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THE SYNTHESIS OF HAMINOLS A AND B

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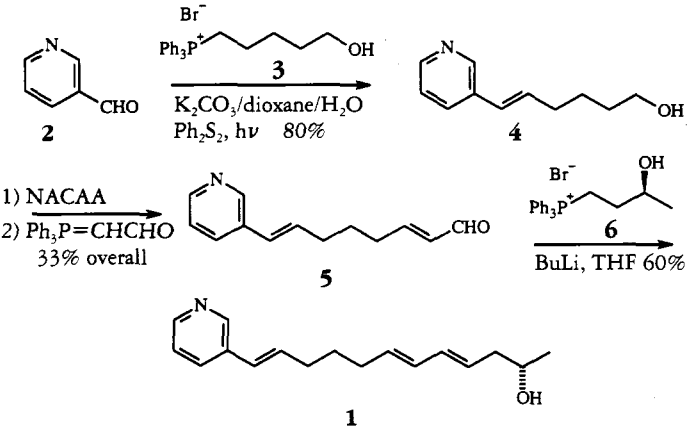
ABSTRACT.—The synthesis of the pyridine-containing metabolites haminols A [**1**] and B from *Haminoea navicula* is reported.

Haminol A [**1**] and its acetate haminol B are rare pyridine-containing marine alkaloids that were isolated from the Mediterranean cephalaspidean mollusk, *Haminoea navicula*, by Spinella and co-workers (1,2). The biological significance and properties of the haminols are largely unknown, although alarm pheromone activity has been observed for **1** as well as antileukemic activity for some near analogues. The amounts available by isolation do not allow a more detailed study of the biological and chemical properties of these compounds. In a continuation of our recent synthetic work on pulo'upone and isopulo'upone (3,4), related pyridine-containing marine products, we now report the chemical synthesis of haminols A [**1**] and B.

The synthesis of haminol A [**1**] using our "photo-Wittig" (5) and chain extension methodology (6–8) is straightforward (Scheme 1). 3-Picolinaldehyde [**2**] reacted smoothly with the phosphonium salt **3** in the presence of K_2CO_3 and a small amount of H_2O as the ylide generating base (9). Only the *E*-isomer of the monoenic pyridyl alcohol derivative **4** was obtained when the Wittig reaction was conducted under irradiation with a daylight lamp in the presence of diphenyl disulfide, whereas under ordinary Wittig conditions the *E*:*Z* ratio was 3:7 (5). The alcohol **4** was best converted to the aldehyde **5** by nicotinic/chromic anhydride betaine (NACAA) oxidation (8) and a routine Wittig alkylidenation. Reaction of **5** with the chiral phosphonium salt **6** [from commercially available (*S*)-(+)-1,3-butanediol] gave enantiomerically pure haminol A [**1**] and its 4-*Z* isomer in the ratio 86:14. Abnormally high *E*:*Z* ratios are found in unstabilized ylide Wittig reactions when anionic groups such as a hydroxyl are present in the proximity of the ylide site (10). The identity and enantiomeric purity of **1** and its 4-*Z* isomer were established by nmr analysis of the



SCHEME 1

Mosher's acid derivatives. Haminol B was prepared from **1** by standard acetylation procedures.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The mass spectra were run on a JEOL JMS-SX102 instrument. The nmr spectra were run on a Varian Gemini 200 spectrometer, using $CDCl_3$ as the solvent and referenced to solvent (δ ^1H 7.29 and ^{13}C 77.3). For prep. reversed-phase hplc, a Hewlett-Packard 1090A chromatograph was employed, using HP Hypersil ODS columns (150×2.1 mm i.d., particle size 5 mm) and elution at 30° with MeCN- triethylammonium phosphate pH 3.0 buffer (7:3, 2.5–3.0 ml/min). Flash chromatography was performed on Si gel (Kieselgel 60, E. Merck, Darmstadt, No. 9385, 230–400 mesh ASTM). Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

