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New 3-Alkylpyridines from Three Mediterranean Cephalaspidean Molluscs: Structure, Ecological Role and Taxonomic Relevance

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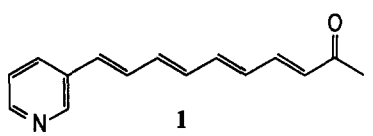
Abstract: Seven new 3-alkylpyridines, showing alarm pheromone activity, have been isolated from three *Haminoea* cephalaspidean molluscs: *H. orteai*, *H. orbignyana* and *H. fusari*. Structures were elucidated by spectral analysis; absolute stereochemistry was determined by applying Mosher's method.

Cephalaspidean molluscs are characterized by a prominent head and by inadequate protection of a shell that is either small and fragile or internal. [2] The first chemical studies on cephalaspideans revealed the presence in the Pacific Aglajide *Navanax inermis* [3] of a series of metabolites , e.g. navenone-A (**1**), which when secreted into the mucus act as alarm pheromones inducing an immediate escape reaction in following conspecifics. Recently, metabolites related to navenones were found in some Mediterranean cephalaspidean molluscs: lignarenone-A (**2**) and -B (**3**) from the Cylichnidae *Scaphander lignarius* [4] and haminol-A (**4**) and haminol-B (**5**) from the Haminoeidae *Haminoea navicula*.[5] Because of the interesting biological properties of haminols, which like navenones act as alarm pheromones, we have begun a chemical investigation of other Mediterranean *Haminoea* species .



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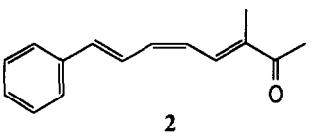

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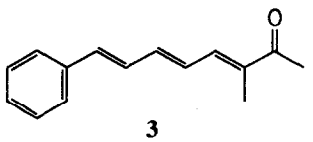

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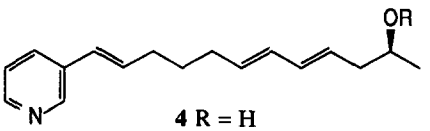


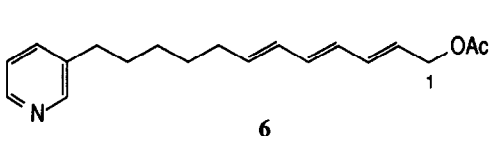
4 R = H
5 R = Ac

Table 1. ^{1}H-NMR Data ($CDCl_3$; 500.13 MHz; m and *J* / Hz in parentheses) of Compounds **6**, **7**, **8**, **9**,**10**,**11** and **12**.

