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Alkaloids from marine organisms. Part 7:☆ Synthesis of bisdemethylaaptamine and bisdemethyloxyaaptamine—a biomimetic approach to the aaptamines?

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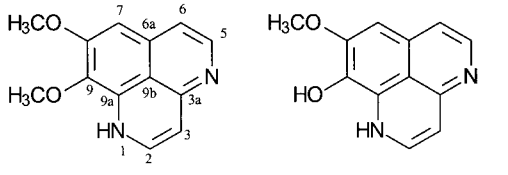
Abstract—Aaptamines are marine alkaloids with a unique 1*H*-benzo[*d*,*e*][1,6]naphthyridine structure and interesting biological properties. Bisdemethylaaptamine and bisdemethyloxyaaptamine were synthesized in four steps on a Bischler–Napieralski route including an oxidative formation of the crucial C^{9a}–N^{1}-bond. This synthetic approach may serve as a model for an oxidative Pictet–Spengler biosynthesis of the aaptamines.

1. Introduction

The aaptamines form a small group of 1*H*-benzo[*d*,*e*][1,6]-naphthyridine alkaloids[2] with interesting biological activities (Scheme 1). Due to their antagonistic effects on α-adrenergic receptors, a cardiac activity has been described for aaptamine (**1**).[3] Also antitumor activity has been reported for aaptamines.[4,5] The inhibition of Ehrlich tumor cell growth seems to be the strongest for those compounds with a free phenolic group at C-9 (**2** and **4**).[6]



aaptamine (**1**) demethylaaptamine (**2**)

demethyloxyaaptamine (**3**) isoaaptamine (**4**)

Scheme 1. Natural 1*H*-benzo[*d*,*e*][1,6]naphthyridine alkaloids.

A patent claims the inhibition of protein kinase C by iso-aaptamine derivatives.[7] The first aaptamines **1**–**3** were isolated by Nakamura et al.[8] from the marine sponge *Aaptos aaptos*.[9] Later on it was shown that the presence of these alkaloids is not limited to the genus *Aaptos*. Besides the *O*-methyl compounds **1**–**3**, the new *N*-methylaaptamine **4** (isoaaptamine) was isolated from sponges of the genus *Suberites*.[6]

So far eight synthetic approaches to these unique alkaloids have been published.[10,11] However, none of these efforts was designed to mimic a possible biosynthesis of the aaptamine system. In this paper we report on a concise four-step synthesis of bisdemethylaaptamine (**8**) based on biosynthetic considerations.[12] As shown in Scheme 2, the aaptamine skeleton can be assumed to be derived from L-dopa (**5**) and a biosynthetic equivalent of β-alanine aldehyde (**6**).[13] A biochemical Pictet–Spengler condensation followed by oxidative closure of the piperidine ring C should yield the perhydro derivative **7**.[14] Decarboxylation and dehydrogenation of **7** would then afford bisdemethyl-aaptamine **8**, from which the natural aaptamine alkaloids could be formed by methylation. Interestingly, the hypothetical precursor **9**[15] of the sponge alkaloid halitulin appears to originate from the same two building blocks **5** and **6**, which points to a common biosynthetic origin of these compounds.

2. Results

According to our hypothesis bisdemethylaaptamine (**8**) was synthesized from homoveratrylamine (**10**) and *N*-trifluoro-acetyl-β-alanine (**11**) (Scheme 3). Coupling of the two

☆ For Part 6, see Ref. 1.

Keywords: marine metabolites; biomimetic reactions; Bischler–Napieralski reaction; oxidative C–N bond formation.

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† X-Ray crystallography.

