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Synthesis of haminol-A and haminol-B, polyenic alarm pheromones of Cephalaspidean molluscs

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Abstract

Two stereocontrolled palladium-catalyzed cross-couplings of 1-alkenyl boronic acids and aryl/alkenyl halides (the Suzuki–Miyaura reaction) are the key steps in an enantioselective approach to the polyene fragment of haminols A and B, alarm pheromones isolated from *Haminoea navicula*, a Cephalaspidean Opisthobranch mollusc. Chirality rested on the use of (*S*)-propylene oxide as the starting material.

1. Introduction

The lack of adequate external protection makes Cephalaspidean molluscs quite vulnerable to predators.[1] It is not unexpected, therefore, that these Opisthobranchs have evolved to secrete chemicals for communication among conspecifics and as a defense mechanism against predators. Although there is no evidence for the use of chemicals as defensive weapons, classical field observations with the Cephalaspidean *Navanax inermis* from the Pacific Coast,[2] and *Haminoea navicula* from the Mediterranean Sea,[3] revealed that the mixture of components secreted into the slime trail by the molested animals induced an escape response in the following conspecifics. Furthermore, recent disection studies[4] showed that related compounds isolated from another Mediterranean species, *H. callidegenita*, are exclusively located in the external part (parapodia) of the mollusc, and are absent in the internal organs, a trend in keeping with their putative alarm pheromone activity.

With regard to their chemical nature, existing studies on the chemical composition of Cephalaspidea reveal that the major components of polypropionate biogenetic origin feature a polyenic structure as a side chain attached to a (hetero)aromatic ring.[2–5] Nine polyenic pyridines, a class of compounds uncommon among marine natural products, have been isolated from the Haminoeidae so far: haminols A **1a** and B **1b** in *Haminoea navicula*,[3] haminol C **2** in *H. orteai*,[5] and haminols 1–2 **3a,b** and 3–6 **4a,b** and **5a,b** in

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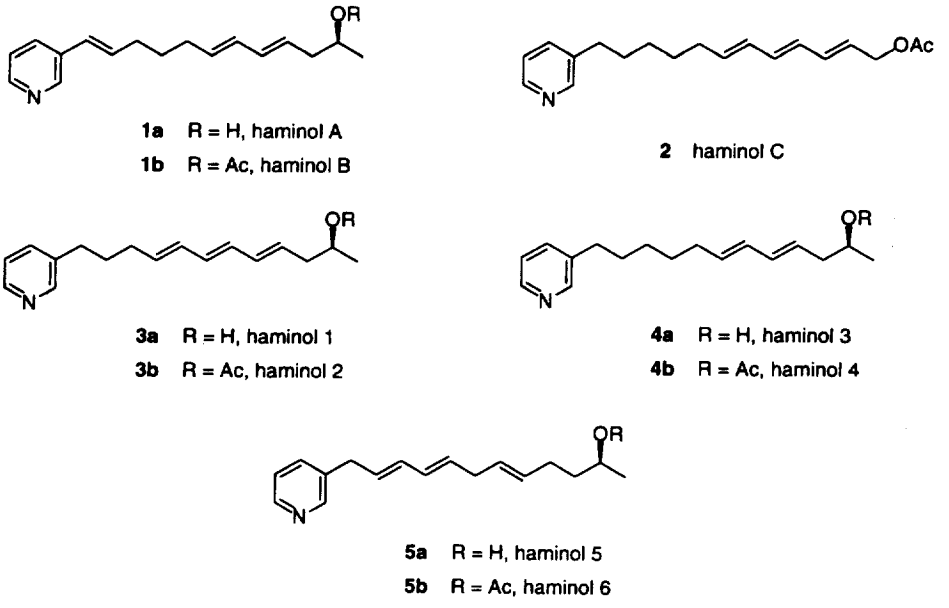


