Skeleton Diversity by Cyclopropanation of Tricyclic Acylenamines

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

Aiming at the structural diversification of phakellin- and isophakellin-type pyrrole-imidazole alkaloids on the skeleton level, the reaction of dipyrrolopyrazinones and pyrroloindolizines with dichlorocarbene was investigated. Conversions resulted in ring expansion affording novel chlorinated and brominated dipyrroloazepinones, pyridopyrroloazepinones, and dipyrrolopyrazinones. Structures of the tetracyclic products with hitherto unknown architectures have been secured by X-ray analyses.

Key words: Alkaloids, Azepinones, Cyclopropanation, Dichlorocarbene, Ring Expansion

Introduction

Diversity-oriented synthesis (DOS) addresses different levels of complexity [1]. Whereas functionalizations of scaffolds are common, variations on the skeleton level have rarely been investigated. A challenging case is represented by the strained tetracyclic phakellin- and isophakellin-type pyrrole-imidazole alkaloids which have been isolated from marine sponges. We wondered whether it would be possible to go beyond the naturally occurring skeletons by functionalization of tricyclic precursors.

Structural analogs of dibromophakellstatin (**1**) are interesting because of the antitumor activity of (−)-**1** [2, 3]. Structures [4] and total syntheses [5] of the pyrrole-imidazole alkaloids have been reviewed. We were also interested in analogs of dibromoisophakellin (**2**) which differs from **1** by the orientation of the pyrrole ring (Fig. 1) [6].

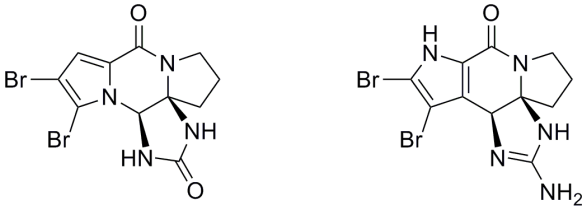
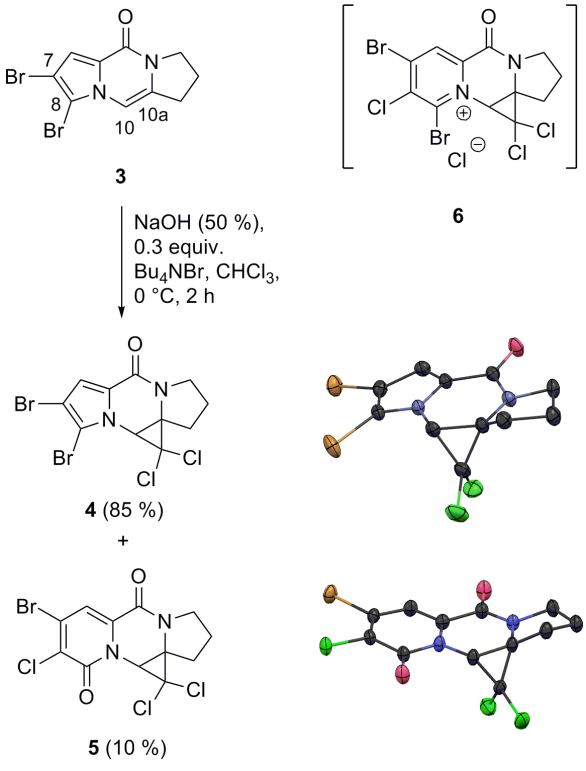


Fig. 1. Pyrrole-imidazole alkaloids (−)-dibromophakellstatin (**1**) and (−)-dibromoisophakellin (**2**).

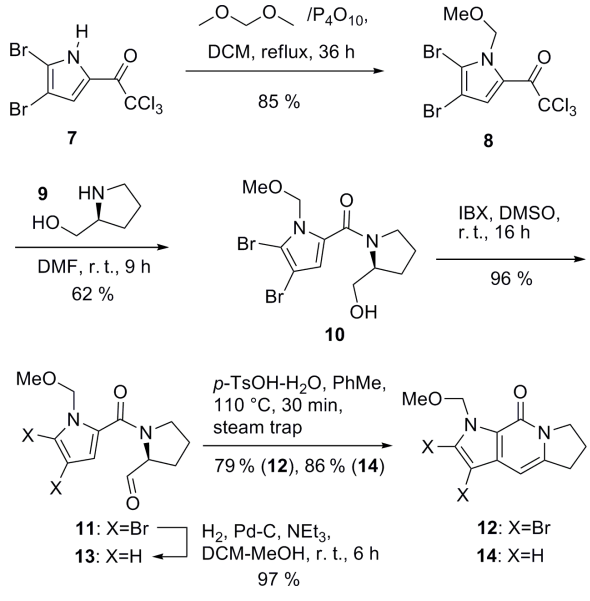
Results and Discussion

As precursor of phakellin-type adducts, we chose the dibrominated dipyrrolopyrazinone **3** (Scheme 1), which can be assembled from pyrrole and prolinol in five steps [7]. Position C10 of the acylenamine double bond of **3** attacks oxygen and nitrogen electrophiles forming an acyliminium ion, which can be exploited for the anellation of an imidazolidinone ring [8], enabling the enantioselective total synthesis of (−)-dibromophakellstatin (**1**) [9].

