Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 5, pp. 801–810, 1997
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Printed in Great Britain
PII: S0957-4166(97)00025-6 0957-4166/97 $17.00 + 0.00

Enantioselective synthesis of haminol-1, an alarm pheromone of a Mediterranean mollusc

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Abstract: The first enantioselective synthesis of (−)-(R)-haminol-1 is described in this paper. The chiral part of the molecule was prepared by reduction of an optically active β-ketosulfoxide. The all-trans trienic part was stereoselectively synthesized via reductive elimination of a 1,6-dibenzoate-2,4-diene with sodium amalgam. © 1997 Elsevier Science Ltd. All rights reserved.

Cephalospidean molluscs are characterized by a prominent head and by inadequate protection of a shell that is either small and fragile or internal. The first chemical studies revealed the presence of navenone-B,[1] in *Navanax inermis* and lignarenone-B[2] in *Scaphander lignarus*. These two molecules which have been synthesized in our laboratory[3], act as alarm pheromones inducing an immediate escape reaction. Recently seven new 3-alkylpyridines[4] showing also alarm pheromone activity have been isolated from three *Haminoe* cephalospidean molluscs: *H. Orteai, H. Orbignyana* and *H. Fusari*. The metabolite pattern of *H. Orbignyana* was characterized by two metabolites, a secondary alcohol haminol-1, **1** and its acetate, **2**.

We report in this paper a short and efficient enantioselective synthesis of haminol-1, **1** and its acetate **2** (Figure 1).

As shown on the retrosynthetic scheme (Scheme 1), the all-trans-trienic part of the molecule can be prepared in high stereoselectivity from **3** following our previous work[5] on the reductive elimination of 1,6-dibenzoate-2,4-dienes with sodium amalgam, the precursor, the 1,6-dihydroxy-2,4-diyne **4**, being obtained by condensation of diacetylene on the appropriate aldehydes. The synthesis of the chiral hydroxyaldehyde **5** was based on the stereoselective reduction of chiral β-ketosulfoxides.[6]

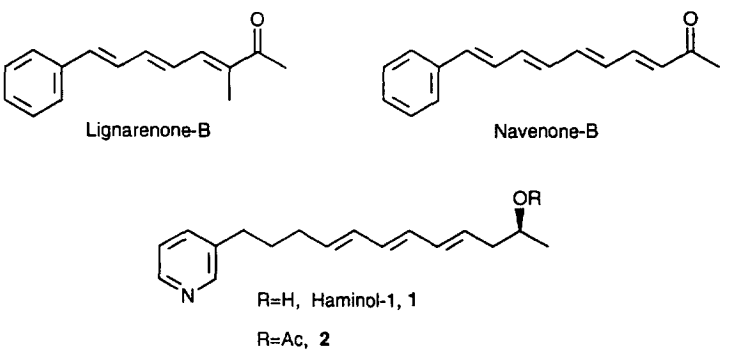

Figure 1.

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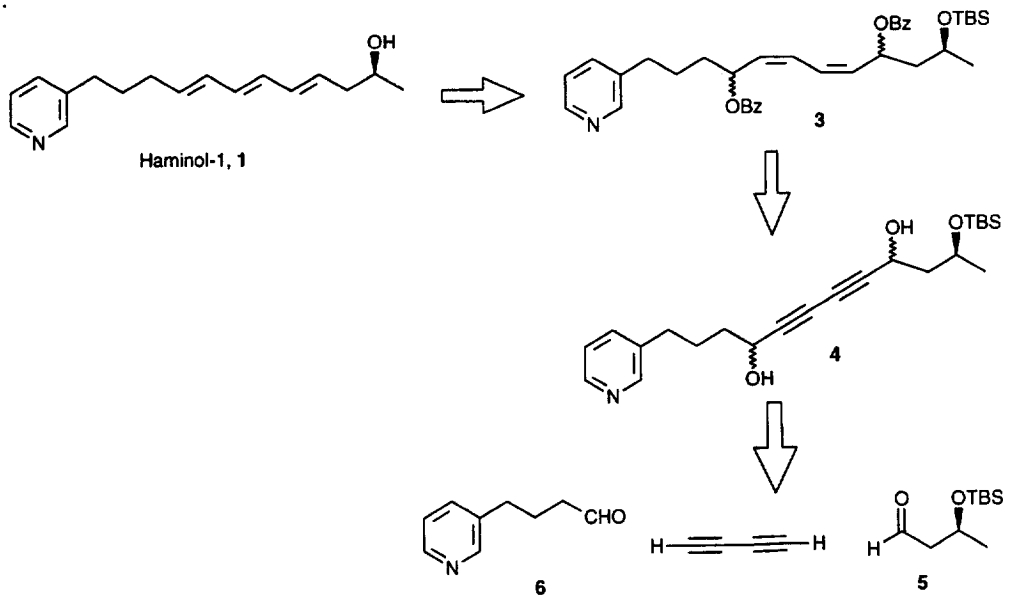
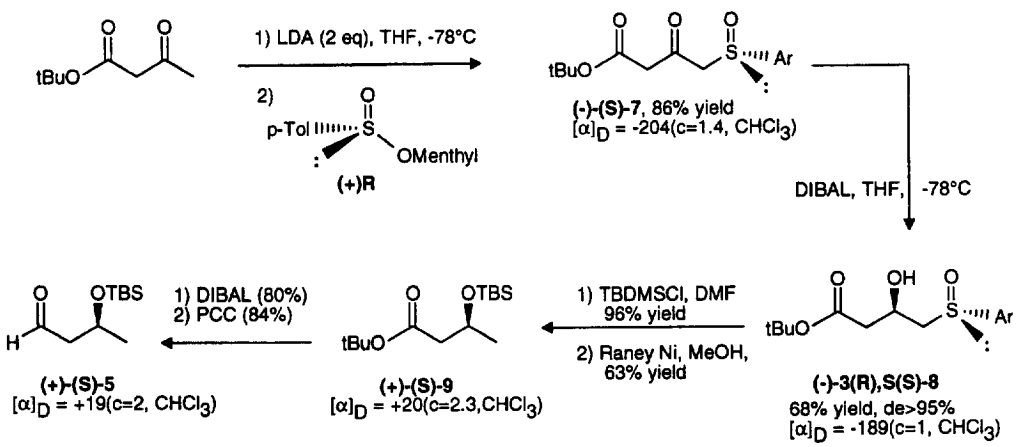


Scheme 1.

