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NEW EXAMPLES OF ACYCLIC AND CYCLIC C-15 ACETOGENINS FROM *LAURENCIA PINNATIFIDA*. REASSIGNMENT OF THE ABSOLUTE CONFIGURATION FOR E AND Z PINNATIFIDIENYNE.

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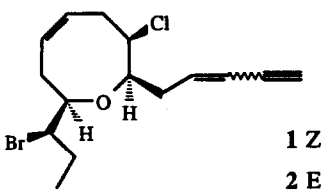
Summary: Seven new C-15 acetogenins have been isolated from *Laurencia pinnatifida*, their structures being established by spectroscopic methods and chemical correlations. The absolute configuration of E and Z pinnatifidienyne have been reassigned on the basis of X-ray analysis.

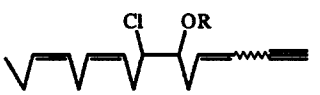
A variety of structurally unusual non-isoprenoid metabolites have been isolated mainly from red algae of the genus *Laurencia*. The vast majority of these are cyclic ethers, those containing an oxocane ring being the most common examples.[1] In recent years, these biologically active marine natural products have received much attention as synthetic targets to develop new methods for enantioselective synthesis of medium ring ethers.[2]

In this paper we wish to report the isolation from the red alga *Laurencia pinnatifida* of new examples of this fascinating family of compounds as well as the revision of the absolute configuration previously reported for Z and E pinnatifidienyne and their biogenetical precursor **3**.[3]



1 Z isomer

2 E isomer



3 Z isomer : R=Ac

4 E isomer : R=Ac

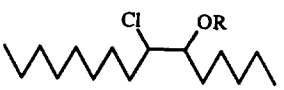
5 Z isomer : R=H

6 E isomer : R=H

Compound **4**, oil, $[\alpha]_D^{25}$=-12.9, was isolated as a minor component of its mixture with compound **3**. The ^{1}H-NMR spectrum of this mixture showed clearly that compounds **3** and **4** were Z and E isomers in the enyne terminal moiety. The attempts at its chromatographic resolution through either silica gel or Sephadex LH-20 chromatographies failed. Only small amounts of the major component, the Z isomer **3**, could be isolated by using neutral alumina column chromatography. However, when this chromatographic method was applied to the mixture of their chlorhydrines **5** and **6**, which was obtained by treatment of **3** and **4** with K_2CO_3/MeOH at 0°C, the isomers were easily separated and pure compounds **5** and **6** obtained. Acetylation of these gave **3** and **4**, respectively.

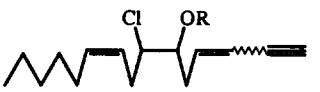
Comparison of the spectral data of compound **4** with those observed for **3** confirmed the geometrical relationship between them. Thus, the ^{1}H-NMR spectrum of **4** showed the characteristic signals at δ 6.10 (J=7.5, 7.5 and 15.3 Hz), δ 5.53 (J=2.2 and 15.3 Hz) and δ 2.79 (J= 2.2 Hz) for an E isomer at C-3, the rest of the signals being very

similar to those observed for compound **3**. Moreover, both compounds were fully hydrogenated to give an identical compound, 6-acetoxy-7-chloropentadecane **7**.



