Improved Conversion of Dihydrooroidin to Oroidin and Ugibohlin

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Dedicated to Professor Hubert Schmidbaur on the occasion of his 75th birthday

Dihydrooroidin was converted to the marine natural product oroidin in 75 % overall yield by chlorination of the 2-aminoimidazole unit in DMF, followed by dehydrochlorination. The natural product ugibohlin was synthesized for the first time by ring opening of dibromoisophakellin, which was obtained in a quantitative manner by heating the free base of dibromophakellin in neutral aqueous solution.

Key words: 2-Aminoimidazole, Dibromophakellin, Marine Natural Products, *N*-Methyldibromoisophakellin, Pyrrole-Imidazole Alkaloids

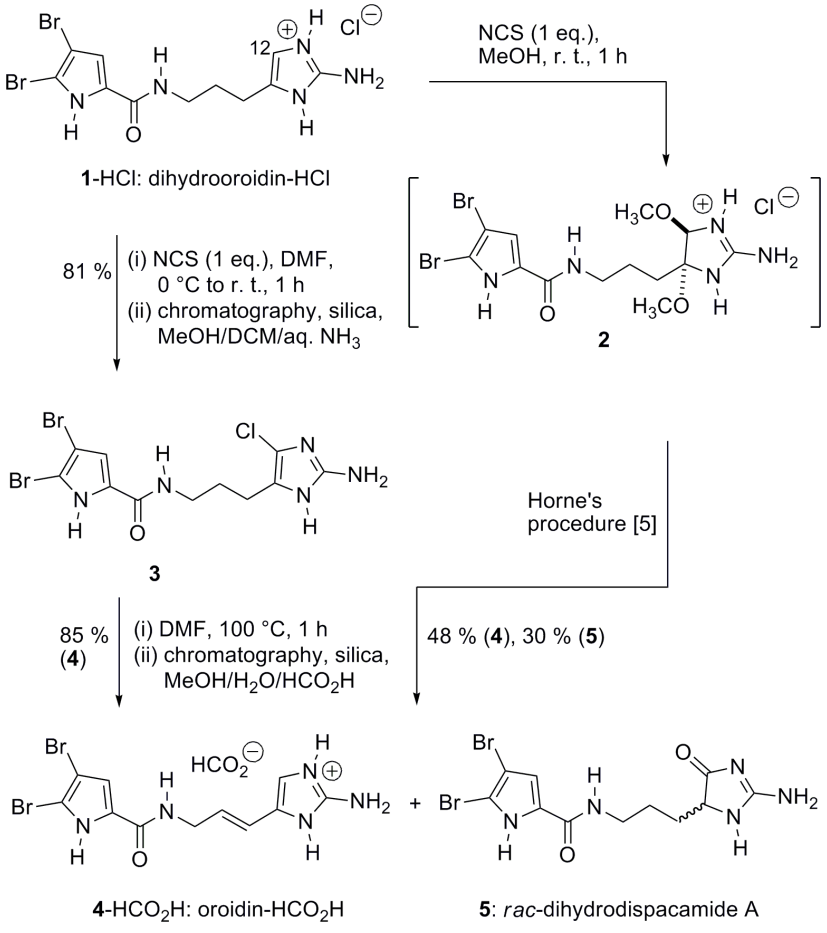
Oroidin (**4**, Scheme 1) serves as parent compound of the marine pyrrole-imidazole alkaloids [1] and was identified as the fish feeding deterrent principle of sponges of the genus *Agelas* [2]. Recently, oroidin (**4**) became a lead structure against bacterial biofilm formation [3]. Several total syntheses of oroidin (**4**) have been reported [4, 5], all of which contain steps with only moderate yields. Since large quantities of oroidin (**4**) are needed for research on the chemistry of pyrrole-imidazole alkaloids, we decided to reinvestigate the conversion of dihydrooroidin (**1**) to oroidin (**4**).

Horne and coworkers had achieved the oxidative dimethoxylation of **1** (75 %) by treatment with Br_2/KO*t*Bu/MeOH, followed by thermal elimination of two molecules of MeOH (Scheme 1) [5]. However, a mixture of oroidin (**4**, 48 %) and dihydrodispacamide A (**5**, 30 %) had been obtained. Avoiding the formation of **5** could double the overall yield of that final step. Ideally, a halogen substituent would have to be installed at C-12 of dihydrooroidin (**1**), followed by dehydrohalogenation. Acidic conditions should be avoided, because it is known that when dihydrooroidin (**1**) is treated with NBS/TFA, spirocyclization occurs [6], as it does with Br_2/HOAc [7]. In the absence of an internal amide nucleophile, bromination of the 2-aminoimidazole would be possible in TFA [8].