	6	**7**	**8**	**9**	**10**	**11**	**12**
1	4.60 *(d 6.7)*	1.20 *(d 6.1)*	1.20 *(d 6.3)*	1.20 *(d 6.2)*	1.21 *(d 6.3)*	1.19 *(d 6.2)*	1.21 *(d 6.4)*
2	5.72 *(bdt 15.2; 6.7)*	3.84 *(m)*	4.93 *(m)*	3.84 *(m)*	4.92 *(m)*	3.81 *(m)*	4.89 *(m)*
3	6.30 *(dd 15.2; 10.6)*	2.29 *(ddd 13.5;5.3;5.9)*	2.35 *(ddd 13.5;6.3;6.8)*	2.27 *(bdd 14.0;7.4)*	2.27 *(ddd 14.0;7.2;6.9)*	1.55 *(m)*	1.67 *(m)*
		2.21 *(ddd 13.5;6.9;6.7)*	2.30 *(ddd 13.5;6.1;6.8)*	2.16 *(bdd 14.0;7.4)*	2.33 *(ddd 14.0;7.2;6.9)*		1.55 *(m)*
4	6.11 *(dd 14.9; 10.6)*	5.65 *(ddd 14.2;5.9;6.7)*	5.57 *(dt 13.9;6.8)*	5.55 *(dt 14.7;7.4)*	5.48 *(dt 14.4;7.2)*	2.10 *(m)*	2.04 *(m)*
5	6.22 *(dd 14.9; 10.5)*			6.09 *(dd 14.7;10.4)*	6.01 *(m)*	5.46 *(m)*	5.42 *(m)*
6	6.07 *(dd 15.0; 10.5)*	6.05-6.16	6.02-6.10	6.01 *(dd 14.7;10.4)*	6.01 *(m)*	5.46 *(m)*	5.42 *(m)*
7	5.73 *(bdt 15.0; 7.0)*	(four protons)	(four protons)	5.60 *(dt14.7;7.2)*	5.59 *(dt 14.4;7.0)*	2.76 *(m)*	2.75 *(m)*
8	2.10 *(m)*			2.06 *(m)*	2.06 *(m)*	5.62 *(dt 14.4;7.2)*	5.62 *(dt 14.6;6.8)*
9	1.41 *(m)*	5.69 *(dt 14.7 ; 7.4)*	5.67 *(dt 14.2;7.1)*	1.42 *(m)*	1.41 *(m)*	6.05 *(m)*	6.05 *(m)*
10	1.35 *(m)*	2.14 *(dt 7.1 ; 7.4)*	2.14 *(m)*	1.34 *(m)*	1.35 *(m)*	6.05 *(m)*	6.05 *(m)*
11	1.62 *(m)*	1.73 *(m)*	1.72 *(m)*	1.61 *(m)*	1.61 *(m)*	5.69 *(dt 14.4;6.9)*	5.70 *(dt 14.6;6.8)*
12	2.60 *(t 7.7)*	2.62 *(t 7.7)*	2.61 *(t 7.7)*	2.60 *(t 7.6)*	2.60 *(t 7.7)*	3.40 *(d 6.9)*	3.40 *(d 6.8)*
2'	8.44 *(bs)*	8.44 *(bs)*	8.43 *(bs)*	8.43 *(bs)*	8.44 *(bs)*	8.45 *(bs)*	8.45 *(bs)*
4'	7.49 *(bd 7.7)*	7.49 *(bd 7.7)*	7.48 *(bd 7.6)*	7.48 *(bd 7.8)*	7.48 *(bd 7.6)*	7.50 *(bd 7.5)*	7.49 *(bd 7.6)*
5'	7.22 *(bdd 7.7; 4.5)*	7.21 *(bdd 7.7 ; 4.9)*	7.20 *(bdd 7.6;4.8)*	7.20 *(bdd 7.8;4.9)*	7.21 *(bdd 7.6;4.8)*	7.21 *(bdd 7.5;4.5)*	7.22 *(bdd 7.6;4.8)*
6'	8.44 *(d 4.5)*	8.44 *(d 4.9)*	8.43 *(d 4.8)*	8.43 *(d 4.9)*	8.44 *(d 4.8)*	8.45 *(d 4.5)*	8.45 *(d 4.8)*
CH_3CO	2.07 *(s)*		2.01 *(s)*		2.02 *(s)*		2.02 *(s)*

Authoritative literature[6] lists only two *Haminoea* species, *H. navicula* and *H. hydatis*, in the Mediterranean Sea . However, there is great confusion over the taxonomy of *Haminoea* in part due to the fact that early studies only describe the shells without specific anatomical differentiations. We collected populations of *Haminoea* molluscs from Fusaro Lake (Gulf of Naples), where the shells of some species of the genus had previously been described.[7] Three different species were identified : *H. orbignyana* , *H. orteai* and *H. fusari*. *H. orteai* and *H. orbignyana* were described previously only from the Spanish coast,[8] whereas *H. fusari* is a new species. *H. hydatis* and *H. navicula* were absent. TLC (SiO_2; *n*-hexane/ethyl acetate 1:1) analysis of the acetone extracts from the three molluscs revealed very similar chromatographic patterns.