7 R=Ac

8 R=H



9 Z isomer : R=H

10 E isomer : R=H

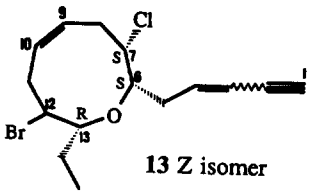
11 Z isomer : R=Ac

12 E isomer : R=Ac

Compounds **9-12** were also isolated as a mixture of geometrical isomers, these being obtained as pure compounds following the same chromatographic procedure for the mixture of **3** and **4**. Their molecular formula could not be established on the basis of their mass spectra, due to the loss of the chlorine atom in the main observed fragmentations. However, they were deduced from the HRMS of its octahydro derivative **7**, which showed a molecular formula of $C_{17}H_{33}O_2Cl$. Compound **9**, oil, $[\alpha]_D^{25}$=-9.1, showed in the ^{13}C-RMN spectrum the presence of two double bonds (δ 112.0, 124.2, 133.6, 140.3), one of them belonging to a Z enyne system, which was characterized by its spectroscopical data (see experimental part). The homonuclear COSY map displayed clearly all the proton-proton connectivities, the heteroatoms being placed at C-6 and C-7 and the double bond between C-9 and C-10. The geometry of the double bond was unambiguously established as Z for the H-10 signal at δ 5.53 (J= 10 Hz) when the H-11 signal at δ 2.04 was irradiated. Moreover, the chlorine atom was placed at C-7 due to the shift to lower field (δ 3.8→5.17) observed for the H-6 signal when **9** was acetylated at r.t. to give a compound identical with **11**, establishing its structure as (3Z, 9Z)-6-hydroxy-7-chloro-pentadeca-3,9-dien-1-yne.

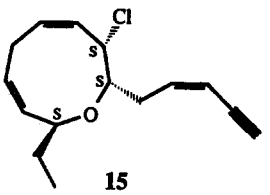
The structures of compounds **10-12** were established on the basis of their spectroscopical data and by trivial chemical correlations with **9** and between them. Catalytic hydrogenation of **9** and **10** gave 6-hydroxy-7-chloropentadecane **8**, while **11** and **12** gave **7**.

Together with these linear compounds were isolated the Z and E isomers, **13** and **14**, having the molecular formula $C_{15}H_{20}OBrCl$ (HRMS.: $C_{15}H_{20}O^{81}Br^{35}Cl$; 332.0383; calc. 332.0365). Their spectroscopical data showed, in addition to the terminal E or Z enyne system, the presence of a double bond and the absence of a hydroxyl group, which indicated that the oxygen atom must be involved in an ether linkage. Furthermore, through the correlations observed in the homonuclear COSY experiment of the E isomer **14**, we could place the position of the double bond between C-9 (H-9: δ 5.59) and C-10 (H-10: δ 5.61) as well as those of the heteroatoms at the carbons C-6 (H-6: δ 3.51), C-7 (H-7: δ 4.08), C-12 (H-12: δ 4.21) and C-13 (H-13: δ 3.20). The nature of these heteroatoms was easily established by correlating the assigned proton signals to carbons in the COSY (HETCOR) experiment. Thus, we observed the correlation between H-6 and C-6 (δ 80.8) as well as between H-13 and C-13 (δ 83.3) which established the ether linkage between carbons C-6 and C-13 indicating the presence of an oxonane ring in the molecule. Moreover, the correlation between the proton signal at δ 4.08 and the carbon signal at δ 61.6 placed the chlorine atom at C-7, while that observed between H-12 (δ 4.21) and the carbon signal centered at δ 54.2 placed the bromine atom at C-12. Compound **13** showed to be the Z isomer of **14** in the enyne system on the basis of its spectroscopic data (see experimental part) and through the chemical correlations shown in Scheme I. Only three examples of this class of C-15 acetogenins brasilenyne **15**,[4] obtusenyne **16**[5] and 12-epi-obtusenyne **17**[6] have been reported, the last two being diastereomers of **13** and **14**.



13 Z isomer

14 E isomer



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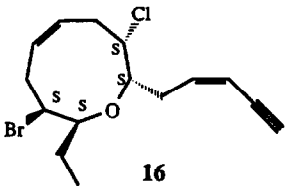

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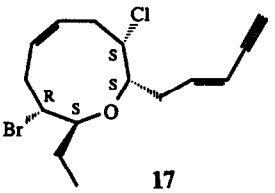
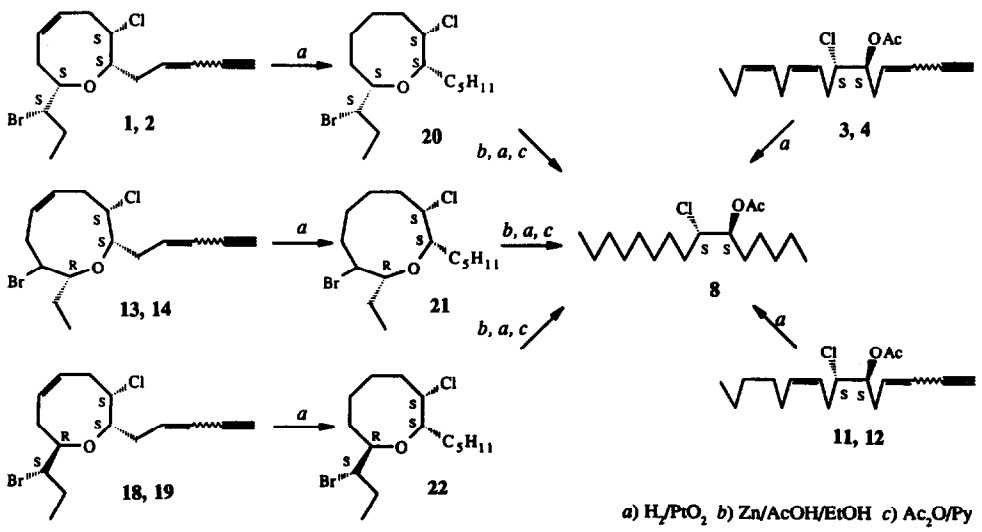


