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Synthesis and absolute configuration of three natural *ent*-halimanolides with biological activity

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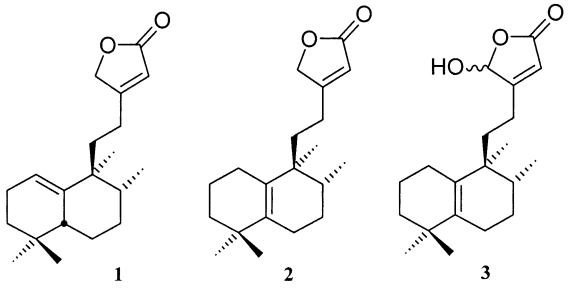
Abstract—The first three natural *ent*-halimanolides known until now have been synthesized from *ent*-halimic acid. Their structure have been confirmed as well as their absolute configurations established. Bestmann methodology has been used for the synthesis of butenolides and for the γ-hydroxybutenolides synthesis the Boukouvalas method has been employed. Biological testing has been carried out on these compounds.

Annonaceae plants are a rich source of bioactive substances such as acetogenins.[1–4] The occurrence of natural diterpenes possessing hydroxybutenolides units has been reported frequently in plants of the genera *Polyalthia*, *Acritopappus*, *Premna* and *Cyathocalux* (*Annonaceae*).[5–7] It is interesting to note that many species of these genera are widely used in folk medicine,[8] and that some natural diterpene hydroxybutenolides show significant biological activity such as antifeedant, antimicrobial, and cytotoxic activities.

In 1995, Hara and co-workers reported the isolation of a great number of clerodanes and *ent*-halimanes from *Polyalthia langifolia*;[9] among them the first three natural *ent*-halimanolides known until now **1**, **2** and **3**. These compounds are the first *ent*-halimane diterpenes which have been isolated from *Annonaceae* plants. Their structures were elucidated by spectroscopic methods. Recently, the synthesis of the enantiomer[10] of **3** from (+)-hardwickiic acid (clerodane diterpene) has been reported. The present work reports the synthesis of **1**, **2** and **3**, starting from *ent*-halimic acid, confirming the structure and establishing the absolute configuration of these natural products.

ent-Halimic acid is the main component of *Halimium viscosum* (Villarino de los Aires) and has been used as the starting material in the synthesis of *ent*-halimanolides,[11] sesterterpenolides[12] similar to dysidiolide,[13] that show high anti-tumor activity, and chettaphanin I and II.[14] Our recent synthesis was achieved as shown in Scheme 1.



1 **2** **3**

The first step in the synthesis is a reduction of an ester group to the hydrocarbon level, that was achieved through two different routes.

Route A, *ent*-halimic acid methyl ester **4,** was reduced with lithium aluminum hydride and the resulting diol **5**, converted, using *N*,*N*-dimethyphosphoramidic chloride in *n*-BuLi,[15] to the corresponding di-*N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (di-TMPDA) derivate **6** (97% yield). Treatment of **6** with lithium naphthalenide (LN)[16] as the reducing agent, gave the desired product **9** (38% yield) along with the alcohol **8** (25% yield) resulting from the oxygen–phosphorus bond cleavage and the TMPDA derivate **7** (35% yield). The compounds **7** and **8** can be recycled to give **9**.

