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The Alkyne Pathway to Keramadine from the Marine Sponge *Agelas* sp.

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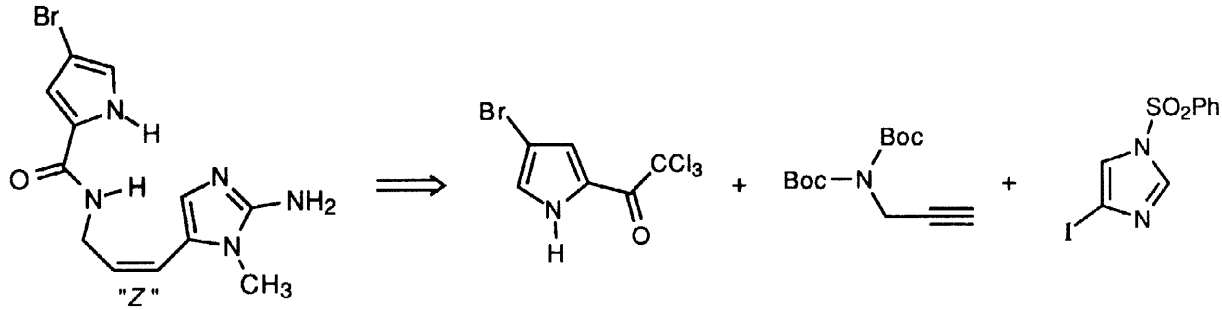
Abstract: A novel synthesis of the pyrrole-imidazole alkaloid keramadine (**1**) from the marine sponge *Agelas* sp. is described. Regiocontrol is reached by the Pd-catalyzed alkynylation of 1-benzenesulfonyl-4-iodoimidazole, followed by N-methylation employing trimethyloxonium tetrafluoroborate. Key step is the double hydrogenation of a 5-alkynyl-2-azidoimidazole which simultanously generates the (*Z*)-double bond and the amino function of **1**.

Keywords: alkaloids; aminoimidazoles; marine natural products; total synthesis.

Marine sponges have been a rich source of structurally diverse pyrrole-imidazole alkaloids. The common skeleton of these secondary metabolites was first observed in oroidin[1] and several modes of its cyclization and dimerization have been found since then in nature.[2] Keramadine (**1**) was isolated from *Agelas* sp. in low yields as an antagonist on serotonergic receptors of the rabbit aorta.[3] From a synthetic point of view, **1** appears to be a promising starting material for partial syntheses of cyclized oroidin alkaloids such as the agelastatins[4].



1: keramadine 2 3 4

Scheme 1. Retrosynthesis of the marine natural product keramadine (1).

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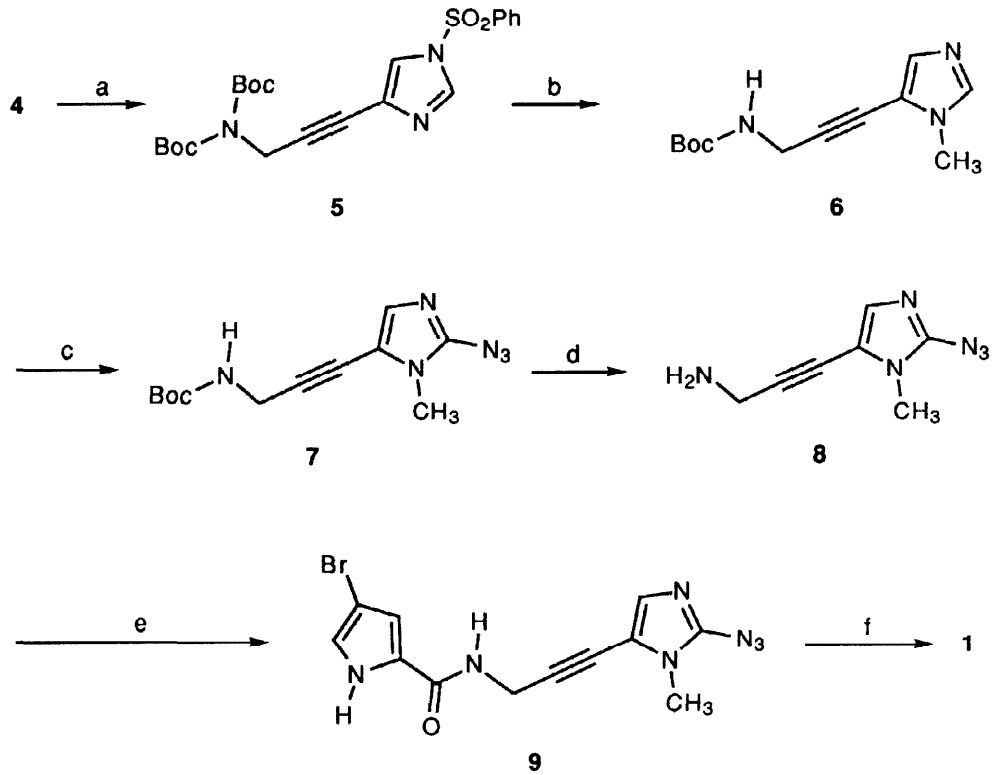
Among the non-cyclized oroidin alkaloids, solely keramadine (**1**) possesses a (Z)-double bond in vinyl position of a trisubstituted imidazole ring. A synthesis designed to render gram quantities of **1** had to be short and regio- as well as stereoselective.

