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Synthesis of the dipyrrolopyrazinone core of dibromophakellstatin and related marine alkaloids

Delphine E. N. Jacquot, Holger Hoffmann,† Kurt Polborn and Thomas Lindel*

Department Chemie der Universität, Butenandtstr. 5-13, D-81377 München, Germany

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Abstract—The dipyrrolopyrazinone (ABC) core of the phakelline-type pyrrole–imidazole alkaloids from marine sponges was synthesized starting from L-prolinol and 2-trichloroacetylated pyrroles. On oxidation of the condensation product with IBX, immediate cyclization occurs. It was found that the presence of a bromine substituent in the 8-position of the resulting tricyclic *N*,*O*-hemiacetal exclusively favors the *cis* relative configuration at the stereogenic centers C10 and C10a. Via an intermediate tertiary *N*-acyliminium ion, the pyrazinone core was dihydroxylated by treatment with *m*-CPBA in the presence of water. The simultaneous functionalization of the C10 and C10a positions is an important step towards the synthesis of the cytotoxic natural product dibromophakellstatin

The pyrrole–imidazole alkaloids constitute a very prominent class of natural products exclusively found in marine sponges. The growing interest in this class is in particular driven by the close biogenetic relationship between these structurally diverse alkaloids.[1] As an important ecological function, the pyrrole–imidazole alkaloids exhibit a fish feeding deterrent activity which is essential for the survival of the entire sponge genus *Agelas*.[2] Considerable cytotoxicity has been reported, e.g. for dibromophakellstatin (**1a**, Fig. 1) isolated from *Phakellia mauritiana* in 1997.[3]

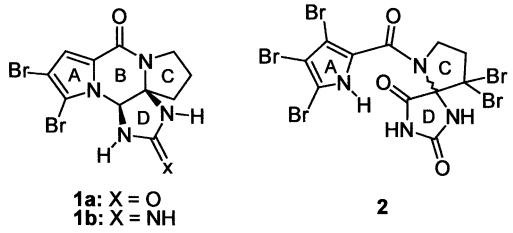

Figure 1. The marine pyrrole–imidazole alkaloids dibromophakellstatin (**1a**), dibromophakellin (**1b**), and the ACD synthetic intermediate **2**.

Foley and Büchi obtained the non-cytotoxic dibromophakellin (**1b**, Fig. 1)[4] which differs from **1a** by the presence of a guanidine instead of a urea function in ring D.[5] We could show that the synthesis of the ACD analog **2** is possible in one step via oxidative *spiro*-cyclization of an alkylidene hydantoin precursor.[6]

In this paper, the efficient synthesis and dihydroxylation of unsymmetrical dipyrrolopyrazinones is reported as alternative to the biomimetic approach. The ABC core structure of **1** is also present in the complex pyrrole–imidazole alkaloid palau'amine[7] the total synthesis of which is currently under intense investigation.[8] The ABC system of **1** has not been synthesized.[9] Our results may also be of interest with respect to the oxidation of pyrazines involved in chemoluminescence phenomena.[10]

Condensation of the differently brominated pyrrolyltrichloromethyl ketones **3a–c** with the unprotected, ambident nucleophile L-prolinol (**4**) in acetonitrile gave the tertiary amides **5a–c** as major products in satisfactory yields (Scheme 1). The only by-product (14%) resulted from the additional acylation of the primary hydroxyl group and could be converted to **5a–c** by simple saponification. Very conveniently, oxidation of the primary alcohol **5a–c** was achieved employing IBX in DMSO.[11] The resulting aldehydes immediately cyclize to the *N*,*O*-hemiacetals **6a–c**. That cyclization appears to occur in this facile manner, only if a six-ring is formed. The homologue of **6a–c** would prefer the open-chain form.[6,9]

Keywords: *N*-acyliminium compounds; dihydroxylation; marine natural products; *N*,*O*-ketal; pyrrole–imidazole alkaloids.

* Corresponding author. Tel.: +(0)89-2180-7733; fax: +(0)89-2180-7734; e-mail: thomas.lindel@cup.uni-muenchen.de

† Present address: Aventis Pharma Deutschland GmbH, Natural Product Research, D-65926 Frankfurt, Germany.