In particular, the extract of *H. orteai* was partially identical to that previously described for *H. navicula* , exhibiting two spots associated to haminol-A (**4**) and -B (**5**), but with a third minor metabolite named haminol-C. Haminol-C (**6**) has the same elementary composition ($C_{19}H_{25}NO_2$) as haminol-B (**5**) . Its ^{1}H-NMR spectrum confirmed the presence of a 3- alkylpyridine on the basis of four downfield resonances between δ 7.22 and 8.44 (table 1). The alkyl chain included an acetoxy group linked to a methylene vinylic to a conjugated triene (λ_{max} 278, 268, 262 nm). A series of ^{1}H-^{1}H NMR decoupling experiments allowed assignment of all couplings of the vinyl protons, which suggested an all-*trans* stereochemistry for the three double bonds. The ^{1}H-NMR spectrum was completed by resonances assigned to five methylenes whose sequence was established by analysis of ^{1}H-^{1}H NMR COSY cross peaks.



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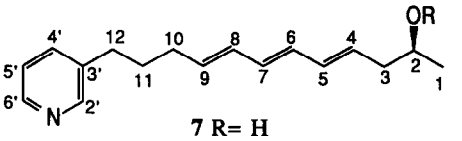

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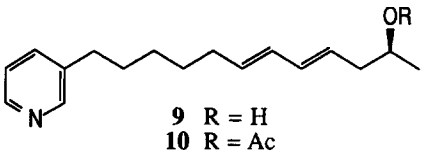
8 R= Ac



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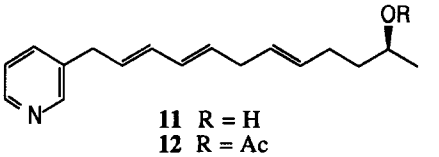
10 R = Ac



11 R = H
12 R = Ac

The metabolite pattern of *H. orbignyana* was characterized by two metabolites, a secondary alcohol (haminol-1, **7**) and its acetate (haminol-2, **8**), isomers of haminol-A (**4**) and -B (**5**), differing only by a C-8 and not a C-11 double bond. Haminol-2 (**8**), $C_{19}H_{25}NO_2$ (EIMS *m/z* 299.1893, M^+, calcd 299.1885), had highly diagnostic ^{1}H-NMR spectrum characterized by the resonances of a pyridine substituted with a linear C_{12} alkyl chain, starting with three methylenes linked to an all -*trans*- conjugated triene, in turn connected to fragment **a** (-CH_2-CH(CH_3)-O-CO-CH_3). All assignments were confirmed by 2D (^{1}H-^{1}H COSY and ^{1}H-^{13}C HETCOR) and 1D (^{1}H-^{1}H decoupling) NMR experiments (table 1). The *trans* configuration of the side chain double bonds was suggested by the values of $J_{4,5}$ (13.9 Hz) and $J_{8,9}$ (14.2 Hz), whereas that of the central double bond was supported by the ^{13}C - NMR values (experimental) of the sp^2 carbons [9]. The spectral data of haminol-1 (**7**) supported the suggested structure, which was confirmed by the identity of its acetate with

haminol-2 (**8**). Absolute *S* -stereochemistry at C-2 was inferred by an application of Mosher's method which will be described below.

H. fusari exhibits external morphological characteristics quite different from those of the other two species co-occurring in the same habitat; furthermore, its metabolite pattern is unique by including along with haminol-1 (**7**) and -2 (**8**), two other alcohol-acetate couples, haminol-3 (**9**), -4 (**10**), -5 (**11**) and -6 (**12**) in addition to some minor components of polypropionic nature, whose structures are as yet undetermined. Haminol-4 (**10**) was recovered from a fraction slightly less polar than haminol-2 (**8**) by preparative TLC on SiO_2 which separated **10** from the more polar haminol-6 (**12**). It should be noted that haminols are highly unstable and that chromatography, even when conducted very rapidly and protected from light, yields only small amounts of pure products. Haminol-4 (**10**) had elementary composition of C_{19} H_{27} N O_2 (EIMS *m/z* 301.2050, M^+, calcd 301.2042) equivalent to a dihydroderivative of haminol-2 (**8**); on the basis of ^{1}H-NMR spectra it should be the 8,9-dihydro derivative. In fact, the ^{1}H-NMR spectra displayed, analogously with haminol-C (**6**), all ^{1}H-NMR resonances (table 1) attributable to a pyridine ring, β-substituted with a linear alkyl chain starting with 5 methylenes and, analogously to haminol-2 (**6**), the resonances of partial structure **a** . The spectrum was completed by well resolved signals of an all-*trans* 1,4 - disubstituted butadiene. The structure was confirmed by a series of 2D and 1D NMR experiments (table 1). Haminol-3 (**9**) was transformed by acetylation to a product identical in all aspects with haminol-4 (**10**). The last alcohol-acetate couple is characterized again by a triene, but with a characteristic double bond pattern in the alkyl chain. In fact haminol-6 (**12**) showed in its ^{1}H-NMR spectrum a diagnostic resonance at δ 2.75, assigned to a doubly vinylic methylene, while another diagnostic resonance at δ 3.40 (doublet, J = 6.8 Hz) was readly assigned to the methylene protons between the pyridine ring and a conjugated diene. Partial structure **a** was linked to the isolated double bond through another methylene. The all-*trans* stereochemistry of the double bonds was assigned on the basis of the ^{1}H-NMR coupling constants of the diene protons and of C-7 ^{13}C-NMR chemical shift (δ 35.5 ppm). Also in this case the structure of haminol-5 (**11**) was supported by the identity of its acetate with haminol-6 (**12**).

