Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 2048–2056
Tetrahedron
www.elsevier.com/locate/tet

New derivatives and ring systems of annulated pyrrolobenzo[1,4]diazepines

Andreas Schmidt [a,*], Anika Sabine Lindner [a], Abbas Gholipour Shilabin [a], Martin Nieger [b]

[a] *Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstrasse 6, D-38678 Clausthal-Zellerfeld, Germany*
[b] *Laboratory of Inorganic Chemistry, 00014 University of Helsinki, Finland*

Received 1 November 2007; received in revised form 17 December 2007; accepted 20 December 2007
Available online 14 January 2008

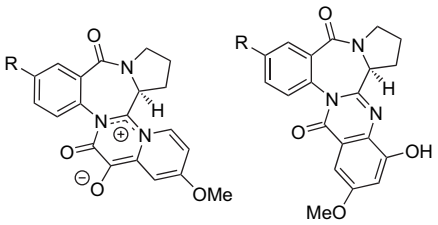
Abstract

(*S*)-11-Thioxo-2,3,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5(10*H*)-one was subsequently reacted with amino acid esters and base to give new 6:7:5:5, 6:7:5:6, and 6:5:7:7 ring systems. The 6:7:5:5 ring system, (*S*)-11,12,13,13a-tetrahydro-2*H*-benzo[*e*]imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine-3,9-dione, exhibits a considerable CH-acidity at position 2, which was exploited in Knoevenagel reactions, a Wittig reaction, enol ester formations, and methylations.

Keywords: Knoevenagel reactions; Circumdatin; Pyrrolobenzodiazepine

1. Introduction

Benzodiazepines form a well-known and widely applied class of biologically active compounds[1] and are representatives of the family of *privileged structures*.[2] In the area of molecular recognition considerable efforts have been devoted to the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) that can recognize and bind to specific sequences of DNA. They are potential regulators of gene expression with possible application as therapeutic agents in the treatment of genetic disorders including cancer.[3] Furthermore, they can be used as affinity-cleavage reagents in molecular biology.[4] The PBD ring system is also found in natural antitumor antibiotics from *Streptomyces* species such as Anthramycin,[5] Tomaymycine,[6] Abbeymycin,[7] Chicamycin A,[8] DC-81,[9] Mazethramycin,[10] Neothramycin A and B,[11] Prothracarcin,[12] Sibanomicin,[13] Sibiromycin,[14] and Porothramycin B.[15] A pentacyclic system was postulated recently as structure of Circumdatin A **1** and B **2** from *Aspergillus* species[16] (Scheme 1).



1: R = OMe
2: R = H
3: R = OMe
4: R = H

Scheme 1. The Circumdatins A, B, D, E.

All naturally occurring compounds possess the (*S*)-configuration at the α-carbon atom of the pyrrolidine ring [i.e., C(11a)], which causes an isohelicity with the minor groove of the double-stranded *B*-form of DNA. In continuation of our interest in alkaloids and model compounds of alkaloid structures,[17] nucleobase betaines,[18] and ionic heteroaromatics[19] we became interested in this class of compounds and synthesized some model

* Corresponding author. Fax: +49 (0)5323 722858.
E-mail address: schmidt@ioc.tu-clausthal.de (A. Schmidt).

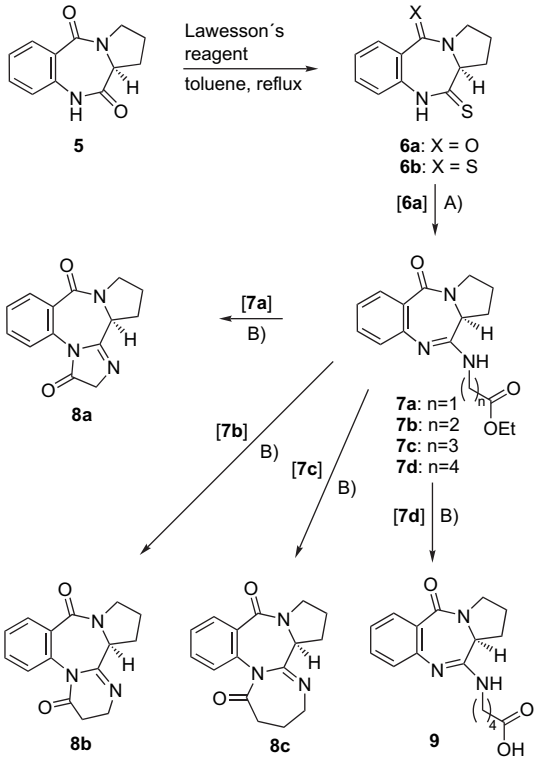
0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.12.044

compounds of the proposed betainic structures of Circumdatin A and B.[26] We report here the syntheses and reactions of first representatives of the new 6:7:5:5 ring system 3,9,11,12,13,13a-hexahydro-2*H*-benzo[*e*]imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine, its 6:7:5:6 derivative, 2,3,4,10,12,13,14,14a-octahydrobenzo[*e*]-pyrimido[2,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine, and its 6:7:5:7 derivative, 5,8a,13b-triaza-benzo[*g*]cyclohepta[*e*]azulene. The 6:5:7:6 ring system is the partial structure of the Circumdatin family of alkaloids from *Aspergillus* species such as Circumdatin D **3** and E **4**,[20,21] as well as of numerous other natural products such as the Benzomalvins A–C, Asperlicins, Sclerogenin,[20] and nonpeptidal cholecystokinin antagonists from microbial sources.[21,22]

2. Results and discussion

2.1. Syntheses and spectroscopic features

Reaction of the benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine **5** from *Isatis indigotica*[23] with Lawesson's reagent in toluene gave monothiolactam **6a**[24] or dithiolactam **6b** depending on the reaction conditions (Scheme 2). Thus, higher temperatures gave high yields of dithiolactam **6b** while lower temperatures resulted in monothiolactam **6a** as the exclusive reaction product.



Scheme 2. Synthesis of new ring systems starting from monothiolactam **6a**. Reaction conditions: (A) EtOOC–$(CH_2)_n$–$NH_3^+Cl^-$, $HgCl_2$, NEt_3; (B) (1) NaOH, dioxane, H_2O; (2) HCl.

Monothiolactam **6a** reacted with glycine ethyl ester hydrochloride, β-alanine ethyl ester hydrochloride, ethyl 4-amino-butanoate hydrochloride, and ethyl 5-amino-pentanoate hydrochloride, respectively, in the presence of $HgCl_2$ and triethylamine to the corresponding iminoesters **7a–d** in high yields. Signals were observed between δ=5.30 and 5.72 ppm in the ^{1}H NMR spectra taken in $CDCl_3$, suggesting secondary amine protons which are not involved in tautomerism in solution. Indicative for the N(10)=C(11)–NH partial structure, HH-COSY experiments showed correlations between these NH groups and the CH_2 groups of the side chains. This is in contrast to other derivatives which we described earlier.[25,26] The structure of **7b** was also confirmed by an X-ray single crystal analysis which is shown in Figure 1. Single crystals were obtained by slow evaporation of **7b** in MeOH. Intermolecular hydrogen bonds were detected between N(71)–H and C(1)=O [H···O distance=209(1) pm; crystallographic numbering] and between C(6)–H and C(74)=O [H···O distance=236 pm]; close contacts were measured between C(11)–H and N(8)–H [H···N distance=248 pm].

Ring closure of **7a–c** was easily accomplished by 2 N NaOH in a mixture of dioxane/water (2:1) at room temperature. Thus, the new 6:7:5:5, 6:7:5:6, and 6:7:5:7 ring systems **8a–c** were obtained in excellent yields. Tetracycle **8a** was also prepared on reaction of **7a** with sodium hydride in anhydrous DMF at room temperature. Using starting material **7d** under analogous reaction conditions resulted in the formation of carboxylic acid **9** instead of the expected 6:7:5:8 ring system.