Our novel synthesis of keramadine (**1**) for the first time employs alkyne precursors to build up a trisubstituted (Z)-2-amino-5-vinylimidazole (scheme 1).[5] While N-unsubstituted analogues could undergo double bond isomerization through diazafulvene intermediates[6], the N-methylation of the natural product keramadine (**1**) seems to stabilize its configuration. Therefore, the methylation of its imidazole ring had to take place prior to the stereoselective generation of the vinyl double bond. 1-Benzenesulfonyl-4-iodoimidazole (**4**) appeared to be succeptible to both alkynylation and regioselective methylation.[7] As the alkyne component, fully Boc-protected propargylic amine (**3**) was chosen. The pyrrole unit could be introduced employing the trichloromethyl ketone **2**.[8]



Scheme 2. The stereoselective alkyne pathway to keramadine (**1**). a: **3**, $Pd(PPh_3)_2Cl_2$ (0.05 equiv.), CuI (0.1 equiv.), DIPA (3.0 equiv.), THF, r. t., 24 h, 90 %; b: $(CH_3)_3OBF_4$ (1.5 equiv.), CH_2Cl_2, r. t., 12 h, 80 %; c: *n*-BuLi (2.1 equiv.), THF, -75° C, $TosN_3$ (1.5 equiv.), 10 min, 60 %; d: TFA (40 equiv.), CH_2Cl_2, r. t., 24 h, quant.; e: **2** (1.1 equiv.), DMF, r. t., 8 h, 60 % from **8**; f: H_2/Pd-Lindlar, THF/MeOH (5:1), r. t., 24 h, quant. conversion, 55 % after chromatography.

Pd-catalyzed coupling of **3** and **4** was achieved in 90 % yield in the presence of copper iodide (Sonogashira conditions[9]) providing regiochemically pure 4-alkynylimidazole **5** (scheme 2). The benzenesulfonyl group serves the double purpose of both activating the imidazole ring for the carbon-carbon bond formation and protecting the reaction product against quaternization in the subsequent methylation. Treatment of **5** with trimethyloxonium tetrafluoroborate ("Meerwein's salt") in dry dichloromethane, followed by methanolysis of the intermediate imidazolium salt led to the regiochemically pure 1-methyl-5-alkynylimidazole **6**. Simultanously, one of the two Boc protecting groups was removed. For the introduction of the nitrogen substituent in the 2-position of the imidazole, azidation was preferred over diazotation. Deprotonation of **6** with *n*-butyllithium and treatment with tosyl azide[10] gave the 2-azidoimidazole **7** in a yield of 60 %. After quantitative removal of the carbamate (TFA), the skeleton of keramadine (**1**) was completed by treatment of **8** with the monobrominated pyrrolyltrichloromethyl ketone **2**. In the final step, double hydrogenation of **9** (Lindlar catalyst) simultanously reduced the azide function to the amino group and the triple bond to the desired (*Z*)-double bond.