Enantiomerically pure β-hydroxy butyraldehyde **5** was prepared from the corresponding β-hydroxy butyric ester[7] **9** (Scheme 2). Condensation of the dianion of t-butylacetoacetate on (+)-menthyl-(+)-(R)-p-toluene sulfinate[8] afforded the β-ketosulfoxide **7** in 86% yield.

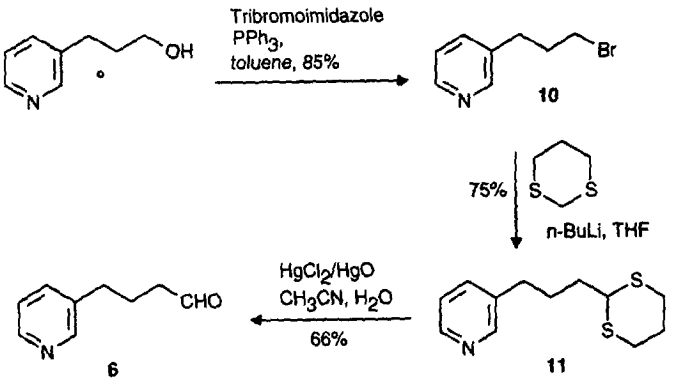


Scheme 2.

The β-ketosulfoxide **7** was then reduced with DIBAL[7] to give in 68% yield the [2R,S(S)]-β-hydroxysulfoxide **8** as the sole diastereomer (the non-equivalence in ^{1}H NMR ($\Delta\nu$=62Hz) between the methylene protons α to the sulfoxide group is consistent with the 2R,S(S) configuration).[6a,b] The final comparison with natural haminol acetate,[4] will indeed confirm the absolute configuration assignment. Compound **8** was then protected with TBDMSCl in high yield and desulfurized with Raney nickel. Finally the ester group was reduced to the corresponding alcohol and oxidized to the aldehyde **5**, in two high yield steps.

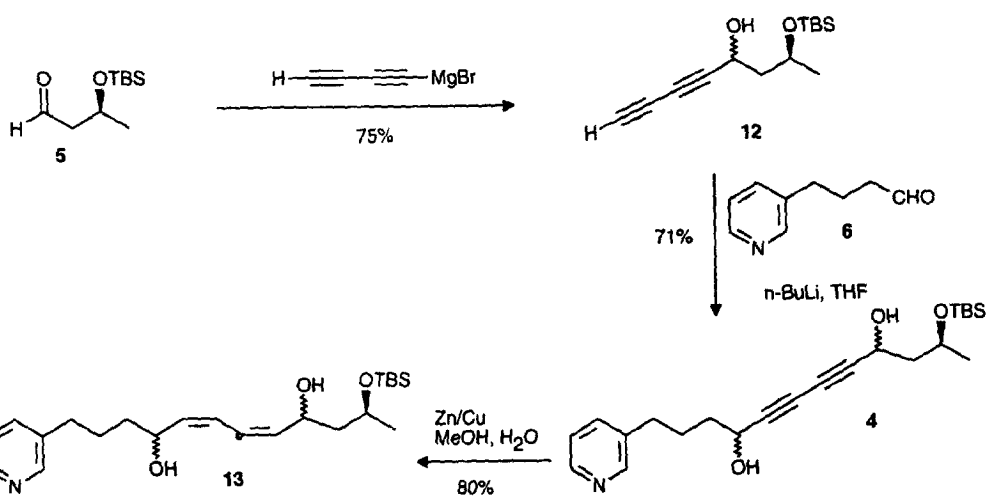
4-(3′-Pyridyl)-butanal, **6**, was obtained by homologation of commercially available 3-(3′-pyridyl)-1-propanol which was first transformed into the bromide **10** with tribromoimidazole and triphenyl

phosphine[9] (85% yield). Then condensation of **10** with the anion of 1,3-dithiane afforded the thioacetal **11** which was then hydrolyzed with mercuric chloride to give the aldehyde **6** in 66% yield (Scheme 3).



Scheme 3.

Condensation of diacetylene magnesium bromide to the aldehyde **5** gave in 75% yield the adduct **12** which was metallated with 2 eq. of butyl lithium and added to the aldehyde **6** to obtain the diyne diol **4** in 71% yield (Scheme 4).

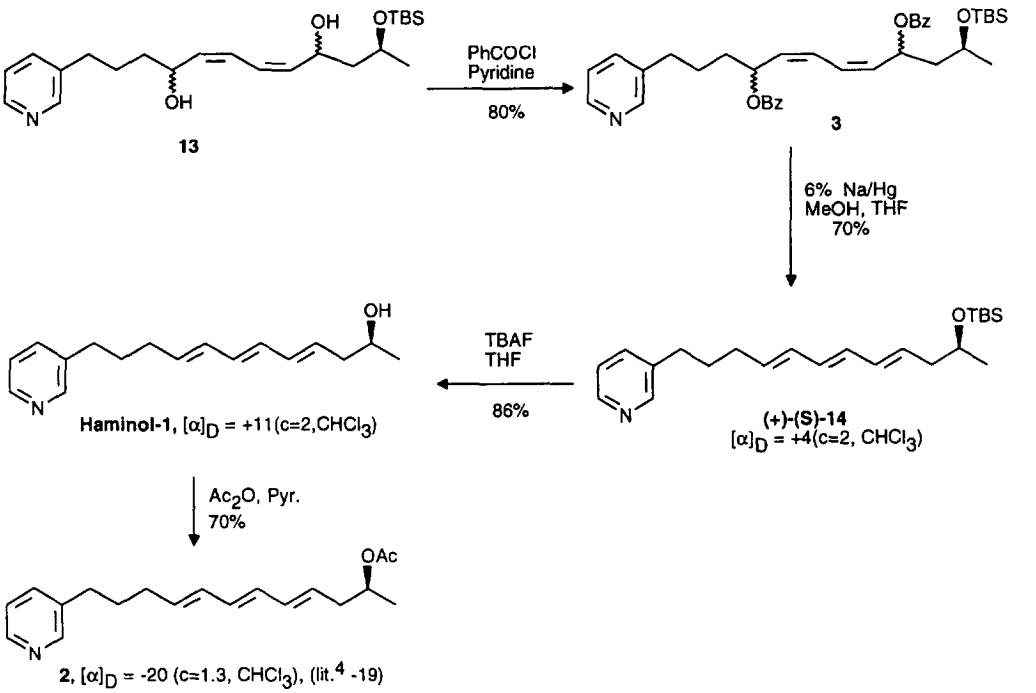


Scheme 4.