6-(3-Pyridyl)-5(E)*-hexen-1-ol* [**4**].—3-Picolinaldehyde [**2**] (0.50 g, 4.7 mmol), the phosphonium salt **3** (11) (3.0 g, 7.0 mmol), K_2CO_3 (0.80 g), Ph_2S_2 (0.10 g), and H_2O (0.14 ml) were stirred in dioxane (10 ml) under Ar at 90° under daylight lamp irradiation (Osram Dulux S, 11 W). After 20 h, the dioxane was removed under reduced pressure, 10 ml of EtOAc were added, and the mixture filtered and extracted with 1 M aqueous HCl. Shaking the aqueous phase with EtOAc (2×10 ml) removed the triphenylphosphine oxide by-product. After neutralization, the aqueous phase was saturated with NaCl and extracted with EtOAc (2×10 ml) to give, after flash chromatography, 0.64 g (78%) of **4** as an oil: ^1H nmr δ 1.65 (5H, m, H-2, H-3, and OH), 2.30 (2H, m, H-4), 3.71 (2H, t, J=6.1 Hz, H-1), 6.35 (2H, m, H-5 and H-6), 7.23 (1H, ddd, J=7.9, 4.8, and 0.9 Hz, H-5′), 7.67 (1H, dt, J=7.8 and 1.8 Hz, H-4′), 8.44 (1H, dd, J=4.6 and 1.7 Hz, H-6′), 8.56 (1H, dd, J=4.8 and 2.2 Hz, H-2′); ^{13}C nmr δ 25.7 (C-3), 32.6 (C-2), 33.1 (C-4), 63.0 (C-1), 123.6 (C-5′), 127.0 (C-6), 132.7 (C-4′), 133.4 (C-5), 133.7 (C-3′), 148.3 (C-2′ and C-6′); hrms *m/z* calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1151.

6-(3-Pyridyl)-5(E)*-hexen-1-al.*—The pyridylhexenol **4** (0.50 g, 23 mmol) was added to a suspension of NACAA (8) (1.6 g, 0.70 mmol) in CH_2Cl_2 (20 ml) and pyridine (4 ml). After stirring for 20 min at room temperature, the reaction mixture was filtered through a pad of Si gel (70–230 mesh). The eluate was monitored by tlc and the fractions containing the product collected to give 0.32 g (65%) of the title aldehyde as an oil: ^1H nmr δ 1.86 (2H, quintet, "J"=7 Hz, H-3), 2.31 (2H, q, J=7.1 Hz, H-4), 2.54 (2H, td, J=7.3 and 1.6 Hz, H-2), 6.27 (1H, dt, J=15.8 and 6.5 Hz, H-5), 6.41 (1H, br d, J=16.3 Hz, H-6), 7.24 (1H, ddd, J=8.0 and 4.8 Hz, 0.8 Hz, H-5′), 7.67 (1H, br d, J=9.0 Hz, H-4′), 8.46 (1H, dd, J=4.8 and 1.5 Hz, H-6′), 8.57 (1H, d, J=1.5 Hz, H-2′), 9.77 (1H, t, J=1.6 Hz, H-1); ^{13}C nmr δ 21.6 (C-3), 32.6 (C-4), 43.3 (C-2), 123.6 (C-5′), 127.6 (C-6), 132.1 (C-5), 132.7 (C-4′), 133.1 (C-3′), 148.2 (C-2′), 148.4 (C-6′), 202.4 (C-1); hrms *m/z* calcd for $C_{11}H_{13}NO$ 175.0997, found 175.0992.

