmol), EDC (171 mg, 892 μmol) and pyridine (70.6 mg, 893 μmol) according to GP 3. Workup without further purification on silica gel af-

forded 180 mg (54%) of the crude coupled product which was deprotected in CH_2Cl_2 (3 mL) with TFA (1.51 g, 13.2 mmol). Workup, heating at 90 °C in DMF (1 mL) for 15 h, evaporation of the solvent in vacuo and purification of the residue by column chromatography on silica gel (75 g, MeOH/CH_2Cl_2, 100 : 5) yielded 77.5 mg (32% from **9b**) of **14b** (≡**15b**) as pale yellow crystals, m.p. >210 °C (MeOH/H_2O, dec.). – $[\alpha]_D^{20}$ = +103.7 (*c* = 0.63 in MeOH). – IR (KBr): $\tilde{\nu}$ = 3270 (NH) cm^{-1}, 2848, 1690 (C=O), 1649 (C=O), 1448, 1426, 1399, 1340, 1176, 1103, 962, 745, 492. – ^1H NMR (CD_3OD): δ = 0.56–0.65 (m, 1 H, cpr-H), 0.89–0.98 (m, 1 H, cpr-H), 1.07–1.22 (m, 2 H, cpr-H), 2.63 (s, 3 H, CH_3N), 3.28 (dd, *J* = 5.6, *J* = 14.6 Hz, 1 H, C*H*HC$_8H_6N$), 3.44 (dd, *J* = 5.6, *J* = 14.6 Hz, 1 H, CH*H*C$_8H_6N$), 3.71 (d, *J* = 18.0 Hz, 1 H, 7′-H), 3.78 (s, 1 H, 9a′-H), 3.82 (d, *J* = 18.0 Hz, 1 H, 7′-H), 5.13 (t, *J* = 5.6 Hz, 1 H, 4′-H), 6.82–6.96 (m, 2 H, Ar-H), 6.94 (s, 1 H, Ar-H), 7.18 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.40 (d, *J* = 7.5 Hz, 1 H, Ar-H). – ^{13}C NMR (CD_3OD): δ = 7.69 (–, cpr-C), 9.89 (–, cpr-C), 27.95 (–), 29.06 (+, CH_3N), 42.91 (C_{quat}, cpr-C), 45.35 (–, C-7′), 58.48 (+, C-4′ or C-9a′), 60.67 (+, C-9a′ or C-4′), 110.92 (C_{quat}, C-3′′), 112.77 (+, C-7′′), 119.34 (+, C-6′′), 120.36 (+, C-4′′), 122.91 (+, C-5′′), 125.00 (+, C-2′′), 129.22 (C_{quat}, C-3a′′), 138.26 (C_{quat}, C-7a′′), 164.97 (C_{quat}, C=O), 165.55 (C_{quat}, C=O), 170.77 (C_{quat}, C=O). – MS (70 eV); *m*/*z* (%): 352 (36) [M^+], 317 (2), 263 (2), 223 (30) [M^+ – C_9H_7N], 186 (16), 130 (100) [$C_9H_8N^+$]. – $C_{19}H_{20}N_4O_3$ (352.4): calcd. C 64.76, H 5.72, N 15.90; found C 64.96, H 5.74, N 15.92.