Compounds **12** and **4** are a mixture of diastereomers with respect to the asymmetric propargylic carbons, which were directly used in the next step. The triple bonds of the diol **4** were then submitted to the stereoselective reduction with Zn/Cu[10] to get the corresponding (Z,Z)-diene diol **13** in 80% yield (Scheme 4).

The compound **13** was then converted into the dibenzoate diene **3** using standard conditions (Scheme 5).

Application of the reductive elimination reaction with sodium amalgam[5] to compound **3** gave the triene **14** as a unique product in 70% yield. The E,E,E geometry of the double bonds in the triene **14** was established by ^{1}H NMR in the presence of Pr(fod)$_3$. The absence of any other isomer was confirmed by ^{13}C NMR showing only one set of six vinylic carbons.



Scheme 5.

Finally deprotection of the compound **14** afforded haminol-1 in 86% yield. Acylation of **1** gave the acetate **2**, $[\alpha]_D=-20$ (c=1.3, MeOH) identical in all respects with the known alkylpyridine,[4] $[\alpha]_D=-19$ (c=1.3, MeOH). The ^1H and ^{13}C NMR and IR data are identical with those found in literature.[4]

Experimental part

(+)-Menthyl-(+)-(R)-p-toluene sulfinate

To a solution of thionyl chloride (50 mL; 0.7 mol) in toluene (500 mL) was added, in 2 h, p-toluene sulfinic acid sodium salt (dried overnight by azeotropic distillation with toluene, 50 g; 0.281 mol) at 0°C and under argon. After stirring for 10 min, the mixture was evaporated in vacuo and the residue diluted with anhydrous diethylether (250 mL). A solution of (+)-menthol (43.9 g.; 0.281 mol) in dry pyridine (50 mL) was added dropwise at 0°C. After stirring at 0°C for 1.5 h, the reaction was quenched with water (200 mL) and the organic layer was washed with 10% HCl (2×200 mL), with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was diluted with acetone (200 mL), treated with 3–4 drops of concentrated HCl and allowed to crystallize overnight at 5°C. After successive crystallizations, the collected crystals were recrystallized in hot acetone to yield 73 g of (+)-menthyl-(+)-(R)-p-toluene sulfinate (88%) as a white solid. $[\alpha]_D=+202$ (c=2, acetone); mp=110°C.

(−)-(S)-t-Butyl-3-oxo-4-(p-tolylsulfinyl)-butyrate, 7

To a solution of diisopropylamine (20.2 mL; 0.143 mol) in dry THF (450 mL) was added dropwise nBuLi (1.55 M in hexane, 87.6 mL; 0.136 mol) at −78°C and under argon. After stirring for 1 h, tert-butyl acetoacetate (11.10 mL; 67.92 mmol) was added dropwise at the same temperature. The mixture was allowed to reach 0°C and stirred for 2 h. A solution of (+)-menthyl-(+)-(R)-p-toluene sulfinate (10 g; 33.96 mmol) in dry THF (200 mL) was then added dropwise at −78°C. After 1 h at the same temperature, the reaction was quenched with saturated aqueous ammonium chloride (100 mL), acidified to pH 3 with 5% aqueous HCl and diluted with ethyl acetate (200 mL). The aqueous layer was

extracted with ethyl acetate and the collected extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (ethyl acetate/hexane: 1/2) to elute menthol then ethyl acetate gave 8.7 g of β-ketosulfoxide **7** (86%) as a yellow oil. Compound **7** was shown to be partially enolized.

A: Ketonic form/B: enolic form; A/B=73/27; Rf=0.25 (AcOEt/hexane=3/7); $[\alpha]_D=-204$ (c=1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz): δ: 1.45 (s, 9H, t-BuO, A); 1.48 (s, 9H, t-BuO, B); 2.43 (s, 3H, Me p-Tol); 3.46 (dd, AB, 2H, H-2, A, J=16Hz, Δν=14Hz); 3.50 (dd, AB, 2H, H-4, B, J=13Hz, Δν=22Hz); 3.97 (dd, AB, 2H, H-4, A, J=13.5 Hz, Δν=18Hz); 5.00 (s, 1H, H-2, B); 7.34 and 7.55 (d, AA′BB′, 4H, Arom., J=8Hz); 12.13 (s, 1H, OH, B); ^{13}C NMR ($CDCl_3$, 50MHz): δ: 21.4 (Me p-Tol); 27.9 ($(CH_3)_3C$, A); 28.1 ($(CH_3)_3C$, B); 51.9 (C-2, A); 63.7 (C-4, B); 67.4 (C-4, A); 81.6 (Me_3CO); 95.9 (C-2, B); 123.9 and 129.9 (Arom. CH, B); 123.9 and 130.1 (Arom. CH, A); 139.2 and 142.0 (Arom. Cq, A); 140.0 and 142.2 (Arom. Cq, B); 165.2 and 165.5 (C-1 and C-3, B); 171.6 (C-1, A); 194.8 (C-3, A); IR ($CHCl_3$): 1700, 1630, 1140, 1080 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.83; H, 6.80.

(−)-[3R,S(S)]-t-Butyl-3-hydroxy-4-(p-tolylsulfinyl)-butyrate, 8

To a solution of the β-ketosulfoxide **7** (1.48 g; 5 mmol) in dry THF (40 mL) was added dropwise DIBAL (1 M in toluene, 6 mL) at −78°C and under argon. After 0.5 h, the reaction was quenched with methanol (1 mL); then ethyl acetate (50 mL) and saturated aqueous sodium tartrate (50 mL) were added and the mixture was stirred until separation in two distinct phases. The aqueous layer was extracted with ethyl acetate (2×30 mL) and the collected extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (ethyl acetate/hexane: 1/1) yielded 1 g of β-hydroxysulfoxide **8** (68%) as a yellow oil.