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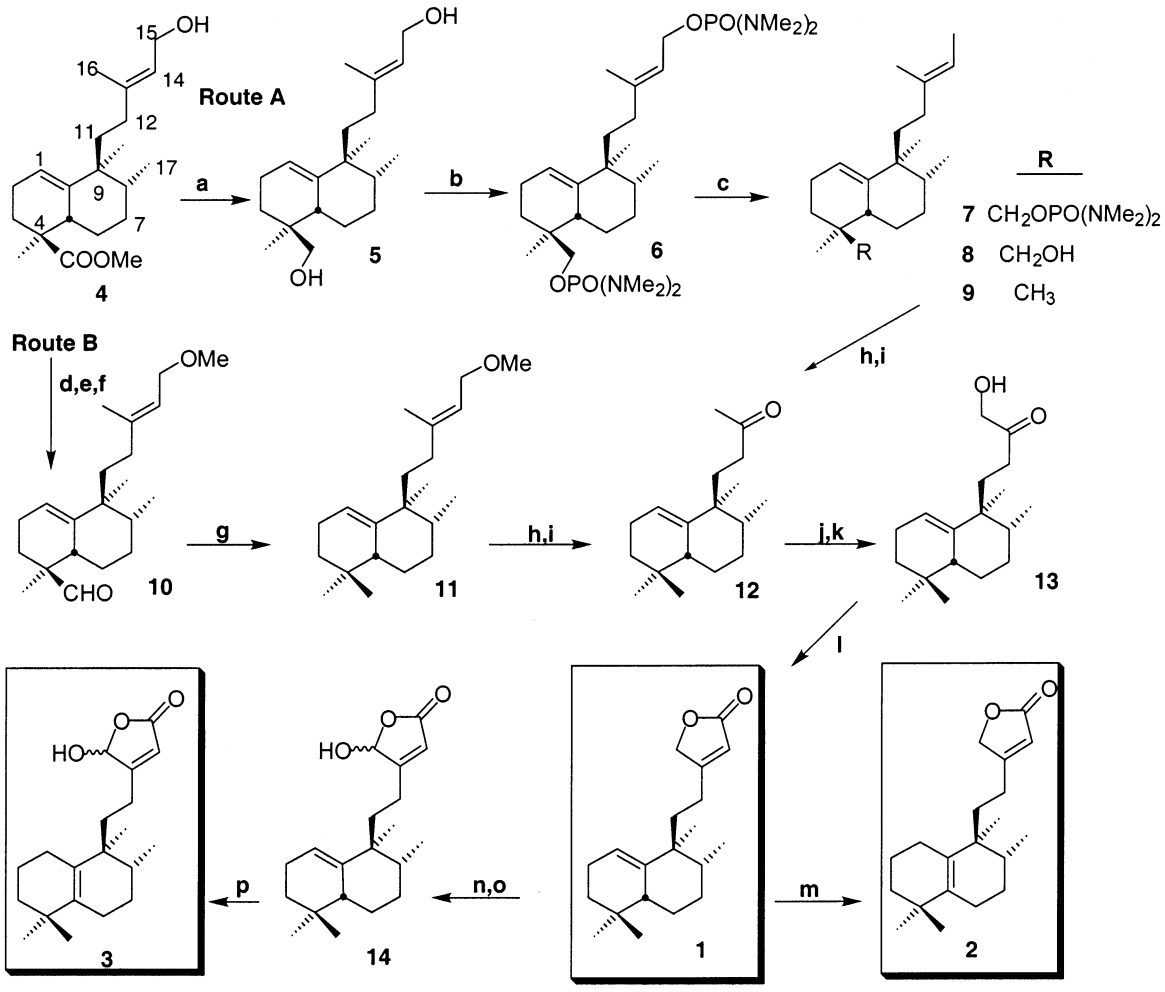

Scheme 1. *Reagents and conditions*: (a) LAH, Et_2O, 1 h (97%); (b) $(NMe_2)_2POCl$, *n*-BuLi, TMDEA, THF, −78°C, rt, 1 h (97%); (c) LN (0.24 M), THF, 6 h [**9** (38%); **8** (25%); **7** (35%)]; (d) NaH, MeI, THF, 2 h (92%); (e) LAH, Et_2O, 1 h (96%); (f) TPAP, NMO, CH_2Cl_2, 30 min (91%); (g) diethylene glycol, NH_2–NH_2·H2O, KOH, 175–230°C, 23 h (85%); (h) *m*-CPBA, CH_2Cl_2, 1 h 30 min (92%); (i) H_5IO_6, THF, H_2O, 12 h (91%); (j) LDA, TMSCl, THF, −78°C, 1 h (97%); (k) OsO_4, NMO, $^tBuOH/THF/H_2O$ (7:2:1), 20 h (96%); (l) $Ph_3P{=}C{=}C{=}O$, C_6H_6, 85°C, 3 h (91%); (m) I_2/C_6H_6 (10^{-2} M), 85°C, 16 h (99%); (n) LDA, TBDMSTf, THF, −78°C, 1 h (94%); (o) *m*-CPBA, CH_2Cl_2, 4 h (77%); (p) HI/C_6H_6 (5×10^{-2} M), 85°C, 4 h (99%).