Single crystals of **8a** were obtained by slow evaporation of a saturated solution in acetone. The compound crystallized monoclinic. The results of the X-ray single crystal structure analysis including the crystallographic numbering are shown in Figure 2. The pyrrolobenzodiazepine ring system adopts a twisted conformation with the seven-membered ring in

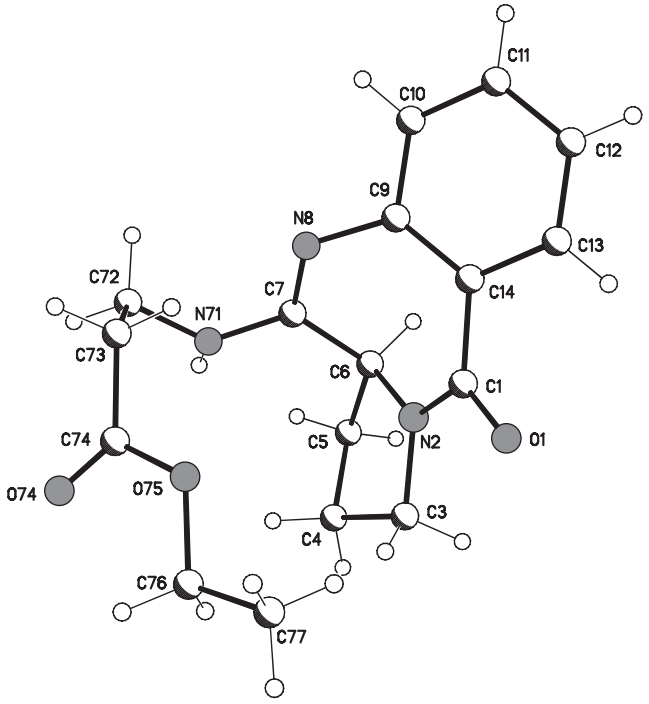


Figure 1.

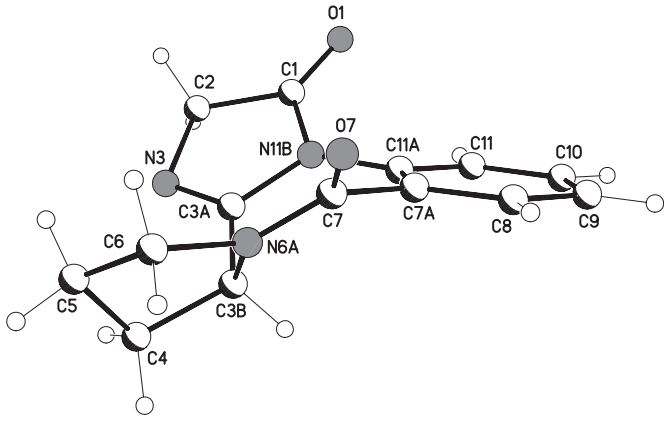
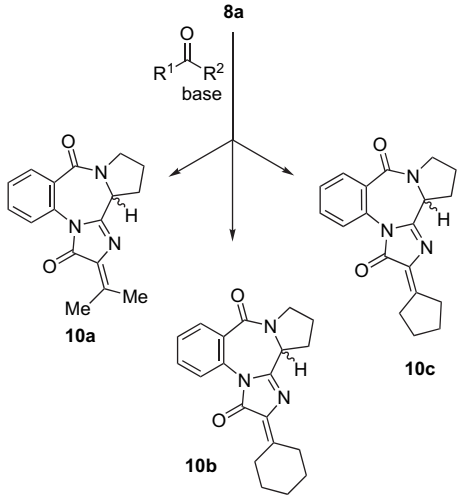


Figure 2.

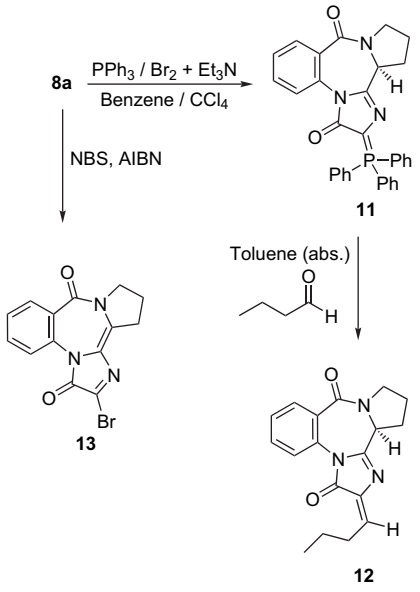
a boat conformation. Accordingly, the dihedral angles of N11B–C3A–C3B–N6A (crystallographic numbering) and C11A–C7A–C7–N6A are −63.2(2)° and 42.4(2)°, respectively. Moreover, torsion angles of −2.2(2)° [C3B–N6A–C7–C7A] and −177.3(1)° [C7–C7A–C11A–N11B] were determined. The bond distance of C3A–N3 is 127.4(2) pm which corresponds to imino $C(sp^2)=N(sp^2)$ double bond. The C3A–C3B bond is a single bond with a bond length of 150.0(2) pm. A close intermolecular contact was measured between C(11)–H and O(7) [H···O distance=245 pm].

The new ring system **8a** has a CH-acidic methylene group in the imidazoline ring. Thus, acetone in the presence of K_2CO_3 at reflux temperature furnished the Knoevenagel product **10a** in good yield (Scheme 3). Treatment of **8a** with cyclohexanone under analogous conditions gave **10b**, and cyclopentanone gave **10c**. Under these conditions, however, almost complete racemization occurred.



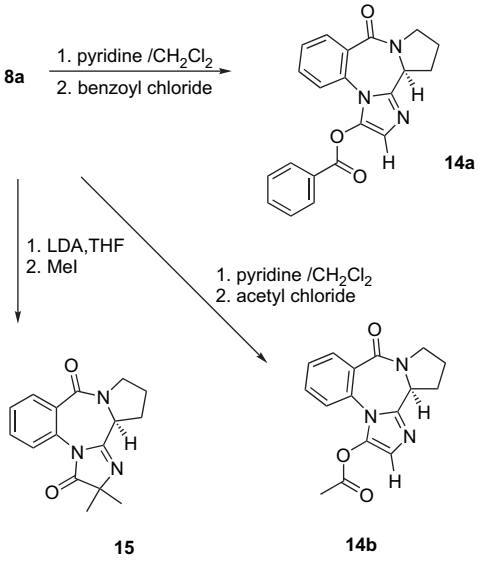
Scheme 3. Exploiting the CH-acidity of ring system **8a**.

These reactions could also be performed as domino cyclocondensation reactions to afford **10a** and **10b** in one step starting from monothiolactam **6a**, or, alternatively, using *n*-BuLi in THF. An alternative approach to exocyclic double bonds in position 2 of **8a** was the reaction via Wittig ylide **11**, which was formed on treatment of **8a** with bromine and triphenylphosphine in good yields (Scheme 4). Reaction with butyraldehyde then yielded **12**. Bromination of **8a** with NBS and AIBN, however, resulted in the formation of 2-bromo derivative **13** as intensely yellow colored compound, which is unstable on storage. Under these conditions, the chiral C11a-position of the pyrrolobenzodiazepine partial structure is oxidized.



Scheme 4.

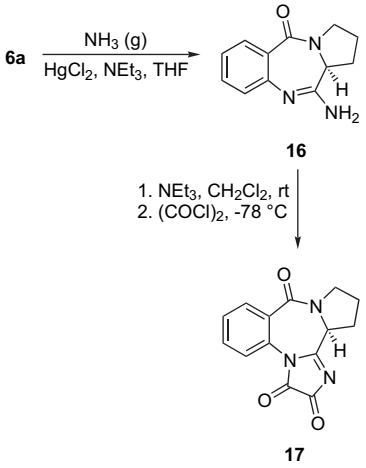
Additional functionalizations of **8a** were achieved on *Einhorn* reaction with benzoyl chloride in pyridine and dichloromethane, which resulted in the formation of ester **14a** (Scheme 5). Under analogous reaction conditions acetyl chloride reacted to **14b**, which could not be isolated in pure form. However, peaks at *m*/*z*=297, 282, and 254 in mass spectrometry could be assigned to the proposed structure, which obviously decomposed during the work-up procedure



Scheme 5. Acylations and methylations of **8a**.

to reconstitute dilactam **5**. Methylation of **8a** resulted in the formation of **15**, as proved by HSQC- and HMBC-NMR-measurements. In HMBC-analysis couplings between C-2 at 68.5 ppm and the methyl groups at 1.37 and 1.44 ppm were found.