Rf=0.30 (AcOEt/hexane=1/1); $[\alpha]_D=-189$ (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz): δ: 1.42 (s, 9H, t-BuO); 2.42 (s, 3H, Me p-Tol); 2.46 (d, 2H, H-2, J=6.5Hz); 2.69–3.08 (AB of ABX, 2H, H-4, J_{AB}=13.5 Hz, J_{AX}=10Hz, J_{BX}=2.5 Hz, Δν=62Hz); 4.12 (d, 1H, OH, J=3.5Hz); 4.51–4.59 (m, X of ABX, 1H, H-3); 7.34 and 7.54 (AA′BB′, 4H, Arom., J=8Hz); ^{13}C NMR ($CDCl_3$, 50MHz): δ: 21.4 (Me p-Tol); 28.0 ($(CH_3)_3$ CO); 42.0 (C-2); 61.8 (C-4); 63.6 (C-3); 81.6 (Me_3CO); 123.9 and 130.1 (Arom. CH); 139.9 and 141.6 (Arom. Cq); 170.6 (C-1); IR ($CHCl_3$): 3600–3100, 1710, 1080 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_4S$: C, 60.38; H, 7.43. Found: C, 60.31; H, 7.33.

(+)-[3(R),S(5)]-t-Butyl-3-(t-butyldimethylsilyloxy)-4-(p-tolylsulfinyl)-butyrate

To a solution of β-hydroxysulfoxide **8** (418 mg; 1.4 mmol) in dry DMF (7 mL) was added imidazole (238 mg; 3.5 mmol) and tert-butyldimethylsilyl chloride (317 mg; 2.1 mmol) at room temperature and under argon. The mixture was stirred overnight, hydrolyzed with water (20 mL), extracted with diethylether (60 mL) and stirred until separation in two distinct layers. The aqueous layer was extracted with diethylether (2×30 mL) and the collected extracts were washed with saturated aqueous ammonium chloride (3×30 mL), with brine, dried over magnesium sulfate and evaporated in vacuo. Chromatography on silica gel (ethyl acetate/hexane: 1/4) yielded 555 mg of silylated β-hydroxysulfoxide (96%) as a pale yellow oil.

Rf=0.30 (AcOEt/hexane=1/4); $[\alpha]_D=-136$ (c=2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz): δ: 0.15 and 0.23 (s, 6H, MeSi); 0.94 (s, 9H, t-BuSi), 1.43 (s, 9H, t-BuO); 2.41 (s, 3H, Me p-Tol); 2.47–2.52 (AB of ABX, 2H, H-2, J_{AB}=15Hz, J_{AX}=6Hz, J_{BX}=4.5Hz, Δν=14Hz); 2.95–3.01 (AB of ABX, 2H, H-4, J_{AB}=13Hz, J_{AX}=8.5Hz, J_{BX}=4Hz, Δν=15Hz); 4.52–4.65 (m, X of ABX, 1H, H-3); 7.31 and 7.53 (d, AA′BB′, 4H, Arom. J=8Hz); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.9 and −4.6 (MeSi); 18.0 (Me_3CSi); 21.3 (Me p-Tol); 25.7 ($(CH_3)_3CSi$); 28.0 ($(CH_3)_3CO$); 43.4 (C-2); 64.0 (C-3); 66.4 (C-4); 80.3 (Me_3CO); 123.6 and 129.9 (Arom. CH); 141.1 and 141.4 (Arom. Cq); 169.3 (C-1); IR ($CHCl_3$): 2960, 1740, 1090 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_4SSi$: C, 61.16; H, 8.77. Found: C, 61.33; H, 8.71.

(+)-(S)-t-Butyl-3-(t-butyldimethylsilyloxy)-butyrate, 9

To a solution of the preceding silylated β-hydroxysulfoxide (5.4 g; 13.1 mmol) in methanol (150 mL) was added activated Raney nickel at room temperature and under argon. (The Raney nickel was activated by washing with distilled water and then washing with methanol). The reaction was followed by TLC and stirred until silylated β-hydroxysulfoxide disappeared. The mixture was filtered over celite and evaporated in vacuo. Purification by Kugelrohr distillation (bp=95°C/0.4 mm Hg) yielded 2.23g of silylated β-hydroxyester **9** (63%) as a colorless oil.

Rf=0.70 (diethylether/hexane=1/10); $[\alpha]_D$=+20 (c=2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200MHz): δ: 0.06 and 0.07 (s, 6H, MeSi); 0.99 (s, 9H, t-BuSi); 1.20 (d, 3H, H-4, J=6Hz); 1.45 (s, 9H, t-BuO); 2.21–2.47 (AB of ABX, 2H, H-2, J_{AB}=14.7Hz, J_{AX}=6.8Hz, J_{BX}=6Hz, Δν=34Hz); 4.18–4.27 (m, X of ABX, 1H, H-3); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.9 and −4.5 (MeSi); 18.0 (Me_3CSi); 23.7 (C-4); 25.8 (($CH_3)_3CSi$); 28.1 (($CH_3)_3CO$); 46.0 (C-2); 65.7 (C-3); 80.1 (Me_3CO); 170.9 (C-1); IR ($CHCl_3$): 2960, 1740 cm^{-1}. Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.01. Found: C, 61.02; H, 10.92.

(+)-(S)-3-(t-Butyldimethylsilyloxy)-butanol

To a solution of silylated β-hydroxyester **9** (1.66 g; 6.73 mmol) in a diethylether/pentane mixture (500 mL; 1/9;) was added dropwise DIBAL (1 M in toluene, 20.5 mL; 10 mL/h) at 0°C and under argon. The mixture was stirred for 0.5 h at the same temperature, quenched with 10% aqueous HCl (100 mL) and the aqueous layer extracted with ethyl acetate (3×100 mL). The collected extracts were washed with water (2×200 mL), with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (diethylether/hexane: 3/7) yielded 1.08 g of (+)-(S)-3-(t-butyldimethylsilyloxy)-butanol (80%) as a colorless oil.

Rf=0.25 (diethylether/hexane=1/4); $[\alpha]_D$=+29 (c=2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200MHz): δ: 0.04 and 0.05 (s, 6H, MeSi); 0.85 (s, 9H, t-BuSi); 1.15 (d, 3H, H-4, J=6.1Hz); 1.51–1.77 (m, 2H, H-2); 2.93 (s, broad, 1H, OH); 3.65–3.76 (m, 2H, H-1); 3.99–4.10 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.4 and−5.0 (MeSi); 17.9 (Me_3CSi); 23.4 (C-4); 25.8 (($CH_3)_3CSi$); 40.5 (C-2); 60.4 (C-1); 68.3 (C-3); IR ($CHCl_3$): 3550–3200, 2960 cm^{-1}. Anal. Calcd for $C_{10}H_{24}O_2Si$: C, 58.77; H, 11.84. Found: C, 58.65; H, 11.89.