The starting material dihydrooroidin (**1**) was synthesized as the hydrochloride following the Büchi/Horne protocol [5, 7, 8] and was reacted with NCS/MeOH to the dimethoxylated product **2** without participation of the internal amide nucleophile (Scheme 1). This indicated that spirocyclization does not take place under neutral conditions. Earlier, Horne and coworkers had successfully applied the same conditions to the free amine lacking the pyrrolylcarbonyl unit of dihydrooroidin (**2**) [5]. It remained to be answered whether spirocyclization of **1** would occur in neutral non-nucleophilic solvents.

We were pleased that dihydrooroidin hydrochloride (**1**-HCl) was converted to 12-chloro-8,9-dihydrooroidin (**3**) on reaction with NCS (1 eq.) in DMF in a yield of 81 % within 1 h at r. t. Compound **3** proved to be stable at r. t., and it was isolated as the free base after chromatography employing an ammonia-containing mobile phase. In the ^{13}C NMR spectrum ([D$_6$]DMSO) of **3**, the chlorinated carbon appears at δ = 119 ppm, as determined by HMBC analysis. Spirocyclization did not occur. The reaction of 2-aminoimidazolium chlorides with NCS under neutral conditions probably does not involve a dication. Simultaneous transfer of one of the 2-aminoimidazolium protons to the succinimide oxygen is likely.

On heating of **3** in DMF to 100 °C for 1 h, clean formation of oroidin (**4**) occurred (85 %). Below 100 °C, elimination of HCl was sluggish, whereas at higher temperatures, decomposition occurred. Dihydrodispacamide A (**5**) was not formed as a byproduct. The sequence can be carried out without workup



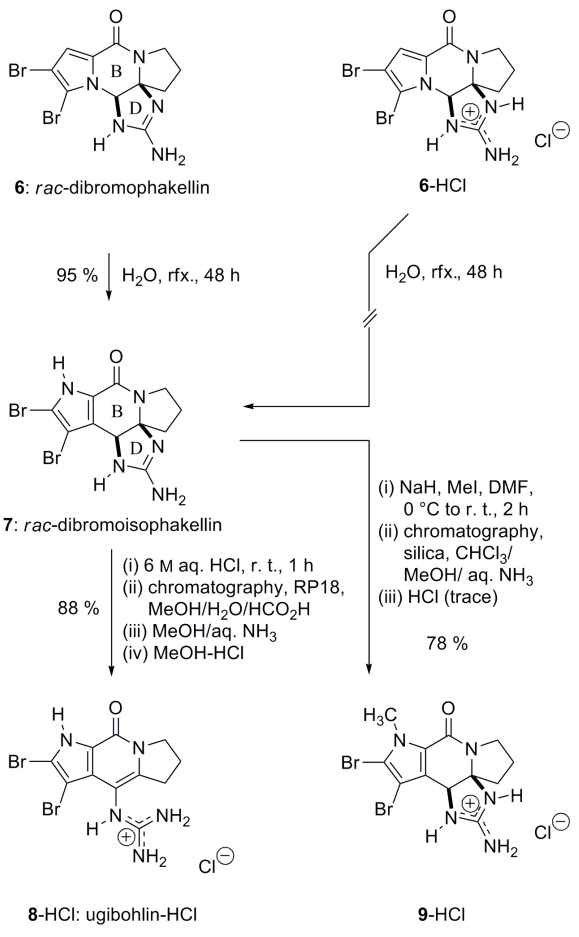
Scheme 1. Improved protocol for the conversion of dihydrooroidin hydrochloride (**1**-HCl) to the key pyrrole-imidazole alkaloid oroidin (**4**).

of compound **3** in one step and 75 % yield. With NBS (1 eq.) in DMF, dihydrooroidin hydrochloride (**1**-HCl) afforded the bromo analog, which was more difficult to purify than **3**.