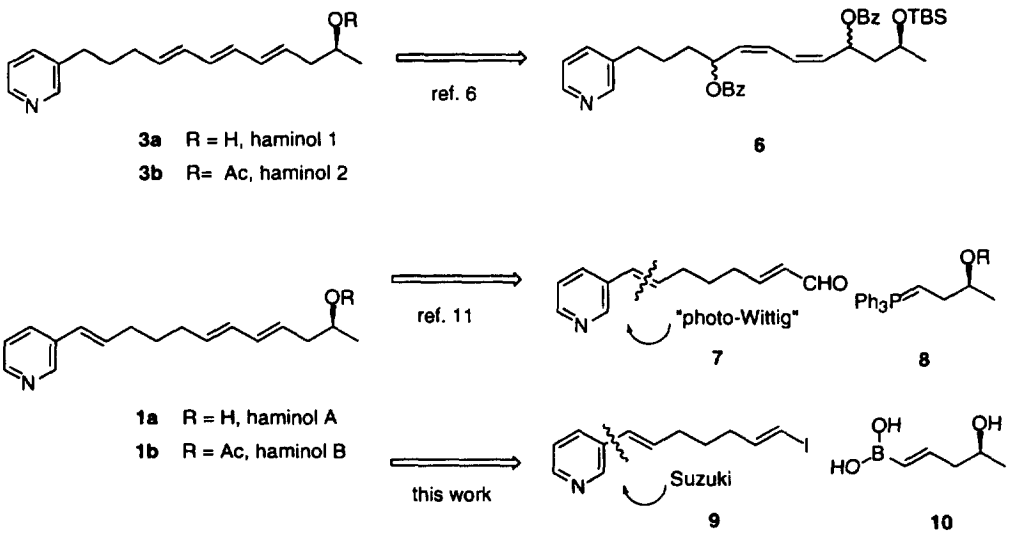
Fig. 1.

H. orbignyana, and *H. fusari*, respectively.[5] These compounds invariably comprise of a 12 carbon side chain with a variety of unsaturation patterns, and, with the exception of haminol C, a stereogenic center at C-2 with absolute *S*-stereochemistry (Fig. 1).

The enantioselective synthesis of haminols 1 and 2 **3a,b** has recently been reported by Solladié et al. using the reductive elimination of benzoate groups derived from 1,6-diol-2,4-dienes **6** as a key step to acquire the all-*E* conjugated triene subunit (Scheme 1).[6] As a complement to our recently reported stereocontrolled synthesis of haminol C,[7] we report here our approach to haminols A and B **1a,b**, in which the side chain is elaborated in a stereocontrolled fashion, by palladium-catalyzed cross-coupling of boronic acids and electrophiles (Suzuki–Miyaura reaction).[8] Based on our experience in the synthesis of fully-conjugated polyenes[9] we considered the elaboration of the diene present in **1a** and **1b** by coupling of appropriately substituted fragments, alkenylboronic acid **10** and alkenyliodide **9** (Scheme 1).[8] Since *E*-alkenyliodides can be stereoselectively obtained from aldehydes using chromium-mediated iodoalkenylation,[10] the stereochemical integrity of the remaining double bond relied upon an additional Suzuki coupling[8] involving 3-bromopyridine and the appropriate alkenylboronic acid. The control of the double bond stereochemistry in our convergent synthesis thus constitutes an improvement from the approach of Hase et al. (Scheme 1) which features two Wittig reactions (the first, a photochemically driven variant; the second the condensation of **7** and **8** proceeding with an 86/14 stereochemical ratio) starting from 3-formylpyridine.[11]

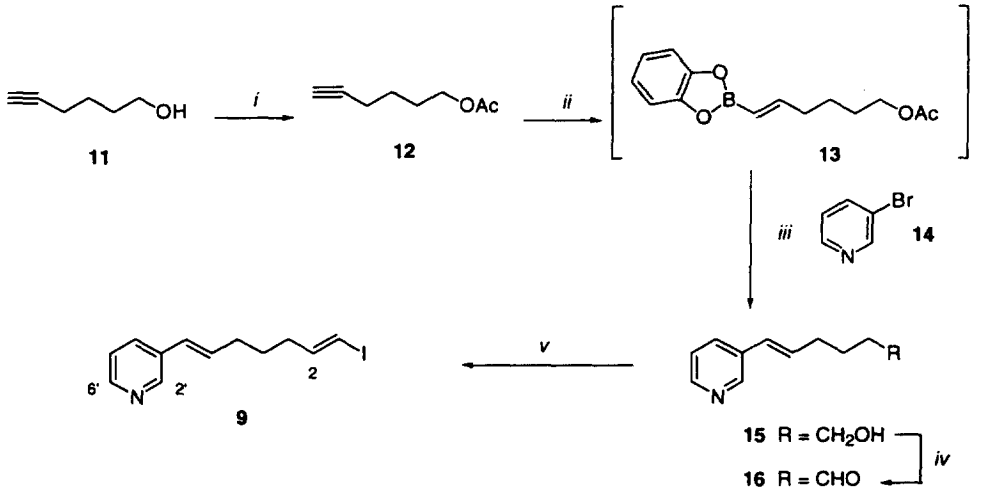
2. Results and discussion

Schemes 2 and 3 depict the synthesis of the required alkenyl fragments **9** and **10**. Due to the unstable nature of boronic acids derived from enynols,[12a] it was found to be more convenient[12b] to generate it in situ from the boronate **13**, obtained by hydroboration of hex-5-in-1-ol acetate **12**, since the basic conditions of the Suzuki coupling ensure concomitant acetate hydrolysis. Thus, treatment of **12** (obtained by acetylation of hex-5-yn-1-ol **11**)[12c] with catecholborane at 80°C for 3 h[13] provided the



Scheme 1.

