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Synthesis of the marine sponge alkaloid oroidin and its analogues via Suzuki cross-coupling reactions

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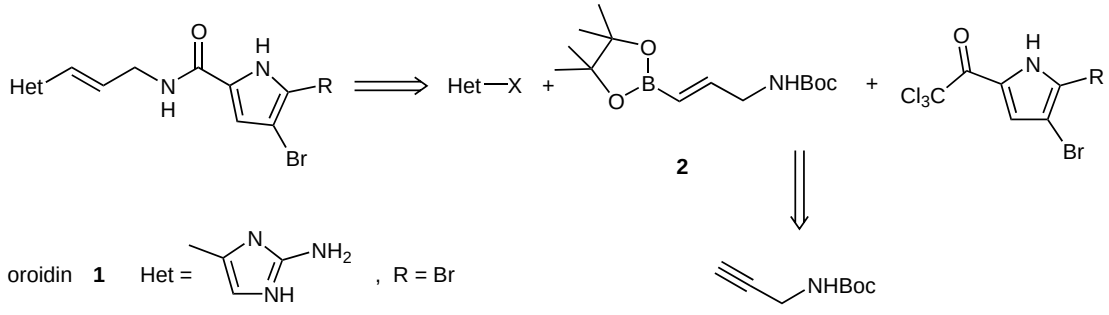
Abstract—A new synthesis of the natural product oroidin was described using a Suzuki coupling reaction as key step. This method was extended to the synthesis of various analogues of oroidin and hymenidin.

Marine sponges are the source of the greatest diversity of marine natural products. Among these is the pyrrole–imidazole alkaloid family, where the common skeleton is observed in oroidin **1**.[1] Various modes of cyclization give rise to a large number of natural products with different geometries and functionalizations. Many of these compounds display a broad range of biological properties including antibacterial, antiinflammatory, anticancer and antiviral activities. With respect to the discovery of new biologically active molecules, it is therefore promising to explore new approaches for the synthesis of oroidin **1** and its structural analogues. Four syntheses of this natural product have been hitherto reported. These previous preparations were based on a Wittig–Schweizer reaction,[2] a cyclization reaction of an α-haloketone with *N*-acetylguanidine,[3] and the preparation and transformation of 2-amino-4,5-dialkoxy-4,5-dihydroimidazoline.[4] While this work was in progress, another route has been described using a Sonogashira alkynylation.[5] In this paper, we present an alternative approach for the synthesis of oroidin **1** and its analogues, which involves the vinylboronate **2** as key building block. Scheme 1 illustrates a retrosynthetic analysis, in which the (*E*)-allylic amide is assembled in a stereoselective manner via a palladium-catalyzed cross-coupling reaction.

The boronate **2** was easily prepared from the commercially available propargylamine. Protection as a *N*-Boc derivative[6] was followed by hydroboration with diisopinocampheylborane (Ipc_2BH), prepared in situ from (−)-α-pinene and BH_3–SMe_2. Dealkylation with acetaldehyde and ester exchange with pinacol was then effected. The stable isomerically pure (*E*)-boronic ester **2** was obtained in a 54% yield after purification by silica gel chromatography.[7] *N*-Trityl-4(5)-iodoimidazole **3** was separately prepared by iodination of imidazole, followed by sodium sulfite reduction of the triiodo



Scheme 1.