With dihydrooroidin (**1**) in hands, we also cyclized the compound to *rac*-dibromophakellin (**6**) following the Büchi/Horne procedure [6, 7] in order to study the isomerization of **6** to the thermodynamically more stable natural product dibromoisophakellin (**7**, Scheme 2). Dibromophakellin [11] and dibromoisophakellin [9, 12] occur in *Agelas* sponges in both enantiomeric forms. For a detailed NMR analysis of **6**, **7**, and also **4**, see reference [10]. It was known that **6** can be converted to **7** by treatment with K_2CO_3/PhCl in about 50 % yield [6]. We found that refluxing the free base **6** under neutral conditions in water for 48 h affords **7** in nearly quantitative yield. Interestingly, dibromophakellin-HCl (**6**-HCl) did not react under the same conditions.

Under protonating conditions, dibromophakellin (**6**) undergoes opening of ring D at the *N*,*N*-ketal moiety forming a tricyclic vinylguanidine [11]. In our hands, treatment of its isomer *rac*-dibromoisophakellin (**7**) with 6 M aqueous HCl at r. t. afforded the natural product ugibohlin (**8**, 88 %), originally isolated from the marine sponge *Axinella carteri* [12]. Ugibohlin-HCl (**8**-HCl) proved to be better soluble in [D_6]DMSO than the HCO_2H adduct first obtained after RP chromatography (Scheme 2). The natural product *N*-methyldibromoisophakellin (*rac*-**9**) [13] was obtained by treatment of *rac*-**7** with NaH/MeI in DMF (78 %). Conversion of **9** to the hydrochloride had to be carried out under very diluted conditions [1 N aqueous HCl/MeOH (1 : 500)], because opening of ring D occurred when employing higher concentrations of acid.

Cleavage of ring B by heterolysis of the *N*,*N*-acetal of *rac*-dibromophakellin (**6**) with electron shift to the pyrrole carboxamide requires that the guanidine moi-



Scheme 2. Conversion of *rac*-dibromophakellin (**6**) to ugibohlin hydrochloride (**8**-HCl) and *rac*-*N*-methyldibromoisophakellin hydrochloride (**9**-HCl).

ety of ring D is not protonated. Otherwise, two positive charges would initially be located at the aminoimidazoline ring. Probably for that reason, the hydrochloride **6**-HCl does not open on the pyrrole side, whereas the neutral free base **6** does. Cleavage of ring D by heterolysis of the *N*,*N*-ketal of **6** or **7** will shift the electrons of the C–N bond to the guanidine unit with formation of an acyliminium ion. Protonating reaction conditions are required, whereas reaction even of the hydrochloride salt **6**-HCl under neutral conditions did not occur.

In summary, the conversion of dihydrooroidin (**1**) to oroidin (**4**) is now possible in 75 % overall yield, making the pathway *via* **3** the most practical in providing large quantities of the key metabolite oroidin (**4**). The conversion of dibromophakellin (**6**) to dibromoisophakellin (**7**) is now a quantitative process in water. The natural products ugibohlin (**8**) and *N*-methyldibromoisophakellin (**9**) have been synthesized for the first time.

Experimental Section

General

NMR spectra were taken with Bruker DRX-400 (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C) and Bruker AV II-600 (600.1 MHz for ^{1}H; 150.9 MHz for ^{13}C) instruments, referenced to the solvent signal or TMS. All measurements were carried out at 300 K. Mass spectra were obtained with a Thermo Finnigan LTQ FT and a Finnigan MAT 95 XLT spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer. UV/Vis spectra were measured with a Varian Cary 100 Bio UV/Vis spectrometer. Melting points were determined with a Büchi Melting Point B 540 apparatus and are uncorrected. Chemicals were purchased from commercial suppliers and used without further purification. Silica gel 60 (40 – 63 μm, Merck) was used for column 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.