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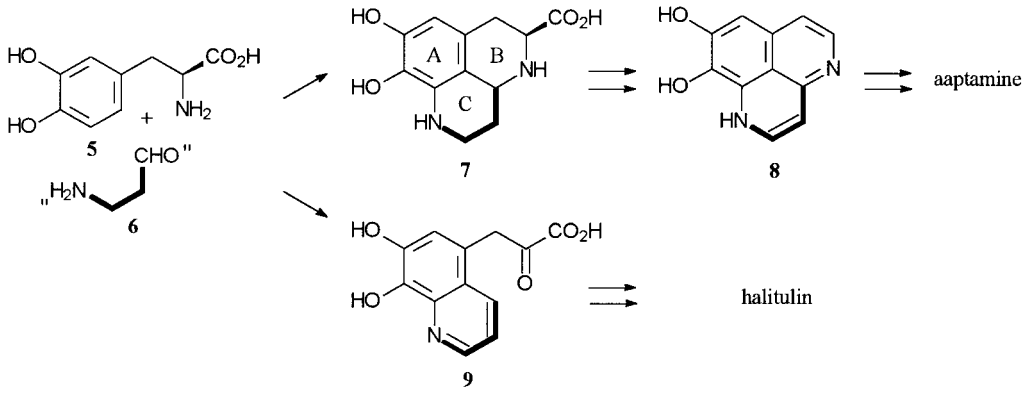


Scheme 2. Proposed biosynthesis of the aaptamine alkaloids and the halitulin precursor **9**.

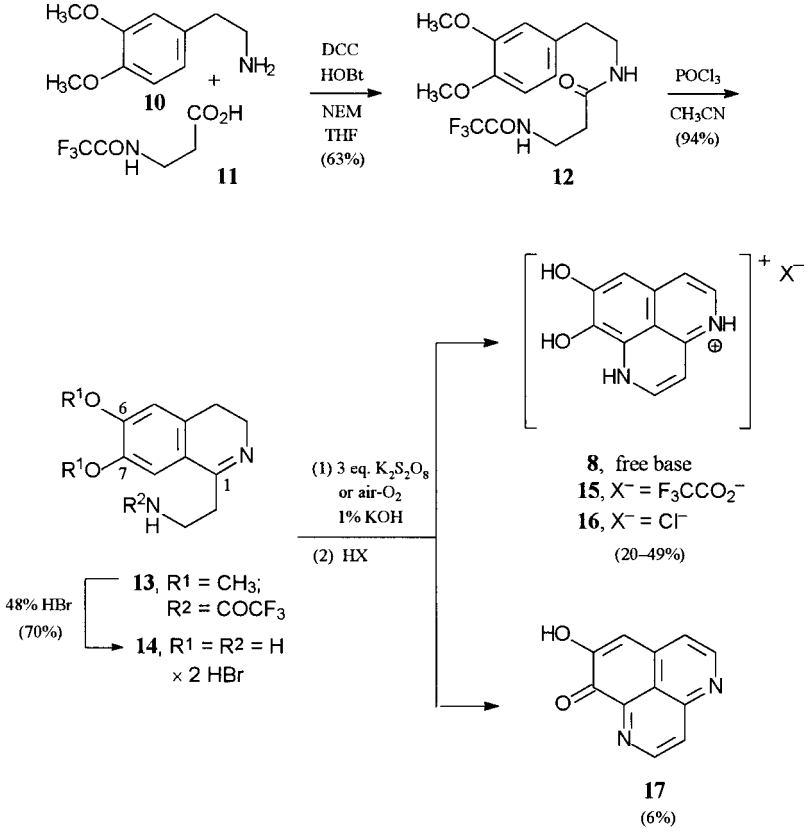
components followed by Bischler–Napieralski cyclization of the resulting amide **12** afforded the dihydroisoquinoline **13** in high yield, whose structure was confirmed by X-ray crystallography (Scheme 4). On treatment with aqueous hydrobromic acid, **13** underwent cleavage of the methyl ether and trifluoroacetamido groups and afforded the catecholamine **14** in form of its stable and analytically pure bishydrobromide. As **14** precipitated from the reaction mixture, no cumbersome purification had to be carried out with this air-sensitive, amphoteric compound.

At this point, the envisaged biomimetic key step had to be carried out. In fact, oxidative cyclization of **14** in 1% aqueous KOH with potassium peroxodisulfate or air yielded bisdemethylaaptamine (**8**) besides minor amounts of its oxidation product bisdemethyloxyaaptamine (**17**). Due to the instability of the free base, **8** was purified as trifluoroacetate **15** or hydrochloride **16** by gel chromatography (20% overall yield).