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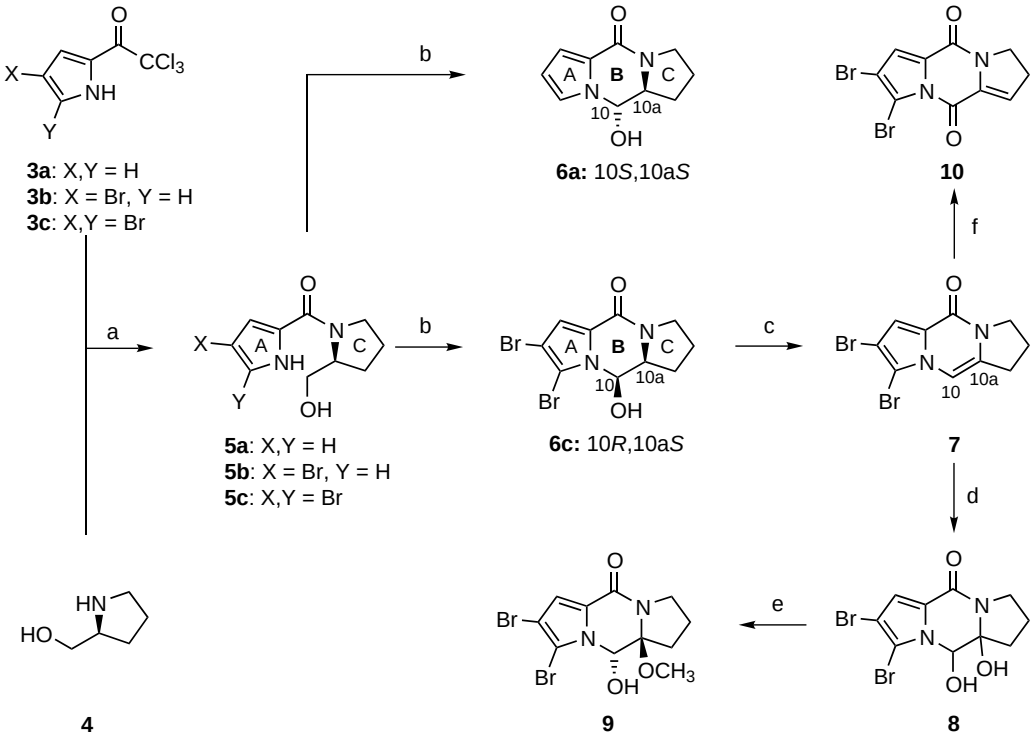

Scheme 1. Oxidative cyclization to diastereomeric non- and dibrominated pyrrolopyrazinones; dihydroxylation of the C10–C10a double bond of **7** and facile reacetalization at the quaternary carbon atom C10a. (a) **4** (1.1 equiv.), Na_2CO_3 (1.9 equiv.), CH_3CN, 30 min, rt then **3a–c** (1 equiv.), 4 h, reflux; (b) IBX (2 equiv.), DMSO, 12 h, rt, 77%; (c) $POCl_3$ (1.5 equiv.), pyridine, 6 h, 0°C to rt, 79%; (d): *m*-CPBA (1.2 equiv.), CH_2Cl_2, 12 h, 0°C to rt, 62%; (e) $CHCl_3$/MeOH (1:1), reflux, 1 h, 67%; (f) dry *m*-CPBA (1.2 equiv.), CH_2Cl_2, 0°C to rt, 2 days, 41%.

The difference in heats of formation of both possible diastereomers of the tricycles **6a** and **6c** was expected to be in the range of only 4 kJ mol^{-1} (MM2).[12] For the 7,8-dibrominated tricyclus **6c**, the observed coupling constant $^3J_{10\text{-H},10a\text{-H}}$ of 2.6 Hz corresponds to the calculated dihedral angle of the (10*R*,10a*S*)- (50°) rather than of the (10*S*,10a*S*)-diastereomer (170°). To our surprise, cyclization of the non-brominated analog **5a** gave the (10*S*,10a*S*)-diastereomer **6a** as the preferred isomer with a coupling constant $^3J_{10\text{-H},10a\text{-H}}$ of 9.7 Hz. Very small enthalpy differences appear to govern the anomeric equilibrium of brominated 10-hydroxy-2,3,10,10a-tetrahydro-1*H*-dipyrrolo[1,2-a;1′,2′-d]pyrazin-5-ones. The 7-monobrominated analog **5b** lacking the 8-bromination cyclizes to a product mixture (DMSO-d_6) favoring the (10*S*,10a*S*)-diastereomer.[13]