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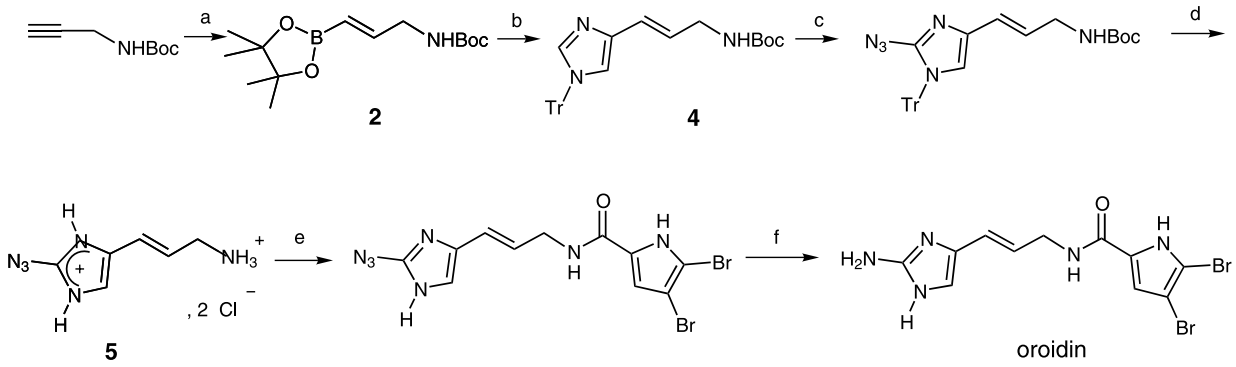
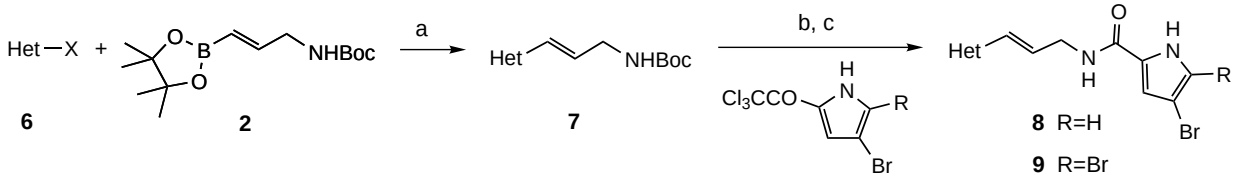


Scheme 2. *Reagents and conditions*: (a) (i) Ipc_2BH, THF, 0°C, 6 h, (ii) CH_3CHO (30 equiv.), rt, 16 h, (iii) pinacol (1.2 equiv.), THF, rt, 16 h, 54%; (b) **3**, $Pd(OAc)_2$, $(o\text{-Tolyl})_3P$ (5%), K_2CO_3 (2 M, 2.5 equiv.), DME, reflux, 18 h, 51%; (c) (i) *n*-BuLi (3 equiv.), THF, −78°C, 15 min, (ii) TsN_3 (1.5 equiv.), −78°C, 15 min, 64%; (d) MeOH (50 equiv.), CH_3COCl (50 equiv.), AcOEt, rt, 18 h, 95%; (e) 4,5-dibromo-2-trichloroacetylpyrrole, Na_2CO_3 (1 equiv.), DMF, rt, 6 h, 25%; (f) H_2/Pd-Lindlar, MeOH, 1 atm, rt, 3 h, 89%.

derivative and finally tritylation, as reported previously.[8] Palladium-catalyzed coupling of **3** with vinyl boronate **2** gives the alkenylimidazole **4** in only 26% yield using the usual catalyst $Pd(PPh_3)_4$ and potassium carbonate in DME.[9] No significant improvement was observed by modifying solvent and base, probably due to a partial deprotection of the trityl group, which was then responsible for the unsatisfactory purification of the final product. The use of $Pd(Oac)_2$ and $(o\text{-Tolyl})_3P$ as catalytic system increased the yield up to 51% with no detectable (*Z*)-isomer. After azidation of the imidazole 2-position employing *n*-BuLi/tosyl azide according to reported procedures,[2b,5] simultaneous removal of the Boc and trityl protecting groups by dry HCl, generated from MeOH and acetyl chloride, afforded the dihydrochloride **5**. The pyrrole moiety was then introduced by coupling with 4,5-dibromo-2-trichloroacetylpyrrole.[10] Clean reduction of the azido function by hydrogenation on Lindlar catalyst led to oroidin **1** (Scheme 2).[11]