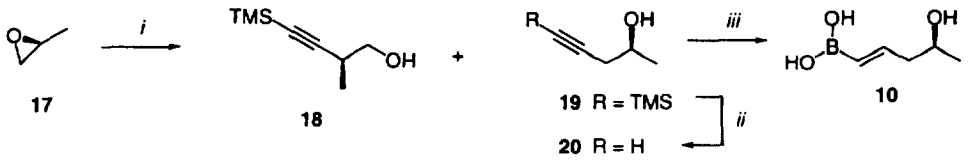
unstable boronate **13**, which without purification was coupled to 3-bromopyridine **14** under the conditions optimized by Miyaura–Suzuki for aryl–vinyl coupling ($Pd(PPh_3)_4$, 3 N NaOH, THF, 85°C)[14] to afford alcohol **15** in 64% combined yield. Swern oxidation[15] of unstable alcohol **15** provided aldehyde **16** in 72% yield. Compound **16** was stereoselectively converted to the *E* alkenyl iodide **9** (72% yield) using Takai's procedure,[10] with flame-dried $CrCl_2$.[16]



Reagents and conditions: *i.* Ac_2O, Py, 25 °C. *ii.* catechol borane, 80 °C, 3h. *iii.* **13**, 3N NaOH, $Pd(PPh_3)_4$, THF, 85 °C, 1h, 64% combined yield. *iv.* 1. $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C. 2. Et_3N, 25 °C, 72 %. *v.* $CrCl_2$, CHI_3, THF, 0 °C, 72%.

Scheme 2.

For the preparation of **10**, regioselective ring opening of (*S*)-propylene oxide **17** with the alane obtained by treating trimethylsilylacetylene with *n*-BuLi/Et_2AlCl[17] afforded homopropargyl alcohols **18** and **19**[18] in a 1:20 ratio (93% yield), and these compounds were separated by HPLC. Deprotection of **19** (TBAF, 25°C, 15 min, 71%) was followed by hydroboration of the resulting **20**[19] with catecholborane[12a]



Reagents and conditions: *i.* 1. TMSCCH, *n*-BuLi, Et_2AlCl, toluene, 0 to 25 °C, 2h. 2. (*S*)-propylene oxide **17** toluene, - 10 °C, then 0 °C, 3h, 93% **18**:**19** 1/20 . *ii.* TBAF, THF, 25 °C, 15 min, 71%. *iii.* catechol borane, 25 °C, 1h, then -20 °C, 12 h. 2. H_2O, 25 °C, 1h, 45%.

Scheme 3.

and hydrolysis of the boronate/borate esters to provide alkenylboronic acid **10**. The assessment of the enantiomeric purity of intermediates shown in Scheme 3 was based on the analysis of the esters obtained upon their separate treatment with (*R*) and (*S*) Mosher's reagent [MTPACl, α-methoxy-α-trifluoromethylphenacetyl chloride].[20] Signals for the diastereomeric esters could be resolved by ^{1}H NMR spectroscopy, and integration of the signals for the methyl and methoxy groups allowed an estimation of >96% ee for **18**, and >98% ee for **19**, **20** and **10**.

The alkenyl iodide **9** was coupled to alkenylboronic acid **10** (Scheme 1) at room temperature using the modified Suzuki conditions due to Kishi (10% aqueous TlOH);[21] the reaction was complete in 2 h affording a 70% yield of the conjugated polyenol **1a**,[3] $[\alpha]_D^{25}$ 4.5 (*c* 0.17, MeOH) with retention of stereochemistry of both coupling partners. Acetylation of haminol A **1a**[3] then provided haminol B **1b**,[3] $[\alpha]_D^{25}$ −23.1 (*c* 0.024, MeOH), in 65% yield. Their ^{1}H NMR spectra (400 MHz) matched the published[3] spectral data for haminols A and B, respectively. Additionally, optical rotations for **1a** and **1b** are coincidental with those of the natural product,[3] which further confirms the preservation of the stereochemistry of (*S*)-propylene oxide along the synthetic sequence.