(+)-(S)-3-(t-Butyldimethylsilyloxy)-butanal, 5

Pyridiniumchlorochromate (PCC) (3.45 g; 16.02 mmol) and sodium acetate (330 mg; 4 mmol) were dried in a flask under vacuum. Dry dichloromethane was added (20 mL) then, dropwise, a 0.4 M dichloromethane solution of the preceding alcohol (1.64 g; 8.01 mmol) at room temperature and under argon. After 2 h at the same temperature, the mixture was diluted with diethylether and filtered through florisil 60–100 mesh. Evaporation in vacuo of the organic layer yielded 1.37 g of the aldehyde **5** (84%).

Rf=0.60 (diethylether/hexane=1/4); $[\alpha]_D$=+19 (C=2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200MHz): δ: 0.04 and 0.06 (S, 6H, MeCSi); 0.85 (s, 9H, t-BuSi); 1.22 (d, 3H, H-4, J=6Hz); 2.48 (AB of ABXM, 2H, H-2, J_{AB}=16Hz, J_{AX}=7Hz, J_{BX}=6Hz, J_{AM}=J_{BM}=2.5Hz, Δν=36Hz); 4.33 (sextet, X of ABXM, 1H, H-3, J=6Hz); 9.77 (t, M of ABXM, 1H, H-1, J_{AM}=J_{BM}=2.5Hz); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.9 and −4.3 (MeSi); 18.0 (Me_3C Si); 24.2 (C-4); 25.8 (($CH_3)_3C$ Si); 53.0 (C-2); 64.6 (C-3); 202.1 (C-1); IR ($CHCl_3$): 2920, 1720 cm^{-1} .

1-Bromo-3-(3′-pyridyl)-propane, 10

To a solution of 3-(3′-pyridyl)-propanol (2.12 g; 15.5 mmol) in dry toluene (350 mL) were added tribromoimidazole (6.61 g.; 21.7 mmol), imidazole (1.47 g; 21.7 mmol) and triphenylphosphine (5.7 g; 21.7 mmol). The solution was heated for 2 h then filtered, washed with water (3×500 mL), with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Triphenylphosphine oxide was eliminated by several precipitations with cold diethylether and the organic layer evaporated in vacuo.

Chromatography on silica gel (ethyl acetate/hexane: 7/3) yielded 2.67g of the bromide **10** (86%) as a pale yellow oil that was immediatly used because of its unstability.

Rf=0.50 (AcOEt/hexane=7/3); ^{1}H NMR ($CDCl_3$, 200MHz): δ: 2.10–2.25 (m, 2H, H-2); 2.81 (t, 2H, H-3, J=7.8Hz); 3.40 (t, 2H, H-1, J=6.4Hz); 7.21–7.28 (m, 1H, H-5′); 7.52–7.60 (m, 1H, H-4′), 8.48 (m, 2H, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 50MHz): δ: 31.0 and 32.4 and 33.5 (C-1 and C-2 and C-3); 123.5 (C-5′); 135.9 (C-3′); 136.2 (C-4′); 147.4 and 149.6 (C-2′ and C-6′); IR ($CHCl_3$): 2930 cm^{-1}.

*1-(1″,3″-Dithianyl)-3-(-3′-pyridyl)-propane, **11***

To a solution of 1,3-dithiane (2.37g; 19.7 mmol) in dry THF (60 mL) was added dropwise n-butyl lithium (1.45 M in hexane, 14.96 mL; 21.7 mmole; 3 mL/min.) at −40°C and under argon. The mixture was stirred for 2.5 h at −20°C. Then 1-bromo-3-(-3′-pyridyl)-propane **10** (3.59 g; 13.9 mmol) in dry THF (80 mL) was added dropwise on the dithiane anion at −40°C. After 2 h at the same temperature, the reaction was quenched with water (100 mL) and the aqueous layer was extracted with dichloromethane (3×100 mL). The collected organic layers were washed with water (2×300 mL), with aqueous 7% sodium hydroxide (300 mL), with water (300 mL), with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (ethyl acetate/hexane: 3/2) yielded 3.2 g of thioacetal **11** (75%).

Rf=0.50 (AcOEt/hexane=7/3); ^{1}H NMR ($CDCl_3$, 200MHz): δ: 1.76–1.91 (m, 5H, H-1 and H-2 and axial H-5″); 2.01–2.13 (m, 1H, equatorial H-5″); 2.62 (t, 2H, H-3, J=7.3Hz); 2.80–2.87 (m, 4H, H-4″ and H-6″); 4.04 (t, 1H, H-2″, J=6.5Hz); 7.21 (dd, 1H, H-5′, $J_{5'-6'}$=5.2Hz, $J_{5'-4'}$=7.7Hz); 7.48 (dt, 1H, H-4′, $J_{4'-5'}$=7.7Hz, $J_{4'-6'}$=2Hz); 8.43 (m, 2H, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 50MHz): δ: 25.9 and 27.9 and 30.4 and 32.4 and 34.8 (C-1 and C-2 and C-3 and C-4″ and C-5″ and C-6″); 47.2 (C-2″); 123.3 (C-5′); 135.7 (C-4′); 136.9 (C-3′); 147.4 and 149.9 (C-2′ and C-6′); IR ($CHCl_3$): 2920 cm^{-1}.

*4-(3′-Pyridyl)-butanal, **6***

To a mixture of mercuric chloride (7.82 g; 28.8 mmole) and mercuric oxide (3.12 g; 14.4 mmol) in acetonitrile/water (160 mL; 8/2) was added the thioacetal **11** (3.13 g; 13 mmol) dissolved in the same solvent mixture (100 mL) and the reaction was heated 4 h at 80°C. The mixture was filtered, washed with aqueous ammonium acetate 5 M (200 mL), with water (300 mL), with brine, dried over magnesium sulfate, filtered and evaporated in vacuo to yield 1.28 g of the aldehyde **6** (66%) as a pale yellow oil.

