# Synthesis and Absolute Configuration of the Supposed Structure of Cladocoran A and B

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**Abstract:** The proposed structures of cladocoran A and B, sesterterpenoid γ-hydroxybutenolides, were synthesized from *ent*-halimic acid.

**Key words:** cladocoran A and B, *ent*-halimic acid, dysidiolide, diterpenes, sesterterpenes

The proposed structures of cladocoran A and B, sesterterpenoid γ-hydroxybutenolides, were synthesized from *ent*-halimic acid (Figure 1), the major component of *Halimium viscosum* (Villarino de los Aires). Interestingly, since our synthetic compounds **1** and **2** are not identical to cladocoran A or B, the structures of these marine sesterterpenoids must be revised.

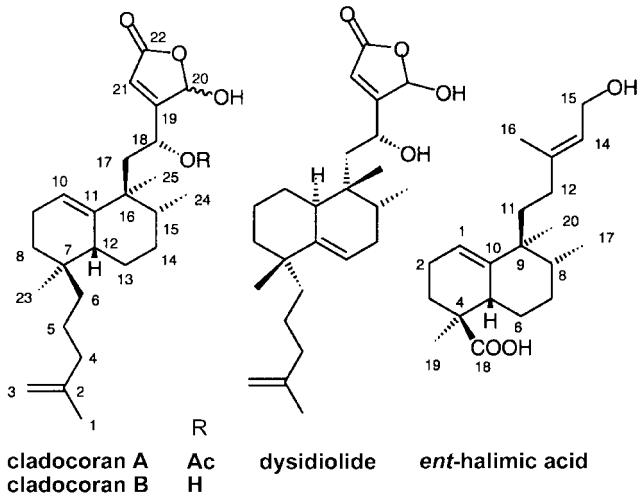


**Figure 1**

Cladocoran A and B, isolated from the mediterranean coral *Cladocora cespitosa* by Fontana et al.[1] in 1998, are novel sesterterpenoids possessing an unprecedented skeleton. Both of them occur in the organic extract as a mixture of α- and β-epimers at $C_{20}$.

Cladocoran A and B share more than one analogy with dysidiolide,[2] a natural inhibitor of protein phosphatase cdc 25A ($IC_{50}$ = 9.4 μM), which is essential for cell proliferation. Dysidiolide inhibits the growth of A-549 human lung carcinoma and P388 murine leukemia cell lines at low micromolar concentrations.[3]

Because of its atypical structure and its potentially important physiological activity, dysidiolide has attracted considerable attention as a target for total synthesis, ten total syntheses having been reported to date.[3–11]

Cladocoran A and B have a γ-hydroxybutenolide group previously associated with phospolipase $A_2$ inhibition,[12–15] but no total synthesis has yet been reported.

In this work we describe the synthesis of the supposed structure for cladocoran A and B, compounds **1** and **2**. Physical properties of the compounds synthesized by us do not correspond with those reported for cladocoran A and B. Compounds **1** and **2** are sesterterpenes structurally considered as "isopropenyl-*ent*-halimanes" with the stereogenic centers that match the decalin fragment plus an additional isopropenyl group. The synthesis for compounds **1** and **2** was planned starting from *ent*-halimic acid[16] methyl ester **3**, of known absolute configuration, due to its structural analogy. At present, *ent*-halimic acid is being employed in the synthesis of natural *ent*-halimanolides.[17]

The synthesis of **1** and **2** from *ent*-halimic acid methyl ester **3** presented two main problems: manipulation of side chains on $C_{18}$ (south chain) and on $C_9$ (north chain) to achieve the introduction of the γ-hydroxybutenolide group, and control of stereochemistry for the hydroxyl group to be placed at $C_{12}$ of *ent*-halimic acid methyl ester **3**.

The retrosynthetic route for **1** and **2** from *ent*-halimic acid methyl ester **3** is presented in Scheme 1.

The γ-hydroxybutenolide moiety of **1** and **2** was to be obtained from **A** following Faulkner[18] methodology. **A** could be obtained by addition of furyllithium to an aldehyde such as **B**. The elongation of the south chain of **3** by an isoprene unit was to be done in two steps: adding one carbon by Wittig condensation to give an intermediate such as **B** and then the four remaining carbons by $S_N2$ substitution, due to the difficulty of achieving substitution at a neopentyl carbon.

Degradation of the north chain had to take account of the annular double bond of **3**, so the oxidation on $\Delta^{13}$ would have to be chemoselective. Initially, attention was focused on degradation of **3** to obtain a compound such as **B**.