The results confirm the utility of the Suzuki reaction for the highly stereoselective synthesis of unstable natural products with polyolefinic structure. The variety of chain lengths, unsaturation patterns and stereochemistry of the alarm pheromones of Opisthobranchs already reported by our group[7,9] (navenone B, 3-methylnavenone B, lignarenone A, lignarenone B, and the pyridine derivatives navenone A, haminol A, haminol B, and haminol C) attest to the generality of the approach exemplified above.

3. Experimental

Solvents were dried according to published methods and distilled before use. HPLC grade solvents were used for the HPLC purification. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed using Merck silica gel 60 particle size (0.040–0063 μm). Proton (^{1}H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on Bruker AMX-300 [300 MHz (75 MHz for ^{13}C)] and AMX-400 [400 MHz (100 MHz for ^{13}C)] Fourier transform spectrometers, and chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) or chloroform ($CHCl_3$, 7.24 ppm for ^{1}H and 77.00 ppm for ^{13}C) as an internal reference. ^{13}C multiplicities (s, singlet; d, doublet; t, triplet; q, quartet) were assigned with the aid of the DEPT pulse sequence. Infrared spectra (IR) were obtained on a MIDAC Prospect Model FT-IR spectrophotometer. Absorptions are recorded in wavenumbers (cm^{-1}). Optical rotations were recorded on an Autopol IV polarimeter at the sodium D line.

3.1. (E)-6-(3-Pyridyl)-hex-5-en-1-ol 15

Catecholborane (0.4 mL, 3.8 mmol) was added to alkyne **12**[12c] (0.532 g, 3.80 mmol) in a Schlenk tube, and the solution was heated at 80°C for 3 h with vigourous stirring. Upon cooling to room temperature, the mixture was diluted with THF (10 mL), and slowly added, via cannula, to a flask containing a solution of 3-bromopyridine (0.5 g, 3.166 mmol) and $Pd(PPh_3)_4$ (0.366 g, 0.317 mmol) in anhydrous THF (10 mL). A 3 N NaOH aqueous solution was then added, and the resulting mixture was heated at 85°C for 1 h. After cooling to room temperature, the suspension was poured into ethyl acetate (20 mL), washed with H_2O (3×10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography (silica gel, 60:40 hexane:ethyl acetate) furnished alcohol **15** in 64% combined yield. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.5–1.7 (4H, m, $2H_2$+$2H_3$), 2.26 (2H, t, J=6.4 Hz, $2H_4$), 2.4–2.5 (1H, br, OH), 3.63 (2H, t, J=6.2 Hz, $2H_1$), 6.28 (1H, dt, J=16.0, 6.4 Hz, H_5), 6.35 (1H, d, J=16.0 Hz, H_6), 7.20 (1H, dd, J=7.9, 4.8 Hz, $H_{5'}$), 7.64 (1H, dt, J=7.9, 1.8 Hz, $H_{4'}$), 8.39 (1H, d, J=4.8 Hz, $H_{6'}$), 8.52 (1H, s, $H_{2'}$). ^{13}C NMR (100.13 MHz, $CDCl_3$): δ 25.3 (t), 32.2 (t), 32.8 (t), 62.5 (t), 123.4 (d), 126.4 (d), 128.4 (s), 132.5 (d), 133.2 (d), 147.7 (d), 147.8 (d). IR (NaCl): ν 3600–3100 (s, broad, OH), 2932 (s, C–H), 2859 (s, C–H), 1417 (m), 1063 (m) cm^{-1}. MS *m/z* (%): 177 (M^+, 16), 149 (21), 144 (29), 132 (31), 131 (35), 130 (76), 118 (61), 117 (62), 106 (100), 105 (24), 93 (40), 91 (27), 86 (68), 84 (92). HRMS: calcd for $C_{11}H_{15}NO$, 177.1154; found, 177.1156.