Route B has, as the key step, a Huang–Minlon reduction. Protection of the hydroxy group[17] of **4** followed by reduction at C_{18} and subsequent oxidation with TPAP[18] led very satisfactorily to aldehyde **10**. The unstable aldehyde **10** was treated under Huang–Minlon[19] conditions to afford the desired compound **11** in 85% yield.

To functionalize C_{16} it was necessary to degrade the side chain of **9** and **11**, by *m*-CPBA oxidation[20] and subsequent cleavage with H_5IO_6.[21] The reaction with *m*-CPBA was totally regioselective, with no derivative of the annular double bond being observed. The resulting epoxides were treated with H_5IO_6, giving methyl ketone **12** in excellent yield.

In order to introduce the butenolide ring fragment in the side chain by means of Bestmann cetene[22] it is necessary to functionalize C_{16} as a hydroxy group. This was achieved by reaction of **12** with LDA in presence of TMSCl[23,24] followed by oxidation[25] of the intermediate silyl enol ether with OsO_4 to afford the hydroxy ketone **13** in excellent yield.

It is known that, phosphacumulene ylides are building blocks for the synthesis of heterocycles since they can react with molecules having a group capable of cyclization with the ylide function after addition.[21] Thus, hydroxy ketone **13** adds to Ph_3-P=C=C=O giving an intermediate ylide which cyclize by intramolecular Wittig reaction with formation of a double bond to give butenolide **1**.

The butenolide **2** was obtained from **1** by isomerization $\Delta^{1(10)}$ a $\Delta^{5(10)}$. The isomerization reaction was carried out by heating a solution of the butenolide **1** and I_2 (10^{-2} M) in benzene at 85°C affording **2** in almost quantitative yield. Physical properties of the synthesized compounds, **1**[26] and **2**[27] are identical to those described for the natural products 1(10),13*E*-*ent*-halimadien-15,16-olide[9] and 5(10),13*E*-*ent*-halimadien-15,16-olide,[9] respectively.

The synthesis of the γ-hydroxybutenolide of **3** was performed using the Boukouvalas[28] method: 2-trialkylsilyloxyfurans undergo rapid oxidative cleavage upon treatment with dimethyldioxirane or peracids, and subsequent hydrolysis of the so obtained (*Z*)-4-oxo-2-alkenoates affords γ-hydroxybutenolides. Thus, reaction of **1** with TBDMSTf[29–31] in the presence of LDA followed by reaction of the intermediate 2-trialkylsilyloxyfurane with *m*-CPBA afforded **14** in good yield, after chromatography.

Finally, compound **3** was obtained in quantitative yield by acidic isomerization of **14** using HI in benzene at 85°C. Physical and spectroscopic data of the synthetic product **3**[32] were in good agreement with those reported for the natural product 16-hydroxy-5(10),13-*ent*-halimadien-15,16-olide.[9]

In conclusion *ent*-halimic acid, a diterpene of known absolute configuration,[33] has been transformed into natural *ent*-halimanolides **1**, **2** and **3**, confirming their structure and establishing their absolute configuration. Several compounds were evaluated for their potential biological activity, showing that the compound **1** possesses cytotoxic and antiviral activity [HELAM cells ($IC_{50}=5.0$), MDCK ($IC_{50}=5.1$) and influenza virus ($IC_{50}=6.8$)].