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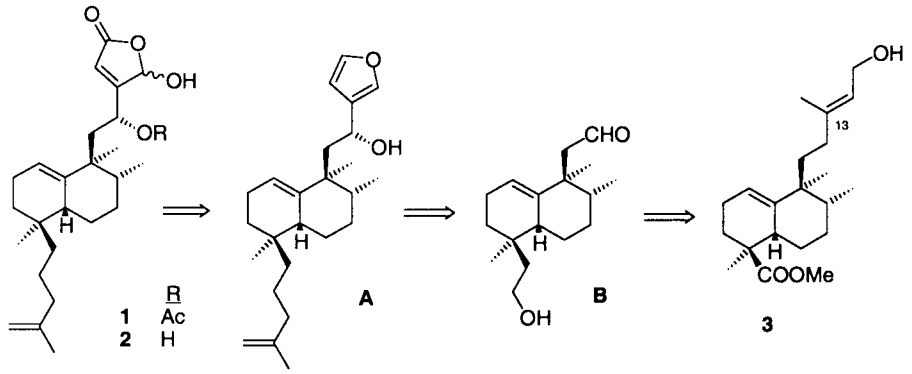
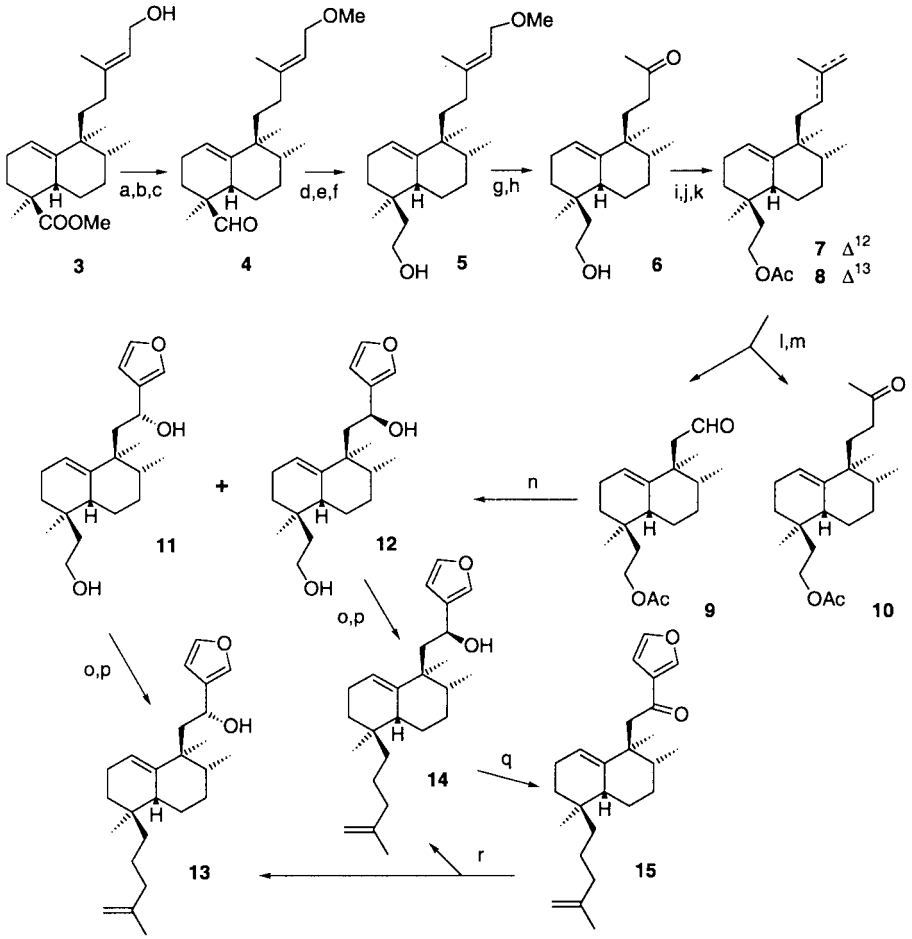