Rf=0.30 (AcOEt/hexane=7/3); ^{1}H NMR ($CDCl_3$, 200MHz): δ: 1.96 (quintet, 2H, H-3, J=7.5Hz); 2.49 (td, 2H, H-2, J=7.2Hz, J=1.3Hz); 2.65 (t, 2H, H-4, J=8Hz); 7.19–7.25 (m, 1H, H-5′); 7.47–7.53 (m, 1H, H-4′); 8.46 (m, 2H, H-2′ and H-6′); 9.78 (t, 1H, H-1, J=1.3Hz); ^{13}C NMR ($CDCl_3$, 50MHz): δ: 23.2 (C-3); 32.0 (C-4); 42.9 (C-2); 123.7 (C-5′); 136.1 (C-4′); 136.9 (C-3′); 147.5 and 149.6 (C-2, C-2′ and C-6′); 201.7 (C-1); IR ($CHCl_3$): 2940, 1725 cm^{-1}.

*(+)-2(S)-4-Hydroxy-2-(t-butyldimethylsilyloxy)-5,7-octadiyne, **12***

To a solution of potassium hydroxide (12.75 g; 0.23 mol) in dimethyl sulfoxide/water (25 mL; 17/83) was added dropwise 1,4-dichlorobutyne (6.25g; 50 mmol) at room temperature. The mixture was heated at 95°C for 1.5 h and the resulting gaseous butadiyne (2.05 g; 41 mmol) was trapped in dry THF at −60°C. To this solution was added dropwise ethyl magnesium bromide 1M (18.4 mL) at −20°C and under argon. The resulting anion was stirred for an additional hour at room temperature and a solution of the aldehyde **5** (1.24 g; 6.12 mmol) in dry THF (10 mL) was added dropwise at 0°C. After 2 h at the same temperature, the reaction was quenched with saturated aqueous ammonium chloride (30 mL) and the aqueous layer extracted with diethylether (3×30 mL). The collected extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (diethylether/hexane: 1/4) yielded 1.16 g (75%) of the adduct **12** as a pair of diastereomers in a ratio 1/2 (dark brown oil/dark brown solid).

Liquid diastereomer: Rf=0.46 (diethylether/hexane=1/4); $[\alpha]_D$=+44 (c=0.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz): δ: 0.11 and 0.14 (s, 6H, MeSi); 0.89 (s, 9H, t-BuSi); 1.21 (d, 3H, H-1, J=6.2Hz); 1.85 (t, 2H, H-3, J=5.3Hz); 2.17 (s, 1H, H-8); 3.68 (d, 1H, OH, J=6.3Hz); 4.31 (sextet, 1H, H-2, J=6.1Hz); 4.64 (q, 1H, H-4, J=5.6Hz); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.8 and −4.0 (MeSi); 18.0 (Me_3CSi); 23.6 (C-1); 25.9 ($(CH_3)_3CSi$); 44.5 (C-3); 60.7 (C-2); 67.2 and 68.2 (C-4 and C-5 and C-6 and C-7 and C-8); IR ($CHCl_3$): 3500–3300, 3320, 2960 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.56; H, 9.46.

Solid diastereomer: Rf=0.36 (diethylether/hexane=1/4); mp=59–61°C; $[\alpha]_D$=+55 (c=0.16, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz): δ: 0.09 and 0.10 (s, 6H, MeSi); 0.88 (s, 9H, t-BuSi); 1.21 (d, 3H, H-1, J=6.1Hz); 1.74–2.02 (m, 2H, H-3); 2.18 (s, 1H, H-8); 2.88 (d, 1H, OH, J=3.7Hz); 4.02–4.12 (m, 1H, H-2); 4.57–4.62 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.8 and −4.0 (MeSi); 18.0 (Me_3CSi); 24.3 (C-1); 25.7 ($(CH_3)_3CSi$); 46.3 (C-3); 61.5 (C-2); 67.2 and 67.5 and 68.4 and 69.3 (C-4 and C-5 and C-6 and C-7 and C-8); IR ($CHCl_3$): 3500–3300, 3310, 2960 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.67; H, 9.48.

2(S)-4,9-Dihydroxy-2-(t-butyldimethylsilyloxy)-12-(3'-pyridyl)-dodeca-5,7-diyne, ***4***

To a solution of the adduct **12** (1.03 g; 4.08 mmoles) in dry THF (40 mL) was added dropwise nBuLi (1.49 M, 5.48 mL; 8.16 mmol) at 0°C and under argon. The mixture was stirred for 1 h at room temperature and a solution of the aldehyde **6** (305 mg; 2.04 mmol) in dry THF (30 mL) was added dropwise at −78°C. After 1.5 h at room temperature, the reaction was quenched with saturated aqueous ammonium chloride (100 mL) and the aqueous layer extracted with diethylether (3×100 mL). The collected extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (ethyl acetate) yielded 584 mg of the diyne diol **4** (71%) as a yellow oil.

Rf=0.50 (AcOEt); ^1H NMR ($CDCl_3$, 200MHz): δ: 0.08 and 0.10 and 0.11 (s, 6H, MeSi); 0.87 and 0.89 (s, 9H, t-BuSi); 1.17 (d, 3H, H-1, J=6.1Hz); 1.68–1.92 (m, 6H, H-3 and H-10 and H-11); 2.66 (t, 2H, H-12, J=6.9Hz); 4.01–4.40 (m, 1H, H-2); 4.47 (t, 1H, H-9, J=5.9Hz); 4.57–4.69 (m, 1H, H-4); 7.22 (dd, 1H, H-5', $J_{5'-6'}$=4.8Hz, $J_{5'-4'}$=7.7Hz); 7.50 (dt, 1H, H-4', $J_{4'-5'}$=7.7Hz, $J_{4'-6'}$=2Hz); 8.43 (m, 2H, H-2' and H-6'); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.8 and −4.1 and −4.0 (MeSi); 18.0 (Me_3CSi); 23.8 and 24.2 (C-1); 25.9 ($(CH_3)_3CSi$); 26.5 and 32.6 and 36.9 (C-10 and C-11 and C-12); 45.4 and 46.8 (C-3); 60.1 and 61.1 and 61.9 and 66.5 and 67.0 (C-2 and C-4 and C-9); 80.6 and 80.7 and 80.8 and 80.9 (C-5 and C-6 and C-7 and C-8); 123.7 (C-5'); 136.6 (C-4'); 137.7 (C-3'); 146.8 and 149.3 (C-2' and C-6'); IR ($CHCl_3$): 3500–3300, 2940 cm^{-1}. Anal. Calcd for $C_{23}H_{35}NO_3Si$: C, 68.78; H, 8.78. Found: C, 68.89; H, 8.75.