Cyclopropanation of the electron-rich C10-C10a double bond of dipyrrolopyrazinone **3** (Scheme 1) turned out to be surprisingly facile on reaction with 50 % NaOH/$CHCl_3$ in the presence of nBu$_4$NBr [3]. Acyliminium ion formation and ring opening do not take place. Tetracycle **4** structurally corresponds to the replacement of the imidazolidinone moiety of dibromophakellstatin (**1**) by a dichlorocyclopropane unit and was isolated in 85 % yield after 2 h. Reinvestigation revealed that side product **5** containing a ring-expanded pyridopyrazinone partial structure was also formed. The unprecedented structures of the proton-poor compounds **4** [3] and **5** could be secured by X-ray analyses [10]. If the reaction time was increased from 2 h to 12 h, the percentage of **5** rose



Scheme 1. Cyclopropanation of dipyrrolopyrazinone **3**. Yields of **4** and **5** change to 35 % each after 12 h. Molecular structures of **4** [3] and **5** in the crystal (displacement ellipsoids at the 50 % probability level, hydrogen atoms omitted for clarity).



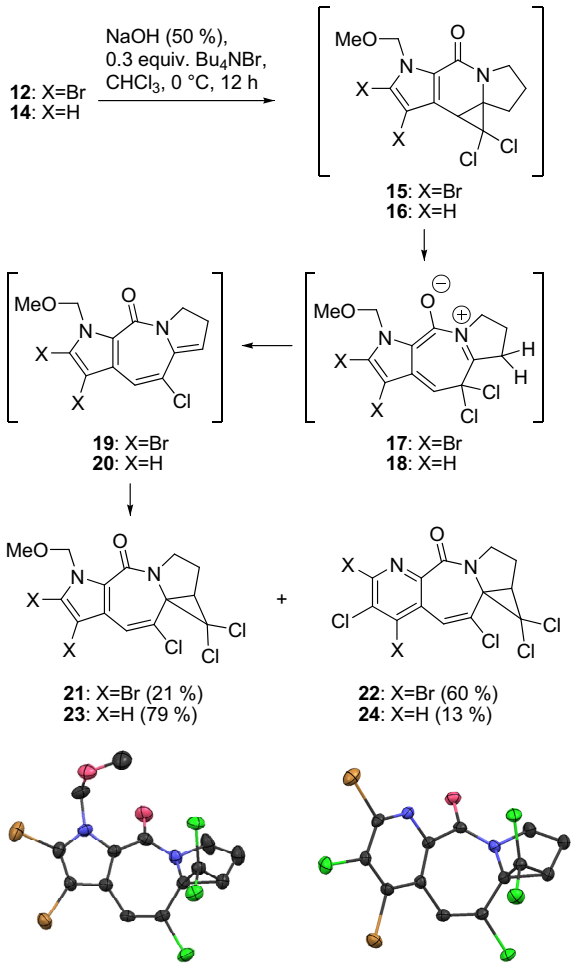
Scheme 2. Synthesis of dipyrrolopyridinones **12** and **14** with inverted pyrrole rings.

from 10 % to 35 %. Ring expansions of pyrroles to 3-chloropyridines on reaction with electrophilic dichlorocarbene are known [11]. Reaction takes place at the more electron rich C7-C8 double bond. Formation of the pyridinone ring of **5** probably proceeds through hydrolysis of intermediate **6** with replacement of the α-bromo substituent.

Encouraged by the stability of tetracycle **4**, we envisaged the synthesis of alternative tetracycles with an inverted pyrrole ring as it occurs in the structure of dibromoisophakellin (**2**). MOM protection of pyrrolyltrichloromethylketone **7** [12] is possible on reaction with methylal/P_4O_{10} [13], avoiding the use of carcinogenic MOM chloride (Scheme 2). Presence of the MOM protecting group prevented participation of the pyrrole nitrogen atom in the upcoming cyclization. After coupling of **8** with prolinol (**9**) to the tertiary amide **10**, oxidation with IBX afforded aldehyde **11** which was cyclized immediately under acid catalysis, affording pyrroloindolizine **12** in 40 % overall yield, as calculated from **7**. Interestingly, the MOM group was not hydrolyzed even in refluxing toluene in the presence of *p*-TsOH. The non-brominated pyrrolo[2,3-*f*]indolizine **14** was accessible after hydrogenation of **11** affording **13**, followed by cyclization [14]. Differing from the dibrominated aldehyde **11**, the non-brominated compound **13** could be stored in substance without cyclization to the *N*,*O*-acetal.

On reaction of the dibrominated pyrrolo[2,3-*f*]indolizine **12** with dichlorocarbene, we did not obtain cyclopropanes as observed in the reaction of pyrrolo[1,2-*a*]pyrazinone **3** (Scheme 1). Instead, expansion of the central six-membered ring was observed, affording the tetracyclic dipyrroloazepinone **21** (21 %, Scheme 3) and pyridopyrroloazepinone **22** (60 %). In the absence of pyrrole bromination (**14**), the product ratio changed in favor of dipyrroloazepinone **23** (79 %), accompanied by pyridopyrroloazepinone **24** (13 %). The constitutions of all proton-poor products **21** – **24** have been secured by crystal structure analyses [10].