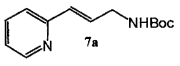
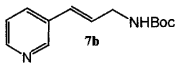
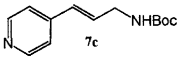
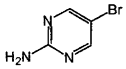
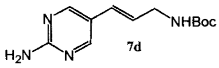
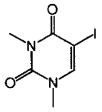
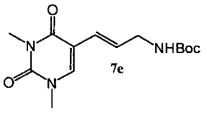
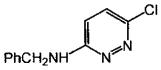
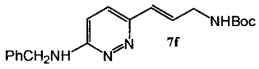
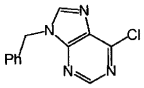
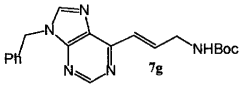
Having in hand a convenient method to prepare the oroidin skeleton, we then extended this approach to the synthesis of analogues of oroidin (R = Br) and hymenidin (R = H) (Scheme 3). We first replaced the aminoimidazole moiety with various heterocycles ranging in size and basicity. All these modifications were effected from the boronate **2**. Suzuki cross-coupling reactions with appropriate functionalized heterocycles (Het–Hal **6a**–**g**) were realized in the presence of $Pd(PPh_3)_4$ as catalyst and potassium carbonate in DME. Different haloheterocycles were used: commercially available 2- and 3-bromopyridin, 4-iodopyridin (entries a, b and c), 2-amino-5-bromopyrimidin (entry d), 5-iodo-1,3-dimethyluracil (entry e) while *N*-benzyl-6-chloro-3-aminopyridazin has been first prepared from benzylamine and 3,6-dichloropyridazin (entry f)[12] and 9-benzyl-6-chloropurine by benzylation of 6-chloropurine with benzyl bromide[13] (entry g) (Table 1). The *N*-Boc allylamines **7a**–**g** were obtained in good to moderate yields (43–82%) after purification by column chromatography with no detectable traces of the (*Z*) isomers.[14] Deprotection of the amino group was effected for some of them, using the same procedure as previously described for oroidin. Acylation of the resulting hydrochloride with 4-bromo- or 4,5-dibromo-2 trichloroacetylpyrrole proceeded in the presence of sodium carbonate in DMF in low unoptimized yields.[15]

In summary, oroidin and several of its analogues were synthesized stereoselectively via Suzuki reaction as key step, followed by an amide coupling with pyrrol-2-yltrichloromethyl ketone. In view of the recent preparation of diversely substituted alkenyl boronates **2**[16] and the large availability of heterocycles bearing an halide or a carboxylic acid group, this approach should allow the preparation of other structurally diversified analogues of some marine sponge alkaloids.



Scheme 3. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, 5%, K_2CO_3 (2 M, 2.5 equiv.), DME reflux, 18 h (see Table 1 for yields); (b) MeOH (50 equiv.), CH_3COCl (50 equiv.), AcOEt, rt, 6 h, quantitative; (c) 4-bromo- or 4,5-dibromo-2 trichloroacetylacetylpyrrole, Na_2CO_3, DMF, rt, 6 h, R = H: **8a** 23%; **8d** 43%; **8e** 27%; **8f** 29%. R = Br: **9a** 26%; **9e** 30%.

Table 1. Synthesis of *N*-Boc allylamines **7a–g** by Suzuki cross-coupling reactions

Entry	Het-X	Compound 7	Yield (%)[a]
a			65
b			82
c			70
d			43
e			56
f			69
g			65

[a] Yield of isolated product after purification by column chromatography.

