Synthesis of the Marine Natural Product Oroidin and Its *Z*-Isomer†

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Pyrrole−imidazole alkaloids continue to be discovered as biologically active natural products in marine sponges.[1] The various modes of cyclization and dimerization of the $C_{11}N_5$ skeleton of the major metabolite oroidin ((*E*)-**1**, Scheme 1)[2] give rise to a variety of natural products with different geometries and functionalizations, economically based on a common precursor. With respect to structural diversity as a central issue of modern drug discovery,[3] it is an intriguing question if oroidin ((*E*)-**1**) itself or structural analogues thereof can be used to find new modes of cyclization and dimerization in advance to their discovery from natural sources. In 1982, Foley and Büchi biomimetically cyclized 9,10-dihydrooroidin to racemic dibromophakellin.[4] Recent work on the preparation of cyclized pyrrole−imidazole alkaloids includes the total syntheses of hymenialdisine[5] and agelastatin A[6] and incomplete approaches to palau'amine, styloguanidine,[7] and phakellstatin.[8]

Four syntheses of the natural product oroidin ((*E*)-**1**) have been reported to date,[9] while its very interesting (*Z*)-isomer (*Z*)-**1** has not yet been characterized. Ahond, Poupat, et al. prepared keramadine (**2**) as well as imidazole-*N*-tritylated (*Z*)-oroidin, which isomerized to (*E*)-**1** under acidic deprotection conditions.[9c] In this paper, we present an alternative synthetic approach to (*Z*)-oroidin ((*Z*)-**1**), oroidin ((*E*)-**1**), and keramadine (**2**)[10] employing alkyne intermediates (Scheme 1). Our synthesis of (*E*)-**1** for the first time allows stable isotopic labeling of the double bond protons 9-H and 10-H. (*E*)-**1** is of ecological importance because of its function as a chemical defendant in Caribbean sponges of the genus *Agelas*.[11]

The (*Z*)-vinyl double bond of the *N*-methylated keramadine (**2**, Scheme 1) is stereochemically stable, but it was unclear how the *N*-free (*Z*)-oroidin ((*Z*)-**1**) would behave. To date, aplysinamisine I from the sponge *Aplysina aerophoba* is the only natural product exhibiting a (*Z*)-2-amino-5-vinylimidazole subunit.[12] Our syntheses of (*Z*)-oroidin ((*Z*)-**1**) and keramadine (**2**) from *Agelas* sp. take advantage of the Sonogashira alkynylation[13] of the regiochemically pure 4-iodoimidazoles **4**[14] and **10**,[15] respectively (Scheme 1). Pd-catalyzed coupling of **4** resp. **10** with Boc-protected propargylic amine (**3**)[16] gives the alkynylimidazoles **5** and **11**, respectively, in high yields. After azidation of the imidazole 2-position employing *n*-BuLi/tosyl azide[17] and simultaneous removal of the Boc and trityl protecting groups yielding the dihydrochloride **7**, the pyrrole moiety was introduced via coupling with the pyrrolyltrichloromethyl ketone **8**.[18] The overall sequence to (*Z*)-**1** concludes with the double hydrogenation of the 5-alkynyl-2-azidoimidazole **9**, generating both the (*Z*)-double bond and the 2-amino function. In the synthesis of keramadine (**2**), the desired imidazole substitution pattern is achieved via treatment of the alkynylated imidazole **12** with trimethyloxonium tetrafluoroborate, yielding **12** after methanolysis, followed by azidation providing **13**. (*Z*)-Oroidin ((*Z*)-**1**) and keramadine (**2**) were obtained in 30% (five steps) and 25% (six steps) overall yields, respectively.

Clean conversion of (*Z*)- to (*E*)-oroidin is observed under acidic conditions (6 N aqueous HCl/MeOH (1:1) at 60 °C, Scheme 2). When the analogous experiment was performed in an NMR tube in DCl/D_2O, no incorporation of deuterium into positions 9 or 10 of the resulting (*E*)-oroidin ((*E*)-**1**) was observed. This indicates that under the chosen acidic conditions a 5-alkylidene-2-imino tautomer such as **18** is not formed,[9c,17b,19] because this

† This paper is dedicated to Professor Dr. Richard Neidlein on the occasion of his 70th birthday.