The instability of the initially formed cyclopropanes **15** and **16** may be explained by participation of the α,β-unsaturated enone partial structure conjugated with the cyclopropane ring, leading to enhanced polarization and facilitated cleavage of the cyclopropane bond (Scheme 3). This is prevented, if, as in compounds **4** and **5**, the pyrrole nitrogen atom interrupts the conjugation of the cyclopropane ring with the car-



Scheme 3. Ring expansion of pyrroloindolizines **12** and **14** to the novel tetracycles **21** – **24**. Molecular structures of **21** and **22** in the crystal (displacement ellipsoids at the 50 % probability level, hydrogen atoms omitted for clarity).

bonyl group. Comparable behavior has been observed for dihydroisoquinolines [15].

Intermediates **17** and **18** will undergo elimination of HCl forming the electron-rich acylenamines **19** and **20**, respectively. In the absence of any β proton, nucleophilic attack of water at the intermediate acyliminium ion would be expected, as it has been reported for berberine derivatives [16]. We were not able to isolate enamides **19** and **20** which underwent additional cyclopropanation to the novel tetracycles **21** and **23**, respectively.

Tetracyclic pyridopyrroloazepinones **22** and **24**, respectively, are probably formed from **21** and **23** by cyclopropanation and ring opening of the pyrrole. The pyridinium ion generated after ring expansion of the cyclopropanated pyrrole is not hydrolyzed to the pyridone, but the MOM group is cleaved off. The ratios of the di- and non-brominated products **21**, **22** and **23**, **24**, respectively, suggest that the dibrominated pyrroloazepinone ring is electron-richer than its non-brominated analog.

In summary, our new project on the synthesis of novel structural diversity inspired by the pyrrole-imidazole alkaloids has led us to complex tetracyclic heterocycles with unprecedented skeletons. For the phakellin series, introduction of a cyclopropane unit instead of the imidazolidine or guanidine ring is possible. In the isophakellin series, ring opening to the azepinone occurs. The pyrroloazepinone partial structures of **21** and **23** occur in pyrrole-imidazole alkaloids related to the kinase inhibitor hymenialdisine [17]. Pyridoazepinones are much less frequent and have been synthesized as ligands of the peripheric benzodiazepine receptor [18].

Experimental Section

General

Melting points were determined with a Büchi Melting Point B 540 and are uncorrected. NMR spectra were taken with a Varian NMR-System 300 MHz, a Varian NMR-System 400 MHz INOVA 400 and a Varian NMR-System 600 MHz (300.0, 400.0, and 600 MHz) for ^{1}H, 75.7, 100.5, and 150.8 MHz for ^{13}C (referenced on solvent signals or TMS). All measurements were carried out at 300 K. Mass spectra were obtained with Finnigan MAT95Q and Thermo Finnigan LTQ FT spectrometers. IR spectra were recorded with a Perkin-Elmer PE 1600 FT-IR spectrometer. UV/Vis spectra were measured with a Perkin-Elmer Lambda-16 UV spectrometer. Crystal structures were determined with an Enraf-Nonius Kappa-CCD diffractometer with graphite-monochromatized MoK_α radiation. Chemicals were purchased from commercial suppliers and were used without further purification. Silica gel 60 (0.040 – 0.063 mm, Merck) was used for flash chromatography. For reversed phase chromatography LiChroprep RP-18 (40 – 63 μm, 94 g, Merck) was used in a column with 3 cm diameter, which was regenerated by washing with MeOH.

*Cyclopropanation of **3***

Aqueous NaOH (4.00 mL, 50 %) was slowly added to a solution of pyrazinone **3** [7] (332 mg, 1.00 mmol) and nBu$_4$NBr (97.0 mg, 0.30 mmol) in $CHCl_3$ (10 mL) under stirring. After 2 h, aqueous saturated NH_4Cl solution (50 mL) was added to the brown mixture, followed by extrac-

tion with CH_2Cl_2 (3 × 100 mL). The unified organic phases were extracted with water and dried over $MgSO_4$. After concentration to dryness, the residue was purified by column chromatography [silica, EtOAc-isohexane (1 : 1)], affording tetracycles **4** (352 mg, 85 %) and **5** (40.0 mg, 10 %) as colorless solids.