17

Together with the above depicted metabolites, the Z and E dihydrorhodophytins **18** and **19** were also isolated as minor compounds.[4,7] These were diastereomers of **1** and **2**, but they possess an S,S absolute configuration at C-6 and C-7 instead of the R,R configuration observed for **1** and **2**, as has been established by their X-ray analyses.[3] On the basis of the coexistence in the alga of these cyclic compounds with enantiomeric precursors, we felt it was important to discard the possibility that compounds **3** and **4** were a mixture of enantiomers enriched in one of them. We therefore designed a set of chemical transformations in order to obtain pure (6R, 7R)-6-hydroxy-7-chloro-pentadecane from compounds **1-4** and its enantiomer from **18** and **19**. These chemical transformations are summarized in Scheme 1, the chemical transformation of compounds **13** and **14** being included. Unexpectedly, all

Scheme I



of them gave an identical compound, which not only discarded the possibility of the existence in the alga of a mixture of enantiomers but also pointed to the need to revise the absolute configuration obtained from the X- ray analyses for compounds **1** and **2** or **18** and **19**. In order to decide which of these compounds should be reinvestigated, we have revised all the examples of lauroxane published until now.[1,8] Thus, we have found that in the lauroxanes with either ethyl or bromopropyl side chains, the lauroxonanes and the lauroxepanes always had an S,S and R,R absolute configuration, respectively, at C-6 and C-7. Likewise, in the lauroxocane group, if the ether linkage was established through the carbon C-6, as in the lauroxonanes, the chirality was also S,S, while if the carbon involved was C-7 the chirality was R,R as in the lauroxepanes. Since two examples, the chlorofucin[9] and the pinnatifidienynes, failed to fulfil this rule, we decided to revise the absolute configuration of these last compounds.

Compound **1** crystallized in the monoclinic system, space group $P2_1$, $\underline{a}$= 5.572 (5), $\underline{b}$= 17.141(10), $\underline{c}$=8.855(5), β= 104.12(6), v= 820.2(10)Å^3, z= 2, Dc= 1.343 g.cm^{-3}, μ= 48.7 cm^{-1}. The intensity of 1188 unique reflections was measured up to θ= 60° with a Siemens AED computer-controlled four-circle diffractometer, using graphite monochromated CuKα(λ= 1.5418 Å) radiation and ω: θ scan mode. 1042 reflections were judged as observed with I>3σ (I) and corrected for Lorentz and polarization factors. The bromine and chlorine atoms were located on a Patterson synthesis [10] and used as a fasing model for structure completion by F_o synthesis.[11]

In the course of the isotropic refinement of the parameters of the non-hydrogen atoms an empirical absorption correction was applied,[12] correction factors being between 0.710 and 2.960. The hydrogen atoms were placed at a calculated position[13] (C-H 1.00 Å, U 0.06). A weighting scheme to obtain flat dependence of ΔF versus F_o and sin θ/λ was carried out.[14] A final full-matrix weighted anisotropic refinement (fixed isotropic contribution for H-atoms)[11] converged to R= 0.055 and Rw= 0.048 for the correct enantiomer, shown in Figure 1. The absolute configuration was determined as 6(S), 7(S), 12(S), 13(S) by comparison of 23 Bijvoet pairs with $F_o \geq 10\,\sigma(F_o)$ which are in the ranges $5.0 \leq Fo \leq 50.0$ and $0.2 \leq \sin\theta/\lambda \leq 0.4$ Å^{-1}. The averaged Bijvoet differences are 1.300 for the correct enantiomer versus 3.008 for the wrong one.[15] Atomic coordinates and bond angles are given in Table 1. Bond distances and angles agree well with generally accepted values and there were no abnormally short intermolecular contacts.