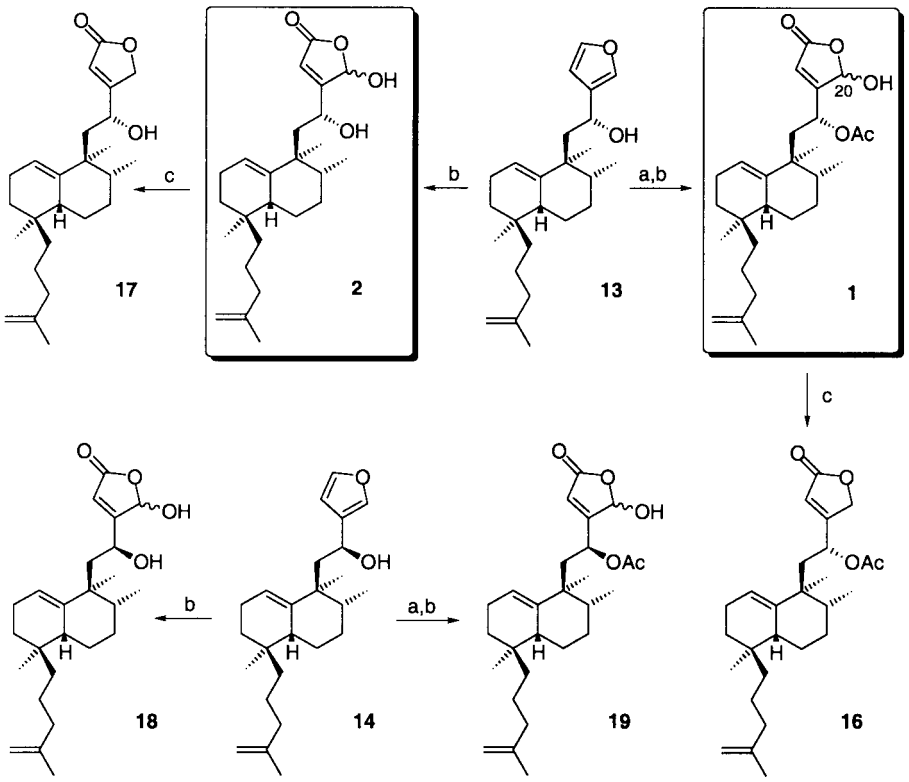

**Scheme 1**

In Scheme 2 the route followed for the synthesis of the north side chains of **1** and **2** is shown, together with the extension of the south side chain by one carbon atom.

Methylation of the hydroxy group[19] of **3** followed by reduction at $C_{18}$ and subsequent oxidation with TPAP[20] led very satisfactorily to aldehyde **4**. Extension of the south chain by one carbon atom was accomplished by reaction of **4** with $Ph_3P$=CHOMe,[21] acid hydrolysis of the resulting enol ether and reduction with LAH to give **5**. North side chain degradation was done by oxidation with $OsO_4$ and treatment with LTA,[22] to give methyl ketone **6** in an excellent yield.




**Scheme 2** a) NaH, MeI, THF, 3 h, (90%); b) LAH, $Et_2O$, 1 h, (97%); c) TPAP, NMO, $CH_2Cl_2$, 30 min, (85%); d) $(MeOCH_2PPh_3)^+Cl^-$, HMDS-Na, THF, –78 °C, 20 min, (92%), e) *p*-TsOH, acetone, 0.03 M, 4 h, (98%), f) LAH, $Et_2O$, 30 min, (96%); g) $OsO_4$, NMO, *t*-BuOH/THF/$H_2O$ (7:2:1), 24 h, (99%); h) LTA, $C_6H_6$, 20 min, (95%); i) MeMgBr, $Et_2O$, –78 °C, 1 h 30 min, (91%); j) $Ac_2O$, pyridine, 5 h, (95%); k) $POCl_3$, pyridine, 0 °C to r.t., 30 min, (75%); l) *m*-CPBA, $CH_2Cl_2$, 0 °C to r.t., 1 h 30 min, (90%); m) $H_5IO_6$, THF, $H_2O$, 15 min, (91%); n) 3-Bromofurane, BuLi, THF, –78 °C, 20 min, (90%), *R*/*S*: 3/7; o) TsCl, pyridine, 4 h, (92%); p) $CH_2$=C($CH_3$)-$CH_2MgCl$, THF, 12 h, (93%); q) TPAP, NMO, $CH_2Cl_2$, 45 min, (90%); r) LAH, $Et_2O$, 30 min, (81%), *R*/*S*:3/1.




**Scheme 3** a) $Ac_2O$, pyridine, 8 h (93%); b) $^1O_2$, hν, Rose Bengal, DIPEA, $Cl_2CH_2$, -78 °C, 2 h 30 min, (84%); c) $NaBH_4$, EtOH, 10 min, (88%).