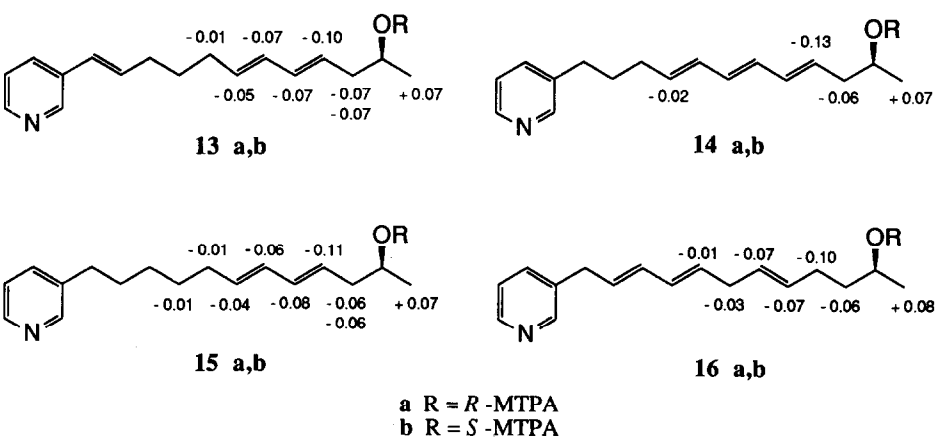
All haminols, with the exception of haminol-C (**6**) , are characterized by a secondary alcohol at C-2 exhibiting, analogously to haminols A and B, absolute *S*-stereochemistry, which was determined by treating the alcohols, haminol-1 (**7**), -3 (**9**) and -5 (**11**), separately with *S* and *R* Mosher's reagent (MTPACl, 2-methoxy - 2-(trifluoromethyl)-phenylacetyl chloride) and observing for the pair of esters **14 (a,b)**,**15 (a,b)**,**16 (a,b)** some diagnostic shifts in the ^{1}H-NMR spectra (table 2) at both sides of the chiral center. All values (Fig. 1) are in excellent agreement with those expected for a secondary aliphatic alcohol with absolute *S* - stereochemistry. [10] *S* -stereochemistry at C-2 of haminol-A (**4**) was previously assigned by treatment of **4** with *R*(-)-1-(1-naphtyl)-ethyl-isocyanate, followed by Lemieux degradation and methylation, leading to the ester which exhibited a diagnostic ^{1}H-NMR chemical shift (δ 3.58) for the carbomethoxy protons. [5] Applying Mosher 's method to haminol-A (**4**) confirmed *S* - stereochemistry at C-2 (**13 a,b** ; table 2).