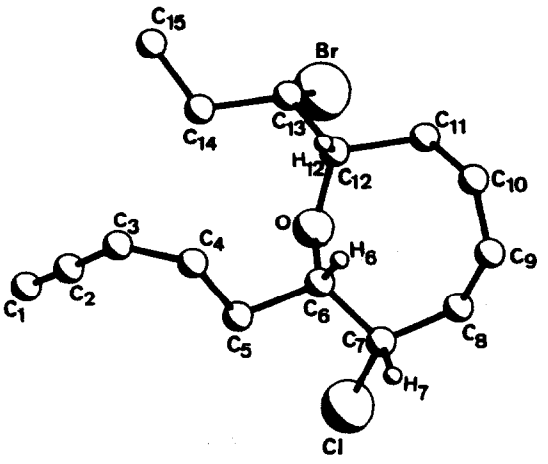


Figure 1

C6 - C7	1.537(23)	Br - C13	1.952(18)
C1 - C7	1.789(20)	C7 - C8	1.495(20)
O - C6	1.434(13)	C8 - C9	1.502(34)
O - C12	1.428(17)	C9 - C10	1.321(30)
C1 - C2	1.155(40)	C10 - C11	1.524(24)
C2 - C3	1.395(35)	C11 - C12	1.574(20)
C3 - C4	1.358(26)	C12 - C13	1.522(19)
C4 - C5	1.554(27)	C13 - C14	1.531(23)
C5 - C6	1.549(22)	C14 - C15	1.530(27)

C6 - O - C12	114.0(10)	C8 - C9 - C10	123.7(18)
C1 - C2 - C3	177.8(23)	C9 - C10 - C11	125.2(19)
C2 - C3 - C4	132.1(21)	C10 - C11 - C12	113.5(14)
C3 - C4 - C5	117.6(17)	O - C12 - C11	111.5(12)
C4 - C5 - C6	109.4(13)	C11 - C12 - C13	111.3(11)
O - C6 - C5	108.7(11)	O - C12 - C13	108.3(12)
C5 - C6 - C7	114.6(11)	Br - C13 - C12	113.8(11)
O - C6 - C7	108.0(11)	C12 - C13 - C14	112.7(13)
C1 - C7 - C6	113.0(12)	Br - C13 - C14	110.4(14)
C6 - C7 - C8	113.9(12)	C13 - C14 - C15	113.3(15)
C1 - C7 - C8	110.2(13)	C7 - C8 - C9	113.0(15)

Table 1. Interatomic distances (Å) and angles (°) with e.s.d.'s in ( ).

These results imply that the previous absolute configuration we have published for the pinnatifidienynes was incorrect and that the correct is that of their enantiomers. The absolute configuration of the linear compounds **3**, **4** and **9-12**, as well as that of the lauroxonane derivatives **13** and **14**, was established as follows. At C-6 and C-7, it must be S,S in accordance with the chemical transformations shown in Scheme I. Moreover, for compounds **13** and **14**, taking this fact into account and by comparison with their diastereomers **16** and **17**, the absolute configuration at C-13 must be R, while at C-12 it is still undefined.

These results are noteworthy, because the new examples of lauroxonane derivatives **13** and **14** still possess an S, S absolute configuration at C-6 and C-7. On the other hand, this study showed that the pinnatifidienynes **1** and **2** are not an exception in the C-6 ether link lauroxocane series and may indicate the necessity to revise the absolute configuration of the chlorofucin.

EXPERIMENTAL PART

Collection, extraction and chromatographic separation.