3.2. (E)-6-(3-Pyridyl)-hex-5-enal 16

A solution of alcohol **15** (0.12 g, 0.7 mmol) in CH_2Cl_2 (2 mL) was added to a cold (−60°C) solution of DMSO (0.13 mL, 0.76 mmol) and oxalyl chloride (0.07 mL, 0.8 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at −60°C for 15 min and, after addition of triethylamine (0.15 mL, 0.21 mmol), was warmed to room temperature, and poured into H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine (3×5 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography (silica gel, eluant gradient from hexane to 70:30 hexane:ethyl acetate) furnished aldehyde **16** as a yellow oil in 72% yield. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.83 (2H, quintet, J=7.4 Hz, $2H_3$), 1.9–2.0 (br, –OH), 2.27 (2H, dt, J=7.4, 6.8 Hz, $2H_4$), 2.51 (2H, dt, J=7.4, 1.4 Hz, $2H_2$), 6.25 (1H, dt, J=15.9, 6.8 Hz, H_5), 6.38 (1H, d, J=15.9 Hz, H_6), 7.23 (1H, dd, J=7.6, 4.7 Hz, $H_{5'}$), 7.65 (1H, d, J=7.6 Hz, $H_{4'}$), 8.44 (1H, br s, $H_{6'}$), 8.56 (1H, br s, $H_{2'}$), 9.79 (1H, d, J=1.5 Hz, H_1). ^{13}C NMR (100.13 MHz, $CDCl_3$): δ 21.3 (t), 32.2 (t), 43.1 (t), 123.4 (d), 127.3 (d), 131.9 (d), 132.4 (d), 132.9 (s), 147.8 (d), 148.0 (d), 202.2 (d). IR (NaCl): ν 3026 (m, C–H), 1720 (m, C=O) cm^{-1}. MS *m/z* (%): 175 (M^+, 17), 132 (16), 131 (100), 130 (94), 118 (29), 117 (29), 91 (14). HRMS: calcd for $C_{11}H_{13}NO$, 175.0997; found, 175.0997.

3.3. (1E,6E)-1-Iodo-7-(3-pyridyl)-hepta-1,6-diene 9

A solution of CHI_3 (0.56 g, 1.42 mmol) in THF (5 mL) was added to a cooled (0°C) suspension of $CrCl_2$ (0.55 g, 4.46 mmol, previously flame-dried under argon) in THF (5 mL). A solution of aldehyde **16** (0.12 g, 1.50 mmol) in THF (5 mL) was then added, and the resulting mixture was stirred at 0°C for 30 min. The reaction mixture was poured into a saturated aqueous NH_4Cl (10 mL)/saturated aqueous $NaHCO_3$ (10 mL) mixture, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine (2×10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography of the residue (SiO_2, 95:5 CH_2Cl_2:MeOH) afforded 0.132 g (72%) of compound **9** as a yellow oil, which was used in the next step without further purification. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.6 (2H, quintet,

J=7.4 Hz, $2H_4$), 2.1–2.2 (2H, m, $2H_3$), 2.2–2.3 (2H, m, $2H_5$), 6.03 (1H, d, J=14.4 Hz, H_1), 6.2–6.3 (1H, m, H_6), 6.38 (1H, d, J=16.0 Hz, H_7), 6.53 (1H, dt, J=14.4, 7.4 Hz, H_2), 7.22 (1H, dd, J=8.0, 4.7 Hz, $H_{5'}$), 7.65 (1H, dd, J=8.0, 1.4 Hz, $H_{4'}$), 8.43 (1H, d, J=4.7 Hz, $H_{6'}$), 8.55 (1H, br s, $H_{2'}$). ^{13}C NMR (100.13 MHz, $CDCl_3$): δ 27.6 (t), 29.7 (t), 34.1 (t), 75.0 (d), 123.4 (d), 126.9 (d), 128.4 (d), 132.5 (d), 140.7 (s), 145.9 (d), 147.8 (d), 147.9 (d).

3.4. (S)-(−)-5-Trimethylsilylpent-4-yn-2-ol **19**

n-BuLi (2.48 mL, 2.77 M in THF, 6.87 mmol) was added dropwise to a cooled (0°C) solution of trimethylsilylacetylene (1.95 mL, 13.76 mmol) in toluene (12 mL). After stirring at 0°C for 30 min, Et_2AlCl (7.6 mL, 1.8 M in hexanes, 13.76 mmol) was slowly added, and the resulting mixture was stirred at room temperature for 2 h. After the solution was cooled down to −10°C, a solution of (*S*)-propylene oxide in toluene (4 mL) was added, and the resulting mixture was stirred at that temperature for 10 min and then at 0°C for 3 h. Water (10 mL) and aqueous 10% citric acid (10 mL) were slowly added, and the mixture was extracted with ether (4×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (SiO_2, 80:20 hexane:ethyl acetate) to afford 1.01 g (93%) of a mixture of regioisomers (1:20 **18:19**) as determined by ^{1}H NMR spectroscopy, which could be separated by HPLC (Prep Nova-Pak®, HR silica 60 Å, 19×300 mm; 10:90 ethyl acetate:hexane; 7 mL/min; t_R=25.9 min for **18**; t_R=28.2 min for **19**).