4: M. p. 115 °C (from MeOH, decomp.). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (m, 2H, $NCH_2CH_2CH_2$), 2.34 (m, 1H, NCH_2CHHCH_2), 2.58 (m, 1H, NCH_2CHHCH_2), 3.62 (m, 1H, $NCHHCH_2CH_2$), 4.01 (m, 1H, $NCHHCH_2CH_2$), 4.23 (s, 1H, $NCHCCl_2$), 6.98 (s, 1H, CBrCBrCH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3 ($NCH_2CH_2CH_2$), 30.4 ($NCH_2CH_2CH_2$), 43.9 ($NCHCCl_2$), 45.4 ($NCH_2CH_2CH_2$), 54.8 ($NCCH_2$), 60.9 (CCl_2), 101.9 (CBrCBrCHC), 108.1 (CBrCBrCHC), 115.7 (CBrCBrCHC), 124.9 (CBrCBrCHC), 154.5 (CO). – MS (FTESIMS): *m/z* (%) = 413/415/417/419 (34.8/100/95.4/25.7) [M+H$^+$]. – IR (ATR): ν = 3052 (w), 2951 (w), 2887 (w), 1657 (s), 1634 (m), 1526 (w), 1414 (s), 1342 (m), 1325 (m), 1258 (m), 1182 (s), 1101 (m), 950 (m), 882 (s), 843 (s), 755 (m), 692 (s), 640 (s) cm^{-1}. – UV ($CHCl_3$): λ_{max} (lg ε) = 243 nm (4.10), 288 (3.89). – HRMS ((+)-ESI): *m/z* = 412.8452 (calcd. 412.8459 for $C_{11}H_9{}^{79}Br_2{}^{35}Cl_2N_2O$, [M+H]$^+$).

5: M. p. 193 °C (from CH_2Cl_2/MeOH (9 : 1), decomp.). – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.19 (m, 2H, $NCH_2CH_2CH_2$), 2.35 (m, 1H, NCH_2CHHCH_2), 2.62 (m, 1H, NCH_2CHHCH_2), 3.65 (m, 1H, $NCHHCH_2CH_2$), 4.01 (m, 1H, $NCHHCH_2CH_2$), 4.68 (s, 1H, $NCHCCl_2$), 7.46 (s, 1H, CClCBrCH). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.7 ($NCH_2CH_2CH_2$), 30.1 ($NCH_2CH_2CH_2$), 41.9 ($NCHCCl_2$), 46.4 ($NCH_2CH_2CH_2$), 52.8 ($NCCCl_2$), 60.9 (CCl_2), 113.0 (CClCBrCHC), 130.6 (CClCBrCHC), 130.9 (CClCBrCHC), 134.5 (CClCBrCHC), 153.5 [C(CO)N], 157.0 [N(CO)CCl]. – MS (EI, 70 eV): *m/z* (%) = 396/398/400/402 (2.72/8.18/3.64/0.91) [M$^+$], 362/364/366/368 (62.6/88.6/43.3/5.45), 325/327/329 (78.5/100/24.9). – IR (ATR): ν = 3116 (w), 3049 (w), 1653 (s), 1591 (m), 1441 (m), 1395 (m), 1347 (m), 1247 (w), 1033 (w), 896 (w), 733 (m) cm^{-1}. – UV ($CHCl_3$): λ_{max} (lg ε) = 335 nm (4.00), 349 (3.99), 365 (3.69). – HRMS ((+)-ESI): *m/z* = 395.8830 (calcd. 395.8835 for $C_{12}H_8{}^{79}Br^{35}Cl_3N_2O_2$, [M]$^+$).

*2,2,2-Trichloro-1-(4,5-dibromo-1-methoxymethyl-1H-pyrrol-2-yl)-ethanone (**8**)*

Trichloromethylketone **7** [12] (10.0 g, 27.0 mmol) was dissolved in a mixture of $CH_2(OMe)_2$ with CH_2Cl_2 (1 : 1, 80 mL). P_2O_5 (10.0 g, 35.2 mmol) was added, and the suspension was stirred and refluxed for 36 h. At 0 °C, the brown reaction mixture was poured onto pre-cooled aqueous $NaHCO_3$ solution (250 mL, saturated) and extracted thrice with Et_2O (200 mL). The unified organic phases were dried over $MgSO_4$ and concentrated to dryness. The residue was purified by column chromatography [silica, EtOAc-isohexane (5 : 95)], affording product **8** (9.51 g, 85 %) as a yellow solid. M. p. 8. – 86 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3H, NCH_2OCH_3), 5.83 (s, 2H, NCH_2OCH_3), 7.64 (s, 1H, CBrCH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.5 (NCH_2OCH_3), 78.2 (NCH_2OCH_3), 95.2 (CCl_3), 101.8 (CHCBrCBr), 119.5 (CHCBrCBr), 123.4 (CHCBrCBr), 126.0 (CHCCO), 171.6 (CHCCO). – MS (EI, 70 eV): *m/z* (%) = 411/413/415 (2/5/6) [M$^+$], 294/296/298 (15/31/15), 45 (100). – IR (ATR): ν = 3195 (w), 2950 (w), 2939 (w), 1645 (s), 1480 (m), 1390 (m), 1375 (m), 1335 (m), 1101 (m), 1054 (m), 881 (m), 791 (m), 696 (m) cm^{-1}. – HREIMS: *m/z* = 410.7833 (calcd. 410.7831 for $C_8H_6{}^{79}Br_2{}^{35}Cl_3NO_2$, [M]$^+$).