Laurencia pinnatifida was collected in shallow water at low tide on the Island of Tenerife in April 1988. The air dried alga (4 kg) was extracted with acetone and the solvent evaporated in vacuo to afford 40 gr of crude extract. This extract was chromatographed on a silica gel column eluting with a mixture of n-hexane:ethyl acetate of increasing polarity and 60 fractions of 250 ml each were collected. The fractions eluted with n-hexane:EtOAc 95:5 were combined, the solvent evaporated and rechromatographed on a medium pressure silica gel and a Sephadex LH-

20 column to afford pure compounds **1** (125 mg), **2** (200 mg), **18** (25 mg), **19** (50 mg), a mixture of **3** and **4** (54 mg) and a mixture of **11** and **12** (35 mg). The fractions eluted with n-hexane:EtOAc 90:10 were also rechromatographed following the same chromatographic procedure to give compounds **13** (16 mg), **14** (41 mg) and the mixture of **9** and **10** (50 mg). This mixture, as well as that of **5** and **6** obtained by treatment of the mixture of **3** and **4** with K_2CO_3/MeOH at 0°C, was chromatographed on a neutral alumina (70-120 mesh) column eluted with n-hexane:EtOAc (99:1) to give pure compounds.

Compound 3.- oil, $[\alpha]_D^{25}$=+18.5 ($CHCl_3$, c, 0.85). IR ν_{max}^{cm-1}: 3300, 2980, 2920, 2890, 2100, 1730, 1420, 1380 and 1080. UV λ_{max}^{EtOH}=224 nm (ε=13300). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 7.7,H-15); 2.04 (2H, m,H-14); 2.11 (3H, s,H-17); 2.52 (2H, m, H-11); 2.76 (2H, m, H-5); 2.78 (2H, m, H-8); 3.13 (1H, d, 2.3, H-1); 3.95 (1H, m, H-7); 5.17 (1H, m, H-6); 5.45 (4H, m, H-9 and H-10); 5.57 (1H, dd, 2.3, 11.1, H-3); 5.97 (1H, ddd, 7.4, 11.1, 14.7,H-4). ^{13}C-NMR ($CDCl_3$) δ: 14.3 (C15), 20.7 (C17), 20.9 (C14), 25.8 C11, 32.3, 32.5 (C8 and C5), 62.6 (C7), 73.5 (C6), 77.3 (C1), 81.7 (C2), 111. 8 (C3), 124.4, 126.5 (C10 and C13), 131.8 , 132.4 (C9 and C12), 139.0 (C4), 170.3 (C16). MS: m/z 294, 296 (no obs.); 251, 253; 199, 201, 169, 171; 151, 129.

Compound 4.- oil, $[\alpha]_D^{25}$=-12.9 ($CHCl_3$, c, 0.35). IR ν_{max}^{cm-1}: 3300, 3000, 2960, 2100, 1735, 1430, 1220, 1030 and 960. UV λ_{max}^{EtOH}=224 nm (ε=13100). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, 7.6, H-15); 2.05 (2H, m, H-14); 2.09 (3H, s, H-17); 2.46 (4H, m, H-8 and H-11); 2.70 (2H, m, H-5); 2.79 (1H, d, 2.2, H-1); 3.87 (1H, ddd, 3.3, 7.3, 10.0, H-7); 5.02 (1H, ddd, 3.2, 6.9, 10.0, H-6); 5.33 (4H, m, H-9 and H-10); 5.53 (1H, dd, 2.2, 15.3, H-3); 6.10 (1H, ddd, 7.5, 7.5, 15.3, H-4). ^{13}C-NMR ($CDCl_3$) δ: 13.9 (C15), 20.7 (C17), 20.9 (C14), 25.8 (C11), 32.2 , 35.2 (C8 and C5), 62.2 (C7), 73.1 (C6) , 77.3 (C1), 82.9 (C2), 112.8 (C3), 124.3, 126.4 (C10 and C13), 131.9, 132.5 (C9 and C12), 139.6 (C4), 170.2 (C17). MS: m/z 294, 296 (no obs.), 251, 253; 199, 201; 169, 171; 151, 129.