Until now, only few chemical studies have been performed on *Haminoea* species. In particular, same halogenated compounds have been reported from the Pacific *H. cymbalum* .[11] However, 3-alkylpyridines seem to be chemical markers for Mediterranean species of *Haminoea* . These compounds could be useful to clarify their complex taxonomy. Preliminary work in progress has confirmed alarm pheromone properties for all haminols comparable to those already reported for haminol-A (**4**) and -B (**5**).[5]

Finally, preliminary biosynthetic experiments failed to obtain labelled haminols because using ^{14}C acetate as precursor we found incorporation only in the fatty acid fraction.

Table 2. ^{1}H-NMR Chemical Shifts ($CDCl_3$; 500.13 MHz) for (*R*) and (*S*) MTPA Derivatives of Haminol -A (**13 a,b**), -1 (**14 a,b**), -3 (**15 a,b**), -5 (**16 a,b**).

	13a	**13b**	**14a**	**14b**	**15a**	**15b**	**16a**	**16b**
proton	(*R*-MTPA ester)	(*S*-MTPA ester)	(*R*-MTPA ester)	(*S*-MTPA ester)	(*R*-MTPA ester)	(*S*-MTPA ester)	(*R*-MTPA ester)	(*S*-MTPA ester)
1	1.34	1.27	1.34	1.27	1.33	1.26	1.34	1.26
2	5.20	5.19	5.20	5.20	5.19	5.19	5.14	5.14
3	2.37	2.44	2.38	2.44	2.32	2.38	1.71	1.77
	2.31	2.38			2.35	2.41		
4	5.39	5.49	5.45	5.58	5.36	5.47	1.93	2.03
5	5.98	6.05			5.98	6.06	5.34	5.41
6	5.98	6.05	6.02-6.07	6.03-6.12	5.92	5.98	5.34	5.41
7	5.57	5.62	four protons	four protons	5.55	5.59	2.73	2.76
8	2.12	2.13			2.05	2.06	5.60	5.61
9	1.58	1.58	5.68	5.70	1.40	1.41	6.05	6.05



a R = *R* -MTPA
b R = *S* -MTPA

Figure 1. $\Delta\delta$ values (δ_R - δ_S; ppm) obtained for *R*- and *S* -MTPA esters of haminol-A (**13 a,b**), haminol-1 (**14 a,b**), haminol-3 (**15 a,b**), haminol-5 (**16 a,b**).

EXPERIMENTAL

General. IR spectra were measured with a Nicolet FT 5DXB spectrophotometer. UV spectra were recorded on a Varian DMS 90 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker WM 500 and Bruker AMX 500 spectrometers; chemical shifts are reported in parts per million referred to the solvent as internal standard (δ 7.26 for proton and δ 77.0 for carbon). Two-dimentional NMR experiments were performed using standard Bruker pulse microprograms. Mass spectra were obtained on AEI MS30 and MS50 Kratos instruments. Merck Kiesel gel 60 (70-230 mesh) was used for silica gel chromatography and preacoted Kiesel gel 60 F_{254} plates were used for analytical and preparative TLC. Spots were visualized by UV (254 nm) and by spraying with 2% $CeSO_4$ in H_2SO_4, followed by heat. R_f values are relative to silica gel chromatography on TLC (20x20 cm) plates using *n*-hexane/ethylacetate 1:1 as eluant.

Biological Material. Specimens of all *Haminoea* species were collected by hand (2 to 4 m) at Fusaro Lake (April-June 1991) and authenticated by L. A. A. and Dr. G. Villani. In particular, *H. fusari* , undescribed until now, was anatomically studied by L. A. A. and Dr. F. J. Garcia at the Universidad de Sevilla. A detailed description of this new species will be reported elsewhere.[12] Voucher specimens are available at the Istituto per la Chimica di Molecole di Interesse Biologico.

Extraction and Isolation of the Metabolites from *H. orteai*.
Specimens of *H. orteai* (400) were soaked in acetone and subjected to ultrasonic treatment for 15 minutes. The acetone solution was saved and the animals were extracted again with fresh acetone. The acetone solutions were filtered and concentrated. The residue was next partitioned between ether and water. The combined ether extracts were dried over Na_2SO_4 and the solvent evaporated to obtain an oil (140.5 mg). Silica gel column chromatography, using eluant with increasing polarity from light petroleum ether- diethyl ether (7:3) to diethyl ether, yielded in order of increasing polarity, haminol-B (**5**, 12 mg), haminol-C (**6**, 3.5 mg) and haminol-A (**4**, 7 mg).