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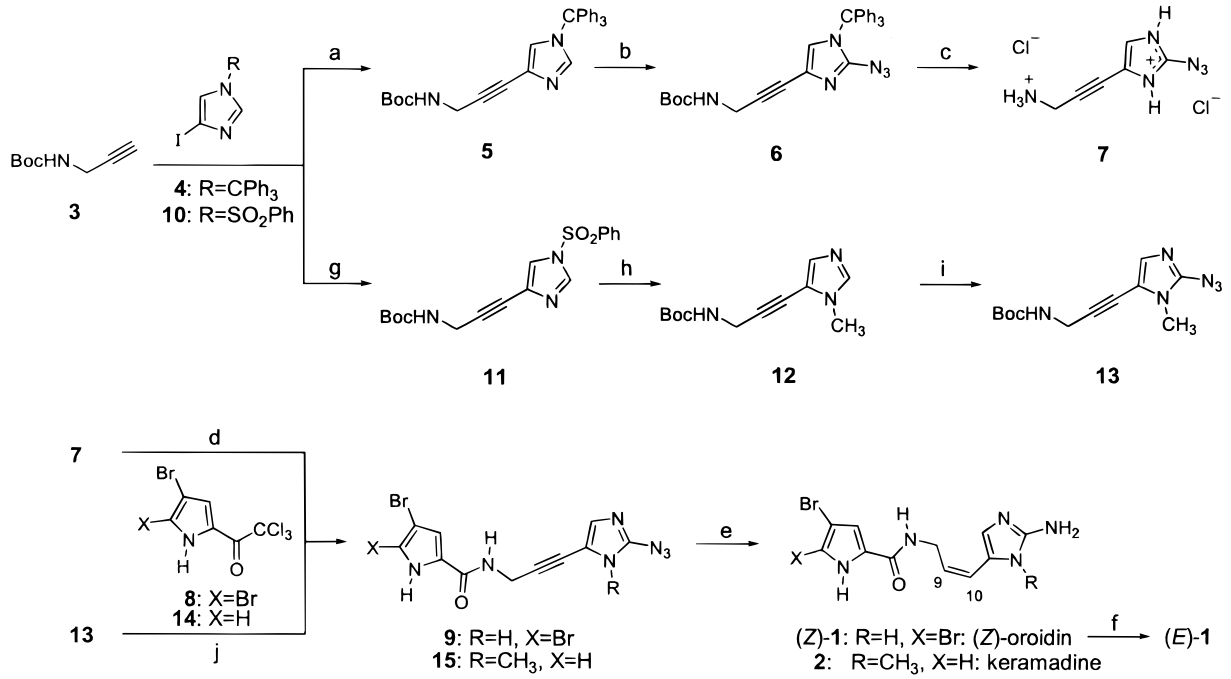
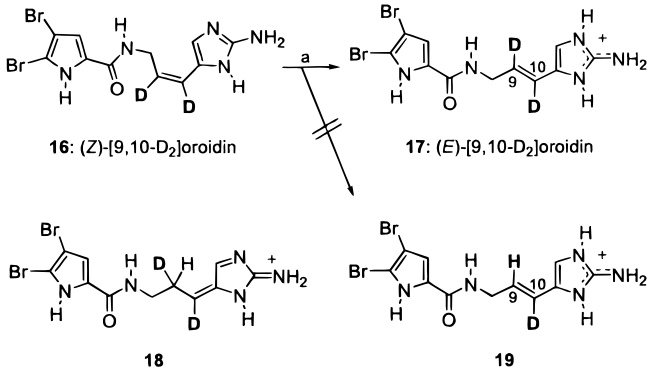
Scheme 1. Unified Synthetic Scheme toward (*Z*)-Oroidin ((*Z*)-1) and Keramadine (2)[a]