We then tried to introduce a keto group in position 2 of **8a**. Thus, thiolactam **6a** was reacted with anhydrous NH_3 and $HgCl_2$ to yield **16** which we described earlier[25] (Scheme 6). Reaction with oxalyl chloride at −78 °C in the presence of triethylamine lead to **17**, which proved to be an unstable compound. After a short period of time, dilactam **5** reconstituted.



Scheme 6.

In summary, we present three new ring systems as derivatives of natural products, and functionalizations to either potentially biologically active compounds or starting materials for further derivatizations.

3. Experimental

3.1. General

The ^1H and ^{13}C NMR spectra were recorded on Bruker ARX-400 and DPX-200 spectrometers and were taken in $CDCl_3$ and DMSO-d_6 at 200 and 400 MHz at 20 °C. The chemical shifts are reported in parts per million relative to internal tetramethylsilane (δ=0.00). Multiplicities are described by using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quadruplet, h=heptet, m=multiplet, br=broad. The mass spectra (EIMS) were measured with a Hewlett-Packard HP 5989B or a Varian SAT2100T with GC3900. Melting points are uncorrected. The CHN analyses were performed in the Institute of Technical Chemistry of the Clausthal University of Technology.

3.2. X-ray crystal structure analysis of *7b* and *8a*

3.2.1. Compound *7b*

Colorless crystals, $C_{17}H_{21}N_3O_3$, M=315.37, crystal size 0.40×0.30×0.10 mm, orthorhombic, space group $P2_12_12_1$ (no. 19): a=8.4072(2) Å, b=12.5881(3) Å, c=15.3652(4) Å, V=1626.11(7) Å^3, Z=4, ρ(calcd)=1.288 Mg m^{-3}, F(000)=672, μ=0.090 mm^{-1}, 15,194 reflections ($2\theta_{max}$=55°) measured on a Nonius Kappa-CCD diffractometer at 123(2) K using Mo Kα radiation (λ=0.71073 Å), 3687 unique [R_{int}=0.040] used for structure solution (Direct Methods, SHELXS-97[27a]) and refinement (full-matrix least-squares on F^2, SHELXL-97[27b]) with 211 parameters and 1 restraint, H-atoms with a riding model, $R1$ ($I>2\sigma(I)$)=0.031, $wR2$ (all data)=0.074, largest diff. peak and hole 0.196 and −0.193 e Å^{-3}. The absolute configuration could not be determined reliably (x=−0.5(8), racemic twin).[27c]

3.2.2. Compound *8a*

Colorless crystals, $C_{14}H_{13}N_3O_2$, M=255.27, crystal size 0.40×0.30×0.20 mm, monoclinic, space group $P2_1$ (no. 4): a=9.3330(2) Å, b=7.0934(2) Å, c=9.9247(3) Å, β=114.714(1)°, V=596.86(3) Å^3, Z=2, ρ(calcd)=1.420 Mg m^{-3}, F(000)=268, μ=0.098 mm^{-1}, 5713 reflections ($2\theta_{max}$=55°) measured on a Nonius Kappa-CCD diffractometer at 123(2) K using Mo Kα radiation (λ=0.71073 Å), 2197 unique [R_{int}=0.023] used for structure solution (Direct Methods, SHELXS-97[27a]) and refinement (full-matrix least-squares on F^2, SHELXL-97[27b]) with 172 parameters and 1 restraint, H-atoms with a riding model, $R1$ ($I>2\sigma(I)$)=0.028, $wR2$ (all data)=0.069, largest diff. peak and hole 0.129 and −0.215 e Å^{-3}. The absolute configuration could not be determined reliably (x=−0.1(10)).[27c]

Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-664431 (**7b**) and CCDC-664432 (**8a**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

3.3. (S)-2,3-Dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-5,11(10H,11aH)-dithione (*6b*)

A mixture of dilactam **5** (2.16 g, 10 mmol) and Lawesson's reagent (2.02 g, 5 mmol) in toluene was stirred overnight at room temperature and then refluxed for 6 h. Evaporation of the solvent in vacuo gave a solid residue, which was purified by flash chromatography [silica, CH_2Cl_2/acetone (100:1)] to give monothiolactam **6a** as yellow solid (R_f=0.05) and pure dithiolactam **6b** as a dark yellow solid (R_f=0.4).

Yield of **6b**: 0.41 g (34%); mp: 254 °C. ^1H NMR (400 MHz, DMSO-d_6): δ=1.92−2.05 (m, 1H, 2-H), 2.14−2.38 (m, 2H, 1,2-H), 2.82−2.92 (m, 1H, 1-H), 3.64−3.79 (m, 1H, 3-H), 3.89−3.99 (m, 1H, 3-H), 4.59 (d, J=7.04 Hz, 1H, 11a-H), 7.22 (d, J=8.02 Hz, 1H, 9-H), 7.31 (t, J=7.49 Hz, 1H, 7-H), 7.54 (td, J=7.73, 1.10 Hz, 1H, 8-H), 8.12 (dd, J=8.02, 7.49 Hz, 1H, 6-H), 12.61 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=22.9 (C-2), 29.6 (C-1), 55.1 (C-3), 65.3 (C-11a), 122.1, 125.9, 132.2, 133.0, 134.7, 135.2, 190.2 (CS), 200.1 (CS). IR (KBr): $\tilde{\nu}$ = = 576, 658, 773, 825, 978, 1046, 1158, 1188, 1371, 1482, 1520, 1599, 2924, 3068, 3105, 3424. MS: 248 (100) [M], 179 (23), 136 (10), 71 (100).

Anal. Calcd for $C_{12}H_{12}N_2S_2$ (248.37): C, 58.1; H, 4.9; N, 11.3. Found: C, 57.6; H, 4.9; N, 11.3.

*3.4. General procedure for preparation of the pyrrolobenzo[1,4]diazepin-5-ones (**7a–d**)*

To a suspension of thiolactam **6a** (0.232 g, 1.0 mmol) and $HgCl_2$ (0.272 g, 1.0 mmol) in acetonitrile (30 mL) was first added the amino acid ethyl ester hydrochloride (1.5 mmol) and then Et_3N (1.0 mL) at room temperature. The mixture was then refluxed for 2–3 h (monitored by TLC), during which time the color changed to black. After cooling, the resulting mixture was filtered through a plug of Celite which was then washed with chloroform. The filtrate was subsequently treated with a saturated $NaHCO_3$ solution (20 mL) and a solution of $Na_2S_2O_3$ (20 mL). The solvents were then removed under reduced pressure to give the crude products which were finally recrystallized.

*3.4.1. (S)-Ethyl 2-(5-oxo-2,3,5,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-11-ylamino)-acetate (**7a**)*

Using glycine ethyl ester hydrochloride as starting material gave an oil. By addition of diethyl ether (15 mL) and stirring for 10 min at room temperature, the crude product was obtained as a pale yellow solid which was filtered off and washed with diethyl ether. Recrystallization from EtOAc/petrol afforded pale yellow crystals.

Yield: 0.25 g (83%); mp: 89–91 °C; $[\alpha]_D^{20}$ +717.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.32 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 2.04–2.18 (m, 2H, 2-H), 2.22–2.38 (m, 2H, 1-H), 3.54–3.61 (m, 1H, 3-H), 3.86–3.92 (m, 1H, 3-H), 4.06 (dd, *J*=7.8, 1.9 Hz, 1H, 11a-H), 4.10–4.27 (m, 2H, $NHCH_2$), 4.27 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 5.46 (br s, 1H, NH), 7.08–7.12 (m, 2H, 8-H, 9-H), 7.38–7.42 (m, 1H, 7-H), 7.96 (dd, *J*=8.3, 1.7 Hz, 1H, 6-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6 (CH_2CH_3), 24.2 (C-2), 27.2 (C-1), 43.7 ($NHCH_2$), 46.9 (C-3), 54.5 (C-11a), 62.1 (CH_2CH_3), 123.1, 127.0, 127.2, 130.5, 132.0, 147.0, 156.2 (C-11), 166.9 (CO), 171.0 (CO). IR (KBr): $\tilde{\nu}$ = 3312 (NH), 3055, 2976, 1784, 1620, 1593, 1541, 1461, 1277, 1199. GC–MS (70 eV) *m/z* (%): 301 (100) [M^+], 255 (42), 226 (10), 186 (13), 158 (25), 131 (14), 102 (16), 70 (17).

Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301.34): C, 63.8; H, 6.3; N, 13.9. Found: C, 63.7; H, 6.1; N, 13.5.

*3.4.2. (S)-Ethyl 3-(5-oxo-2,3,5,11a-hexahydro-1H-benzo[e]pyrrolo-[1,2-a][1,4]diazepin-11-ylamino)-propanoate (**7b**)*

Using β-alanine ethyl ester hydrochloride as starting material afforded a solid which was recrystallized from benzene to yield **7b** as colorless crystals.

Yield: 0.222 g (70%); mp: 122–124 °C; $[\alpha]_D^{20}$ +878.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.28 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.93–2.35 (m, 4H, 1-H, 2-H), 2.64–2.71 (m, 2H, $COCH_2$), 3.48–3.62 (m, 1H, 3-H), 3.57–3.74 (m, 2H, $NHCH_2$), 3.81–3.92 (m, 1H, 3-H), 4.00–4.05 (m, 1H, 11a-H), 4.27 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 5.74 (br s, 1H, NH), 7.04–7.12 (m, 2H, 8-H, 9-H), 7.36–7.44 (m, 1H, 7-H), 7.40 (ddd, *J*=8.1, 7.2, 1.6 Hz, 1H, 6-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.2 (CH_2CH_3), 23.6 (C-2), 26.6 (C-1), 33.0 ($COCH_2$), 36.7 ($NHCH_2$), 46.4 (C-3), 54.4 (C-11a), 60.9 (CH_2CH_3), 122.4, 126.5, 126.6, 130.1, 131.6, 146.7, 156.2 (C-11), 166.9 (CO), 171.0 (CO_2). IR (KBr): $\tilde{\nu}$ = 3283 (NH), 3059, 2973, 2870, 1728, 1603, 1524, 1465, 1342, 1174, 1032. GC–MS (70 eV) *m/z* (%): 315 (100) [M^+], 270 (19), 242 (52), 215 (14), 200 (19), 172 (28), 146 (34), 118 (15), 70 (31).

Anal. Calcd for $C_{17}H_{21}N_3O_3$ (315.37): C, 64.7; H, 6.7; N, 13.3. Found: C, 64.6; H, 6.5; N, 13.3.

*3.4.3. (S)-Ethyl 4-(5-oxo-2,3,5,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-11-ylamino)-butanoate (**7c**)*

Using 4-aminobutyric ethyl ester hydrochloride as starting material gave **7c** as a red oil.

Yield: 0.36 g (98%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.27 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.90–1.98 (m, 2H, 14-H), 2.08–2.32 (m, 4H, 1-H, 2-H), 2.48 (t, *J*=6.7 Hz, 2H, 15-H), 3.32–3.62 (m, 3H, 3-H, 13-H), 3.80–3.91 (m, 1H, 3-H), 4.01 (dd, *J*=7.6, 2.1 Hz, 1H, 11a-H), 4.15 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 5.74 (br s, 1H, NH), 7.02–7.12 (m, 2H, 8-H, 9-H), 7.39 (ddd, *J*=7.4, 1.7 Hz, 1H, 7-H), 7.92 (dd, *J*=7.4, 1.3 Hz, 1H, 6-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=12.3 (CH_2CH_3), 21.4 (C-2), 21.8 (C-1), 24.7 (C-13), 30.5 (C-14), 40.1 (C-12), 44.6 (C-3), 52.6 (C-11a), 58.9 (CH_2CH_3), 120.3, 124.6, 124.8, 128.1, 129.7, 133.6 ($C_{arom.}$), 154.7 (C-11), 164.7 (C=O), 172.7 (C=O). IR (NaCl): $\tilde{\nu}$ = 3355, 2980, 1730, 1608, 1462, 1416, 1216, 1034, 761. LC–MS (ESI): 330.1821 (100) [M].

Anal. Calcd for $C_{18}H_{23}N_3O_3$ (329.29): C, 65.6; H, 7.0; N, 12.7. Found: C, 65.7; H, 7.0; N, 12.5.

*3.4.4. (S)-Ethyl 5-(5-oxo-2,3,5,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-11-ylamino)-pentanoate (**7d**)*

Using 5-aminovaleric ethyl ester hydrochloride gave a red oil.

Yield: 0.68 g (99%); $[\alpha]_D^{20}$ +424.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.27 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.66–1.70 (m, 4H, 2-H, 14-H), 1.74–1.80 (m, 1H, 1-H), 2.05–2.17 (m, 2H, 15-H), 2.30–2.41 (m, 3H, 16-H, 1-H), 3.32–3.47 (m, 2H, 13-H), 3.50–3.64 (m, 1H, 3-H), 3.81–3.93 (m, 1H, 3-H), 4.02 (dd, *J*=7.1, 2.1 Hz, 1H, 11a-H), 4.14 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 5.21 (br s, 1H, NH), 7.02–7.11 (m, 2H, 7-H, 9-H), 7.39 (ddd, *J*=7.6, 1.8 Hz, 1H, 8-H), 7.9 (dd, *J*=7.87 Hz, 1H, 6-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.2 (CH_2CH_3), 21.9 (C-15), 23.8 (C-2), 26.6 (C-1), 28.3 (C-14), 33.6 (C-16), 40.9 (C-13), 46.4 (C-3), 54.4 (C-11a), 60.5 (CH_2CH_3), 122.1, 126.5, 126.7, 129.8, 130.0, 131.5 ($C_{arom.}$), 156.3 (C-11), 166.6 (C=O), 173.9 (C=O). IR (NaCl): 3347, 2939, 1731, 1607, 1539, 1461, 1415, 1162, 1110, 1034, 763. MS: 343 (100) [M^+], 298 (30), 256 (100), 242 (60), 229 (90), 199 (50), 160 (70), 70 (75).

Anal. Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.61; H, 6.92; N, 12.83.

3.5. General procedure for the preparation of 1,3-imidazole-, 1,3-pyrimidine-, and 1,3-diazepin-4-one-pyrrolo-benzo[1,4]diazepin-5-ones (**8** and **9**)

To a solution of the cycloamidine ethyl esters **7a–d** (1.505, 1.575, 1.560 g (5.0 mmol) and 0.343 g (1.0 mmol)) in a mixture of dioxane/water (2:1) (50 mL) was added a solution of NaOH (2 N) (3.0 mL) at 0 °C. The reaction mixture was then stirred for 30 min at room temperature after removing the ice bath, and then acidified to pH=3 with HCl (0.5 N) at 0 °C. Compound **8a** was purified by extraction with chloroform (2×50 mL), drying of the combined organic layers over Na_2SO_4, and evaporation of the solvent under reduced pressure. The resulting solids were extracted with dichloromethane (50 mL) to remove impurities. The aqueous layers were evaporated in vacuo to give solids which were extracted with methanol. After distillation of the solvent **8b** and **8c** were obtained as colorless solids, respectively, and **9** as pale yellow oil.

3.5.1. (S)-11,12,13,13a-Tetrahydro-2H-benzo[e]imidazo-[2,1-c]pyrrolo[1,2-a][1,4]diazepine-3,9-dione (**8a**)

Using **7a** afforded a solid which was recrystallized from acetone to yield **8a** as pale yellow crystals.