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26. **1(10),13*E*-*ent*-halimadien-15,16-olide, 1**: R_f (Hex/AcOEt 8/2) = 0.36; $[\alpha]_D = +82.7$ (*c* 0.39, $CHCl_3$); UV(EtOH): 210 nm; IR (film): 2928, 1780, 1751, 1640, 1451, 1381, 1169, 1138, 1032, 885 and 853 cm^{-1}. ^1H NMR δ 5.80 (1H, s, H-14), 5.39–5.36 (1H, m, H-1), 4.71 (2H, s, H-16), 2.30–2.10 (1H, m, H_A-12), 2.10–1.90 (2H, m, H-2), 2.00–1.90 (1H, m), 1.70–1.50 (3H, m, H-5, H-8 and H_A-6), 1.45–1.35 (1H, m, H_B-12), 1.45–1.10 (5H, m), 1.30–1.20 (1H, m, H_B-6), 0.93 (3H, s, Me-20), 0.86 (3H, s, Me-19), 0.84 (3H, s, Me-18), 0.83 (3H, d, $J=7.0$ Hz, Me-17); ^{13}C NMR δ 120.9 (C_1), 23.0 (C_2) 33.1 (C_3), 31.4 (C_4), 43.6 (C_5), 23.5 (C_6), 29.0 (C_7), 39.0 (C_8), 43.0 (C_9), 140.5 (C_{10}), 36.2 (C_{11}), 23.6 (C_{12}), 171.5 (C_{13},) 114.9 (C_{14}), 174.1 (C_{15}), 73.0 (C_{16}), 15.6 (C_{17}), 25.9 (C_{18}), 28.1 (C_{19}), 22.1 (C_{20}). EIMS (rel. intensity): *m*/*z* 302 (M^+, 1), 191 (37), 135 (28), 107 (33), 91 (62). EIHRMS calcd for $C_{20}H_{30}O_2$: 302.2245, found: 302.2250.
27. **5(10),13*E*-*ent*-halimadien-15,16-olide, 2**: R_f (Hex/AcOEt 8/2) = 0.36; $[\alpha]_D$ +14.3 (*c* 0.81, $CHCl_3$); UV (EtOH) 207 nm; IR (film) 2926, 2868, 1778, 1753, 1638, 1462, 1381, 1360, 1169, 1130, 1034, 885 and 853 cm^{-1}; ^1H NMR δ 5.83 (1H, s, H-14), 4.74 (2H, s, H-16), 2.40–1.10 (15H,

m), 0.99 (3H, s, Me-20), 0.97 (3H, s, Me-19), 0.87 (3H, s, Me-18), 0.86 (3H, d, $J=7.0$ Hz, Me-17); ^{13}C NMR δ 25.2 (C_1), 19.9 (C_2), 39.9 (C_3), 34.6 (C_4), 138.6 (C_5), 25.8 (C_6), 27.1 (C_7), 33.8 (C_8), 40.8 (C_9), 131.3 (C_{10}), 33.6 (C_{11}), 23.7 (C_{12}), 171.2 (C_{13}), 115.0 (C_{14}), 173.9 (C_{15}), 73.0 (C_{16}), 16.0 (C_{17}), 27.6 (C_{18}), 29.6 (C_{19}), 20.9 (C_{20}); EIMS (rel. intensity): m/z 302 (M^+, 1), 287 (1), 274 (1), 227 (8), 191 (60), 171 (8), 135 (8), 121 (7), 105 (9), 91 (14), 69 (20), 55 (60), 43 (80), 41 (100). EIHRMS calcd for $C_{20}H_{30}O_2$: 302.2245, found: 302.2252.

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32. **16-Hydroxy-5(10),13-*ent*-halimadien-15,16-olide, 3**: R_f (Hex/AcOEt 8/2) = 0.16; $[\alpha]_D$ +22.8 (*c* 0.49, $CHCl_3$); IR (film) 3354, 2926, 1744, 1458, 1134 and 951 cm^{-1}; ^{1}H NMR δ 5.98 (1H, s br, H-16), 5.85 (1H, s br, H-14), 2.45–2.10 (2H, m), 2.05–1.90 (4H, m), 1.70–1.10 (9H, m), 0.99 (3H, s, Me-20), 0.97 (3H, s, Me-19), 0.87 (3H, s, Me-18), 0.86 (3H, d, $J=7.0$ Hz, Me-17); ^{13}C NMR δ 25.2 (C_1), 19.8 (C_2), 39.8 (C_3), 34.5 (C_4), 138.4/138.5 (C_5), 25.6/25.7 (C_6), 27.0 (C_7), 33.7 (C_8), 40.6 (C_9), 131.3 (C_{10}), 32.8/32.9 (C_{11}), 22.6 (C_{12}), 170.7 (C_{13}), 117.1 (C_{14}), 171.6 (C_{15}), 98.5 (C_{16}), 16.1 (C_{17}), 27.6 (C_{18}), 29.2 (C_{19}), 20.9 (C_{20}); EIMS (rel. intensity): m/z 256 [M^+–(HOH+CO_2), 15], 191 (30), 149 (58), 128 (14), 105 (40), 77 (78). FABMS (rel. intensity): m/z 301 [M^++1–(HOH), 15], 191 (38), 95 (45), 69 (77).
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