(4′*S*,7′*S*,9a′*R*)- and (4′*R,7′*S**,9a′*S**)-4′-Benzyl-2′-methyl-7′-[2-(methylthio)ethyl)]octahydrospiro(cyclopropane-1,1′-[2*H*]pyrazino-[1,2-*a*]pyrazine)-3′,6′,9′-triones (14c and 15c):** To a solution of (*S*)-BocMetOH (1.49 g, 5.98 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C DCC (618 mg, 3.00 mmol) dissolved in CH_2Cl_2 (2 mL). Stirring was continued for 1 h at 0 °C; the precipitate was removed by filtration and α-amino ester **9a** (288 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the filtrate at 0 °C with stirring, followed by pyridine (980 mg, 12.4 mmol). The reaction mixture was allowed to warm to room temp., and stirring was continued for 3.5 h. To this reaction mixture was added dropwise DCC (206 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) at room temp., and stirring was continued overnight. The precipitate was removed, the filtrate was diluted with CH_2Cl_2 (20 mL) and washed sequentially with cold aqueous HCl (0.5 M, 25 mL), saturated $NaHCO_3$ (4 × 20 mL), brine, and dried (Na_2SO_4). Solvent was evaporated in vacuo and the residue separated on silica gel (100 g, CH_2Cl_2/MeOH, 100 : 2.5) to give 382 mg (74%) of the coupled products (R_f = 0.38) as a glass-like material. These products were dissolved in CH_2Cl_2 (4 mL) and deprotected with TFA (1.34 g, 11.7 mmol) according to GP 3. Standard workup, cyclization in DMF (2 mL) at 80–85 °C for 18 h and evaporation of the solvents in vacuo gave 160 mg (41% from **9a**) of **14c** and **15c**. Separation on silica gel (50 g, CH_2Cl_2/MeOH, 30 : 1) yielded two fractions. – Fraction I (R_f = 0.30): 31 mg (8% from **9a**) of **15c** as colorless crystals, m.p. 158–159 °C (MeOH/H_2O). – $[\alpha]_D^{20}$ = –0.5 (*c* = 0.22 in MeOH). – IR (KBr): $\tilde{\nu}$ = 3426 (NH) cm^{-1}, 3250 (NH), 2920, 1659 (C=O), 1389, 1334, 1291, 1178, 1033, 978, 756, 700. – ^1H NMR ($CDCl_3$ + traces of CD_3OD): δ = 0.78 (dt, *J* = 6.0, *J* = 10.9 Hz, 1 H, cpr-H), 1.09–1.25 (m, 2 H, cpr-H), 1.38 (dt, *J* = 6.0, *J* = 10.7 Hz, 1 H, cpr-H), 1.74–1.88 (m, 2 H, 7′-CH_2 and NH), 2.06 (s, 3 H, H_3CS), 2.25–2.34 (m_c, 1 H, 7′-CH_2), 2.62 (m_c, 2 H, CH_2S), 2.78 (s, 3 H, CH_3N), 3.32 (m_c, 2 H, CH_2Ph), 3.82 (s, 1 H, 9a′-H), 4.06 (dd, *J* = 4.3, *J* = 7.5 Hz, 1 H, 7′-H), 5.28 (t, *J* = 5.8 Hz, 1 H, 4′-H), 7.16–7.27 (m, 5 H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 7.66 (–, cpr-C), 10.05 (–, cpr-C), 15.00 (+, CH_3S), 28.41 (+, CH_3N), 30.05 (–), 32.20 (–), 36.65 (–, CH_2Ph), 40.53 (C_{quat}, cpr-C), 53.22 (+), 56.57 (+), 59.04 (+), 127.18 (+, C-*para*), 128.60 (+, 2 C), 129.33 (+, 2 C), 136.28 (C_{quat}, C-*ipso*), 163.48 (C_{quat}, C=O), 164.47 (C_{quat}, C=O), 168.24 (C_{quat}, C=O). – MS (70 eV); *m*/*z* (%): 389/388/387 (7/24/100) [M^+], 326 (40) [M^+ – C_2H_5S], 313 (95) [M^+ – C_3H_6S], 268 (36) [M^+ – C_7H_7 – C_2H_4], 222 (68) [M^+ – C_7H_7 – C_3H_6S], 165 (32) [222 – C_2H_3NO], 91 (28) [$C_7H_7^+$], 61 (35) [$C_2H_5S^+$]. – $C_{20}H_{25}N_3O_3S$: calcd. 