Yield: 1.084 g (85%); mp: 199–201 °C; $[\alpha]_D^{20}$ +130.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.98–2.31 (m, 3H, 4-H, 5-H), 2.84–2.98 (m, 1H, 4-H), 3.60–3.68 (m, 1H, 6-H), 3.82–3.93 (m, 1H, 6-H), 4.32–4.35 (m, 2H, 2-H), 4.41–4.45 (m, 1H, 3b-H), 7.41 (ddd, *J*=7.9, 7.4, 1.4 Hz, 1H, 10-H), 7.54–7.63 (m, 1H, 9-H), 7.69 (dd, *J*=7.9, 1.1 Hz, 1H, 11-H), 7.99 (dd, *J*=7.8, 1.4 Hz, 1H, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.3 (C-5), 26.0 (C-4), 47.3 (C-6), 53.9 (C-3b), 59.0 (C-2), 122.3, 126.4, 127.8, 129.5, 130.4, 131.1 ($C_{arom.}$), 162.8 (C-3a), 164.0 (CO), 177.4 (CO). IR (KBr): $\tilde{\nu}$ = 2959, 2876, 1749, 1624, 1465, 1340, 1220, 1170, 1026. GC–MS (70 eV) *m/z* (%): 255 (100) [M^+], 226 (25), 198 (14), 184 (16), 172 (16), 158 (34), 130 (36), 103 (31), 69 (23).

Anal. Calcd for $C_{14}H_{13}N_3O_2$ (255.27): C, 65.3; H, 5.1; N, 16.5. Found: C, 65.4; H, 5.1; N, 16.1.

3.5.2. (S)-2,3,12,13,14,14a-Hexahydrobenzo[e]pyrimido-[2,1-c]pyrrolo[1,2-a][1,4]diazepine-4,10-dione (**8b**)

Using **7b** gave a solid which was recrystallized from EtOH/2-propanol to yield **8b** as colorless crystals.

Yield: 1.049 g (78%); mp: 194–196 °C; $[\alpha]_D^{20}$ +485.2 (*c* 1.0, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.87–2.12 (m, 3H, 5-H, 6-H), 2.36–2.48 (m, 3H, 3-H, 5-H), 3.33–3.38 (m, 1H, 7-H), 3.43 (t, *J*=6.9 Hz, 2H, 2-H), 3.57–3.64 (m, 1H, 7-H), 3.91 (d, *J*=7.6 Hz, 1H, 4b-H), 6.96–7.00 (m, 2H, 11-H, 12-H), 7.36 (td, *J*=7.7, 1.1 Hz, 1H, 10-H), 7.70 (dd, *J*=7.7, 1.3 Hz, 1H, 9-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=24.1 (C-6), 26.7 (C-5), 35.1 (C-3), 38.5 (C-2), 47.1 (C-7), 55.1 (C-4b), 121.7, 127.2, 127.5, 130.4, 132.0, 148.6, 158.1 (C-4a), 166.2 (CO), 175.4 (CO). IR (KBr): $\tilde{\nu}$ = 2967, 2873, 1693, 1630, 1455, 1394, 1257, 1202. GC–MS (70 eV) *m/z* (%): 270 (100) [M^++1], 240 (8), 216 (26), 201 (13), 172 (17), 146 (9), 103 (8), 63 (11).

Anal. Calcd for $C_{15}H_{15}N_3O_2$ (269.30): C, 66.9; H, 5.6; N, 15.6. Found: C, 66.6; H, 5.7; N, 15.2.

3.5.3. (5bS)-2,3,4,5b,6,7,8-Octahydro-5,8a,13b-triaza-benzo[g]cyclohepta[e]-azulene-1,8-dione (**8c**)

Using **7c** gave a solid which was recrystallized from EtOH/2-propanol to yield **8c** as colorless crystals.

Yield: 1.01 g (67%); mp: 210 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ=1.81–2.01 (m, 4H, 7-H, 3-H), 2.02–2.29 (m, 1H, 6-H), 2.40 (t, *J*=7.5 Hz, 2H, 2-H), 2.63–2.82 (m, 1H, 6-H), 3.38–3.71 (m, 4H, 4-H, 8-H), 4.51 (d, *J*=7.6 Hz, 1H, 5b-H), 7.38–7.48 (m, 1H, 13-H), 7.60–7.79 (m, 2H, 11-H, 12-H), 7.83 (d, *J*=7.6 Hz, 1H, 10-H). ^{13}C NMR (50 MHz, DMSO-d_6): δ=22.7 (C-7), 23.0 (C-6), 25.5 (C-3), 30.5 (C-2), 42.2 (C-8), 46.5 (C-4), 55.4 (C-5b), 124.3, 126.6, 128.0, 129.9, 132.0, 134.0 ($C_{arom.}$), 162.6 (C-5a), 163.7 (C=O), 174.1 (C=O). IR (NaCl): $\tilde{\nu}$ = 3435, 2881, 1725, 1669, 1634, 1482, 1449, 1415, 1354, 1268, 1225, 1177, 892, 798, 764, 697. GC–MS (70 eV) *m/z* (%): 283 (100) [M+1].

Anal. Calcd for $C_{16}H_{17}N_3O_2$ (283.88): C, 67.8; H, 6.0; N, 14.8. Found: C, 67.6; H, 6.0; N, 14.7.

3.5.4. (S)-(5-Oxo-2,3,5,11a-tetrahydro-1H-benzo[e]pyrrolo-[1,2-a][1,4]diazepin-11-ylamino)pentanoic acid (**9**)

Using **7d** gave a solid which was recrystallized from EtOH/2-propanol to yield **9** as faintly yellow oil.

Yield: 0.252 g (81%); $[\alpha]_D^{20}$ +194.0 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.51–1.70 (m, 4H, 14-H, 15-H), 1.93–2.02 (m, 2H, 2-H), 2.17–2.24 (m, 1H, 1-H), 2.27–2.30 (m, 1H, 16-H), 2.32–2.39 (m, 1H, 16-H), 2.75–2.83 (m, 1H, 1-H), 3.37–3.45 (m, 1H, 3-H), 3.65–3.69 (m, 2H, 13-H, 3-H), 3.78–3.87 (m, 1H, 13-H), 4.52 (d, *J*=8.0 Hz, 1H, 11a-H), 7.41–7.46 (m, 1H, 9-H), 7.62–7.69 (m, 2H, 7-H, 8-H), 7.83 (dd, *J*=7.8, 1.2 Hz, 1H, 6-H), 10.17 (s, 1H, O*H*), 11.89 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.5 (C-15), 23.1 (C-2), 25.7 (C-1), 26.9 (C-14), 33.3 (C-16), 42.8 (C-13), 46.5 (C-3), 55.5 (C-11a), 124.4, 126.6, 128.1, 130.0, 132.1, 134.3, 162.5 (C-11), 163.8 (CO), 173.3 (CO). IR (KBr): $\tilde{\nu}$ = 3396, 1718, 1632, 1260, 1218, 1364, 1205, 1106, 764. GC–MS (70 eV) *m/z* (%): 315 (100) [M^+], 297 (10), 256 (80), 242 (60), 229 (55), 187 (25), 160 (55), 70 (75).

Anal. Calcd for $C_{17}H_{21}N_3O_2$ (315.37): C, 64.7; H, 6.7; N, 13.3. Found: C, 64.8; H, 6.4; N, 13.7.

3.6. General procedure for the preparation of the diazepines (**10a–c**)

To a solution of cycloamidine ethyl ester **7a** (0.301 g, 1.0 mmol) in THF (20 mL) was added K_2CO_3 (0.5 g) and the corresponding ketone (1.0 mL) at room temperature. The mixture was then heated at reflux for 4–6 h (monitoring by TLC). After cooling, the solids were filtered off and the filtrates were evaporated in vacuo. The resulting solids were subjected to flash column chromatography [silica gel, EtOAc/petrol (1:1)] to afford the compounds **10a–c** as faintly yellow solids or oily products.