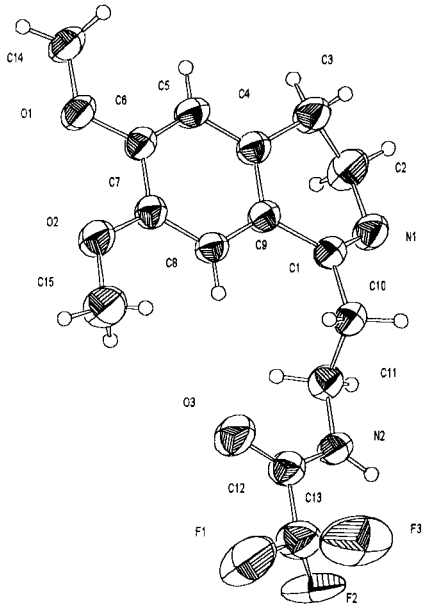
Experiments, to convert the dihydroxy compound **8** or its salts into the natural products **1**–**4** by selective methylation were as yet unsuccessful.

3. Conclusions

Our synthesis illustrates that bisdemethylaaptamine (**8**) can be obtained in one step from the simple catecholamine **14**. The mild conditions of this oxidative ring closure support the idea that the biosynthesis of the aaptamines may follow a similar course (Scheme 2).[14]



Scheme 3. Synthesis of the bisdemethylaaptaminium salts **15**, **16**, and bisdemethyloxyaaptamine (**17**).



Scheme 4. Crystal structure of dihydroisoquinoline **13** (Ortep plot).[16]

4. Experimental

4.1. General

Silica gel 60 230–400 mesh (Merck), MN Polyamide SC 6-AC (Macherey and Nagel, Germany) and Sephadex LH-20 (Pharmacia) were used for chromatography. R_f values were determined on silica gel 60 F254 TLC plates (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 instrument. ^{1}H and ^{13}C chemical shifts are given with respect to TMS or the solvent as internal standard. If there was no certain assignment possible #, ‡ and § indicate an interchangeable assignment of NMR signals. IR spectra were measured on a Perkin–Elmer FT 1000. C, H, N and Br analyses were performed by the microanalytical laboratory of our institute. The X-ray diffraction analyses were carried out on a Enraf–Nonius CAD4 diffractometer at 296 (2) K using MoK$_\alpha$ (λ=0.71069 Å) radiation.[16] The structure was solved with SHELXS 86 and refined by SHELXL 93 program.[17] The full data of the X-ray crystal structure have been deposited at the Cambridge Crystallographic Data Center.[16] Mass spectra were measured with a Finnigan MAT 95Q sector mass spectrometer using EI at 70 eV.