Compound 9.- oil, $[\alpha]_D^{25}$=-9.1 ($CHCl_3$, c, 0.40). IR ν_{max}^{cm-1}: 3550, 3295, 2950, 2930, 2910, 2100 and 1350. UV λ_{max}^{EtOH}=223 nm (ε=15300). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, 7.0, H-15); 1.30 (6H, m, H12-H14); 2.04 (2H, m, H-11); 2.64 (2H, m, H-8); 2.69 (2H, m, H-5); 3.16 (1H, d, 2.3, H-1); 3.80 (1H, ddd, 3.6, 5.6, 7.3, H-6); 3.92 (1H, ddd, 3.6, 6.0, 7.3, H-7); 5.39 (1H, m, H-9); 5.53 (1H, m, H-10); 5.63 (1H, dd, 2.3, 11.0, H-3); 6.10 (1H, ddd, 7.4, 7.4, 11.0, H-4). ^{13}C-NMR ($CDCl_3$) δ: 13.9 (C15), 22.5, 27.4, 29.1, 31.5 (C11-C14), 32.8 , 35.6 (C8 and C5), 67.5 (C7), 72.4 (C6), 80.0 (C2), 82.3 (C1), 112.0 (C3), 124.2 (C10), 133.6 (C9), 140.3 (C4) . MS: m/z 254, 256 (no obs.); 219, 201, 183, 185; 153, 149, 143, 145; 129.

Compound 10.- oil, $[\alpha]_D^{25}$=+17.0 ($CHCl_3$, c, 0.18). IR ν_{max}^{cm-1}: 3500, 3300, 2950, 2100, 1360 and 960. UV λ_{max}^{EtOH}= 227 nm (ε=15800). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, 6.6, H-15); 1.23 (6H, m, H12-H14); 2.04 (2H, m, H-11); 2.46 (1H, m, H-5'); 2.64 (2H, m, H-8), 2.85 (2H, m, H-1 and H-5); 3.76 (1H, m, H-6); 3.92 (1H, m, H-7); 5.38 (1H, m, H-9); 5.45 (1H, m, H-10); 5.61 (1H, m, H-3); 6.19 (1H, ddd, 7.5, 7.5, 15.0, H-4). ^{13}C-NMR ($CDCl_3$) δ: 14.0 (C15), 22.5, 27.4, 29.1, 31.6 (C11-C14), 32.6 , 37.3 (C8 and C5), 67.9 (C7), 72.8 (C6), 79.1 (C2), 81.4 (C1), 111.0 (C3), 124.5 (C10), 133.3 (C9), 139.7 (C4). MS: m/z 254, 256 (no obs.); 219, 201, 183, 185; 153, 129.

Compound 11.- oil, $[\alpha]_D^{25}$=+39.7 ($CHCl_3$= c, 0.47). IR ν_{max}^{cm-1}: 3300, 3000, 2950, 2100, 1720, 1300 and 1050. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, 6.7, H-15); 1.30 (6H, m, H12-H14); 2.02 (2H, m, H-11); 2.11 (3H, s, H-17); 2.51 (2H, m, H-8); 2.78 (2H, m, H-5); 3.15 (1H, d, 2.0, H-1); 3.93 (1H, ddd, 4.0, 5.8, 7.9, H-7); 5.17 (1H, ddd, 4.0, 5.8, 7.3, H-6); 5.38 (1H, m, H-9); 5.52 (1H, m, H-10); 5.59 (1H, dd, 2.0, and 11.0, H-3); 5.96 (1H, ddd, 7.3, 7.3, 11.0, H-4). ^{13}C-NMR ($CDCl_3$) δ: 14.2 (C15), 21.1 (C17), 22.7 , 27.6 , 29.3 , 31.7 (C11-C14), 32.5, 35.3 (C8 and C5), 62.4 (C7), 73.2 (C6), 77.4 (C1), 82.9 (C2), 112.9 (C3), 124.0 (C10), 134.0 (C9), 139.8 (C4), 170.3 (C16). MS: m/z 296, 298 (no obs.); 219, 201, 183, 185; 153, 129.

Compound 12.- oil, $[\alpha]_D^{25}$=-12.9 ($CHCl_3$, c, 1.16). IR ν_{max}^{cm-1}: 3300, 2950, 2930, 2080, 1740 and 1310, 1045.^{1}H-