*3.6.1. 2-(Propan-2-ylidene)-11,12,13,13a-tetrahydro-2H-benzo[e]imidazo][2,1-c]pyrrolo[1,2-a][1,4]diazepine-3,9-dione (**10a**)*

Acetone was used. Yield: 0.23 g (78%); mp: 214–217 °C; $[\alpha]_D^{20}$ −4.8 (*c* 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ=1.96–2.27 (m, 3H, 4,5-H), 2.32 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.95–3.08 (m, 1H, 4-H), 3.62–3.89 (m, 2H, 6-H), 4.46–4.50 (m, 1H, 3b-H), 7.38 (ddd, *J*=7.9, 7.4, 1.4 Hz, 1H, 10-H), 7.57 (ddd, *J*=8.0, 7.4, 1.3 Hz, 1H, 9-H), 7.69 (dd, *J*=7.9, 1.3 Hz, 1H, 11-H), 7.99 (dd, *J*=8.0, 1.4 Hz, 1H, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=19.8 (CH_3), 22.7 (CH_3), 23.4 (C-5), 26.0 (C-4), 47.2 (C-6), 53.6 (C-3b), 123.5, 126.9, 128.9, 131.2, 131.3, 131.9, 136.0, 153.4, 156.4 (C-3a), 165.1 (CO), 166.2 (CO). IR (KBr): $\tilde{\nu}$ = 2942, 2869, 1709, 1641, 1459, 1395, 1334, 1234, 1155, 1064. GC–MS (70 eV) *m/z* (%): 295 (100) [M^+], 280 (31), 227 (14), 199 (17), 130 (30), 102 (34).

Anal. Calcd for $C_{17}H_{17}N_3O_2$ (295.34): C, 69.1; H, 5.8; N, 14.2. Found: C, 68.8; H, 5.9; N, 14.1.

*3.6.2. 2-Cyclohexylidene-11,12,13,13a-tetrahydro-2H-benzo[e]imidazo[2,1-c]pyrrolo[1,2-a][1,4]diazepine-3,9-dione (**10b**)*

Cyclohexanone was used. Yield: 0.24 g (71%); mp: 161–164 °C; $[\alpha]_D^{20}$ 0 (*c* 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ=1.65–1.82 (m, 6H, 3×CH_2), 1.95–2.31 (m, 3H, 4,5-H), 2.79–2.85 (m, 2H, CH_2), 2.94–3.05 (m, 1H, 4-H), 3.07–3.15 (m, 2H, CH_2), 3.62–3.89 (m, 2H, 6-H), 4.44–4.50 (m, 1H, 3b-H), 7.38 (ddd, *J*=7.9, 7.5, 1.4 Hz, 1H, 10-H), 7.57 (ddd, *J*=8.0, 7.5, 1.3 Hz, 1H, 9-H), 7.69 (dd, *J*=7.9, 1.3 Hz, 1H, 11-H), 7.98 (dd, *J*=8.0, 1.4 Hz, 1H, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.4 (C-5), 26.0 (C-4), 26.1 (CH_2), 28.2 (2×CH_2), 28.7 (CH_2), 31.7 (CH_2), 47.2 (C-6), 53.6 (C-3b), 123.5, 126.9, 128.9, 131.2, 131.3, 131.8, 133.4, 156.4, 161.3 (C-3a), 165.2 (CO), 166.7 (CO). IR (KBr): $\tilde{\nu}$ = 2934, 2853, 1715, 1651, 1459, 1396, 1284, 1173. GC–MS (70 eV) *m/z* (%): 335 (100) [M^+], 307 (7), 227 (14), 281 (27), 255 (13), 199 (11), 130 (15), 102 (20).

Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.40): C, 71.6; H, 6.3; N, 12.5. Found: C, 71.7; H, 6.2; N, 12.3.

*3.6.3. 2-Cyclopentylidene-11,12,13,13a-tetrahydro-2H-benzo[e]imidazo[2,1-c]pyrrolo[1,2-a][1,4]diazepine-3,9-dione (**10c**)*

Cyclopentanone was used. Yield: 0.09 g (28%); $[\alpha]_D^{20}$ +4.5 (*c* 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ=1.70–1.79 (m, 1H, 5-H), 1.80–1.97 (m, 4H, 2×CH_2), 1.99–2.11 (m, 1H, 5-H), 2.13–2.23 (m, 2H, CH_2), 2.26–2.10 (m, 1H, 4-H), 2.87–3.08 (m, 3H, 4-H, CH_2), 3.61–3.69 (m, 1H, 6-H), 3.71–3.77 (m, 1H, 6-H), 4.41–4.53 (m, 1H, 3b-H), 7.34–7.45 (m, 1H, 12-H), 7.53–7.62 (m, 1H, 10-H), 7.75–7.79 (m, 1H, 11-H), 7.96–8.01 (m, 1H, 9-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.4 (C-5), 25.4 (C-4), 26.0 (CH_2), 26.5 (CH_2), 33.8 (CH_2), 41.9 (CH_2), 47.2 (C-6), 53.6 (C-3b), 121.0, 123.4, 126.8, 128.8, 131.3, 131.9, 132.9, 157.1 (C-2), 164.4 (C-3a), 165.2 (CO), 166.0 (CO). IR (KBr): $\tilde{\nu}$ = 3229, 2958, 2877, 1717, 1637, 1461, 1396, 1338, 1165, 763, 735. GC–MS (70 eV) *m/z* (%): 321 (100) [M^+], 216 (20), 187 (15), 146 (30), 130 (30), 70 (100).

Anal. Calcd for $C_{19}H_{19}N_3O_2$ (321.37): C, 71.0; H, 6.0; N, 13.1. Found: C, 70.9; H, 6.0; N, 13.2.

*3.7. 2-(Triphenyl-λ^5-phosphanylidene)-3b,4,5,6-tetrahydro-2H-3,6a,11b-triaza-benzo[g]cyclopenta[e]azulene-1,7-dione (**11**)*

A solution of triphenylphosphine (0.131 g, 0.5 mmol) in dry benzene (10 mL) was cooled to 10 °C. With stirring, a solution of bromine (26 μL, 0.5 mmol) in carbon tetrachloride (2 mL) was added during 10 min. When the addition was complete, a solution of triethylamine (0.17 mL, 1.2 mmol) and tetracyclic imidazole (150 mg, 0.5 mmol) in benzene/THF (1:1) (6 mL) was added at once. The solution was refluxed for 10 min. The solid (triethylammonium bromide) was filtered off and the solvent was removed by distillation to leave a red oil which solidified upon addition of *n*-pentane. The crude product was purified by column chromatography using EA/acetone as a solvent to give the product as a yellow colored solid.

Yield: 0.186 g (72%). ^1H NMR (400 MHz, $CDCl_3$): δ=1.94–1.99 (m, 1H, 5-H), 2.11–2.23 (m, 2H, 4,5-H), 2.92–2.99 (m, 1H, 4-H), 3.69–3.76 (m, 1H, 6-H), 3.78–3.84 (m, 1H, 6-H), 4.51 (dd, *J*=7.9, 3.8 Hz, 1H, 3b-H), 7.31 (ddd, *J*=7.8, 7.5, 1.1 Hz, 1H, 10-H), 7.52 (ddd, *J*=8.4, 7.2, 1.5 Hz, 1H, 9-H), 7.55–7.60 (m, 6H, Ph), 7.66–7.70 (m, 3H, Ph), 7.76–7.81 (m, 6H, Ph), 7.99 (dd, *J*=7.8, 1.6 Hz, 1H, 11-H), 8.11 (dd, *J*=8.2, 1.0 Hz, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.1 (C-5), 26.8 (C-4), 47.7 (C-6), 60.8 (C-3b), 123.8, 124.5, 124.8, 125.9, 128.9, 129.0, 129.4, 129.5, 131.4, 131.7, 132.4, 132.5, 132.6, 133.4, 133.5, 133.9, 134.5, 134.6, 142.3, 142.5, 166.3 (CO), 171.6 (CO). MS (70 eV) *m/z* (%): 515 (100).

*3.8. 2-Butylidene-11,12,13,13a-tetrahydro-2H-benzo-[e]imidazo[2,1-c]pyrrolo[1,2-a][1,4]diazepine-3,9-dione (**12**)*

A mixture of the ylide **11** (0.515 g, 1 mmol) and *n*-butanal (1.0 mL) in anhydrous toluene (30 mL) was heated at 70 °C overnight under nitrogen gas. After cooling, the toluene was evaporated under reduced pressure and the residue was purified by flash column chromatography using EA/PE (1:1).