*Chlorodihydrooroidin (**3**)*

At 0 °C, *N*-chlorosuccinimide (30.5 mg, 0.22 mmol) was added to a solution of dihydrooroidin-HCl (**1**-HCl, 100 mg, 0.22 mmol, [5]) in DMF (10 mL). The mixture was stirred at r. t. for 1 h, and the solvent was removed *in vacuo*. The residue was purified by column chromatography [silica, $CHCl_3$/MeOH/25 % aqueous NH_3 (90 : 10 : 1)] to provide compound **3** as a yellow solid (78.8 mg, 0.18 mmol, 81 %). TLC [silica, $CHCl_3$/MeOH/25 % aqueous NH_3 (8 : 2 : 0.1)]: R_f = 0.65. – M. p. 178 °C. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.67 (s, br, 1H, pyrrole-N*H*), 10.63 (s, br, 1H, imidazole-N*H*), 8.15 (t, ^3J = 5.6 Hz, 1H, OCN*H*CH$_2$), 6.92 (s, 1H, pyrrole-C*H*), 5.31 (s, br, 2H, N*H*$_2$), 3.17 (dt, ^3J = 6.9, ^3J = 6.6 Hz, 2H, NHC*H*$_2$CH$_2$), 2.38 (t, ^3J = 7.3 Hz, 2H, NHCH$_2$C*H*$_2$), 1.67 (tt, ^3J = 7.6 Hz, ^3J = 7.2 Hz, 2H, C*H*$_2$CCCl). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 158.8 (C=O), 147.3 (*C*NH$_2$), 128.2 (NH*C*CO), 119.3 (*C*Cl), 117.7 (ClC*C*), 112.4 (pyrrole-*C*H), 104.3 (Br*C*CH), 97.7 (NH*C*Br), 38.1 (NH*C*H$_2$), 29.0 (NHCH$_2$*C*H$_2$), 21.0 (*C*H$_2$CN). – IR (ATR): $\tilde{\nu}$ = 3111 (br), 2940 (br), 1680 (m), 1612 (s), 1564 (s), 1519 (m), 1415 (m), 1320 (m), 1219 (m), 1105 (s), 1053 (s), 974 (s), 823 (s), 752 (m), 652 cm^{-1} (m). – UV (MeOH): λ_{max} (log ε) = 201 (4.11), 213 (3.19), 275 (3.93). – HRFTMS ((+)-ESI): *m*/*z* = 423.9154 (calcd. 423.9169 for $C_{11}H_{11}{}^{79}Br_2{}^{35}ClN_5O$, [M+H]$^+$).

*Oroidin-HCO$_2$H (**4**-HCO$_2$H)*

A solution of *N*-chlorosuccinimide (30.5 mg, 0.22 mmol) and dihydrooroidin-HCl (**1**-HCl, 100 mg, 0.22 mmol, [5]) in

DMF (10 mL) was stirred at r. t. for 1 h and then at 100 °C for 1 h. The solvent was evaporated under reduced pressure, and the residue was purified by reversed phase column chromatography [RP-18, H_2O/MeOH/HCO_2H (60 : 40 : 1)] to give oroidin-HCO_2H (**4**-HCO_2H) as a yellow solid (74.6 mg, 0.17 mmol, 75 %). – TLC [silica, $CHCl_3$/MeOH/25 % aqueous NH_3 (80 : 20 : 1)]: R_f = 0.20. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.45 (t, ^3J = 5.8, 1H, CONHCH$_2$), 8.23 (s, 3H), 7.77 (s, br, 2H, NH$_2$), 6.97 (s, 1H, pyrrole-CH), 6.80 (s, 1H, imidazole-CH), 6.19 (d, ^3J = 16.0 Hz, CHCHC), 6.08 (dt, ^3J = 16.0 Hz, ^3J = 5.2 Hz), 3.95 (dd, ^3J = 5.1 Hz, 2H, NHCH$_2$). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.5 (formate), 158.6 (NHC=O), 148.6 (CNH$_2$), 128.0 (BrCCHC), 125.5 (CHCHCH$_2$), 125.3 (NHCCHCH), 116.9 (NHCCHCH), 112.7 (pyrrole-CH), 111.4 (imidazole-CH), 104.6 (NHCBr), 97.8 (CHCBr), 40.0 (NHCH$_2$CH). – MS ((+)-ESI): *m/z* (%) = 388/390/392 (50/100/50) [M+H]$^+$.