Data for **19**: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.16 (9H, s, $-Si(CH_3)_3$), 1.25 (3H, d, J=6.1 Hz, $3H_1$), 1.8–1.9 (1H, br, –OH), 2.35 (1H, dd, J=16.7, 6.7 Hz, H_3), 2.44 (1H, dd, J=16.7, 5.1 Hz, H_3), 3.95 (1H, m, H_2). ^{13}C NMR (75.89 MHz, $CDCl_3$): δ 0.04 (q), 22.1 (q), 30.3 (t), 66.1 (d), 87.2 (s), 103.2 (s). IR (NaCl): ν 3600–3100 (br, O–H), 2959 (s, C–H), 2926 (s, C–H) cm^{-1}. $[\alpha]_D^{25}$ −3.98 (*c* 4.1, CH_3OH).

Data for **18** [(*S*)-(−)-2-methyl-4-trimethylsilylbut-3-yn-1-ol]: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.17 (9H, s, $-Si(CH_3)_3$), 1.17 (3H, d, J=7.0 Hz, C_2–CH_3), 2.69 (1H, m, H_2), 3.4–3.6 (2H, m, $2H_1$). ^{13}C NMR (75.89 MHz, $CDCl_3$): δ 0.13 (q), 16.9 (q), 30.5 (d), 66.6 (t), 86.6 (s), 108.2 (s). IR (NaCl): ν 3600–3100 (br, O–H), 2959 (s, C–H), 2924 (s, C–H) cm^{-1}. $[\alpha]_D^{25}$ −19.5 (*c* 0.81, $CHCl_3$).

3.5. (S)-(+)-4-Pent-4-yn-2-ol **20**

Tetrabutylammonium fluoride (6.8 mL, 1 M in THF, 6.8 mmol) was added to a solution of compound **19** (0.7 g, 4.53 mmol) in THF (40 mL), and the mixture was stirred at room temperature for 15 min, poured into saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with Et_2O (3×10 mL). The organic extracts were washed with brine (1×10 mL) and H_2O (1×10 mL), dried over Na_2SO_4 and concentrated. Chromatography of the residue (SiO_2, 80:20 hexane:ethyl acetate) yielded 0.254 g (71%) of enynol **20**[19] as a colourless oil. $[\alpha]_D^{25}$ +17.5 (*c* 1.36, $CHCl_3$), lit.[19] $[\alpha]_D^{25}$ +17.8 (*c* 0.22, $CHCl_3$).

3.6. 4(S)-(−)-[(E)-4-Hydroxy-pent-1-en-1-yl]boronic Acid **10**

Catecholborane (0.45 mL, 5.02 mmol) was added slowly (the reaction is very exothermic!) to alkyne **20** (0.532 g, 3.80 mmol) in a Schlenk tube cooled to 0°C, allowing for the release of hydrogen. After stirring at room temperature for 1 h, the mixture was cooled down to −20°C and stirred for 12 h. After addition of water (3 mL), the resulting suspension was stirred at room temperature for 1 h, NaCl was added to saturate the solution, and the resulting mixture was extracted with ethyl acetate (3×10 mL). The organic extracts were washed with H_2O (3×10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography (silica gel, eluting first with 50:50 hexane:ethyl acetate and then with

90:10 CH_2Cl_2:MeOH) furnished boronic acid **10** in 45% yield. $[\alpha]_D^{25}$ −1.3 (*c* 0.23, CH_3OH). ^1H NMR (300.13 MHz, CD_2Cl_2): δ 1.14 (3H, d, *J*=6.3 Hz, $3H_5$), 2.4–2.2 (2H, m, $2H_3$), 3.80 (1H, app. q, *J*=6.3 Hz, H_4), 5.63 (1H, d, *J*=17.7 Hz, H_1), 6.53 (1H, dt, *J*=17.7, 7.0 Hz, H_2). ^{13}C NMR (75.89 MHz, CD_2Cl_2): δ 16.8 (q), 47.1 (t) 67.9 (d), 150.4 (d), 156.3 (d). IR (NaCl): ν 3675–3100 (br, O–H), 2968 (s, C–H), 2929 (m, C–H), 1637 (m), 1345 (s, B–O) cm^{-1}.