Yield: 0.21 g (68%). ^1H NMR (200 MHz, $CDCl_3$): δ=1.22–1.30 (m, 3H, CH_3), 1.54–1.66 (m, 2H, CH_2), 2.06–2.30 (m, 3H, 4,5-H), 2.64 (q, *J*=7.7 Hz, 2H, CH_2), 2.99–3.05 (m, 1H, 4-H), 3.65–3.72 (m, 1H, 6-H), 3.80–3.89 (m, 1H, 6-H), 4.47–4.52 (m, 1H, 3b-H), 6.79 (t, *J*=7.7 Hz, 1H, CH), 7.40 (ddd, *J*=7.6, 7.5, 1.2 Hz, 1H, 10-H), 7.59 (ddd, *J*=8.2, 7.3, 1.5 Hz, 1H, 9-H), 7.74 (dd, *J*=8.1, 1.1 Hz, 1H, 11-H), 8.00 (dd, *J*=7.8, 1.5 Hz, 1H, 8-H).

*3.9. 2-Bromo-12,13-dihydro-3H-benzo[e]imidazo[2,1-c]-pyrrolo[1,2-a][1,4]diazepine-3,9(11H)-dione (**13**)*

To a solution of the tetracyclic imidazole **8a** (0.255 g, 1 mmol) in carbon tetrachloride (12 mL) was added *N*-bromosuccinimide (0.178 g, 1 mmol) and AIBN. The mixture was heated at reflux temperature for 12 h. After cooling, the solid was filtered off and the filtrate was evaporated in vacuo to give

a brownish oil. The crude product was then subjected to flash column chromatography [silica gel, EtOAc/petroleum ether (1:3)] to afford the compound **13** as intensely yellow solid which is unstable.

Yield: 70 mg (21%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.11 (m, 2H, 5-H), 3.42 (t, J=7.7 Hz, 2H, 4-H), 4.16 (t, J=7.7 Hz, 2H, 6-H), 7.35 (td, J=7.7, 1.15 Hz, 1H, 10-H), 7.64 (td, J=7.8, 1.9 Hz, 1H, 9-H), 8.25 (dd, J=8.1, 1.8 Hz, 1H, 12-H), 8.72 (dd, J=8.5, 1.0 Hz, 1H, 8-H). IR (KBr): $\tilde{\nu}$ = 2923, 1752, 1678, 1648, 1489, 1447, 1385, 1360, 1207, 1148, 1022, 985, 751. MS (70 eV) *m/z* (%): 333/331 (80) [M], 224 (100), 198 (30), 170 (28), 142 (29), 130 (40), 102 (70), 76 (75).

*3.10. (S)-9-Oxo-11,12,13,13a-tetrahydro-9H-benzo[e]-imidazo[2,1-c]pyrrolo[1,2-a][1,4]diazepin-3-yl benzoate (**14a**)*

To a solution of **8a** (0.255 g, 1.0 mmol) in 10 mL of abs dichloromethane was added 0.5 mL abs pyridine. At room temperature 0.12 mL (1.0 mmol) freshly distilled benzoyl chloride was added dropwise. The reaction was stirred for 2 h at this temperature (monitored by TLC). The reaction mixture was then evaporated in vacuo to give a brownish oil which was subjected to flash column chromatography [silica gel, EtOAc/petrol (1:1)] to afford the compound **14a** as dark yellow solid.

Yield: 180 mg (51%); mp: 156–159 °C; $[\alpha]_D^{20}$ +172.4 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.07–2.14 (m, 1H, 5-H), 2.21–2.30 (m, 1H, 5-H), 2.32–2.41 (m, 1H, 4-H), 3.10–3.16 (m, 1H, 6-H), 3.65–3.72 (m, 1H, 6-H), 3.84–3.90 (m, 1H, 6-H), 4.59 (dd, J=8.1, 3.2 Hz, 1H, 3b-H), 7.22 (s, 1H, 2-H), 7.46–7.54 (m, 4H, 8-H, 10-H, β-benzoyl), 7.58–7.61 (m, 1H, $H_{arom.}$), 7.62–7.68 (m, 1H, γ-benzoyl), 8.05 (dd, J=8.2, 1.2 Hz, 2H, α-benzoyl), 8.11 (dd, J=7.7, 1.7 Hz, 1H, 9-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.8 (C-5), 26.9 (C-4), 47.5 (C-6), 53.9 (C-3b), 114.8 (C-2), 123.4, 127.7, 127.9, 128.9 (2C), 130.3 (2C), 130.4, 131.3, 131.6, 131.8, 134.4, ($C_{arom.}$), 137.7 (C-1), 143.1 (C-3a), 161.7 (CO), 164.5 (CO). IR (KBr): $\tilde{\nu}$ = 2972, 1745, 1638, 1602, 1556, 1527, 1462, 1417, 1250, 1223, 1180, 1116, 1082, 800, 757, 704. MS: 359 (15) [M^+], 256 (10), 105 (100), 96 (15), 77 (50), 64 (95). HRESIMS calcd for $C_{21}H_{17}N_3O_3$+Na+MeCN: 423.1434; found: 423.1470.

Anal. Calcd for $C_{21}H_{17}N_3O_3$ (359.13): C, 70.1; H, 4.7; N, 11.6. Found: C, 69.8; H, 4.4; N, 11.4.

*3.11. 2,2-Dimethyl-11,12,13,13a-tetrahydro-2H-benzo[e]-imidazo[2,1-c]pyrrolo[1,2-a][1,4]diazepine-3,9-dione (**15**)*

Under an inert gas atmosphere 0.22 mL (1.5 mmol) of diisopropylamine in 5 mL abs THF was cooled to −78 °C. At this temperature 0.61 mL of *n*-BuLi (1.5 mmol, c=2.45 mol/L in hexane) was added dropwise. This mixture was stirred at room temperature for 30 min. After cooling to −78 °C a solution of 0.255 g (1 mmol) **8a** in 10 mL abs THF was added dropwise. After 1 h 0.34 mL (3 mmol) iodomethane was added. The reaction mixture was stirred for 1 h at −78 °C and 2 h at room temperature. After evaporation of the solvent, the residue was purified by column chromatography using EA to afford **15** as yellow oil. The compound is unstable.

Yield: 59 mg (21%); $[\alpha]_D^{20}$ +78.2 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.37 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.03–2.08 (m, 1H, 5-H), 2.10–2.24 (m, 2H, 4-H, 5-H), 2.85–2.92 (m, 1H, 4-H), 3.60–3.68 (m, 1H, 6-H), 3.81–3.88 (m, 1H, 6-H), 4.42 (dd, J=7.6, 2.3 Hz, 1H, 3b-H), 7.46–7.41 (m, 1H, 10-H), 7.53–7.58 (m, 1H, 11-H), 7.60–7.65 (m, 1H, 12-H), 7.90–7.96 (m, 1H, 9-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.3 (C-5), 23.7 (CH_3), 24.1 (CH_3), 26.0 (C-4), 47.3 (C-3b), 53.9 (C-6), 68.5 (C-2), 123.3, 127.2, 128.7, 130.8, 131.2, 132.1 (6$C_{arom.}$), 159.7 (C-3a), 165.2 (C=O), 183.4 (C=O). IR (NaCl): $\tilde{\nu}$ = 3385, 2977, 2880, 1745, 1638, 1461, 1392, 1340, 1285, 1226, 1165, 1135, 1085, 915, 864, 734. MS: 283 (70) [M^+], 255 (15), 240 (10), 186 (70), 117 (90), 102 (15), 90 (30), 84 (30), 70 (50).

HREIMS calcd for $C_{16}H_{17}N_3O_2$+H^+: 283.1399; found: 283.1400.