4.1.1. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-(trifluoroacetylamino)propionamide (12). To a stirred, ice-cold solution of **10** (48.54 g, 267.8 mmol), **11** (49.0 g, 264.7 mmol), *N*-ethylmorpholine (33.3 mL, 263.1 mmol), and *N*-hydroxybenzotriazole (HOBt) (27.03 g, 200 mmol) in THF (400 mL) was added dropwise within 1 h to a 1 M solution of dicyclohexylcarbodiimide (DCC) (60.4 g, 292.7 mmol) in THF. The reaction mixture was warmed to room temperature and stirred for additional 6 h. After cooling to 0°C, the dicyclohexylurea was filtered off. The filtrate was concentrated, the residue dissolved in EtOAc (500 mL) and stirred for 12 h. After filtration, the organic layer was washed with saturated aq. $NaHCO_3$ (3×200 mL), 2N citric acid (200 mL), saturated aq. $NaHCO_3$ (100 mL), and brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Recrystallization from EtOAc–hexanes provided **12** as a colorless solid (58.5 g, 63%): mp 148–149°C; UV/Vis (MeOH) λ_{max} (log ϵ)=228 (3.94), 278 nm (3.46); IR (KBr) 3304 (m, br), 3105 (m), 2941 (s), 1698 (s, $\nu_{C=O}$), 1644 (s, $\nu_{C=O}$), 1591 (w), 1552 (m), 1519 (m), 1459 (m), 1332 (m), 1263 (m), 1239 (m), 1185 (s), 1160 (w), 1026 (s), 938 (w), 877 (w), 804 (w), 766 (w), 729 cm^{-1} (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (t, J=5.7 Hz, 2H), 2.76 (t, J=6.9 Hz, 2H), 3.51 ('q', J=6.9 Hz, 2H), 3.61 ('q', J=5.7 Hz, 2H), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.54 (s, 1H, NH), 6.70 (s, 1H, ArH), 6.72 (d, J=8.6 Hz, 1H, ArH), 6.81 (d, J=8.6 Hz, 1H, ArH), 7.61 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 34.11, 35.11, 35.93, 40.78 (each 1 C, C-2, α-CH_2, β-CH_2, C-3), 55.90 (OCH_3), 55.94 (OCH_3), 111.50 (C-5′), 111.89 (C-2′), ~116 (q, $^1J_{CF}$≈290 Hz, CF_3), 120.66 (C-6′), 130.98 (C-1′), 147.87 (C-4′), 149.17 (C-3′), 157.32 (q, $^2J_{CF}$= 36.9 Hz, *C*OCF_3), 171.03 (C-1); EI-MS *m*/*z* (%)=348 (14) [M^+], 164 (100) [$M^+-C_5H_6F_3N_2O_2$], 151 (25) [$M^+-C_6H_8F_3N_2O_2$]; HR-EI-MS calcd for $C_{15}H_{19}F_3N_2O_4$ 348.1297, found 348.1290. Anal. Calcd C, 51.72, H, 5.50, N, 8.04, found C, 51.95, H, 5.60, N, 8.04.

4.1.2. 6,7-Dimethoxy-1-[2-(trifluoroacetylamino)ethyl]-3,4-dihydroisoquinoline (13). $POCl_3$ (150 mL, 1.6 mmol) was added dropwise (30 min) to a stirred suspension of **12** (50.58 g, 145.2 mmol) in CH_3CN (300 mL, dried over molecular sieves 3 Å), and the stirring was continued for 1 h at room temperature. The resulting mixture was refluxed for approximately 8 h until all the starting material had been consumed (TLC monitoring). After removal of the solvent in vacuo, the residue was poured into ice water and neutralized with saturated aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×200 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2×200 mL) and brine (100 mL), dried ($MgSO_4$), and filtered. Evaporation of the solvent provided isoquinoline **13** as a yellow solid (45.2 g, 94%): mp 144.0–146.8°C; R_f 0.80 (1:1 $CHCl_3$–MeOH); UV/Vis (CH_3CN) λ_{max} (log ϵ)=225 (4.36), 270 (3.89), 304 (3.80), 356 nm (2.25); IR (KBr) 3349 (br, NH), 3256 (m, br), 2934 (s), 1712 (s, $\nu_{C=O}$), 1643 (s), 1628 (m), 1591 (w), 1563 (s), 1519 (s), 1472 (m), 1449 (m), 1261 (m), 1246 (m), 1209 (m), 1197 (m), 1157 (m), 1026 (m, CO), 850 (m), 810 (m), 768 (w), 460 cm^{-1} (w); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.64 (t, J=7.7 Hz, 2H), 2.92 (t, J=5.5 Hz, 2H), 3.66 (t, J=7.7 Hz, 2H), 3.78 ('q', J=5.5 Hz, 2H), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.70 (s, 1H, ArH), 6.94 (s, 1H, ArH), 8.17 (s, 1H, $NHCOCF_3$); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 25.62 (C-4$^{\#}$), 33.98 (C-1′$^{\#}$), 36.38 (C-3‡), 46.62 (C-2′‡), 56.02 (OCH_3), 56.31 (OCH_3), 108.25 (C-8), 110.50 (C-5), 116.11 (q, $^1J_{CF}$=287.7 Hz, CF_3), 121.68 (C-8a), 131.23 (C-3a), 147.76 (C-7§), 151.34 (C-6§), 156.91 (q, $^2J_{CF}$= 36.6 Hz, *C*OCF_3), 164.74 (C-1); EI-MS *m*/*z* (%)=330 (35) [M^+], 261 (30) [M^+-CF_3], 233 (39) [$M^+-C_2F_3O$], 217 (100) [$M^+-C_2H_2F_3NO$]; HR-EI-MS calcd for $C_{15}H_{17}F_3N_2O_3$ 330.1191, found 330.1188. Anal. Calcd C, 54.54, H, 5.19, N, 8.48, found C, 54.59, H, 5.19, N, 8.46.