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7. Experimental procedure: Borane–methyl sulfide complex (1.7 mL, 16.8 mmol) was added dropwise to a solution of (−)-α-pinene (5.4 mL, 33.6 mmol) in 10 mL of freshly distilled THF at 0°C under a nitrogen atmosphere. The mixture was kept at 0°C for 1 h and then allowed to reach rt by removing the cold bath. After 2 h, the resulting suspension of diisopinocampheylborane was cooled to 0°C when *N*-Boc-propargylamine (2.0 g, 12.9 mmol) in 5 mL of THF was slowly added. The reaction mixture was kept at rt for 16 h. The mixture was cooled to 0°C and freshly distilled acetaldehyde (0.25 mmol, 14.3 mL) was added dropwise. After 5 h at rt, the excess of acetaldehyde and the solvent were removed under reduced pressure. 2,3-Dimethylbutane-2,3-diol (2.4 g, 20.1 mmol) and 30 mL of heptane were added and the mixture was kept at rt for 3 h. After washing the solution with water (2×10 mL) and drying the organic layer over magnesium sulfate, the solvent was evaporated and the crude product was purified by silica gel column chromatography. Compound **2**: yield 54%, mp = 72°C, R_f = 0.30 (heptane/ethyl acetate: 80/20). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (s, 12H), 1.45 (s, 9H), 3.84 (t, J = 4.3 Hz, 2H), 4.66 (br s, 1H), 5.58 (dt, J = 1.8 and 17.9 Hz, 1H), 6.59 (dt, J = 4.5 and 17.9 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.6 (CH_3), 29.3 (CH_3), 44.8 (CH_2), 80.2 (C), 84.1 (C), 119.0 (br. CH), 150.3 (CH), 156.6 (C).
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14. Typical procedure: To a solution of boronate **2** (1.0 mmol) in DME (10 mL), under an argon atmosphere, were successively added heteroaryl halide (1.2 mmol), $Pd(PPh_3)_4$ (0.050 mmol) and 1.25 mL of a degassed 2 M K_2CO_3 aqueous solution. The reaction mixture was stirred at reflux temperature for 18 h, then cooled to rt and partitioned between water (20 mL) and ethylacetate (3×20 mL). The combined extracts were washed with brine (10 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography. Compound **7a**: yield 65%, R_f = 0.30 (EtOAc/heptane 20/80). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.96 (t,

$J=5.2$ Hz, 2H), 4.95 (br s, 1H), 6.59 (d, $J=15.8$ Hz, 1H), 6.69 (dd, $J=5.1$ and 15.8 Hz, 1H), 7.12 (ddd, $J=1.1$, 2.6 and 7.4 Hz, 1H), 7.26 (d, $J=7.7$ Hz, 1H), 7.61 (dt, $J=1.8$ and 7.7 Hz, 1H), 8.53 (d, $J=4.8$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.3 (CH_3), 43.1 (CH_2), 80.3 (C), 122.3 (CH), 123.0 (CH), 131.4 (CH), 132.2 (CH), 137.4 (CH), 150.2 (CH), 155.9 (C), 156.6 (C). Compound **7b**: yield 82%, $R_f=0.20$ (EtOAc/heptane 20/80). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.90 (t, $J=5.3$ Hz, 2H), 5.11 (br s, 1H), 6.26 (dt, $J=5.5$ and 15.9 Hz, 1H), 6.49 (d, $J=15.9$ Hz, 1H), 7.22 (dd, $J=4.8$ and 7.8 Hz, 1H), 7.68 (dt, $J=1.5$ and 7.8 Hz, 1H), 8.41–8.50 (m, 1H), 8.52–8.64 (m, $J=1$H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.7 (CH_3), 42.9 (CH_2), 79.9 (C), 123.8 (CH), 127.7 (CH), 129.5 (CH), 132.7 (C), 133.2 (CH), 148.5 (CH), 148.8 (CH), 156.2 (C). Compound **7c**: yield 70%, $R_f=0.20$ (EtOAc/heptane 20/80). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 3.80–3.95 (m, 2H), 4.96 (s large, 1H), 6.42–6.44 (m, 2H), 7.22 (dd, $J=1.5$ and 4.4 Hz, 2H), 8.52 (d, $J=1.5$ and 4.4 Hz, 2H, H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.3 (CH_3), 42.3 (CH_2), 79.7 (C), 120.8 (CH), 128.5 (CH), 131.7 (CH), 144.1 (CH), 144.9 (C), 149.9 (CH), 155.7 (C). Compound yield **7d**: 43%, $R_f=0.35$ (EtOAc/heptane 70/30). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.80–1.95 (br s, 1H), 3.88 (t, $J=5.6$ Hz, 2H), 6.07 (dt, $J=5.8$ and 15.9 Hz, 1H), 6.30 (d, $J=15.9$ Hz, 1H), 8.30 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.4 (CH_3), 39.4 (CH_2), 79.7 (C), 121.0 (C), 124.7 (CH), 125.6 (CH), 155.7 (C), 156.0 (CH), 162.0 (C). Compound yield **7e**: 56%, $R_f=$ 0.35 (EtOAc/heptane 80/20). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.38 (s, 3H), 3.44 (s, 3H), 3.86 (t, $J=5.5$ Hz, 2H, C$\underline{H}_2$), 4.77 (br s, 1H), 6.25 (d, $J=15.8$ Hz, 1H), 6.43 (dt, $J=5.8$ and 15.8 Hz, 1H), 7.23 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.0 (CH_3), 28.3 (CH_3), 37.0 (CH_3), 42.8 (CH_2), 79.4 (C), 110.6 (C), 122.2 (CH), 127.6 (CH), 139.4 (C), 151.1 (C), 155.7 (C), 162.2 (C). Compound yield **7f**: 69%, $R_f=0.40$ (EtOAc/heptane 80/20). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H), 4.01 (t, $J=5.4$ Hz, 2H), 4.62 (d, $J=5.5$ Hz, 2H), 4.80–4.95 (br s, 1H), 5.39 (s large, 1H), 6.34 (dt, $J=5.5$ and 16.0 Hz, 1H), 6.60 (d, $J=9.3$ Hz, 1H), 6.68 (d, $J=16.0$ Hz, 1H), 7.18–7.48 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.8 (CH_3), 42.8 (CH_2), 43.4 (CH_2), 79.9 (C), 113.9 (CH), 125.4 (CH), 127.8 (CH), 128.0 (CH), 129.1 (CH), 138.9 (C), 150.7 (C), 158.4 (C), 156.2 (C). Compound yield **7g**: 65%, $R_f=0.3$ (EtOAc/heptane 80/20). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 9H), 4.06 (t, $J=4.1$ Hz, 2H), 5.35 (s, 2H, CH_2-Ph), 7.01 (d, $J=15.9$ Hz, 1H), 7.16–7.32 (m, 5H), 7.51 (dt, $J=5.1$ and 15.9 Hz, 1H), 7.94 (s, 1H), 8.82 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.8 (CH_3), 42.8 (CH_2), 47.6 (CH_2), 80.0 (C), 125.6 (CH), 128.2 (CH), 128.9 (CH), 129.5 (CH), 131.0 (C), 135.5 (C), 140.5 (CH), 144.5 (CH), 152.3 (C), 152.9 (CH), 153.7 (C), 156.1 (C).