[a] Key: (a) **4**, $Pd(PPh_3)_2Cl_2$, CuI, $^iBu_2NH$, THF, rt, 20 h, 85%; (b) *n*-BuLi (2.1 equiv), THF, −78 °C, TsN_3, 10 min, 70%; (c) (1) TFA, CH_2Cl_2, rt, 5 h; (2) HCl(g), Et_2O/MeOH; (d) **8**, DMF, Na_2CO_3, rt, 6 h, 69%; (e) H_2/Pd−Lindlar, 1 atm, rt, 3 h; **9**: MeOH, 74%; **15**: THF/MeOH (5:1), 12 h, 90%; (f) 6 N HCl/MeOH, 60 °C, 6 h, 56%; (g) **10**, $Pd(PPh_3)_2Cl_2$, CuI, $^iBu_2NH$, THF, rt, 24 h, 92%; (h) $(CH_3)_3OBF_4$ (1 equiv), CH_2Cl_2, rt, 2 h, 87%; (i) *n*-BuLi (2.1 equiv), THF, −78 °C, TsN_3, 10 min, 62%; (j) (1) TFA, CH_2Cl_2, rt, 3 h; (2) **14**, DMF, rt, 6 h, 62%.

Scheme 2. Isomerization of (*Z*)-[9,10-D_2]Oroidin ((*Z*)-16) under Acidic Conditions[a]



[a] Key: (a) 6 N HCl/MeOH (1:1), 60 °C, 6 h, 80%.

tautomerization would have led to the deuteration of C-9. Our finding was confirmed on analysis of (*Z*)-[9,10-D_2]-oroidin (**16**), obtained by reduction of the alkyne **9** with D_2. The isomerization product **17** obtained by treatment with HCl/H_2O showed no signals in the ^1H NMR spectrum for any double bond protons (Scheme 2). From the absence of the monodeuterated oroidin **19** it can be concluded that the tautomer **18** does not play a major role, because otherwise exchange of 9-D of (*E*)-**1** would have occurred.

To our surprise, (*Z*)-oroidin ((*Z*)-**1**) is remarkably stable and remains unchanged in an NMR solvent mixture of DMSO-d_6/TFA-d_1 (1:1) at room temperature, while (*E*)-oroidin ((*E*)-**1**) slowly decomposes to a very complex product mixture under the same conditions. For keramadine (**2**), irradiation with a sunlamp (300 W) in DMSO-d_6/TFA-d_1 (1:1) leads to a 3:1 mixture of (*Z*)- and (*E*)-isomers, both of which are stable under the reaction conditions.

In conclusion, a convenient synthesis of both the hitherto unknown (*Z*)-oroidin and the natural product (*E*)-oroidin ((*Z*)-**1**, (*E*)-**1**)) has been developed. The use of alkyne intermediates allows the selective isotopic labeling of the vinyl double bond of both isomers. Our isomerization study indicates that the deuterated derivatives **16** and **17** may be more suitable as advanced precursors for biosynthetic studies than expected. Following a hypothesis recently forwarded by Scheuer et al.,[20] the putative existence of (*Z*)-oroidin ((*Z*)-**1**) as a natural product would explain the stereochemistry of the dimeric pyrrole-imidazole alkaloid konbu'acidin.[21]

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were acquired at 250 or 360 (^1H) MHz and 62.9 or 90.6 (^{13}C) MHz. Chemical shifts refer to those of residual solvent signals based on $\delta_{TMS} = 0$. All measurements were carried out at 300 K. Mass spectra were taken in EI or FAB (nitrobenzyl alkohol as matrix) mode. Solvents were purified and dried according to standard procedures.[22] Column chromatography was carried out on silica gel (silica gel 60 (60−200 mesh), Merck) and on Sephadex LH20 (Pharmacia). Thin-layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254} Merck).

General Procedure for the Sonogashira Alkyne Coupling. Under an argon atmosphere, Boc-protected propargylamine (**3**, 1.5 equiv) was added to a solution of the protected 4-iodoimidazole (1 equiv), $Pd(PPh_3)_2Cl_2$ (0.025 equiv), CuI (0.05 equiv), and diisobutylamine (3 equiv) in dry THF. After being stirred at room temperature for 20 h, the reaction mixture was filtered and concentrated in vacuo to yield a dark residue that was chromatographed on silica gel with the eluent specified.