4.1.3. 1-(2-Aminoethyl)-6,7-dihydroxy-3,4-dihydroisoquinoline dihydrobromide (14). A suspension of **13** (24.34 g, 73.7 mmol) in 48% aqueous HBr (210 mL) was

refluxed (145°C) until the TLC showed no more starting material (approximately 4–8 h). The reaction mixture was cooled to 5°C and stirred at this temperature for additional 12 h. The resulting yellow precipitate was filtered under argon, immediately washed with Et_2O (3×30 mL) under argon and then dried in vacuo. **14** was obtained as a hygroscopic, bright yellow solid (18.9 g, 70%, analytically pure): mp 200°C (dec); R_f 0.20 (95:5 MeOH–NH_4OH); UV/Vis (MeOH) λ_{max} (log ϵ)=251 (4.06), 313 (3.93), 371 nm (3.83); IR (KBr) 3421 (m, br, NH), 3158 (m, br), 3086 (m, br), 2959 (m, br), 1648 (m), 1614 (m), 1579 (s), 1491 (m), 1468 (m), 1390 (m), 1335 (m), 1305 (s), 1266 (m), 1204 (m), 1161 (m), 1079 (w), 1035 (w), 462 cm^{-1} (w); ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (t, J=8.1 Hz, 2H), 3.37 (m, 4H), 3.78 (t, J=8.1 Hz, 2H), 6.87 (s, 1H, ArH), 7.33 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.66 (C-4), 30.87 (C-1′), 37.43 (C-3[#]), 41.80 (C-2′[#]), 116.0 (C-8[‡]), 116.38 (C-5[‡]), 117.25 (C-8a), 134.72 (C-4a), 144.16 (C-7[§]), 154.62 (C-6[§]), 173.29 (C-1); FAB-MS m/z (%)=207 (100) [M^++H]; Anal. Calcd for $C_{11}H_{16}Br_2N_2O_2$: C, 35.90, H, 4.38, N, 7.61, Br, 43.42, found C, 36.20, H, 4.50, N, 7.64, Br, 43.04.

4.2. General procedure A

Solid **14** (1 mmol) was dissolved in degassed 1% aq. KOH (150 mL) under argon. A 0.05 M solution of potassium peroxodisulfate (2.1 mmol) in degassed 0.5% aq. KOH was added via a syringe pump within 2 h, and the resulting deep violet reaction mixture was immediately worked up as indicated below.

4.3. General procedure B

A solution of **14** (1 mmol) in 1% aq. KOH (250 mL) was stirred vigorously in an open Erlenmeyer flask (1000 mL) at room temperature. After approximately 4–5 h, the solution, yellow in color originally, turned deep violet and was immediately worked up as discussed in the following paragraphs.