It proved to be important to use a mixture of THF and methanol as solvent in order to avoid overreduction. The ratio of isomers (*Z*:*E* ≈ 18:1) could only be determined by integration of the signals of the methylene group (δ 4.14 *resp.* δ 4.04) in [D_4]methanol, but not in [D_6]DMSO which was used as a solvent in course of the original structure elucidation of keramadine (**1**).[3] The overall yield of our six step synthesis is 14 %.[11] By keeping the double bond masked as a triple bond until the last step of the sequence, the risk of its isomerization was minimized. The alkyne pathway appears to be especially well-suited for the preparation of tritiated keramadine (**1**) as a precursor in biosynthetic studies.[12]

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[11] Selected experimental data. **5**: mp. 120 °C. - ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.99-7.86 (m, 3H, *o*-arom. H, N=C*H*N), 7.76-7.66 (m, 1H, *p*-arom. H), 7.65-7.52 (m, 2H, *m*-arom. H), 7.38 (d, *J* = 1.4 Hz, 1H, NC*H*=CCN), 4.54 (s, 2H, NCH_2C=), 1.52 (s, 18H, 2 C(CH_3)$_3$). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 151.6, 137.6, 136.3, 135.2, 130.0, 127.4, 126.9, 120.5, 87.5, 83.1, 74.2, 36.4, 28.1. - MS (EI, 70 eV): *m/z* (%) = 461 (0.02) [M$^+$], 446 (0.2), 405 (2), 305 (85), 164 (100). - IR (KBr): $\tilde{\nu}$ = 3136 cm^{-1}, 3116, 2977, 1756, 1711. - $C_{22}H_{27}N_3O_6S$ (461.53): calcd. C 57.25, H 5.90, N 9.10; found C 57.13, H 5.90, N 8.98.

9: mp. 112 °C (dec.). - ^{1}H NMR (360 MHz, $CDCl_3$/[D$_4$]MeOH): δ = 7.40 (s, 1H, NC=C*H*N), 6.91 (d, *J* = 1.6 Hz, 1H, HNC*H*CBr), 6.77 (d, *J* = 1.6 Hz, 1H, BrCC*H*C), 4.38 (s, 2H, HNCH_2C=), 3.41 (s, 3H, NCH_3). - ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 160.9, 140.5, 132.8, 125.9, 121.8, 115.3, 111.5, 97.1, 92.0, 72.1, 30.1, 30.0.- MS (FAB, NBA); *m/z* (%) = 348/350 (23/22) [M$^+$ + H]. - HRFABMS ($C_{12}H_{11}N_7O^{79}Br$): calcd. 348.0208; found 348.0222.

1: mp. 180 °C (183-187 °C[3]). - ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 12.59 (s, NH), 11.85 (s, NH), 8.46 (t, *J* = 5.9 Hz, 1H, NH), 7.78 (s, 1H, NH), 7.11 (s, 1H, C=C*H*N), 6.99 (m, 1H, NHC*H*=CBr), 6.85 (m, 1H, CBrC*H*=C), 6.26 (d, *J* = 11.7 Hz, 1H, CH_2CH=C*H*C), 5.86 (dt, *J* = 5.9, 11.7 Hz, 1H, CH_2C*H*=CH), 4.02 (m, 2H, NHCH_2CH), 3.39 (s, 3H, NCH_3). The ^{1}H NMR chemical shifts obtained at 70 °C and the ^{13}C NMR chemical shifts are in accordance with those reported in ref. 1. - MS (EI, 70 eV): *m/z* (%) = 323/324/325/326 (62/9/60/5) [M$^+$], 245 (8) [M$^+$ - Br], 151 (100). - HREIMS ($C_{12}H_{14}N_5O^{79}Br$): calcd. 323.0382; found 323.0383.

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