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[3-(1-Triphenylmethyl-1*H*-imidazol-4-yl)prop-2-ynyl]carbamic Acid *tert*-Butyl Ester (5). The iodoimidazole **4** (10 g, 23 mmol) and the alkyne **3** (7.1 g, 46 mmol) were coupled according to the general procedure. Purification by column chromatography (silica gel, petroleum ether/CH_2Cl_2/ether (5/4/1)) afforded a pale yellow solid (9.0 g, 85%) that was recrystallized from ethanol: mp 210 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.36−7.31 (m, 9H), 7.16−7.08 (m, 6H), 7.00 (s, 1H), 4.88 (s, 1H), 4.10 (d, J = 5.3 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.2, 142.0, 138.9, 129.7, 128.3, 128.2, 125.6, 85.6, 79.7, 77.2, 75.7, 31.2, 28.3; IR (KBr) 3266, 1710, 1521 cm^{-1}; EIMS *m*/*z* (rel intensity) 463 (0.4) [M$^+$], 243 (100), 165 (43), 57 (14); HRMS (FAB, PEG) calcd for $C_{30}H_{29}N_3O_2Na$ 486.2157, found 486.2171.

[3-(1-Benzenesulfonyl-1*H*-imidazol-4-yl)prop-2-ynyl]carbamic Acid *tert*-Butyl Ester (11). The iodoimidazole **10** (3 g, 9 mmol) and the alkyne **3** (3.5 g, 23 mmol) were coupled according to the general procedure. Purification by column chromatography (silica gel, petroleum ether/CH_2Cl_2/ether (5/10/2)) afforded a colorless solid (2.99 g, 92%) that was recrystallized from ethanol: mp 145 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.95−7.90 (m, 3H), 7.75−7.65 (m, 1H), 7.60−7.55 (m, 2H), 7.39 (d, J = 1.2 Hz, 1H), 4.10 (d, J = 5.6 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.1, 137.5, 136.3, 135.1, 129.9, 127.3, 126.6, 120.3, 87.8, 78.0, 74.7, 31.00, 28.3; IR (KBr) 3352, 3141, 3119, 2987, 1679, 1511 cm^{-1}; EIMS *m*/*z* (rel intensity) 361 (0.1) [M$^+$], 305 (14), 164 (100), 120 (12), 93 (14), 77 (42), 57 (43); HREIMS calcd for $C_{17}H_{19}N_3O_4S$ 361.1096, found 361.1095. Anal. Calcd for $C_{17}H_{19}N_3O_4S$: C, 56.50; H, 5.30; N, 11.63. Found: C, 56.53; H, 5.34; N, 11.43.

[3-(3-Methyl-3*H*-imidazol-4-yl)prop-2-ynyl]carbamic Acid *tert*-Butyl Ester (12). To a solution of **11** (830 mg, 2.3 mmol) in dry CH_2Cl_2 (30 mL) was added $(CH_3)_3OBF_4$ (340 mg, 2.3 mmol). After the mixture was stirred at room temperature for 2 h, methanol (10 mL) was added. The solvent was removed, and the residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH (20/1)) to yield **12** (468 mg, 87%) as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.22 (s, 1H), 4.93 (s, 1H), 4.18 (d, J = 5.8 Hz, 2H), 3.64 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 155.3, 138.2, 134.5, 115.7, 93.0, 80.2, 71.2, 31.6, 32.0, 28.4; IR (KBr) 3324, 2977, 1704 cm^{-1}; EIMS *m*/*z* (rel intensity) 235 (11), 179 (77), 134 (100), 119 (51), 57 (70); HREIMS calcd for $C_{12}H_{17}N_3O_2$ 235.1321, found 235.1320.

General Procedure for Azidation of the Alkynyl Imidazoles. A solution of the imidazole (**5** or **12**) in dry THF was cooled to −78 °C, followed by addition of *n*-BuLi (2.1 equiv, 1.6 M solution in hexane). The cooling bath was removed for 5 min. After the mixture was recooled to −75 °C, tosyl azide (1.5 equiv) in THF was added to the stirred solution. After 10 min, aqueous buffer (pH 7) was added, and the reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography.