Since the Baeyer–Villiger reaction was not suitable for the removal of two more carbon atoms from the north chain without effecting the annular double bond, an indirect strategy was required. Addition of MeMgBr to methyl ketone **6** gave a crystalline diol; the primary alcohol in this structure was then protected as its acetate. This was followed by dehydration of the tertiary alcohol by $POCl_3$,[23] to give a mixture of tri- and disubstituted olefins **7** and **8** in a ratio of 7:3. Selective oxidation of the side chain double bond of **7** and **8** with *m*-CPBA and subsequent cleavage of the epoxide with $H_5IO_6$[24] led to a mixture **9** and **10** (7:3). Compound **10** can be recycled to give **9**, by the same sequence as before. Compound **9** is the equivalent of aldehyde **B** (Scheme 1); as can be appreciated, this compound can easily be transformed into analogues with both side chains interchanged. This will give rise to a synthesis of dysidiolide analogues, useful compounds for SAR studies.

North side chain transformation was started with addition of 10 equivalents of 3-furyllithium to **9**, to give a good yield of a mixture of **11** and **12** in a 3:7 ratio, which was separable by column chromatography. The structure was determined by NMR studies and the 12*R* absolute configuration in **11** was corroborated by X-ray analysis.[25] (mp: 115–116 °C, hexane/AcOEt) (Figure 2).

Chemoselective esterification of **11** and **12** with TsCl in pyridine permitted the synthesis of the monotosyl derivatives which, upon reaction with 2-methylallylmagnesium chloride, gave **13** and **14** respectively.

The undesired $C_{18}$ epimer **14** may be recycled, via oxidation to the ketone **15** and subsequent reduction to the desired stereoisomer **13**. The reduction of ketone **15** with LAH gives a mixture (*R*/*S*: 3/1) of $C_{18}$ diastereomers **13** and **14** that were separated and recycled. (Scheme 2).

Compound **13** has the required south chain and a north chain with adequate functionality for subsequent transformations. Acetylation of **13**, (Scheme 3) followed by application of the Faulkner[18] furan oxidation methodology for

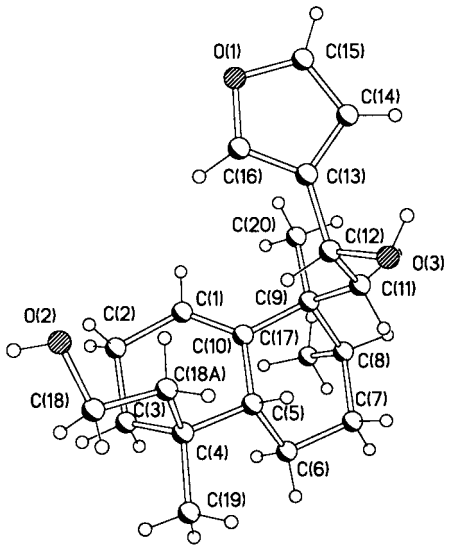



**Figure 2** ORTEP view of compound **11**

the synthesis of γ-hydroxybutenolides, gave **1**. Reaction of **13** with $^1O_2$ under the same conditions gave **2**. Both, **1** and **2**, were obtained as epimeric mixtures at $C_{20}$ in a ratio of 3:1.

Physical properties of these synthesized compounds, **1** and **2**,[26] are not identical to those described for the natural products cladocoran A and B. Initially it was thought that the difference could be at the stereogenic centre of the γ-hydroxybutenolide, so this centre was eliminated by $NaBH_4$ reduction of lactones **1** and **2** to give the butenolides **16** and **17**, but the physical properties of these derivatives were also not coincident with the analogues obtained by reduction of cladocoran A and B.[1]

Due to these facts, similar transformations were carried out on **14** to give **18** and **19** (epimers of **1** and **2**), but the physical properties of these compounds also do not coincide with those of Cladocoran A and B, and therefore the structure of these natural products should be revised.

Spectroscopic studies of cladocorans A and B, **1**, **2**, **18** and **19** show that the side chains are indeed present in the natural products, so the difference might be in the decalin, which would then not correspond to that of *ent*-halimic acid methyl ester **3**.