2(S)-4,9-Dihydroxy-2-(t-butyldimethylsilyloxy)-12-(3'-pyridyl)-dodeca-5,7-diene, ***13***

(The preparation of activated zinc/copper was carried out with a continuous argon flow).

A suspension of zinc dust (6.25 g; 96 mmol) in water (40 mL) was stirred for 15 min. Copper acetate (570 mg; 3.14 mmol) was added and the mixture was stirred for 15 min, then silver nitrate was added (622 mg; 3.66 mmol) and the mixture was stirred for 30 min. The activated zinc dust was washed with 250 mL of each of the following solvents: water, methanol, acetone and diethylether. The activated Zn was added still wet to a mixture methanol/water (30 mL; 1/1) and a solution of the diyne diol **13** (700 mg; 1.74 mmol) in methanol (4.5 mL) was added and stirred for 48 h. Diethylether was added (3×50 mL) and the liquid layers were collected after decantation of the zinc dust, then evaporated in vacuo. The residue obtained was diluted with diethylether (100 mL), dried over magnesium sulfate and evaporated in vacuo. Chromatography on silica gel (ethyl acetate/hexane: 7/3) yielded 554 mg of the diene diol **13** (80%) as a pale yellow oil.

Rf=0.35 (AcOEt); ^1H NMR ($CDCl_3$, 200MHz): δ: 0.04 and 0.05 and 0.06 and 0.07 and 0.09 (s, 6H, MeSi); 0.85 and 0.86 and 0.87 and 0.89 (s, 9H, t-BuSi); 1.12–1.19 (m, 3H, H-1); 1.36–1.81 (m, 6H, H-3 and H-10 and H-11); 2.56–2.66 (m, 2H, H-12); 3.48–4.92 (m, 3H, H-2 and H-4 and H-9);

5.27–6.55 (m, 4H, H-5 and H-6 and H-7 and H-8); 7.16 (dd, 1H, H-5′, $J_{5'-6'}$=4.8Hz, $J_{5'-4'}$=7.7Hz); 7.47 (d, 1H, H-4′, J=7.7Hz); 8.37 (m, 2H, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.9 and −4.8 and −4.7 and −4.4 and −4.1 (MeSi); 17.9 (Me_3CSi); 23.4 and 23.5 and 24.2 and 24.3 (C-1); 25.7 (($CH_3)_3CSi$); 26.4 and 26.7 and 26.8 and 31.7 and 32.6 and 32.9 and 35.7 and 36.9 and 37.2 (C-10 and C-11 and C-12); 44.4 and 45.6 and 46.4 and 47.4 (C-3); 60.6 and 61.5 and 61.7 and 64.2 and 68.5 and 68.7 (C-2 and C-4 and C-9); 123.5 and 123.7 and 123.9 (C-5 and C-6 and C-7 and C-8 and C-5′); 149.3 (C-2′ and C-6′); IR ($CHCl_3$): 3500–3300, 2940 cm^{-1}.

2(S)-4,9-Dibenzoyl-2-(t-butyldimethylsilyloxy)-12-(3′-pyridyl)-dodeca-5,7-diene, 3

To a solution of diene diol **13** (485 mg; 1.2 mmol) in dry pyridine (20 mL) was added dropwise benzoyl chloride (0.305 mL; 2.63 mmol) at room temperature and under argon. After 24 h, the solvent was evaporated in vacuo and the liquid residue was diluted with diethylether (20 mL), washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (ethyl acetate/hexane: 3/7) yielded 575 mg of the dibenzoate diene **3** (79%) as a pale yellow syrup.

Rf=0.70 (AcOEt); ^{1}H NMR ($CDCl_3$, 200MHz): δ: −0.08–0.11 (m, 6H, MeSi); 0.83–0.92 (m, 9H, t-BuSi); 1.14–1.29 (m, 3H, H-1); 1.71–2.04 (m, 6H, H-3 and H-10 and H-11); 2.60–2.65 (m, 2H, H-12); 3.80–4.02 (m, 1H, H-2); 5.50–6.10 and 6.49–6.78 (m, 6H, H-4 and H-5 and H-6 and H-7 and H-8 and H-9); 7.10–7.22 (m, 1H, H-5′); 7.36–7.60 (m, 7H, H-4′ and 6 Arom. H); 7.97–8.08 (m, 4H, Arom.); 8.43 (m, 2H, H-2′and H-6′); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −5.0 and −4.6 and −4.1 and −4.0 (MeSi); 17.9 and 18.1 (Me_3CSi); 23.9 and 24.2 and 24.4 (C-1); 25.9 (($CH_3)_3CSi$); 26.6 and 31.6 and 32.5 and 32.6 and 33.6 and 34.3 (C-10 and C-11 and C-12); 44.5 and 44.9 (C-3); 64.7 and 65.4 and 68.0 and 68.2 and 68.4 and 70.0 and 72.6 (C-2 and C-4 and C-9); 123.3 (C-5′); 126.0 and 126.2 and 126.7 and 128.4 and 129.6 and 129.7 and 129.9 and 130.0 and 130.3 and 130.4 and 130.9 and 131.1 and 131.2 and 131.9 and 132.9 and 133.1 and 135.7 and 137.0 (C-5 and C-6 and C-7 and C-8 and C-3′ and C-4′ and Arom. Cq and Arom. Ct.); 147.4 and 149.9 (C-2′ and C-6′); 165.4 and 165.5 and 165.6 and 165.7 (Arom. Cq); IR ($CHCl_3$): 2940, 1740 cm^{-1}. Anal. Calcd for $C_{37}H_{47}NO_5Si$: C, 72.39; 6.90; N, 2.28. Found: C, 72.29; H, 6.99; N, 2.27.

2(S)-(4E,6E,8E)-2-(t-Butyldimethylsilyloxy)-12-(3′-pyridyl)-dodecatriene, 14

To a solution of dibenzoate diene **3** (460 mg; 0.75 mmol) in a mixture THF/methanol (40 mL; 3/1) was added sodium hydrogenophosphate (745 mg; 5.24 mmol) and 6% sodium amalgam (2.88 g; 7.5 mmol) at −20°C and under argon. After 4 h at the same temperature, the reaction was treated with a mixture diethylether/water (40 mL; 1/1) and the aqueous layer was extracted with diethylether (3×50 mL). The collected organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (diethylether/hexane: 3/7) yielded 195 mg of the triene **14** (70%) as a colorless oil.