Haminol-C (6): R_f = 0.20. UV (CH_3OH) λ_{max} 278 (ε = 25950), 268 (ε = 32970), 262 (ε = 27570) nm. IR (film) ν_{max} 1738 cm^{-1}. EIMS *m/z* 299.1878 (M^+, $C_{19}H_{25}NO_2$ requires 299.1885), 256, 240, 239, 228, 176. ^{1}H-NMR data, Table 1.

Extraction and Isolation of the Metabolites from *H. orbignyana*.
H. orbignyana (480 specimens) were extracted using the procedure previously described for *H. orteai* . The resulting oil (809 mg) was chromatographed on silica gel. Elution with 50% light petroleum ether in diethyl ether afforded haminol-2 (**8**, 72 mg); increasing the content of diethyl ether in the eluant furnished haminol-1 (**7**, 5.2 mg).

Haminol-1 (7): R_f =0.07. UV (CH_3OH) λ_{max} 280 (ε=26800), 268 (ε=34700), 260 (ε=26500). EIMS *m/z* 257.1766 (M^+, $C_{17}H_{23}NO$ requires 257.1780), 213, 172, 132, 106, 93. ^{1}H-NMR data, Table 1.

Haminol-2 (8): R_f =0.17. [α] $_D^{20}$ = - 19° (c = 1.3 , CH_3OH). UV (CH_3OH) λ_{max} 278 (ε=30000), 268 (ε=39090), 258 (ε=30730). IR (film) ν_{max} 1732 cm^{-1}. EIMS *m/z* 299.1893 (M^+, $C_{19}H_{25}NO_2$ requires 299.1885), 239, 212 , 172, 106. ^{1}H-NMR data, Table 1. ^{13}C-NMR ($CDCl_3$; assignments made by ^{1}H - ^{13}C COSY 2D experiment) : δ 19.5 (q, C-1), 70.3 (d, C-2), 39.2 (t, C-3), 128.5 (d, C-4), 131.6 (d, C-5 or C-6 or C-8), 130.7 (d, C-5 or C-6 or C-8), 133.3 (d, C-7 or C-9), 131.1 (d, C-5 or C-6 or C-8), 133.7 (d, C-7 or C-9), 32.1 (t, C-10 or C-12), 30.6 (t, C-11), 32.3 (t, C-10 or C-12), 149.8 (d, C-2' or C-6'), 137.5 (s, C-3'), 135.8 (d, C-4'), 123.3 (d, C-5'), 147.2 (d, C-2' or C-6'), 21.3 (q, $\underline{C}H_3COO$-), 170.5 (s, $CH_3\underline{C}OO$-) .

Extraction and Isolation of the Metabolites from *H. fusari*.

The usual procedure of extraction on 580 specimens of *H. fusari* afforded an oil (344 mg). Silica gel column chromatography, using eluants with increasing content of diethyl ether in light petroleum ether (from 30% to 100%), allowed isolation of four main fractions. Each fraction contained a complex mixture of products whose instability caused heavy losses by degradation during several attempts of separation via column chromatography or HPLC. Only rapid PLC separation on SiO_2 plate (*n*-hexane/ethylacetate 7:3; two migrations) allowed separation, from the less polar fraction (73 mg, R_f = 0.15), of three compounds : haminol-4 (**10**, 18 mg , R_f = 0.17), haminol-6 (**12**, 7.5 mg, R_f = 0.15) and haminol-2 (**8**, 6.0 mg, R_f = 0.14). The second (18 mg, R_f = 0.07) and fourth (26 mg, R_f = 0.02) fractions, in order of increasing polarity, mainly contained polypropionate compounds, whose structures are under investigation. A PLC chromatographic separation of the third haminol fraction (11 mg, R_f = 0.05) afforded haminol-3 (**9**, 2.5 mg, R_f = 0.06), haminol-5 (**11**, 2.0 mg, R_f = 0.05) and haminol-1 (**7**, 1.5 mg, R_f = 0.04).