[3-(2-Azido-3-triphenylmethyl-3*H*-imidazol-4-yl)prop-2-ynyl]carbamic Acid *tert*-Butyl Ester (6). Azidation of **5** (5.5 g, 11.9 mmol) yielded **6** as a pale yellow solid (4.2 g, 70%; silica gel, petroleum ether/ethyl acetate (3/1)): mp 75−80 °C decomp; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.25 (m, 9H), 7.15−7.05 (m, 6H), 6.85 (s, 1H), 4.72 (s, 1H), 4.11 (d, J = 5.5 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 157.8, 142.3, 141.3, 129.6, 128.0, 124.8, 119.6, 86.2, 76.4, 75.7, 60.4, 31.1, 28.4; IR (KBr) 2133, 1718 cm^{-1}; FABMS *m*/*z* (rel intensity) 527 (100) [M + Na$^+$], 477 (71), 421 (63); HRFABMS calcd for $C_{30}H_{28}N_6O_2Na$ 527.2171, found 527.2164.

[3-(2-Azido-3-methyl-3*H*-imidazol-4-yl)prop-2-ynyl]carbamic Acid *tert*-Butyl Ester (13). Azidation of **12** (420 mg, 1.8 mmol) yielded **13** (310 mg, 62%; silica gel, petroleum ether/ethyl acetate (4/1)): mp 126 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.07 (s, 1H), 4.82 (s, 1H), 4.16 (d, J = 5.4 Hz, 2H), 3.38 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 155.3, 141.0, 132.3, 114.7, 93.0, 80.2, 71.3, 31.3, 30.0, 28.3; IR (KBr) 3324, 2979, 2146, 1682 cm^{-1}; EIMS *m*/*z* (rel intensity) 276 (14) [M$^+$], 193 (6), 192(52), 160 (15), 139 (25), 57 (100); HREIMS calcd for $C_{12}H_{16}N_6O_2$ 276.1335, found 276.1334.

3-(2-Azido-1*H*-imidazol-4-yl)prop-2-ynylamine Dihydrochloride (7). TFA (6 mL) was slowly added to a solution of **7** (1.5 g, 2.98 mmol) in CH_2Cl_2 (20 mL). After complete deprotection monitored by TLC (silica gel, $CHCl_3$/MeOH/NH_3 (40:10:1)), the solvent was removed in vacuo. The crude product was purified by column chromatography (Sephadex LH20, methanol). Addition of gaseous HCl to a methanol/ether solution of the free base, followed by filtration, yielded **7** as a colorless solid (0.61 g, 88%): mp 152 °C dec; ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.66 (s, H), 7.38 (s, 1H), 6.38 (s), 3.93 (m, 2H); ^{13}C NMR (91 MHz, DMSO-d_6) δ 145.5, 128.8, 122.8, 88.2, 84.2, 34.0; EIMS *m*/*z* (rel intensity) 162 (4) [M$^+$], 99 (57), 61 (10), 59 (51), 57 (100); IR (KBr) 2889, 2153, 1620, 1564 cm^{-1}; UV (MeOH) λ_{max} (lg ϵ) 252 nm (4.11) and 206 nm (3.75); HREIMS calcd for $C_6H_6N_6$ 162.0654, found 162.0654.

4,5-Dibromo-1*H*-pyrrole-2-carboxylic Acid [3-(2-Azido-3*H*-imidazol-4-yl)prop-2-ynyl]amide (9). 4,5-Dibromopyrrol-2-yltrichloromethyl ketone (**8**, 1.57 g, 4.25 mmol) was added to a solution of **7** (1 g, 4.25 mmol) and Na_2CO_3 (450 mg, 4.25 mmol) in dry DMF (10 mL) at room temperature under argon. After being stirred for 6 h, the reaction mixture was concentrated in vacuo and suspended in water. The precipitate was filtered, dried in vacuo, and purified by column chromatography (silica gel, $CHCl_3$/MeOH (20/1)) to yield **9** as a brownish solid (1.22 g, 69%): mp 132 °C dec; ^{1}H NMR (360 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.64 (t, J = 5.4 Hz, 1H), 7.23 (s, 1H), 6.96 (s, 1H), 4.24 (d, J = 5.4 Hz, 2H). ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 158.5, 139.9, 127.6, 120.9, 120.6, 113.0, 105.1, 98.0, 85.9, 76.4, 28.6; IR (KBr) 3287, 2145, 1638 cm^{-1}; FABMS *m*/*z* (rel intensity) 412/414/416 (3/7/3) [M$^+$ + H]; HRFABMS calcd for $C_{11}H_8N_7O^{79}Br^{81}Br$ 413.9137, found 413.9135.