8-(3-Pyridyl)-2(E),*7*(E)*-octadienal* [**5**].—The preceding aldehyde (210 mg, 1.2 mmol) and Ph_3P=CHCHO (12) (470 mg, 1.5 mmol) were heated in C_6H_6 (10 ml) under Ar at 60°. After 40 h, the product was purified as described for **4**, to give 120 mg (50%) of **5** as an oil: ^1H nmr δ 1.71 (2H, quintet, "J"=7.7 Hz, H-5), 2.32 (2H, m, H-6), 2.46 (2H, m, H-4), 6.14 (1H, ddt, J=15.6 and 7.9 Hz, 1.5 Hz, H-2), 6.27 (1H, dt, J=15.9 and 6.2 Hz, H-7), 6.38 (1H, br d, J=16.0 Hz, H-8), 6.90 (1H, dt, J=15.6 and 6.7 Hz, H-3), 7.22 (1H, ddd, J=7.9 and 4.8 Hz, 0.9 Hz, H-5′), 7.68 (1H, dt, J=8.1 and 1.9 Hz, H-4′), 8.47 (1H, dd, J=4.8 and 1.5 Hz, H-6′), 8.59 (1H, d, J=0.5 Hz, H-2′), 9.55 (1H, d, J=7.8 Hz, H-1); ^{13}C nmr δ 27.6 (C-5), 32.4 (C-4), 32.7 (C-6), 123.7 (C-5′), 127.6 (C-8), 132.3 (C-7), 132.7 (C-4′), 133.2 (C-3′), 133.5 (C-2), 148.2 (C-2′), 148.5 (C-6′), 158.3 (C-3), 194.3 (C-1); hrms *m/z* calcd for $C_{13}H_{15}NO$ 201.1153, found 201.1149.

(S)*-3-Hydroxybutyltriphenylphosphonium bromide* [**6**].—Br_2 (0.28 ml, 5.5 mmol) was added dropwise to a suspension of triphenylphosphine (1.6 g, 6.0 mmol) in pyridine (0.5 ml) and CH_2Cl_2 (15 ml) at 0°. After stirring for 20 min at room temperature, the reaction mixture was cooled to −40° and (*S*)-(+)-1,3-butanediol (0.5 g, 5.5 mmol) in CH_2Cl_2 (5 ml) was added slowly. After stirring for 30 min at −30° followed by gradual warming to 25°, the concentrated crude product was purified by flash chromatography (CH_2Cl_2-EtOAc, 1:1) to afford (*S*)-1-bromo-3-butanol as an oil (0.51 g, 60%). The bromide (0.4 g, 2.6 mmol) and triphenylphosphine (1.0 g, 4.0 mmol) were refluxed in toluene (20 ml) for 5 days under Ar to give 0.88 g (81%) of **6**, mp 230–232°. The identity and stereochemical purity of **6** were established by its X-ray spectrum. (I. Mutikainen, J. Matikainen, S. Kaltia, and T. Hase, unpublished results.)

Haminol A [**1**].—Butyllithium (1.2 ml of 0.9 M solution in hexane; 2.2 equivalents) was added to **6** (250 mg, 0.6 mmol) in THF (10 ml) at −10°. The reaction mixture was stirred for 10 min at this temperature and cooled to −70°. The aldehyde [**5**] (100 mg, 0.5 mmol) in THF (2 ml) was then slowly added The reaction temperature was then allowed to rise to 0°, 0.5 ml H_2O was added and the product was purified by flash chromatography to give 80 mg (60%) of **1** as an oil: ^1H- and ^{13}C-nmr spectra as reported in the literature (2); hrms *m/z* calcd for $C_{17}H_{23}NO$ 257.1780, found 257.1767.

Haminol B.—Haminol A (50 mg, 0.16 mmol) was kept in Ac_2O (0.2 ml) and pyridine (0.2 ml) for 12 h at room temperature under Ar. The solution was then neutralized with saturated $NaHCO_3$, extracted with EtOAc (2×2 ml) and purified by hplc to give 52 mg (90%) of haminol B: $[\alpha]_D$ −25° [*c*=0.01, CH_3OH lit. −24° (2)]; ^{1}H-nmr data as reported in the literature (2); ^{13}C nmr δ 19.7 (C-1), 21.5 (*C*H_3COO), 28.9 (C-9), 32.2 (C-8), 32.7 (C-10), 39.2 (C-3), 70.6 (C-2), 123.5 (C-5′), 126.7 (C-4 and C-12), 130.7 (C-5), 132.5 (C-4′), 133.0 (C-7), 133.3 (C-6), 133.4 (C-3′ and C-11), 148.1 (C-2′ and C-6′), 170.7 (*C*H_3*C*OO); hrms *m/z* calcd for $C_{19}H_{25}NO_2$ 299.1885, found 299.1869.

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