NMR ($CDCl_3$) δ: 0.89 (3H, t, 6.7, H-15); 1.29 (6H, m, H12-H14); 2.01 (2H, m, H-11); 2.11 (3H, s, H-17); 2.53 (3H, m, H-8 and H-5'); 2.75 (1H, m, H-5); 2.84 (1H, d, 2.0, H-1); 3.94 (1H, ddd, 3.3, 6.5, 9.4, H-7); 5.09 (1H, ddd, 3.3, 6.5, 6.5, H-6); 5.39 (1H, m, H-9); 5.48 (1H, m, H-10); 5.60 (1H, dd, 2.0, 15.0, H-3); 6.12 (1H, ddd, 7.4, 8.0, 15.0, H-4). ^{13}C-NMR ($CDCl_3$) δ: 14.2 (C15), 21.1 (C17), 22.7 , 27.6 , 29.2 , 32.4 (C11-C14), 32.5, 35.2 (C8 and C5), 62.9 (C7), 73.6 (C6), 77.3 (C1), 81.2 (C2), 111.9 (C3), 124.1 (C10), 133.8 (C9), 139.1 (C4), 170.4 (C16). MS: m/z 296, 298 (no obs.); 219, 201, 183, 185; 153, 129.

Compound 13.- oil, $[\alpha]_D^{25}$=-15.4 ($CHCl_3$, c, 0.31). UV λ_{max}^{EtOH}=222 nm (ε=12500). IR ν_{max}^{cm-1}: 3300, 3000, 2965, 2940, 2100, 1450, 1380 and 1325. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, 7.4, H-15); 1.89 (2H, dq, 7.6, 7.8, H-14); 2.44 (2H, m, H-8); 2.59 (2H, m, H-11); 2.84 (2H, m, H-5); 3.15 (1H, d, 2.4, H-1); 3.22 (1H, m, H-13); 3.58 (1H, ddd, 3.2, 5.9, 8.9, H-6); 4.06 (1H, ddd, 3.2, 5.7, 8.9, H-7); 4.26 (1H, ddd, 3.2, 5.6, 8.9, H-12); 5.56 (1H, m, H-3); 5.57 (1H, m, H-9); 5.60 (1H, m, H-10); 6.03 (1H, dt, 7.5, 10.6, H-4). ^{13}C-NMR ($CDCl_3$) δ: 9.6 (C15), 27.6 (C14), 33.5 (C8), 34.1 (C11), 34.7 (C5), 54.1 (C12), 61.8 (C7), 80.9 (C6), 82.8 (C1), 83.4 (C13), 111.1 (C3), 128.6 (C9), 130.0 (C10), 140.1 (C4). MS: m/z 330, 332, 334; 295, 297, 265, 267, 269; 185.

Compound 14.- powder, $[\alpha]_D^{25}$=-39.7 ($CHCl_3$, c, 0.80). UV λ_{max}^{EtOH}=223 nm (ε=12800). IR ν_{max}^{cm-1}: 3320, 3000, 2960, 2920, 2100, 1450, 1335 and 1000. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, 7.5, H-15); 1.88 (2H, m, H-14); 2.45 (2H, m, H-8); 2.51 (1H, m, H-5); 2.57 (2H, m, H-11); 2.71 (1H, m, H-5'); 2.84 (1H, d, 2.2, H-1); 3.20 (1H, ddd, 3.3, 5.3, 8.8, H-13); 3.51 (1H, ddd, 3.2, 5.3, 8.8, H-6); 4.08 (1H, ddd, 3.2, 5.7, 10.5, H-7); 4.21 (1H, ddd 3.3, 5.5, 8.8, H-12); 5.59 (1H, m, H-9); 5.61 (1H, m, H-10); 5.64 (1H, m, H-3); 6.12 (1H, ddd, 7.6, 7.6, 15.5, H-4). ^{13}C-NMR ($CDCl_3$) δ: 9.72 (C15), 27.7 (C14), 33.4 (C8), 34.2 (C11), 37.1 (C5), 54.2 (C12), 61.6 (C7) 77.0 (C1), 80.8 (C6), 83.3 (C13), 112.3 (C3), 128.5 (C9), 130.1 (C10), 140.6 (C4). HRMS:$C_{15}H_{20}{}^{81}Br^{35}Cl$ 332.0383; calc. 332.0365. MS: m/z 330, 332, 334; 295, 297; 265, 267, 269; 251, 253; 229, 231; 185, 167, 169; 157, 159.