4-Bromo-1*H*-pyrrole-2-carboxylic Acid [3-(2-Azido-3-methyl-3*H*-imidazol-4-yl)prop-2-ynyl]amide (15). A solution of **13** (1.3 g, 4.7 mmol) in CH_2Cl_2 (20 mL) under argon was treated with TFA (6 mL) and stirred at room temperature for 3 h. After complete deprotection was confirmed by TLC, the solvents were evaporated. The residue was suspended in DMF (10 mL) and neutralized with Na_2CO_3. To the stirred suspension was added 4-bromopyrrol-2-yltrichloromethyl ketone (**14**, 2.05 g, 7.05 mmol) at room temperature under argon. After being stirred for 6 h, the reaction mixture was concentrated in vacuo and suspended in water. The precipitate was filtered, dried in vacuo, and purified by column chromatography (silica gel, $CHCl_3$/MeOH (20/1)) to yield a pale brown solid (1.01 g, 62%): mp 112 °C dec; ^{1}H NMR (360 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.65 (t, J = 5.9 Hz, 1H), 7.14 (s, 1H), 7.00 (m, 1H), 6.88 (m, 1H), 4.30 (s, 2H), 3.33 (s, 3H); ^{13}C NMR (90.6 MHz, DMSO-d_6) δ 159.2, 140.1, 131.5, 126.2, 121.6, 114.5, 111.8, 94.9, 94.3, 69.9, 29.8, 28.7; FABMS *m*/*z* (rel intensity) 348/350 (23/22) [M$^+$ + H]; HRFABMS calcd for $C_{12}H_{11}N_7O^{79}Br$ 348.0208, found 348.0222. Anal. Calcd for $C_{12}H_{10}N_7O_1Br$ C: 41.40; H, 2.89; N, 26.17. Found: C, 41.13; H, 3.05; N, 26.37.

General Procedure for Double Lindlar Hydrogenation. A solution of the alkynyl azido imidazole in THF/MeOH was hydrogenated in the presence of Lindlar catalyst (5% Pd on $CaCO_3$, poisoned with Pb) at room temperature at atmospheric pressure. After complete hydrogenation (monitored by TLC) the reaction mixture was filtered and the solvent was removed. Purification by column chromatography yielded the free base.

(*Z*)-Oroidin ((*Z*)-1). According to the general procedure (Lindlar catalyst, 80 mg; MeOH, 40 mL), **9** (200 mg, 0.48 mmol) was hydrogenated. Purification by column chromatography (Sephadex LH20, methanol) afforded a colorless solid (140 mg, 74%, $Z/E \approx$ 16:1): ^{1}H NMR (360 MHz, methanol-d_4) δ 6.82 (s, 1H), 6.81 (s, 1H), 6.20 (d, J = 11.5 Hz, 1H), 5.75 (dt, J = 11.5, 6.5 Hz, 1H), 4.07 (dd, J = 6.5, 1.5 Hz, 2H); ^{13}C NMR (90.6 MHz, DMSO-d_6/TFA-d_1 (1:1)) δ 162.7, 148.2, 130.6, 128.5, 124.4, 116.9, 114.9, 113.0, 105.6, 99.5, 39; ^{13}C NMR (90.6 MHz, methanol-d_4) δ 162.3, 149.1, 131.0, 128.6, 125.3, 117.3, 114.9, 113.6, 106.8, 100.4, 39.5; UV (MeOH) λ_{max} (log ϵ) 208 (4.02), 278 nm (4.31); FABMS *m*/*z* (rel intensity) 388/390/392 (17/35/20) [M$^+$ + H]; HRFABMS calcd for $C_{11}H_{12}N_5O^{79}Br^{81}Br$ 389.9389, found 389.9401.