*Dibromophakellin (**6**) and dibromophakellin-HCl (**6**-HCl)*

NBS (35.6 mg, 0.2 mmol) was added to a solution of dihydrooroidin-HCl (**1**-HCl, 42.8 mg, 0.1 mmol, [5]) in TFA (1 mL) in one portion, and the reaction was stirred for 5 min. The solvent was evaporated under reduced pressure, and the resulting residue was quenched with THF/Et_3N (1 : 1, 2 mL). Evaporation of the solvent afforded an oil, which was diluted with acetone (0.5 mL) and triturated with Et_2O (3 mL). After filtration, the solid was purified by column chromatography [silica, $CHCl_3$/MeOH/25 % aqueous NH_3 (90 : 10 : 1)] affording dibromophakellin (**6**) as the free base. Treatment with MeOH/12 N aqueous HCl (10 : 1) provided dibromophakellin-HCl (**6**) as a colorless solid (38.9 mg, 0.9 mmol, 91 %) after evaporation. – TLC [silica, $CHCl_3$/MeOH/25 % aqueous NH_3 (8 : 2 : 0.1)]: R_f = 0.5. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.34 (s, br, 1H, NH$_2$CNHC), 9.78 (s, br, 1H, CHNHC), 8.41 (s, br, 2H, NH$_2$), 7.01 (s, 1H, BrCCH), 6.31 (s, 1H, NCHNH), 3.73 – 3.44 (m, 2H, NCH$_2$), 2.44 – 2.03 (m, 4H, NCH$_2$CH$_2$CH$_2$). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 156.3 (CNH$_2$), 153.6 (CO), 124.9 (CHCCO), 114.8 (CBrCH), 106.1 (NCBr), 101.9 (CBrCH), 82.3 (NCHCN), 68.2 (NCHCN), 44.7 (NCH$_2$), 38.5 (NCCH$_2$), 19.0 (CH$_2$CH$_2$CH$_2$). – MS (EI, 70 eV): *m/z* (%) = 389/391/393 (50/100/50) [M]$^+$.

*Dibromoisophakellin-HCl (**7**-HCl)*

Dibromophakellin (**6**, 38.9 mg, 0.1 mmol) was suspended in 10 mL H_2O and refluxed for 48 h. After evaporation of H_2O, the residue was washed with Et_2O (3 × 5 mL), acetone (1 × 5 mL), and recrystallized from water. A solution of dibromoisophakellin (**7**) in MeOH (10 mL) was treated with 12 N aqueous HCl (10 µL) to form dibromoisophakellin-HCl (**7**-HCl) after evaporation of the solvent (40.8 mg, 0.09 mmol, 96 %). Reversed-phase column chromatography of **7**-HCl [RP-18, H_2O/MeOH/HCO_2H (60 : 40 : 1)] provided **7**-HCO_2H. – TLC [silica, $CHCl_3$/MeOH/NH_3 (8 : 2)]: R_f = 0.18. – **7**-HCl: M. p. 172 °C. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.35 (s, 1H, BrCNH), 9.80 (s, 1H, CNHC), 8.97 (s, 1H, CHNHC), 7.94 (s, 2H, CNH$_2$), 5.22 (s, 1H, CCHNH), 3.61 – 3.56 (m, 1H, NCHH), 3.48 – 3.41 (m, 1H, NCHH), 2.23 – 2.21 (m, 2H, NCH$_2$CH$_2$), 2.23 – 1.99 (m, 2H CH$_2$C). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 156.8 (NH$_2$CNH$_2$), 154.6 (NCO), 122.7 (NHCCO), 122.3 (CCBr), 108.3 (NHCBr), 96.2 (CCBr), 83.9 (CCCH$_2$), 53.9 (CCCH$_2$), 44.1 (NCH$_2$), 38.9 (CCH$_2$CH$_2$), 19.1 (CH$_2$CH$_2$CH$_2$). – **7**-HCO_2H: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.72 (s, br, 2 H, BrCNH, NH$_2$CNH), 8.30 (s, 2H), 5.16 (s, 1H, CCHNH), 5.10 (s, br, 2H, NHCNH$_2$), 3.58 – 3.53 (m, 1H, NCHH), 3.52 – 3.44 (m, 1H, NCHH), 2.21 – 2.17 (m, 2H, NCH$_2$CH$_2$), 2.21 – 1.99 (m, 2H CH$_2$C). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.5 (formate), 157.7 (NH$_2$CNH$_2$), 155.1 (NCO), 122.9 (NHCCO), 122.8 (CCBr), 109.0 (NHCBr), 95.7 (CCBr), 83.9 (CCCH$_2$), 53.8 (CCCH$_2$), 43.7 (NCH$_2$), 38.9 (CCH$_2$CH$_2$), 19.0 (CH$_2$CH$_2$CH$_2$). – HRFTMS ((+)-ESI): *m/z* = 389.9381 (calcd. 389.9388 for $C_{11}H_{12}{}^{79}Br^{81}BrN_5O$, [M+H]$^+$).