4.3.1. 8,9-Dihydroxy-1*H*-benzo[*d*,*e*][1,6]naphthyridin-4-ium monotrifluoroacetate (15, bisdemethylaaptamin-4-ium monotrifluoroacetate). 14 (368 mg, 1.0 mmol) was oxidized according to the general procedure A. The reaction mixture was acidified (pH 3–4) with TFA and diluted with degassed H_2O (100 mL). The green aqueous phase was extracted under argon with EtOAc (400 mL) in a liquid-liquid extractor for 12 h. After phase separation, the organic layer was concentrated in vacuo to afford crude **15** (160 mg, 51%) as a brown solid. Adsorption chromatography (MN Polyamide SC 6-AC; hexanes→EtOAc→1:1:0.001 EtOAc–MeOH–TFA) followed by gel chromatography (Sephadex LH-20; 1:0.001 MeOH–TFA) provided **15** as a brown solid (104 mg, 28%): mp 247°C (dec from 148°C); R_f 0.86 (95:5 MeOH–NH_4OH); UV/Vis (MeOH) λ_{max} (log ϵ)=206 (4.31), 246 (4.43), 271 (4.19), 315 (3.63), 363 (3.67), 409 nm (3.58); (1% aq. KOH) λ_{max} (log ϵ)=231 nm (4.25), 268 (4.29), 364 (3.56), 548 (br, 3.47); (6N HCl): λ_{max} (log ϵ)=243 nm (4.32), ~270 (sh, 4.06), 311 (3.59), 359 (3.54), 397 (3.56); IR (KBr) 3430 (s), 3137 (m), 1679 (m), 1657 (s), 1627 (s), 1611 (s), 1576 (m), 1437 (m), 1394 (w), 1339 (s), 1227 (m), 1204 (s), 1181 (s), 1138 (m), 1080 (m), 723 cm^{-1} (w); ^1H NMR (300 MHz, d_6-DMSO) δ 6.23 (d, J=7.0 Hz, 1H, 3-H), 6.67 (d, J=7.3 Hz, 1H, 6-H), 6.82 (s, 1H, 7-H), 7.13 (dd, J=7.0, 5.0 Hz, 1H, 5-H), 7.69 ('t', J=6.6 Hz, 1H, 2-H), 9.84 (s, br, 1H, OH), 11.31 (s, br, 1H, OH), 11.89 (d, J=5.3 Hz, 1H, HN^1), 12.43 (d, J=3.9 Hz, 1H, HN^4); ^{13}C NMR (75 MHz, d_6-DMSO) δ 97.46 (C-3), 104.30 (C-7), 112.45 (C-6), 116.14 (C-9b), 116.98 (q, $^1J_{CF}$=297.6 Hz, CF_3), 127.82 (C-5), 128.27 (C), 129.28 (C), 130.02 (C), 141.84 (C-2), 150.04 (C), 151.39 (C), 158.54 (q, $^2J_{CF}$=32.3 Hz, $COCF_3$); EI-MS m/z (%)=200 (100) [M^+], 171 (19) [M^+−H–CO], 143 (5) [M^+−2CO–H]; HR-EI-MS calcd for $C_{11}H_8N_2O_2$ 200.0586, found 200.0576; Anal. Calcd for $C_{13}H_9F_3N_2O_4{\cdot}2H_2O$: C, 44.58, H, 3.74, N, 8.00, found C, 44.84, H, 3.61, N, 8.53.

4.3.2. 8,9-Dihydroxy-1*H*-benzo[*d*,*e*][1,6]naphthyridin-4-ium chloride (16, bisdemethylaaptamin-4-ium chloride). 14 (925 mg, 2.51 mmol) was oxidized according to the general procedure A. Immediately, a 1 M aqueous solution of $BaCl_2$ (4.16 g, 20.0 mmol) was added dropwise to the violet reaction mixture. After removal of the precipitate by filtration over a G3 glass frit, the filtrate was acidified (pH 3–4) with conc. HCl and diluted with degassed H_2O (100 mL). The yellow aqueous phase was extracted under argon with EtOAc (400 mL) in a liquid–liquid extractor for 12 h. After phase separation, the organic layer was concentrated in vacuo to afford crude **16** as a brown solid. Ion exchange chromatography [Dowex 50 WX8; H_2O (500 mL)→4N HCl (500 mL)] followed by gel chromatography (2×, Sephadex LH-20; 1:0.00075 MeOH-conc. HCl) provided **16** as a brown solid (288 mg, 49%; 129 mg, 22% after rechromatography): mp>272°C (dec); R_f 0.86 (95:5 MeOH–NH_4OH); UV/Vis (MeOH) λ_{max} (log ϵ)=248 (4.26), 270 (4.20), 315 (3.52), 362 (3.57), 410 nm (3.46); IR (KBr): 3401 (m, br), 3131 (s), 1657 (s), 1626 (s), 1610 (s), 1575 (m), 1437 (m), 1393 (m), 1339 (s), 1227 (m), 1179 (w), 1091 (w), 1080 (w), 939 (w), 847 cm^{-1} (w); ^1H NMR (300 MHz, d_6-DMSO) δ 6.29 (d, J=6.5 Hz, 1H, 3-H), 6.68 (d, J=7.0 Hz, 1H, 6-H), 6.86 (s, 1H, 7-H), 7.13 (dd, J=7.1, 5.0 Hz, 1H, 5-H), 7.70 ('t', J=6.5 Hz, 1H, 2-H), 9.86 (s, br, 1H, OH), 11.12 (s, br, 1H, OH), 11.89 (d, J=6.2 Hz, 1H, HN^1), 12.43 (s, br, 1H, HN^4); ^{13}C NMR (75 MHz, d_6-DMSO) δ 97.39 (C-3), 104.50 (C-7), 112.37 (C-6), 116.10 (C-9b), 127.63 (C-5), 128.19 (C), 129.19 (C), 129.91 (C), 141.69 (C-2), 149.94 (C), 151.18 (C); EI-MS m/z (%)=200 (100) [M^+], 171 (27) [M^+−H–CO], 154 (12), 143 (8) [M^+−2CO–H]; HR-EI-MS calcd for $C_{11}H_8N_2O_2$ 200.0586, found 200.0576.