*(2S)-(4,5-Dibromo-1-methoxymethyl-1H-pyrrol-1-yl)-(2-hydroxymethyl-pyrrolidin-1-yl)-methanone (**10**)*

A solution of L-prolinol (**9**, 2.63 g, 26.0 mmol) in DMF (3 mL) was added to a stirred solution of trichloromethylketone **8** (8.29 g, 20.0 mmol) in DMF. After 9 h at r. t., aqueous 2 N HCl (150 mL) was added, and the mixture was extracted thrice with Et_2O (150 mL). The unified organic phases were extracted with water, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography [silica, EtOAc-isohexane (8 : 2)] affording product **10** as a colorless solid (4.94 g, 62 %). M. p. 100 – 101 °C (decomp.). $[\alpha]_{365}^{25}$ = – 91.0 (*c* = 7.54 mg/mL, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 – 1.86 (m, 2H, NCHHCHCHCH), 1.88 – 2.00 (m, 1H, NCHHCHCHH), 2.04 – 2.21 (m, 1H, NCHHCHHCH), 3.28 (s, 3H, CHHOCH$_3$), 3.46 – 3.59 (m, 1H, NCHCHHCHH), 3.60 – 3.70 (m, 1H, HOCHCH), 3.71 – 3.85 [m, 2H, ($NCHHCH_2CH_2$), (HOCHCH)], 4.22 – 4.41 (m, 2H, $HOCH_2CH$), 5.46 (d, ^2J = 9.4 Hz, $NCHHOCH_3$), 5.74 (d, ^2J = 9.4 Hz, $NCHHOCH_3$), 6.58 (s, 1H, CBrCBrCH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 ($NCH_2CH_2CH_2$), 28.3 ($NCH_2CH_2CH_2$), 50.9 ($NCH_2CH_2CH_2$), 56.2 (NCH_2OCH_3), 61.4 ($HOCH_2CH$), 66.5 ($HOCH_2CH$), 77.2 (NCH_2OCH_3), 99.4 (NCBrCBrCHC), 109.9 (NCBrCBrCHC), 116.1 (NCBrCBrCHC), 128.2 (NCBrCBrCHC), 162.4 (CO). – MS (FTMS, ESI+): *m/z* (%) = 395/397/399 (39.4/100/43.9) [M+H$^+$]. – IR (ATR): ν = 3350 (br.; m), 2963 (w), 2901 (w), 2879 (w), 1591 (vs), 1513 (m), 1441 (s), 1417 (m), 1274 (m), 1097 (s), 901 (m), 759 (m) cm^{-1}. – UV ($CHCl_3$): λ_{max} (lg ε) = 286 nm (4.40). – HRMS ((+)-ESI): *m/z* = 394.9597 (calcd. 394.9606 for $C_{12}H_{17}{}^{79}Br_2N_2O_3$, [M+H]$^+$).

*(2S)-1-(1-Methoxymethyl-1H-pyrrol-2-carbonyl)-pyrrolidine-2-carbaldehyde (**13**)*

A solution of alcohol **10** (3.96 g, 10.0 mmol) in DMSO (5 mL) was added to a solution of IBX (4.76 g, 17.0 mmol) in DMSO (20.0 mL). After 16 h at r. t., water (100 mL)

was added, and the mixture was extracted thrice with Et_2O (200 mL). The unified organic phases were extracted with water, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography [silica, EtOAc-isohexane (1 : 1)] affording synthetic intermediate **11** as a colorless oil (3.80 g, 96 %), which was immediately used in the next step.

A portion of **11** (1.88 g, 4.78 mmol) was dissolved in MeOH/CH_2Cl_2 (100 mL, 1 : 1), and Pd/C (2.00 g, 0.95 mmol, 10 mol-% Pd) and triethylamine (1.32 mL, 9.56 mmol) were added. The mixture was kept in a hydrogen atmosphere, until the reaction was complete (6 h). 2 N HCl (150 mL) was added, and the mixture was extracted thrice with CH_2Cl_2 (200 mL). The unified organic phases were dried over $MgSO_4$ and concentrated. Aldehyde **13** (1.19 g, 97 %) was obtained as a colorless oil. $[\alpha]_{365}^{25} = -399$ (c = 1.71 mg/mL, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 – 2.01 (m, 3H, NCHHC*HH*CH*H*), 2.08 – 2.19 (m, 1H, NCHHCHHC*H*H), 3.23 (s, 3H, NCHHOC*H*$_3$), 3.79 – 3.85 (m, 2H, NC*HH*CHHCHH), 4.57 (m, 1H, OHCC*H*), 5.43 (d, ^2J = 10.0 Hz, NCH*H*OCH$_3$), 5.66 (d, ^2J = 10.0 Hz, NC*H*HOCH$_3$), 6.16 (m, 1H, NCHC*H*CHC), 6.60 (m, 1H, NCHCHC*H*C), 6.92 (m, 1H, NC*H*CHCHC), 9.54 (s, 1H, C*H*O). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (NCH$_2$*C*H$_2$CH$_2$), 26.1 (NCH$_2$CH$_2$*C*H$_2$), 49.8 (N*C*H$_2$CH$_2$CH$_2$), 56.0 (NCH$_2$O*C*H$_3$), 65.5 (OHC*C*H), 78.7 (N*C*H$_2$OCH$_3$), 107.9 (NCH*C*HCHC), 115.2 (NCHCH*C*HC), 124.7 (NCHCHCH*C*), 126.5 (N*C*HCHCHC), 162.1 [C(*C*O)N], 199.4 (OH*C*). – MS (FTMS, ESI+): *m/z* (%) = 237 (100) [M+H$^+$]. – IR (ATR): ν = 2939 (w), 2822 (w), 1728 (m), 1603 (s), 1536 (m), 1431 (s), 1391 (m), 1289 (m), 1263 (m), 1080 (s), 1044 (m), 913 (m), 728 (s), 610 (m) cm^{-1}. – HRMS ((+)-ESI): *m/z* = 237.1228 (calcd. 237.1239 for $C_{12}H_{17}N_2O_3$, [M+H]$^+$).