Keramadine (2). According to the general procedure (Lindlar catalyst, 40 mg; THF/MeOH (5/1, 10 mL)), **15** (100 mg, 0.29 mmol) was hydrogenated. Purification afforded a colorless solid (84 mg, 90%). Addition of TFA to the methanolic solution of the free base, followed by concentration in vacuo yielded the trifluoroacetate of **2** as a colorless solid: mp 180 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 12.59 (s), 11.85 (s), 8.46 (t, J = 5.9 Hz, 1H), 7.78 (s, 1H), 7.11 (s, 1H), 6.99 (m, 1H), 6.85 (m, 1H), 6.26 (d, J

= 11.7 Hz, 1H), 5.86 (dt, J = 5.9, 11.7 Hz, 1H), 4.02 (m, 2H), 3.39 (s, 3H); ^{13}C NMR (90.6 MHz, DMSO-d_6) δ 159.5, 146.5, 133.4, 126.6, 123.7, 121.3, 113.7, 111.8, 111.5, 94.9, 37.6, 29.2; IR (KBr) 3300, 3148, 1683, 1558 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 222 (3.91), 272 nm (4.15); EIMS m/z (rel intensity) 323/324/325/326 (62/9/60/5) [M$^+$], 245 (8) [M$^+$ − Br], 151 (100); HREIMS calcd for $C_{12}H_{14}N_5O^{79}Br$ 323.0382, found 323.0383.

Oroidin ((*E*)-1). (*Z*)-Oroidin (**1**) (200 mg, 0.51 mmol) was dissolved in methanol (6 mL). After addition of aqueous HCl (25%, 4 mL), the solution was heated for 6 h at 60 °C. Purification by column chromatography (Sephadex LH20, methanol) afforded a colorless solid (111 mg, 56%): ^{1}H NMR (360 MHz, methanol-d_4) δ 6.82 (s, 1H), 6.74 (s, 1H), 6.30 (d, J = 16.4 Hz, 1H), 6.01 (dt, J = 16.4, 5.5 Hz, 1H), 4.04 (dd, J = 5.5, 1.5 Hz, 2H); ^{13}C NMR (90.6 MHz, methanol-d_4) δ 161.6, 149.3, 128.6, 127.6, 127.0, 117.6, 114.3, 111.9, 106.3, 100.0, 41.6; UV (MeOH) λ_{max} (log ϵ) 203 (4.30), 275 nm (4.33); FABMS m/z (rel intensity) 388/390/392 (16/29/17); HRFABMS calcd for $C_{11}H_{12}ON_5{}^{79}Br^{81}Br$ 389.9389, found 389.9421.

Deuteration of 9. According to the general procedure (Lindlar catalyst, 20 mg; MeOH, 10 mL), **9** (100 mg, 0.24 mmol) was reacted with deuterium. Purification by column chromatography (Sephadex LH20, methanol) afforded (*Z*)-[9,10-D$_2$]oroidin (**16**) as a colorless solid (47 mg, 50%): ^{1}H NMR (360 MHz, methanol-d_4) δ 6.84 (s, 1H), 6.82 (s, 1H), 4.08 (s, 2H); FABMS m/z (rel intensity) 390/392/394 (50/100/49); HRFABMS calcd for $C_{11}H_{10}D_2ON_5{}^{79}Br^{81}Br$ 391.9514, found 391.9492.

Isomerization of 16. (*Z*)-[9,10-D$_2$]Oroidin (**16**) (40 mg, 0.10 mmol) was dissolved in 3 mL of methanol. After addition of 2 mL of aqueous HCl (25%), the solution was heated for 6 h at 60 °C. Purification by column chromatography (Sephadex LH20, methanol) afforded **17** as a colorless solid (21 mg, 53%): ^{1}H NMR (360 MHz, methanol-d_4) δ 6.82 (s, 1H), 6.73 (s, 1H), 4.04 (s, 2H); FABMS m/z (rel intensity) 390/392/394 (12/19/10); HRFABMS calcd for $C_{11}H_{10}D_2ON_5{}^{79}Br^{81}Br$ 391.9514, found 391.9514.

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Supporting Information Available: NMR spectra for compounds (*Z*)-**1**, (*E*)-**1**, **2**, **16**, and **17**; HPLC elution profiles and mass spectra of **16** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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