4.3.3. Bisdesmethyloxyaaptamine (17, 8-hydroxybenzo[*d*,*e*][1,6]naphthyridin-9-one). 14 (250 mg, 0.68 mmol) was oxidized according to the general procedures A or B and worked up as described above for compound **16**. Minor amounts of crude **17** (30 mg, 22%) were obtained as a second fraction. Further gel chromatography (Sephadex LH-20; MeOH) yielded **17** as a green solid (8 mg, 6%): mp >250°C (dec); R_f 0.40 (5:1, Chloroform–MeOH); UV/Vis (MeOH) λ_{max}=210 (s), 230 (s), 295 (m), 360 (m), 375 (m), 410–430 nm (w, sh); IR (KBr) 3436 (s, br), 1630 (s), 1486 (w), 1385 (w), 1285 (s), 1195 (m), 1090 cm^{-1} (m); ^1H NMR (300 MHz, d_6-DMSO) δ 6.97 (s, 1H), 7.63 (d, J=4.5 Hz, 1H), 8.19 (d, J=5.6 Hz, 1H), 9.05 (d, J=4.5 Hz, 1H), 9.07 (d, J=5.6 Hz, 1H); (300 MHz, $CDCl_3$, TMS) δ 6.91 (s, 1H,

7-H), 7.50 (d, J=4.4 Hz, 1H, 6-H), 8.22 (d, J=5.5 Hz, 1H, 2-H), 9.12 (d, J=4.4 Hz, 1H, 5-H), 9.22 (d, J=5.5 Hz, 1H, 3-H); EI-MS: m/z (%)=200 (100) [MH_2^+], 199 (14) [M^++H], 198 (12) [M^+], 170 (47), 160 (31), 142 (26).

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12. (a) Fugmann, B. PhD Thesis, Universität Bonn, 1985. (b) von Nussbaum, F. PhD Thesis, Universität München, 1998.
13. β-Alanine aldehyde (**6**) is the formal Michael addition product of acrolein and ammonia, both precursors in Baldwin's hypothesis for the biosynthesis of manzamine alkaloids (Baldwin, J. E.; Claridge, T. D. W.; Cushaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2661–2663). Alternatively, aminoaldehyde **6** could be derived from aspartic acid by a decarboxylation/reduction sequence.
14. In the biosynthesis of necatorone[2] an analogous biosynthetic pathway, starting from 2-aminobenzaldehyde and tyrosine is followed: von Nussbaum, F.; Eizenhöfer, T.; Klamann, J.-D.; Spiteller, P.; Heinrich, M.; Steglich, W. Unpublished results.
15. 3-(7,8-Dihydroxyquinolin-5-yl)pyruvic acid (**10**) has been proposed by Kashman as a biosynthetic precursor of halitulin: Kashman, Y.; Koren-Goldshlager, G.; Garcia Gravalos, M. D.; Schleyer, M. *Tetrahedron Lett.* **1999**, *40*, 997–1000.
16. Further details of the X-ray analysis (CCDC 154819) are available on request from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).
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