Pyrrolo[2,3-f]indolizine ***12***

TsOH · H_2O (38.0 mg, 0.2 mmol) was added to a solution of aldehyde **11** (1.58 g, 4.00 mmol) in toluene (40 mL). The mixture was heated to reflux for 30 min employing a steam trap. After cooling, saturated aqueous $NaHCO_3$ solution (50 mL) was added, and the mixture was extracted thrice with CH_2Cl_2 (100 mL). The unified organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography [silica, EtOAc/isohexane (7 : 3)] affording pyridone **12** as a colorless solid (1.19 g, 79 %). M. p. 148 – 150 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (dt, ^3J = 7.5 Hz, ^3J = 7.1 Hz, 2H, NCH$_2$C*H*$_2$CH$_2$), 3.09 (dt, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 2H, NCH$_2$CH$_2$C*H*$_2$), 3.38 (s, 3H, NCH$_2$OC*H*$_3$), 4.16 (t, ^3J = 7.1 Hz, 2H, NC*H*$_2$CH$_2$CH$_2$), 6.02 (s, 2H, NC*H*$_2$OCH$_3$), 6.30 (d, ^4J = 1.2 Hz, *H*CCCH$_2$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (NCH$_2$*C*H$_2$CH$_2$), 31.2 (NCH$_2$CH$_2$*C*H$_2$), 47.9 (N*C*H$_2$CH$_2$CH$_2$), 56.0 (NCH$_2$O*C*H$_3$), 76.4 (N*C*H$_2$OCH$_3$), 93.7 (H*C*CCH$_2$), 95.3 (NCBr*C*BrC), 117.0 (N*C*BrCBrC), 122.5 (N*C*CO), 132.4 (NCBrCBr*C*), 142.6 (HC*C*CH$_2$), 153.1 (*C*O). – MS (FTMS, ESI+): *m/z* (%) = 375/377/379 (33.0/100/52.3) [M+H$^+$]. – IR (ATR): ν = 2960 (w), 1651 (s), 1591 (vs), 1471 (m), 1440 (m), 1402 (m), 1297 (m), 1277 (m), 1220 (m), 1091 (s), 1044 (m), 900 (m), 801 (s), 762 (m), 699 (m), 670 (m) cm^{-1}. – HRMS ((+)-ESI): *m/z* = 374.9333 (calcd. 374.9344 for $C_{12}H_{13}{}^{79}Br_2N_2O_2$, [M+H]$^+$).

Pyrrolo[2,3-f]indolizine ***14***

TsOH · H_2O (38.0 mg, 0.2 mmol) was added to a solution of aldehyde **13** (945 mg, 4.00 mmol) in toluene (40 mL). The mixture was heated to reflux for 30 min employing a steam trap. After cooling, saturated aqueous $NaHCO_3$ solution (50 mL) was added, and the mixture was extracted thrice with CH_2Cl_2 (100 mL). The unified organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography [silica, EtOAc/isohexane (8 : 2)] affording pyridone **14** as a yellowish solid (750 mg, 86 %). M. p. 11 – 119 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (dt, ^3J = 7.5 Hz, ^3J = 7.1 Hz, 2H, NCH$_2$C*H*$_2$CH$_2$), 3.04 (dt, ^3J = 7.6 Hz, ^4J = 1.1 Hz, 2H, NCH$_2$CH$_2$C*H*$_2$), 3.32 (s, 3H, NCH$_2$OC*H*$_3$), 4.15 (t, ^3J = 7.1 Hz, 2H, NC*H*$_2$CH$_2$CH$_2$), 5.88 (s, 2H, NC*H*$_2$OCH$_3$), 6.28 (d, ^3J = 2.9 Hz, 1H, NC*H*CH), 6.35 (br.; s, 1H, C*H*CCH$_2$), 7.17 (d, ^3J = 2.9 Hz, NCHC*H*). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7 (NCH$_2$*C*H$_2$CH$_2$), 30.9 (NCH$_2$CH$_2$*C*H$_2$), 47.4 (N*C*H$_2$CH$_2$CH$_2$), 55.7 (NCH$_2$O*C*H$_3$), 77.8 (N*C*H$_2$OCH$_3$), 95.9 (*C*HCCH$_2$), 103.0 (N*C*HCHC), 122.0 (*C*NCHCH), 130.5 (NCH*C*HC), 133.4 (NCHCH*C*), 140.9 (N*C*CH$_2$CH$_2$CH$_2$), 154.5 (*C*O). – MS (EI, 70 eV): *m/z* (%) = 218/219 (40.4/5.77) [M$^+$], 203/204 (100/13.5), 187/188 (41.4/8.89), 175/176 (39.7/5.94), 173/174 (13.5/3.93). – IR (ATR): ν = 3077 (w), 2989 (w), 2930 (w), 2814 (w), 1652 (s), 1585 (vs), 1499 (m), 1443 (m), 1399 (m), 1320 (m), 1236 (m), 1194 (m), 1072 (s), 955 (s), 808 (s), 781 (s), 673 (s) cm^{-1}. – HRMS ((+)-ESI): *m/z* = 218.1066 (calcd. 218.1055 for $C_{12}H_{14}N_2O_2$, [M]$^+$).