15. A representative procedure is as follows: To a mixture of 50 mmol of methanol and 10 mL of ethyl acetate cooled at 0°C was added dropwise 50 mmol of acetylchloride. After 1 h at 0°C, a solution of the *N*-Boc amine **7** (1 mmol) was slowly added to the reaction mixture. Stirring was continued at rt for 6 h. The solvent was then evaporated and the residue was dissolved in 5 mL of dried DMF. Neutralization with sodium carbonate was followed by addition of pyrrol-2-yltrichloromethyl ketone. After being stirred at rt for 6 h, the reaction mixture was concentrated in vacuo and the residue suspended in water. The precipitate was filtered and purified by silica gel column chromatography. Selected data for **8e**: yield 27%. $R_f=0.10$ ($CHCl_3$/MeOH = 95/5). ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.19 (s, 3H), 3.32 (s, 3H), 3.95 (t, $J=5.4$ Hz, 2H), 6.19 (d, 1H, $J=15.8$ Hz), 6.48 (dt, $J=5.5$ and 15.8 Hz, 1H), 6.94 (s, 1H), 6.99 (s, 1H), 7.92 (s, 1H), 8.37 (t, $J=5.4$ Hz, 1H), 11.84 (br s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 27.4 (CH_3), 36.4 (CH_3), 40.5 (CH_2), 94.8 (C), 108.3 (CH), 111.3 (C), 121.1 (CH), 122.0 (CH), 126.1 (CH), 126.7 (C), 141.7 (CH), 150.5 (C), 159.2 (C), 161.6 (C).
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