The spectral data of these compounds (**1**) $[\alpha]_D^{25}$=+39.2 ($CHCl_3$, c. 1.07), (**2**) $[\alpha]_D^{25}$=+4.6 ($CHCl_3$, c, 0.70), mp=54-56°C, (**18**) $[\alpha]_D^{25}$=+63.5 ($CHCl_3$,c,1.2), mp=35-36°C and (**19**) $[\alpha]_D^{25}$=+33.2 ($CHCl_3$, c, 0.95), mp=40-41°C, were identical with those published[3,4,7].

Treatment of 3, 4, 11 and 12 with K_2CO_3. An excess of potassium carbonate was added to a magnetically stirred solution of the mixture of compounds **3** and **4** (20 mg) or **11** and **12** (50 mg) in MeOH at 0°C. After total reaction, the resultant mixtures were filtered off and the solvent evaporated to give a crude mixture of **5** and **6** or **9** and **10**. These mixtures, respectively, were chromatographed on a medium-pressure neutral alumina column by using n-hexane:ethyl acetate 99:1 affording pure compounds **5** (5 mg), **6** (8 mg), **9** (11 mg) and **10** (18 mg).

Compound 5.- oil, $[\alpha]_D^{25}$=-16.7 ($CHCl_3$, c, 0.87). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 7.6); 2.03 (2H, m); 2.67 (4H, m); 2.82 (2H, m); 3.13 (1H, d, 2.3); 3.80 (1H, m); 3.93 (1H, ddd, 3.5, 6.0, 7.7); 5.44 (4H, m); 5.60 (1H, dd, 2.1, 10.8); 6.10 (1H, ddd, 7.3, 10.9, 14.9).

Compound 6.- oil, $[\alpha]_D^{25}$=-20.9 ($CHCl_3$, c, 1.02). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 7.6); 2.05 (2H, m); 2.44 (2H, m); 2.63 (2H, m); 2.78 (1H, m); 2.82 (2H, m); 3.78 (1H, m); 3.92 (1H, ddd, 2.9, 7.4, 9.5); 5.39 (4H, m); 5.59 (1H, dd, 2.1, 15.8); 6.22 (1H, ddd, 7.4, 7.4, 15.3).

Catalytic hydrogenation method.- We have followed the methodology described previously for this class of compound[3] and, as expected, the yields were always up to 90%. All compounds obtained were purified by silica gel chromatography, except those resulting from the hydrogenation of the mixtures of **1** and **2** and **18** and **19**, which were treated with Zn/AcOH/EtOH as crude compounds.

Compound 7.- Catalytic hydrogenation of **3** and **4** as well as **11** and **12** gave **7**: oil, ^{1}H-NMR ($CDCl_3$) δ: 0.87 (6H,

m); 1.28 (18H, m); 1.66 (4H, m); 2.09 (3H, s); 3.92 (1H, ddd, 3.6, 3,6, 8.4); 5.05 (1H, ddd, 3.6, 6.7, 6.7). HRMS: M^++1 at m/z 305.2223.(calc. for $C_{17}H_{34}O_2{}^{35}Cl$, 305.2247). MS: m/z 305, 307; 245, 247; 227, 209, 143.

Compound 8.- Catalytic hydrogenation of **5** and **6** as well as **9** and **10** gave **8**: oil, ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, m); 1.30 (18H, m); 1.58 (2H, m); 1.82 (2H, m); 3.71 (1H, m); 3.90 (1H, m). MS: m/z M^+ 262,264 (no obs.); 245, 247; 227, 209.

Compound 21.- The crude compound obtained from the catalytic hydrogenation of **13** and **14** was chromatographed on a silica gel give the octahydroderivative **21**: oil, ^{1}H-NMR ($CDCl_3$) δ: 0.87(3H, t, J=3.5); 0.98 (3H, t, J=7.4); 1.90 (16H, m); 3.36 (1H, ddd, J=3.0, 4.8, 7.9); 3.50 (1H, m); 4.28 (1H, dt, J=2.8, 9.7); 4.41 (1H, dt, J=2.8, 9.7). MS: m/z 338, 340, 342; 267, 269; 240, 242; 201, 203.

Treatment of 20, 21 and 22 with Zn/AcOH/EtOH. We have followed the methodology described previously for this class of compound[3]. In all cases the crude resultant compounds were hydrogenated to give an identical product **8**, wich was in turn converted into **7** by the standard method.

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