*3.7. 2(S)-(+)-(4E,6E,11E)-12-(3-Pyridyl)-dodeca-4,6,11-triene-2-ol (haminol A, **1a**)*

Iodide **9** (0.073 g, 0.245 mmol) in THF (2 mL) was added to a suspension of $Pd(PPh_3)_4$ (0.028 g, 0.0024 mmol) in anhydrous THF (3 mL). After stirring for 30 min, a solution of boronic acid **10** (0.071 g, 0.269 mmol) in THF (5 mL) and 10% aqueous TlOH (1.68 mL, 0.76 mmol) were added sequentially. After stirring at room temperature for 2 h, the reaction mixture was diluted with Et_2O (10 mL) and filtered through Celite. The filtrates were washed with saturated aqueous $NaHCO_3$ (3×10 mL) and the aqueous layer was extracted with ethyl acetate (3×10 mL). The organic layers were dried over $MgSO_4$ and concentrated. Chromatography (SiO_2, gradient from hexane to ethyl acetate) afforded 0.040 g (72%) of compound **1a** as a yellow oil.[3,11] $[\alpha]_D^{25}$ +4.5 (*c* 0.17, CH_3OH); lit.[3] $[\alpha]_D^{25}$ +5.0 (*c* 0.3, CH_3OH). ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.22 (3H, d, *J*=6.2 Hz, $3H_1$), 1.60 (2H, quintet, *J*=7.4 Hz, $2H_9$), 2.1–2.2 (3H, m, H_3+$2H_8$), 2.2–2.3 (3H, m, H_3+$2H_{10}$), 3.84 (1H, app. sextet, *J*=6.2 Hz, H_2), 5.57 (1H, dt, *J*=14.4, 7.1 Hz, H_4), 5.66 (1H, dt, *J*=14.4, 7.1 Hz, H_7), 6.05 (1H, dd, *J*=14.4, 10.4 Hz, H_5), 6.12 (1H, dt, *J*=14.4, 10.4 Hz, H_6), 6.29 (1H, dt, *J*=15.9, 6.3 Hz, H_{11}), 6.37 (1H, d, *J*=15.9 Hz, H_{12}), 7.2–7.3 (1H, m, $H_{5'}$), 7.66 (1H, d, *J*=7.9 Hz, $H_{4'}$), 8.44 (1H, br, $H_{6'}$), 8.57 (1H, br, $H_{2'}$). IR (NaCl): ν 3600–3100 (br, O–H), 2963 (m, C–H), 2926 (m, C–H) cm^{-1}.

*3.8. 2(S)-(−)-(4E,6E,11E)-2-Acetoxy-12-(3-pyridyl)-dodeca-4,6,11-triene (haminol B, **1b**)*

Ac_2O (0.03 mL, 0.56 mmol) was added to a solution of alcohol **1a** (0.017 g, 0.066 mmol) in pyridine (0.06 mL) and the mixture was reacted at room temperature for 4 h. After evaporation of solvents, the residue was dissolved in $CHCl_3$ (5 mL), washed with H_2O (3×2 mL), aqueous saturated $NaHCO_3$ (2 mL) and brine (2 mL), and concentrated. Chromatography (silica gel, ethyl acetate) afforded acetate **1b** in 65% yield.[3,11] $[\alpha]_D^{25}$ −23.1 (*c* 0.024, CH_3OH); lit.[3] $[\alpha]_D^{25}$ −24.0 (*c* 0.4, CH_3OH). ^1H NMR (400.13 MHz, CD_2Cl_2): δ 1.23 (3H, d, *J*=6.3 Hz, $3H_1$), 1.61 (2H, quintet, *J*=7.5 Hz, $2H_9$), 2.01 (3H, s, $COCH_3$), 2.2–2.1 (3H, m, H_3+$2H_8$), 2.4–2.3 (3H, m, H_3+$2H_{10}$), 4.90 (1H, app. sextet, *J*=6.3 Hz, H_2), 5.54 (1H, dt, *J*=14.1, 7.1 Hz, H_4), 5.65 (1H, dt, *J*=14.1, 7.1 Hz, H_7), 6.0–6.1 (2H, m, H_5+H_6), 6.3–6.4 (1H, m, H_{11}), 6.40 (1H, d, *J*=16.1 Hz, H_{12}), 7.23 (1H, dd, *J*=7.8, 4.8 Hz, $H_{5'}$), 7.68 (1H, d, *J*=7.8 Hz, $H_{4'}$), 8.42 (1H, br, $H_{6'}$), 8.56 (1H, br, $H_{2'}$). IR (NaCl): ν 2928 (m, C–H), 2856 (m, C–H), 1740 (s, C=O), 1259 (s), 1252 (s), 1027 (s), 799 (s) cm^{-1}. MS *m/z* (%): 299 (M^+, 4), 278 (41), 277 (76), 240 (27), 239 (100), 201 (23), 183 (10), 171 (19), 158 (18), 145 (11), 144 (13), 133 (16), 132 (63), 130 (33), 119 (19), 118 (29). HRMS: calcd for $C_{19}H_{25}NO_2$, 299.1885; found, 299.1886.