Although the Dess–Martin oxidation is suitable for the synthesis even of racemization-prone α-amino aldehydes,[14] we found it instructive to analyze the absolute configuration of the *N*,*O*-acetal **6c**, because the effects of IBX in DMSO (instead of periodinane in dichloromethane) were unclear. Comparative ^{1}H NMR-analysis of both Mosher esters[15] obtained from **6c** proved that exclusively the (10*R*,10a*S*)-enantiomer was formed on oxidation of **5c** with IBX. Fig. 2 gives the ^{1}H NMR-chemical shift differences of the two Mosher esters, apparently the first obtained from *N*,*O*-acetals. The (10*S*,10a*S*)-diastereomer was not observed.

The conversion of the tertiary carbon C10a to a hemiketal would be an important step forward. Direct oxidation of the acylated pyrrolidine system to an *N*-acyliminium ion was expected to occur at the secondary (C3) rather than the tertiary carbon atom (C10a).[16] Therefore, we decided to study the behavior of the olefin **7**, obtained by dehydration of **6c** employing $POCl_3$/pyridine (Scheme 1). Surprisingly, unsymmetrically saturated dipyrrolopyrazinones of the kind

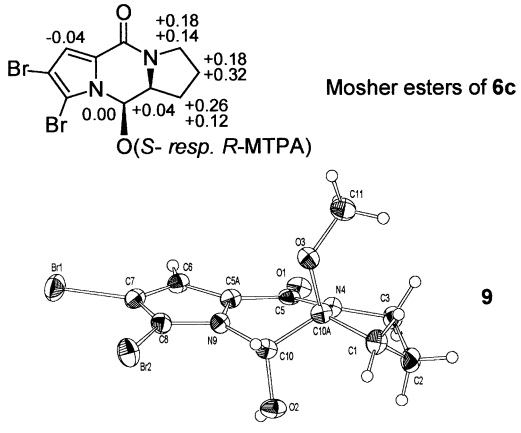

Figure 2. Configuration of dibromophakellstatin ABC subsystems: $\Delta\delta_H = \Delta(\delta_S - \delta_R)$ of the diastereomeric Mosher esters of **6c** and ORTEP plot of the methanol adduct **9** in the crystal (selected torsional angle: O2–C10–C10a–O3 = −167°).

of **7** have not been reported in the literature. The only similar example is oxygen-free and has recently been reported by Li and Marks.[17] Due to the polarization of the C10–C10a double bond electrophiles were expected to attack at C10. e.g. Reaction of **7** with NBS/*n*-BuOH led to the bromination of C10 and the introduction of an *n*-butoxy substituent at C10a. We were pleased to observe that on reaction of **7** with *m*-CPBA in the presence of water the diol **8** was obtained. In the absence of water, the α,β-unsaturated α-aminoamide **10** was the major product, together with minor amounts of the saturated analog. There was no intermediate epoxide detectable in any case, although there are examples reported.[10a]

As for the formation of the monohydroxy compounds **6a** and **6c**, the stereochemical outcome of the reaction was unclear. Due to the quaternary character of C10a the relative configuration of the diol **8** could not be concluded from its ^{1}H NMR spectrum. Fortunately, on treatment of **8** with excess methanol, the methoxy compound **9** could be isolated as a crystalline solid. X-Ray analysis (Fig. 2) proved the methoxy group to be in the *trans*-position to the hydroxy group at C10.[18,19]

In the natural product dibromophakellstatin (**1**) the *cis*-connection of ring D is strongly favored for sterical reasons. The ease by which the hydroxy group at C10a is exchanged by a methoxy and also by an ethoxy group encourages us to develop an intramolecular *N*-acyliminium pathway towards the full ABCD skeleton, starting from the enantiomerically pure *N*,*O*-hemiacetal **6c**. The functionalized ABC systems **8** and **9** are currently among the most advanced synthetic precursors of the cytotoxic dibromophakellstatin.