387.1616; found 387.1616 (HRMS). – 2D-NOESY NMR experiment showed cross-peaks between the signals of 9a′-H and CH_2Ph and strong cross-peaks between 9a′-H and 7′-H. – Fraction II (R_f = 0.24): 60 mg (16% from **9a**) of **14c** as colorless crystals, m.p. 138–139 °C (MeOH/H_2O). – $[\alpha]_D^{20}$ = +3.5 (*c* = 0.31 in MeOH). – IR (KBr): $\tilde{\nu}$ = 3458 (NH) cm^{-1}, 3254 (NH), 2919, 1685 (C=O), 1653 (C=O), 1497, 1425, 1329, 1293, 1226, 1161, 1030, 937, 748, 701. – ^1H NMR ($CDCl_3$ + traces of CD_3OD): δ = 0.80–0.95 (m, 1 H, cpr-H), 1.15 (dt, *J* = 6.6, *J* = 10.9 Hz, 1 H, cpr-H), 1.25–1.40 (m, 2 H, cpr-H), 1.82–1.93 (m, 3 H), 1.98 (s, 3 H, CH_3S), 2.02 (m_c, 1 H, CH_2S), 2.42 (s, 1 H, NH), 2.73 (s, 3 H, CH_3N), 3.15 (dd, *J* = 9.3, *J* = 14.0 Hz, 1 H, C*H*HPh), 3.36 (dd, *J* = 4.9, *J* = 14.0 Hz, 1 H, CH*H*Ph), 4.06 (t, *J* = 4.2 Hz, 1 H, 7′-H), 4.21 (s, 1 H, 9a′-H), 5.46 (dd, *J* = 4.9, *J* = 9.2 Hz, 1 H, 4′-H), 7.15–7.35 (m, 5 H, Ar-H). – ^{13}C NMR ($CDCl_3$ + traces of CD_3OD): δ = 6.54 (–, cpr-C), 8.06 (–, cpr-C), 14.98 (+, CH_3S), 27.79 (+, CH_3N), 28.16 (–), 31.85 (–), 36.51 (–, CH_2Ph), 41.98 (C_{quat}, cpr-C), 53.38 (+), 55.87 (+), 57.92 (+), 127.11 (+, C-*para*), 128.49 (+, 2 C), 129.30 (+, 2 C), 136.06 (C_{quat}, C-*ipso*), 162.89 (C_{quat}, C=O), 164.40 (C_{quat}, C=O), 167.86 (C_{quat}, C=O). – MS (70 eV); *m*/*z* (%): 389/388/387 (7/24/100) [M^+], 326 (27) [M^+ – C_2H_5S], 313 (68) [M^+ – C_3H_6S], 296 (46) [M^+ – C_7H_7], 268 (58) [M^+ – C_7H_7 – C_2H_4], 222 (40) [M^+ – C_7H_7 – C_3H_6S], 165 (33) [222 – CH_3NCO], 144 (30), 109 (16), 91 (23) [$C_7H_7^+$]. – $C_{20}H_{25}N_3O_3S$: calcd. 387.1616; found 387.1616 (HRMS).

X-Ray Crystal Structure Analysis of 14c:[6] Single crystal from MeOH/H_2O, 0.60 × 0.50 × 0.50 mm, *T* = 133 K, Stoe-Siemens-Huber four circle diffractometer, Mo-K_α (graphite monochromator); λ = 71.073 pm, empirical formula $C_{20}H_{25}N_3O_3S$, space group $P2_12_12_1$; unit cell dimensions: *a* = 873.6 pm; *b* = 933.2 pm; *c* = 4737.8 pm; α = 90°; β = 90°; γ = 90°; d_{calcd} = 1.333 g/cm^3, *V* = 3.8625 nm^3, *Z* = 4, μ(Mo-K_α) = 0.193 mm^{-1}; range for data collection: 1.72 ≤ θ ≤ 23.25°; index ranges: –9 ≤ *h* ≤ 9, –10 ≤ *k* ≤ 10, –55 ≤ *l* ≤ 44; 5558 independent reflections [*R*(int) = 0.0683]. Structure solutions: Direct methods (SHELXS-97[8]) and structure refinement (SHELXL-97[9]); full-matrix least-squares on F^2, *R* values: *R*1 = 0.0586, *wR*2 = 0.0717 (for all data with 500 parameters and no restraints); goodness-of-fit on F^2 = 0.996. Flack-x-parameter = 0.004(7); extinction coefficient = 0.0046; largest diff. peak and hole 238 and –172 e nm^{-3}.

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