Rf=0.50 (AcOEt/hexane=2/3); $[\alpha]_D$=+4 (c=2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200MHz): δ: 0.04 (s, 6H, MeSi); 0.88 (s, 9H, t-BuSi); 1.12 (d, 3H, H-1, J=6.1Hz); 1.72 (quintet, 2H, H-11, J=7.6Hz); 2.08–2.25 (m, 4H, H-3 and H-10); 2.61 (t, 2H, H-12, J=7.7Hz); 3.81 (sextet, 1H, H-2, J=6Hz); 5.68–6.10 (m, 6H, H-4 and H-5 and H-6 and H-7 and H-8 and H-9); 7.20 (dd, 1H, H-5′, $J_{5'-6'}$=4.8Hz, $J_{5'-4'}$=7.7Hz); 7.49 (dt, 1H, H-4′, $J_{4'-5'}$=7.7Hz, $J_{4'-6'}$=2Hz); 8.43 (m, 2H, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 50MHz): δ: −4.6 and −4.5 (MeSi); 18.2 (Me_3CSi); 23.6 (C-1); 26.0 (($CH_3)_3CSi$); 30.7 (C-11); 32.0 and 32.2 (C-10 and C-12); 43.3 (C-3); 66.7 (C-2); 123.3 (C-5′); 131.0 and 131.3 and 131.4 and 131.7 and 132.4 and 133.2 (C-4 and C-5 and C-6 and C-7 and C-8 and C-9); 135.8 (C-4′); 137.5 (C-3′); 147.3 and 150.0 (C-2′ and C-6′); IR ($CHCl_3$): 2930 cm^{-1}. Air-sensitive compound.

The double bonds stereochemistry was established by ^{1}H NMR in presence of $Pr(fod)_3$: to a solution of **14** (10 mg, 0.027 mmol) in deuterated chloroform, was added $Pr(fod)_3$ (28 mg, 0.027 mmol) in 7 portions. After every addition, an NMR spectrum was recorded. A progressive scattering of the signal corresponding to the olefinic protons was observed allowing the determination of the coupling constants: H-4 and H-9, dt, J=15 Hz and J=8 Hz, H-5, H-6, H-7 and H-8, dd, J=15 Hz and J=10 Hz.

Haminol-1, 1

To a solution of triene **14** (178 mg; 0.48 mmol) in dry THF (30 mL) was added dropwise TBAF (1 M in THF, 0.57 mL) at 0°C and under argon. The reaction was allowed to reach room temperature and stirred overnight. Diethylether (15 mL) and saturated aqueous ammonium chloride (15 mL) were added and the aqueous layer was extracted with diethylether (3×20 mL). The collected organic layers were washed with water (3×50 mL), brine, dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (ethyl acetate) yielded 106 mg of haminol-1 **1** (86%) as a colorless oil.

Rf=0.15 (AcOEt/hexane=2/3); $[\alpha]_D$=+11 (c=2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200MHz): δ: 1.20 (d, 3H, H-1, J=6.2Hz); 1.72 (quintet, 2H, H-11, J=7.5Hz); 2.06–2.26 (m, 4H, H-2 and H-10); 2.61 (t, 2H, H-12, J=7.6Hz); 3.84 (m, 1H, H-2); 5.60–6.20 (m, 6H, H-4 and H-5 and H-6 and H-7 and H-8 and H-9); 7.22 (dd, 1H, H-5′, $J_{5'-6'}$=4.8Hz, $J_{5'-4'}$=7.7Hz); 7.49 (bd, 1H, H-4′, J=7.7Hz); 8.43 (m, 2H, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 50MHz): δ: 23.0 (C-1); 30.6 (C-11); 32.1 and 32.3 (C-10 or C-12); 42.9 (C-3); 67.3 (C-2); 123.4 (C-5′); 130.1 (C-4); 130.9 and 131.2 and 131.5 (C-5 and C-6 and C-8); 133.3 and 133.7 (C-7 and C-9); 136.0 (C-4′); 137.6 (C-3′); 147.1 and 149.8 (C-2′ and C-6′); IR ($CHCl_3$): 3650–3500, 2920 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.40; N, 5.44. Found: C, 79.37; H, 9.38; N, 5.49.

Haminol acetate, 2

To a solution of haminol-1, **1** (98 mg; 0.38 mmol) in dry pyridine (6 mL) was added dropwise acetic anhydride (40 µl; 0.42 mmol) at 0°C and under argon. The reaction was allowed to reach room temperature and stirred overnight. The solvent was evaporated in vacuo and the residue was diluted with diethylether (15 mL), dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography on silica gel (ethyl acetate/hexane: 1/1) yielded 80 mg of haminol acetate, **2** (70%) as a colorless oil.

Rf=0.55 (AcOEt/hexane=1/1); $[\alpha]_D$=−20 (c=1.3, MeOH); (lit.[4], −19, c=1.3, MeOH); ^1H NMR ($CDCl_3$, 200MHz): δ: 1.20 (d, 3H, H-1, J=6.2Hz); 1.71 (quintet, 2H, H-11, J=7.4Hz); 2.00–2.37 (m, 9H, H-3 and H-10 and H-11 and CH_3CO); 4.93 (m, 1H, H-2); 5.40–6.10 (m, 6H, H-4 and H-5 and H-6 and H-7 and H-8 and H-9); 7.20 (dt, 1H, H-5′, $J_{5'-6'}$=4.8Hz; $J_{5'-4'}$=7.7Hz); 7.49 (bd, 1H, H-4′, J=7.7Hz); 8.43 (m, 2H, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$, 50MHz): δ: 19.6 (C-1); 21.4 (CH_3CO_2); 30.7 (C-11); 32.2 and 32.4 (C-10 and C-12); 39.3 (C-3); 70.4 (C-2); 123.2 (C-5′); 128.6 (C-4); 130.8 and 131.2 and 131.7 (C-5 and C-6 and C-8); 133.4 and 133.9 (C-7 and C-9); 135.9 (C-4′); 137.6 (C-3′); 147.4 and 150.0 (C-2′ and C-6′); 170.7 (CH_3CO_2); IR ($CHCl_3$): 2940, 1730 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.24; H, 8.39; N, 4.65.

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(Received in UK 8 January 1997)