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References

1. (a) Karuso, P. In *Bioorganic Marine Chemistry*, Vol. 1; Scheuer, P. J., Ed.; Springer Verlag: Heidelberg, 1987; pp. 31–60. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1992**, *9*, 323–364, and references cited therein.
2. (a) Sleeper, H. L.; Fenical, W. *J. Am. Chem. Soc.* **1977**, *99*, 2367–2368. (b) Fenical, W.; Sleeper, H. L.; Paul, V. J.; Stallard, M. O.; Sun, H. H. *Pure Appl. Chem.* **1979**, *51*, 1865–1874. (c) Sleeper, H. L.; Paul, V. J.; Fenical, W. *J. Chem. Ecol.* **1980**, 6, 57–70.
3. Cimino, G.; Passeggio, A.; Sodano, G.; Spinella, A.; Villani, G. *Experientia* **1991**, *47*, 61–63.
4. Spinella, A.; Alvarez, L. A.; Cimino, G. *Tetrahedron Lett.* **1998**, *39*, 2005–2008.
5. Spinella, A.; Alvarez, L. A.; Passeggio, A.; Cimino, G. *Tetrahedron* **1993**, *49*, 1307–1314.
6. (a) Solladié, G.; Somny, F.; Colobert, F. *Tetrahedron: Asymmetry* **1997**, *8*, 801–810. (b) Solladié, G.; Colobert, F.; Stone, G. B. *Synlett* **1995**, 1135–1137.
7. Alvarez, R.; Herrero, M.; López, S.; de Lera, A. R. *Tetrahedron* **1998**, *54*, 6793–6810.
8. (a) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749–1758. (b) Suzuki, A. *Pure Appl. Chem.* **1986**, *58*, 629–638. (c) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419–422. (d) Martin, A.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221–230. (e) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213–222. (f) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2485.
9. (a) Torrado, A.; López, S.; Alvarez, R.; de Lera, A. R. *Synthesis* **1995**, 285–293. (b) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435–2454. (c) de Lera, A. R.; Iglesias, B.; Rodríguez, J.; Alvarez, R.; López, S.; Villanueva, X.; Padrós, E. *J. Am. Chem. Soc.* **1995**, *117*, 8220–8231. (d) Alvarez, R.; López, S.; de Lera, A. R. *Nat. Prod. Lett.* **1995**, *6*, 127–132.
10. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
11. Matikainen, J.; Kaltia, S.; Hase, T.; Kuroren, P. *J. Nat. Prod.* **1995**, *58*, 1622–1624.
12. (a) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192–1210. (b) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612–5613. (c) Schlichting, P.; Rohr, U.; Müllen, K. *Liebigs Ann./Recueil* **1997**, 395–407.
13. Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371.
14. (a) Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A. *J. Org. Chem.* **1982**, *47*, 2117–2120. (b) Karabelas, A. K.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1773–1776.
15. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
16. (a) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459. (b) Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327–2328.
17. (a) Fried, J.; Lin, C.-H.; Ford, S. H. *Tetrahedron Lett.* **1969**, 1379–1381. (b) Fried, J.; Lin, C.-H.; Sih, J. C.; Dalven, P.; Cooper, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 4342–4343. (c) Roush, W. R.; Blizzard, T. A.; Basha, F. Z. *Tetrahedron Lett.* **1982**, *23*, 2331–2334. (d) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597–3600.
18. White, J. D.; Somers, T. C.; Reddy, G. N. *J. Am. Chem. Soc.* **1986**, *108*, 5352–5353.
19. (a) Cotterill, S. A.; Gill, M.; Milanovic, N. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1215–1223. (b) Dimitriadis, C.; Gill, M.; Harte, M. F. *Tetrahedron: Asymmetry* **1997**, *8*, 2153–2158.
20. Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147.
21. Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758.