*3.12. 11,12,13,13a-Tetrahydro-2H-benzo[e]imidazo[2,1-c]-pyrrolo[1,2-a][1,4]diazepine-2,3,9-trione (**17**)*

To a suspension of **15** (0.215 g, 1.0 mmol) in 10 mL of abs dichloromethane was added 0.55 mL of triethylamine at room temperature. After cooling to −78 °C, oxalyl chloride (0.104 mL, 1.2 mmol) was added dropwise to the mixture, whereupon the color changed to orange. After stirring for 2 h at this temperature the reaction mixture was quenched with water. The organic layer was separated, washed with water, and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was subjected to flash column chromatography [silica gel, EtOAc/petrol (1:1)] to afford the compound **16** as yellow solid which decomposed rapidly so that we were prevented from a characterization. MS (70 eV) of a freshly prepared sample: *m/z* (%): 269 (10) [M^+], 216 (15), 160 (15), 146 (15), 102 (20), 92 (40), 70 (100). After a short period of time, dilactam **5** reconstituted as evidenced by MS and NMR measurements.

References and notes

1. (a) Da Settimo, F.; Taliani, S.; Trincavelli, M. L.; Montali, M.; Martini, C. *Curr. Med. Chem.* **2007**, *14*, 2680; (b) Lueddens, H.; Korpi, E. R. *Handbook of Contemporary Neuropharmacology*; John Wiley and Sons: New York, NY, 2007; Vol. 2, p 93; (c) Bacon, E. R.; Chatterjee, S.; Williams, M. *Comprehensive Medicinal Chemistry II*; Elsevier: Amsterdam, 2006; Vol. 6, p 139.
2. Herpin, T. F.; Van Kirk, K. G.; Salvino, J. M.; Yu, S. T.; Labaudiniere, R. F. *J. Comb. Chem.* **2000**, *2*, 513.
3. (a) Kamal, A.; Khan, M. N. A.; Reddy, K. S.; Ahmed, S. K.; Kumar, M. S.; Juvekar, A.; Sen, S.; Zingde, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5345; (b) Antonow, D.; Cooper, N.; Howard, P. W.; Thurston, D. E. *J. Comb. Chem.* **2007**, *9*, 437; (c) Kamal, A.; Reddy, D. R.; Reddy, P. S. M. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 803; (d) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L. *Tetrahedron Lett.* **2006**, *47*, 6553; (e) Kang, G.-D.; Howard, P. W.; Thurston, D. E. *Chem. Commun.* **2003**, 1688; (f) Cooper, N.; Hagan, D. R.; Tiberghien, A.; Ademefun, T.; Matthews, C. S.; Howard, P. W.; Thurston, D. E. *Chem. Commun.* **2002**, 1764; (g) Kamal, A.; Ramu, R.; Khanna, G. B. R.; Saxena, A. K.; Shanmugavel, M.; Pandita, R. M. *ARKIVOC* **2005**, *III*, 83; (h) Hurley, L. H.; Boyed, F. L. *TIPS* **1988**, *9*, 402; (i) Zhilina, Z. V.; Ziemba, A. J.; Trent, J. O.; Reed, M. W.; Gorn, V.; Zhov, Q.; Duan, W.; Hurley, L.; Ebbinghaus, S. W. *Bioconjugate Chem.* **2004**, *15*, 1182; (j) Kumar, R.; Lown, J. W. *Mini-Rev. Med. Chem.* **2003**, *3*, 323.

4. Dervan, P. B. *Science* **1986**, *232*, 464.
5. (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791; (b) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793; (c) Arora, S. K. *Acta Crystallogr.* **1979**, *B35*, 2945.
6. (a) Arima, K.; Kohsaka, M.; Tamura, J.; Imanaka, H.; Sakai, H. *J. Antibiot.* **1972**, *25*, 437; (b) Nishioka, Y.; Beppu, T.; Kohsaka, M.; Arima, K. *J. Antibiot.* **1972**, *25*, 660; (c) Tazuka, Z.; Takaya, T. *J. Antibiot.* **1983**, *36*, 142.
7. Hochlowski, J. E.; Andres, W. W.; Theriault, R. J.; Jackson, M.; McAlpine, J. B. *J. Antibiot.* **1987**, *40*, 145.
8. Konishi, M.; Ohkuma, H.; Naruse, N.; Kawaguchi, H. *J. Antibiot.* **1984**, *37*, 200.
9. Kyowa Hakko Kogyo Co. Ltd. Jpn Kokai Tokyo Koho JP 58180487, 21 Oct 1983; *Chem. Abstr.* **1984**, *100*, 173150.
10. Kunimoto, S.; Masuda, T.; Kanbayashi, N.; Hamada, M.; Naganawa, H.; Miamota, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 665.
11. (a) Takeuchi, T.; Miamota, M.; Ishizuka, M.; Naganawa, H.; Kondo, S.; Hamada, M.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 93; (b) Miyamoto, M.; Kondo, S.; Naganawa, H.; Maeda, K.; Ohno, M.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 340.
12. Shimizu, K.-I.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Fujimoto, K. *J. Antibiot.* **1982**, *35*, 972.
13. (a) Hara, M.; Tamaoki, T.; Yoshida, M.; Morimoto, M.; Nakano, H. *J. Antibiot.* **1988**, *51*, 702; (b) Itoh, J.; Watabe, H.-O.; Ishii, S.; Gomi, S.; Nagasawa, M.; Yamamoto, H.; Shomura, T.; Sezaki, M.; Kondo, S. *J. Antibiot.* **1988**, *41*, 1281.
14. Leber, J. D.; Hoover, J. R. E.; Holden, K. G.; Johnson, R. K.; Hecht, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 2992.
15. Tsunkawa, M.; Kamei, H.; Konishi, M.; Miyaki, T.; Oki, T.; Kawakuchi, H. *J. Antibiot.* **1988**, *41*, 1366.
16. Rahbaek, L.; Breinhold, J.; Frisvad, J. C.; Christophersen, C. *J. Org. Chem.* **1999**, *64*, 1689.
17. (a) Schmidt, A.; Topp, M.; Mordhorst, T.; Schneider, O. *Tetrahedron* **2007**, *63*, 1842; (b) Schmidt, A.; Mordhorst, T.; Nieger, M. *Nat. Prod. Res.* **2005**, *19*, 541; (c) Schmidt, A.; Mordhorst, T. *ARKIVOC* **2003**, *XIV*, 233; (d) Schmidt, A.; Habeck, T.; Kindermann, M. K.; Nieger, M. *J. Org. Chem.* **2003**, *68*, 5977.
18. Schmidt, A.; Lindner, A.; Nieger, M.; Ruiz Delgado, M. C.; Ramírez, F. J. *Org. Biomol. Chem.* **2006**, *4*, 3056.
19. (a) Schmidt, A.; Habeck, T.; Lindner, A. S.; Snovydovych, B.; Namyslo, J. C.; Adam, A.; Gjikaj, M. *J. Org. Chem.* **2007**, *72*, 2236; (b) Schmidt, A.; Snovydovych, B.; Habeck, T.; Dröttboom, P.; Gjikaj, M.; Adam, A. *Eur. J. Org. Chem.* **2007**, 4909; (c) Schmidt, A.; Habeck, T.; Snovydovych, B.; Eisfeld, W. *Org. Lett.* **2007**, *9*, 3515; (d) Schmidt, A.; Mordhorst, T.; Nieger, M. *Synthesis* **2006**, 3987.
20. Rahbaek, L.; Breinholt, J. *J. Nat. Prod.* **1999**, *62*, 904.
21. Grieder, A.; Thomas, A. W. *Synthesis* **2003**, 1707.
22. Bock, M. G.; DiPardo, R. M.; Pitzenberger, S. M.; Homnick, C. F.; Springer, J. P.; Freidinger, R. M. *J. Org. Chem.* **1987**, *52*, 1644.
23. Wu, X.; Liu, Y.; Sheng, W.; Sun, J.; Qin, G. *Planta Med.* **1997**, *63*, 55.
24. Kamal, A.; Howard, P. W.; Reddy, B. S. N.; Thurston, D. E. *Tetrahedron* **1997**, *53*, 3223.
25. Schmidt, A.; Gholipour Shilabin, A.; Nieger, M. *Heterocycles* **2005**, *65*, 625.
26. Schmidt, A.; Gholipour Shilabin, A.; Namyslo, J. C.; Nieger, M.; Hemmen, S. *Eur. J. Org. Chem.* **2005**, 1781.
27. (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467; (b) Sheldrick, G. M. Univ. Göttingen, 1997. (c) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.