Haminol-3 (9) : UV (CH_3OH) λ_{max} 270 (ε=1900), 263 (ε=3400), 231 (ε=17800). MS *m/z* (%) 259 (M^+, 5), 241 (M^+-18, 28), 215 (100), 134 (46).^{1}H -NMR data, Table 1.

Haminol-4 (10) : [α] $_D^{20}$ = -12.5° (c = 0.7 , CH_3OH). UV (CH_3OH) λ_{max} 267 (ε=1960), 262 (ε=2400), 230 (ε=17900). IR (film) ν_{max} 1730 cm^{-1}. EIMS *m/z* 301.2050 (M^+, $C_{19}H_{27}NO_2$ requires 301.2042), 241, 134, 106. ^{1}H-NMR data, Table 1. ^{13}C-NMR ($CDCl_3$; assignments made by ^{1}H - ^{13}C COSY 2D experiment) : δ 19.5 (q, C-1), 70.4 (d, C-2), 39.1 (t, C-3), 126.4 (d, C-4), 130.2 (d, C-5), 133.3 (d, C-6 or C-7), 133.4 (d, C-6 or C-7), 32.4 (t, C-8), 28.7 (t, C-9 or C-10), 29.0 (t, C-9 or C-10), 30.9 (t, C-11), 32.9 (t, C-12), 149.9 (d, C-2' or C-6'), 137.8 (s, C-3'), 135.7 (d, C-4'), 123.2 (d, C-5'), 147.2 (d, C-2' or C-6'), 21.3 (q, $\underline{C}H_3COO$-), 170.6 (s, $CH_3\underline{C}OO$-)

Haminol-5 (11) : UV (CH_3OH) λ_{max} 276 (ε=6590), 265 (ε=8530), 228 (ε=18200). EIMS *m/z* 257.1793 (M^+, $C_{17}H_{23}NO$ requires 257.1780), 239, 213. ^{1}H -NMR data, Table 1.

Haminol-6 (12) :[α] $_D^{20}$ = - 4.2° (c = 0.2, CH_3OH). UV (CH_3OH) λ_{max} 276 (ε=6260), 267 (ε=9640), 216 (ε=26000). IR (film) ν_{max} 1734 cm^{-1} . EIMS *m/z* 299.1879 (M^+, $C_{19}H_{25}NO_2$ requires 299.1885), 197, 144, 132. ^{1}H-NMR data, Table 1. ^{13}C-NMR ($CDCl_3$; assignments made by ^{1}H - ^{13}C COSY 2D experiment) : δ 19.9 (q, C-1), 70.5 (d, C-2), 35.6 (t, C-3), 28.4 (t, C-4), 128.3 (d, C-5 or C-6), 130.5 (d, C-5 or C-6), 35.5 (t, C-7), 132.0 (d, C-8), 132.3 (d, C-9), 130.2 (d, C-10), 129.4 (d, C-11), 36.0 (t, C-12), 150.0 (d, C-2' or C-

6'), 135.8 (s, C-3'), 136.1 (d, C-4'), 123.3 (d, C-5'), 147.6 (d, C-2' or C-6'), 21.4 (q, $\underline{C}H_3COO$-), 170.7 (s, $CH_3\underline{C}OO$-).

Acetylation of Haminols. Haminols (**7**,**9**,**11**; 0.5 mg each) were acetylated with Ac_2O and pyridine overnight at room temperature.

Preparation of Mosher's Esters. Each alcohol (**4**,**7**,**9**,**11**) (1.0 mg), dissolved in anhydrous pyridine, was separately treated with an excess of *S* and *R* 2-methoxy -2-(trifluoromethyl)-phenylacetyl chloride. The solvent was evaporated under a stream of N_2 and the residue purified by PTLC (*n*-hexane-ethylacetate 2:8) yielding the pairs **13 a** and **13 b**, **14 a** and **14 b**, **15 a** and **15 b**, **16 a** and **16 b** respectively (^{1}H-NMR data, Table 2).

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