*Ugibohlin-HCO_2H (**8**-HCO_2H)*

Dibromoisophakellin-HCO_2H (**7**-HCO_2H, 43.5 mg, 0.1 mmol) was dissolved in 6 M aqueous HCl (10 mL). The reaction mixture was stirred at r. t. for 1 h. After evaporation of the solvent, the residue was purified by column chromatography on RP-silica gel [H_2O/MeOH/HCO_2H (60 : 40 : 1 to 80 : 60 : 1.4)]. Ugibohlin-HCO_2H (**8**-HCO_2H) was obtained as a light-yellow powder (38.7 mg, 0.089 mmol, 88 %). A solution of ugibohlin-HCO_2H (**8**-HCO_2H) in 5 mL MeOH was treated with 25 % aqueous NH_3 followed by solvent evaporation. The free base was dissolved in MeOH (10 mL) and treated with 37 % aqueous HCl (20 µL), followed by solvent evaporation under reduced pressure. The residue was washed with Et_2O (3 × 10 mL), acetone (1 × 5 mL), and H_2O (5 mL) affording ugibohlin-HCl (**8**-HCl). – TLC [RP-18, H_2O/MeOH/HCO_2H (100 : 200 : 3)]: R_f = 0.45. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.44 (s, br, 1H, BrCNH), 9.14 (s, br, 1H, CCNH), 7.46 (s, br, 4H, NH$_2$CNH$_2$), 4.14 – 4.08 (m, 1H, NCHH), 4.01 – 3.94 (m, 1H, NCHH), 3.05 – 2.98 (m, 1H, NCH$_2$CHH), 2.97 – 2.82 (m, 1H, NCH$_2$CHH), 2.17 – 2.08 (m, 2H, C=CCH$_2$). – ^{13}C NMR (100 MHz, CD_3OD): δ = 157.7 (NCNH$_2$), 151.9 (NCCO), 142.8 (CH$_2$CC), 127.6 (NHCCO), 123.1 (CBrC), 113.4 (NHCBr), 102.6 (CCCH$_2$), 89.5 (CCBr), 48.2 (NCH$_2$), 28.4 (C=CCH$_2$), 21.2 (NCH$_2$CH$_2$). – HRFTMS ((+)-ESI): *m/z* = 389.9382 (calcd. 389.9388 for $C_{11}H_{12}{}^{79}Br^{81}BrN_5O$, [M+H]$^+$).

*N-Methyldibromoisophakellin-HCl (**9**-HCl)*

At 0 °C, methyl iodide (3.2 µL, 0.5 mmol) and NaH (60 % dispersion in mineral oil, 2.1 mg, 0.5 mmol) were

added to a solution of dibromoisophakellin (**7**, 20 mg, 0.5 mmol) in DMF (2 mL). After 2 h at r. t., saturated aqueous $NaHCO_3$ (5 mL) and *n*-BuOH (5 mL) were added. The aqueous phase was washed twice with *n*-BuOH, and the combined organic phases were dried over $MgSO_4$ and evaporated. The resulting residue was purified by column chromatography [silica, $CHCl_3$/MeOH/25 % aq. NH_3 (80 : 20 : 1)] to provide **9** as the free base. Aqueous HCl (1 N, 11 μL) was added to a solution of **9** (15.6 mg, 0.4 mmol) in MeOH (5 mL) to give *N*-methyldibromoisophakellin-HCl (**9**-HCl, 17.6 mg, 0.4 mmol, 78 %) as a yellow powder. – TLC [silica, $CHCl_3$/MeOH/25% aqueous NH_3 (80 : 20 : 1)]: R_f = 0.20. – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.59 (s, 1H, CN*H*C), 8.64 (s, 1H, CHN*H*C), 7.81 (s, 2H, NHCNH_2), 5.23 (s, 1H, CC*H*NH), 3.93 (s, 3H, BrCNCH_3), 3.63 – 3.56 (m, 1H, NCH*H*CH_2), 3.48 – 3.41 (m, 1H, NC*H*HCH_2), 2.25 – 2.21 (m, 2H, $NCH_2CH_2CH_2$), 2.09 – 1.98 (m, 2H, $NCH_2CH_2CH_2$). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 156.6 (NH*C*NH_2), 154.9 (CH_3NCCO), 123.2 (Br*C*CH), 121.0 (CH_3NC), 114.0 (CH_3NCBr), 95.8 (*C*Br), 83.3 (N*C*CH_2), 53.8 (NH*C*HC), 44.5 (N*C*H_2CH_2), 39.3 (NC*C*H_2), 34.9 (N*C*H_3), 19.03 (NCH_2CH_2). – HRFTMS ((+)-ESI): *m/z* = 403.9536 (calcd. 403.9545 for $C_{12}H_{14}{}^{79}Br^{81}BrN_5O$, $[M+H]^+$).

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