Acknowledgements

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13. After prolonged storage of the cyclization products of **6a** and **6b**, the ratio of the (10*S*,10a*S*)- to the (10*R*,10a*S*)-diastereomer was greater than 9:1 (as judged by ^{1}H NMR-integration, DMSO-d_6).
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18. Preparation and characterization of selected compounds: **6c**: IBX (2.6 g, 9.26 mmol) is suspended in DMSO (15 mL). After 20 min, the solution becomes clear and **5c** (1.63 g, 4.63 mmol) is added. After 12 h, the solution is diluted with water (200 mL). The precipitate is filtered off, dried and extracted three times with CH_2Cl_2 (300 mL). Evaporation to dryness yielded **6c** as a colorless solid (1.25 g, 77%), mp 174°C, TLC [silica gel, AcOEt]: R_f=0.2, $[\alpha]_D^{23}$=+31.9° (*c* 12.2, MeOH). ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.75–2.15 (m, 5H, NCHH$\underline{H}$C$\underline{H}_2$C$\underline{H}_2$), 3.48–3.60 (m, 1H, NC$\underline{H}$HCH$_2$), 3.95–4.05 (m, 1H, 10a-H), 5.60 (dd, *J*=2.6, 7.7 Hz, 1H, 10-H), 6.81 (s, 1H, HC=C), 7.02 (d, *J*=7.7 Hz, 1H, OH). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ=22.5 (C-2), 26.8 (C-1), 44.2 (C-3), 60.2 (C-10a), 75.8 (C-10), 99.9 (C-7), 105.7 (C-8), 113.0 (C-6), 126.3 (C-5a), 154.6 (CO). MS (EI, 70