Tetracycles ***21*** *and* ***22***

Bu_4NBr (96.7 mg, 0.30 mmol) was added to a solution of pyridone **12** (376 mg, 1.00 mmol) in $CHCl_3$ (15.0 mL). At 0 °C, aqueous NaOH solution (50 %, 10 mL) was added within 5 min under vigorous stirring. After 12 h, aqueous saturated NH_4Cl solution (100 mL) was added, followed by extraction with CH_2Cl_2 (3 × 100 mL). The unified organic phases were extracted with water and dried over $MgSO_4$. After concentration to dryness, the residue was purified by column chromatography [silica, EtOAc-isohexane (1 : 1)], affording tetracycles **21** (106 mg, 21 %) and **22** (305 mg, 60 %) as colorless solids, which were recrystallized from MeOH.

21: M. p. 142 – 143 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 – 2.33 (m, 1H, NCHHCH*H*CH), 2.47 – 2.58 (m, 1H, NCHHCH*H*CH), 2.89 (dd, ^3J = 7.8 Hz, ^3J = 1.6 Hz, 1H, NCHHCHHC*H*), 3.31 (s, 3H, NCH_2OCH_3), 3.82 (ddd, ^2J = 12.4 Hz, ^3J = 9.9 Hz, 5.0 Hz, 1H, NCH*H*CHHCH), 4.21 (ddd, ^2J = 12.4 Hz, ^3J = 9.7 Hz, 4.0 Hz, 1H, NCH*H*CHHCH), 5.54 (d, ^2J = 10.3 Hz, $NCHHOCH_3$), 6.25 (d, ^2J = 10.3 Hz, $NCHHOCH_3$), 7.06 (s, 1H, *H*CCCl). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1 (NCH_2CH_2CH), 44.1 (NCH_2CH_2CH), 52.9 (NCH_2CH_2CH), 56.5 (NCH_2OCH_3), 56.8 ($NCCCl_2$), 69.3 (CCl_2), 77.9 (NCH_2OCH_3), 101.0 (NCBr*C*BrC), 114.1 (N*C*BrCBrC), 124.4 (NCBrCBr*C*), 124.7 (N*C*CO), 125.5 (HC*C*Cl), 126.4 (H*C*CCl), 160.0 (*C*O). – MS (FTMS, ESI+): *m/z* (%) = 503/505/507/509/511 (15.2/69.9/100/48.5/6.06) [M+H$^+$]. – IR (ATR): ν = 3245 (w), 3050 (w), 2989 (w), 2954 (w), 2830 (w), 1650 (vs), 1421 (s), 1372 (m), 1311 (m), 1187 (m), 1104 (m), 1080 (m), 913 (m), 826 (m) cm^{-1}. – UV ($CHCl_3$): λ_{max} (lg ε) = 246 nm (4.35), 297 (3.84). – HRMS ((+)-ESI): *m/z* = 502.8335 (calcd. 502.8331 for $C_{14}H_{12}{}^{79}Br_2{}^{35}Cl_3N_2O_2$, [M+H]$^+$).

22: M. p. 115 °C (decomp.). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (m, 1H, NCH_2CHHCH), 2.58 (m, 1H, NCH_2CHHCH), 2.92 (dd, J = 7.9 Hz, J = 1.6 Hz, 1H, NCH_2CHHCH), 4.08 (m, 2H, NCH_2CHHCH), 7.31 (s, 1H, *H*CCCl). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7 (NCH_2CH_2CH), 44.0 (NCH_2CH_2CH), 54.9 (NCH_2CH_2CH), 56.7 ($NCCCl_2$), 69.1 (CCl_2), 130.1 (H*C*CCl), 133.3 (HC*C*Cl), 135.2 (*C*q), 136.9 (*C*q), 141.7 (*C*q), 146.5 (*C*q), 146.8 (*C*q), 162.7 (*C*O). – MS (FTMS, ESI+): *m/z* (%) = 527/529/531/533/535 (18.3/54.8/100/40.0/14.8) [M+Na$^+$]. – IR (ATR): ν = 3052 (w), 2951 (w), 2887 (w), 1657 (s), 1635 (m), 1526 (m), 1414 (s), 1381 (m), 1346 (m), 1325 (m), 1258 (m), 1182 (m), 1101 (m), 882 (m), 844 (s), 756 (m), 691 (m), 640 (s) cm $^{-1}$. – UV ($CHCl_3$): λ_{max} (lg ε) = 249 nm (3.65). – HRMS ((+)-ESI): *m/z* = 526.7498 (calcd. 526.7499 for $C_{13}H_6{}^{79}Br_2{}^{35}Cl_4N_2NaO$, [M+Na]$^+$).

*Tetracycles **23** and **24***

Bu_4NBr (161 mg, 0.50 mmol) was added to a solution of pyridone **14** (327 mg, 1.50 mmol) in $CHCl_3$ (20.0 mL). At 0 °C, aqueous NaOH solution (50 %, 10 mL) was added within 5 min under vigorous stirring. After 12 h, aqueous saturated NH_4Cl solution (50 mL) was added, followed by extraction with CH_2Cl_2 (3 × 100 mL). The unified organic phases were extracted with water and dried over $MgSO_4$. After concentration to dryness, the residue was purified by column chromatography [silica, EtOAc-isohexane (4 : 6 to 6 : 4)], affording tetracycles **23** (411 mg, 79 %) and **24** (69 mg, 13 %) as colorless solids, which were recrystallized from MeOH/CH_2Cl_2 (1 : 9).

23: M. p. 93 – 95 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 – 2.33 (m, 1H, NCHHCH*H*CH), 2.46 – 2.58 (m, 1H, NCHHC*H*HCH), 2.85 (dd, ^3J = 7.8 Hz, ^3J = 1.5 Hz, 1H, NCHHCHHC*H*), 3.23 (s, 3H, $NCHHOCH_3$), 3.83 (ddd, ^2J = 12.2 Hz, ^3J = 9.9 Hz, ^3J = 7.3 Hz, 1H, NCH*H*CHHCH), 4.23 (ddd, ^2J = 12.2 Hz, ^3J = 9.7 Hz, 4.1 Hz, 1H, NC*H*HCHHCH), 5.34 (d, ^2J = 10.1 Hz, 1H, $NCHHOCH_3$), 6.04 (d, ^2J = 10.1 Hz, 1H, $NCHHOCH_3$), 6.18 (d, ^3J = 2.8 Hz, NCHC*H*C), 7.01 (d, ^3J = 2.8 Hz, NC*H*CHC), 7.07 (s, 1H, *H*CCCl). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (NCH_2CH_2CH), 44.0 (NCH_2CH_2CH), 52.3 (NCH_2CH_2CH), 56.3 (NCH_2OCH_3), 57.0 ($NCCCl_2$), 69.5 (CCl_2), 79.6 (NCH_2OCH_3), 108.7 (NCH*C*HC), 122.8 (HC*C*Cl), 123.1 (N*C*CO), 125.0 (NCHCH*C*), 127.6 (N*C*HCHC), 128.6 (H*C*CCl), 161.7 (*C*O). – MS (EI, 70 eV): *m/z* (%) = 346/348/350 (34.4/31.9/9.87) [M$^+$], 231/233 (100/34.3), 204 (11.2). – IR (ATR): ν = 3043 (w), 2946 (w), 2826 (w), 1638 (s), 1533 (m), 1484 (s), 1369 (s), 1339 (m), 1107 (s), 1017 (m), 919 (m), 829 (m), 795 (s), 763 (s), 657 (s) cm^{-1}. – HREIMS: *m/z* = 346.0009 (calcd. 346.0043 for $C_{14}H_{13}{}^{35}Cl_3N_2O_2$, [M]$^+$).

24: M. p. 159 °C (decomp.). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 – 2.34 (m, 1H, NCHHCH*H*CH), 2.50 – 2.62 (m, 1H, NCHHC*H*HCH), 2.91 (dd, ^3J = 7.8 Hz,, ^3J = 1.6 Hz, 1H, NCHHCHHC*H*), 4.04 (ddd, ^2J = 12.4 Hz, ^3J = 9.6 Hz, ^3J = 7.7 Hz, 1H, NCH*H*CHHCH), 4.13 (ddd, ^2J = 12.4 Hz, ^3J = 9.6 Hz, ^3J = 4.0 Hz, 1H, NC*H*HCHHCH), 7.04 (s, 1H, *H*CCCl), 7.60 (d, ^4J = 2.1 Hz, NCHCCl*CH*), 8.71 (br.; s, 1H, NC*H*CClCH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (NCH_2CH_2CH), 43.9 (NCH_2CH_2CH), 54.3 (NCH_2CH_2CH), 56.3 ($NCCCl_2$), 68.8 (CCl_2), 130.0 (H*C*CCl), 130.0 (NCHCCl*CH*C), 132.4 (HC*C*Cl), 133.7 (N*C*CO), 136.1 (NCHCCl*C*HC), 146.0 (NCH*C*ClCHC), 148.7 (N*C*HCClCHC), 164.9 (*C*O). – MS (FTMS, ESI+): *m/z* (%) = 349/351/353 (65.6/100/47.9) [M+H$^+$]. – IR (ATR): ν = 3295 (br.; w), 3041 (w), 2946 (w), 1640 (s), 1535 (m), 1410 (s), 1132 (m), 1095 (m), 919 (s), 845 (s), 680 (s) cm^{-1}. – UV ($CHCl_3$): λ_{max} (lg ε) = 263 nm (4.05). – HRMS ((+)-ESI): *m/z* = 348.9465 (calcd. 348.9469 for $C_{13}H_9{}^{35}Cl_4N_2O$, [M+H]$^+$).

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