eV): m/z (%) = 348/350/352 (4/8/4) [M^+], 319/321/323 (2/4/2), 250/252/254 (2/4/2), 71 (8), 70 (100), 42 (8). IR (KBr): $\tilde{\nu}$ = 3445 cm^{-1}, 3139, 2975, 2885, 1621, 1556, 1448, 1352, 1303, 1099, 969, 729. UV (CF_3CH_2OH): λ_{max} (log ε) = 288 nm (4.05), 236 (4.03), 206 (4.14). $C_{10}H_{10}Br_2N_2O_2$ (350.0): calcd C, 34.32; H, 2.88; N, 8.00. Found C, 34.18; H, 2.99; N, 7.95. **8**: *m*-CPBA (696 mg, 2.94 mmol) is added to a solution of **7** (795 mg, 2.39 mmol) in dry CH_2Cl_2 (50 mL) at 0°C under an argon atmosphere. The reaction mixture is allowed to warm to room temperature. After 12 h, the precipitate is filtered off and washed with Et_2O. **8** is obtained as a colorless powder (545 mg, 62%), mp 164°C, TLC [silica gel, AcOEt/MeOH (1:1)]: R_f = 0.71. ^{1}H NMR (DMSO-d_6, 360 MHz): δ = 1.85–1.99 (m, 2H, $NCH_2C\underline{H}HC\underline{H}H$), 2.00–2.13 (m, 1H, $NCH_2CH\underline{H}CH_2$), 2.27–2.40 (m, 1H, $NCH_2CH_2CH\underline{H}$), 3.25–3.45 (m, 1H, $NC\underline{H}HCH_2$), 3.56–3.70 (m, 1H, $NCH\underline{H}CH_2$), 5.39 (d, J = 7.7 Hz, 1H, 10–H), 6.26 (s, 1H, 10a-OH), 6.82 (s, 1H, 6-H), 7.31 (d, J = 7.7 Hz, 1H, 10-OH). ^{13}C NMR (DMSO-d_6, 90.5 MHz): δ = 20.3 (C-2), 35.1 (C-1), 44.0 (C-3), 79.4 (C-10), 90.3 (C-10a), 99.5 (C-7), 106.8 (C-8), 113.2 (C-6), 125.4 (C-5a), 154.6 (CO). MS (EI, 70 eV): m/z (%) = 364/366/368 (10/18/8) [M^+], 250/252/254 (10/16/9), 98 (8), 97 (19), 86 (100), 85 (12), 44 (8), 41 (19). IR (KBr): $\tilde{\nu}$ = 3353 cm^{-1}, 3169, 2982, 2344, 1603, 1548, 1437, 1387, 1344, 1302, 1236, 1185, 1143, 1081, 1023, 987, 973, 900, 867, 846, 809, 790, 740, 668, 644, 617, 596, 562, 434. UV (CF_3CH_2OH): λ_{max} (log ε) = 288 nm (2.77), 228 (3.15), 198 (3.52). $C_{10}H_{10}Br_2N_2O_3$ (366.0): calcd C, 32.82; H, 2.75; N, 7.65; found C, 32.79; H, 2.83; N, 7.40. **9**: The diol **8** (100 mg, 0.27 mmol) is suspended in MeOH–$CHCl_3$ (1:1, 50 mL). As the mixture is heated to reflux, the solution becomes clear. After 1 h, the solution is concentrated to dryness to give a colorless solid. Purification by flash chromatography ($CHCl_3$/MeOH (9:1)) afforded **9** as a colorless solid (70 mg, 67%), mp 75°C, TLC [silica gel, AcOEt]: R_f = 0.36. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.88–2.04 (m, 2H, $NCH_2C\underline{H}HC\underline{H}H$), 2.18–2.26 (m, 1H, $NCH_2CH\underline{H}CH_2$), 2.34–2.44 (m, 1H, $CH_2CH_2CH\underline{H}$), 3.08 (s, 3H, OCH_3), 3.52–3.68 (m, 1H, 3-H), 5.44 (dd, J = 0.4, 8.0 Hz, 1H, 10-H), 6.87 (d, J = 0.4 Hz, 1H, 6-H), 7.47 (d, J = 8.0 Hz, 1H, 10-OH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 21.4 (C-2), 30.6 (C-1), 45.5 (C-3), 50.1 (OCH_3), 77.7 (C-10), 95.1 (C-10a), 99.7 (C-7), 106.8 (C-8), 113.7 (C-6), 124.8 (C-5a), 154.9 (CO). MS (EI, 70 eV): m/z (%) = 378/380/382 (24/49/26) [M^+], 363/365/367 (9/18/9), 347/349/351 (11/20/9), 317/319/321 (14/30/14), 278/280/282 (27/52/24), 250/252/254 (19/36/18), 171/173 (5/5), 112 (10), 100 (52), 99 (100). IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1}, 2956, 1637, 1554, 1433, 1398, 1349, 1289, 1191, 1149, 1100, 1058, 1032, 974, 944, 900, 828, 785, 744, 647, 610, 566, 440. UV (CH_3OH): λ_{max} (log ε) = 287 nm (4.01), 235 (4.01). HREIMS m/z calcd for $C_{11}H_{12}Br_2N_2O_3$: 377.9215. Found 377.9213. **10**: Dry *m*-CPBA (2.5 g, 11.2 mmol) is added to a solution of **7** (2.5 g, 7.5 mmol) in dry CH_2Cl_2 (250 mL) at 0°C under an argon atmosphere. The reaction mixture is allowed to warm to room temperature. After 2 days, the precipitate is filtered off and washed with Et_2O. **10** is obtained as a colorless powder (1.06 g, 41%) mp 185°C, TLC [silica gel, AcOEt]: R_f = 0.38. ^{1}H NMR (DMSO-d_6, 360 MHz): δ = 2.87 (dt, J = 2.9, 8.9 Hz, 2H, 2-H), 4.00 (t, J = 8.9 Hz, 2H, 3-H), 6.73 (t, J = 2.9 Hz, 1H, 1-H), 7.16 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ = 28.7 (C-2), 45.0 (C-3), 104.8 (C-7), 109.2 (C-8), 116.8 (C-6), 128.6 (C-1), 129.0 (C-5a), 133.1 (C-10a), 150.1 (C-10), 151.6 (C-5). MS (EI, 70 eV): m/z (%) = 344/346/348 (18/40/21) [M^+], 250/252/254 (3/5/3), 249/251/253 (3/5/3), 144 (8), 142 (9), 95 (20), 94 (16), 67 (100). IR (KBr): $\tilde{\nu}$ = 3134 cm^{-1}, 3085, 2917, 1727, 1645, 1612, 1566, 1472, 1445, 1418, 1352, 1321, 1298, 1259, 1083, 1012, 945, 920, 858, 814, 732. HREIMS m/z calcd for $C_{10}H_6Br_2N_2O_2$: 345.8776. Found 345.8759.

19. Crystal and data collection parameters, relevant structure refinement parameters, atomic coordinates for the non-hydrogen atoms, positional and isotropic displacement coefficients for hydrogen atoms, a list of anisotropic displacement coefficients for the non-hydrogen atoms and a full list of bond distances and bond angles have been deposited with the Cambridge Crystallographic Data Center. The crystallographic data will be sent on quoting the CCDC numbers 167328 for **9** (e-mail: deposit@ccdc.cam.ac.uk).