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(25) Crystal data for **11**: $C_{21}H_{32}O_3$, M = 332.47, orthorhombic, space group $P2_12_12_1$ (nº 19). a = 7.6504(15), b = 8.771(2), c = 28.694(6) Å, V = 1925.4(7) Å$^3$, Z = 4, $D_c$ = 1.147 mg/m$^3$, m (Cu-$K_\alpha$) = 0.075 mm$^{-1}$, F(000) = 728. Data (3609 collected reflections, and 3331 unique reflections [I > 2sigma (I)]) were measured on a Seifert 3003 SC rotating anode diffractometer with Cu-$K_\alpha$ radiation (graphite monochromator) using 2θ-ω scans at 268 K. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F$^2$ to give the agreement factors $R_1$ =& nbsp;0.0669, ω$R_2$ = 0.1527. Computations were carried on a Digital Alphastation 500 using the SHELXTL$^{TM}$ program. Crystallographic data for the structure of **11** in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 163376. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, (UK), (fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk).
(26) The assignments for the spectra, $^1$H NMR and $^{13}$C NMR for **1** and **2** were done by bidimensional experiments HMQC and HMBC. Spectroscopic and physical data for the mixture of α- and β-epimers at $C_{20}$ in **1**: $R_f$ = 0.41 (*hexane*–EtOAc, 7:3, v/v); $[\alpha]_D$: +20.0 (*c* 0.47, $CHCl_3$); UV/Vis (EtOH): $\lambda_{max}$ = 207 nm (ε 8500); IR(film): $\nu_{max}$ 3422, 3071, 3051, 2938, 2870, 1794, 1771, 1719, 1653, 1458, 1373, 1250, 1123, 1038, 939, 885 cm$^{-1}$; MS (EI): *m/z* (%) = 444(1) [M$^+$], 384(8), 340(13), 301(25), 259(44), 173(58), 105(62), 81(57); HRMS: *m/z* calcd for $C_{27}H_{40}O_5$: 444.2876; found: 444.2911. Data for **major epimer**: $^1$H NMR ($CDCl_3$, 400 MHz): δ = 5.99 (1 H, d, *J* = 9.4 Hz, H-20), 5.92 (1 H, s, H-21), 5.46 (1 H, m, H-10), 5.29 (1 H, dd, *J* = 3.0, 7.0 Hz, H-18), 4.94 (1 H, d, *J* = 9.4 Hz, OH), 4.70 (1 H, s, $H_A$-3), 4.66 (1 H, s, $H_B$-3), 2.56 (1 H, dd, *J* = 7.0, 15.2 Hz, $H_A$-17), 2.01 (3 H, s, -OOCMe), 1.97 (2 H, t, *J* = 7.2 Hz, H-4), 1.88 (2 H, m, H-13), 1.87 (1 H, m, H-12), 1.82 and 1.37 (1 H, m ea, H-14), 1.71 (3 H, s, Me-1), 1.60 (1 H, dd, *J* = 3.0, 15.2 Hz, $H_B$-17), 1.57 (2 H, m, H-9), 1.56 (1 H, m, H-15), 1.41 and 1.19 (1 H, m ea, H-8), 1.35 and 1.23 (1 H, m ea, H-5), 1.28 and

1.21 (1 H, m ea, H-6), 0.97 (3 H, s, Me-25), 0.84 (3 H, d, *J* = 7.2 Hz, Me-24), 0.80 (3 H, s, Me-23); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 22.4 (C-1), 146.0 (C-2), 109.7 (C-3), 38.5 (C-4), 21.5 (C-5), 40.2 (C-6), 34.2 (C-7), 31.7 (C-8), 21.7 (C-9), 121.8 (C-10), 140.1 (C-11), 41.7 (C-12), 22.7 (C-13), 28.4 (C-14), 38.6 (C-15), 42.4 (C-16), 43.1 (C-17), 67.7 (C-18), 168.8 (C-19), 97.7 (C-20), 117.9 (C-21), 169.5 (C-22), 21.5 (C-23), 15.5 (C-24), 23.8 (C-25), 171.2 (-OOCMe), 21.0 (-OOCMe). Data for **minor epimer**: $^1$H NMR ($CDCl_3$, 400 MHz): δ = 6.20 (1 H, br s, H-20), 5.96 (1 H, s, H-21), 5.46 (1 H, m, H-10), 5.44 (1 H, dd, *J* = 3.0, 8.0 Hz, H-18), 4.70 (1 H, s, $H_A$-3), 4.66 (1 H, s, $H_B$-3), 4.38 (1 H, br s, OH), 2.38 (1 H, dd, *J* = 8.0, 15.2 Hz, $H_A$-17), 2.03 (3 H, s, -OOCMe), 1.97 (2 H, t, *J* = 7.2 Hz, H-4), 1.92 (1 H, m, H-12), 1.88 (2 H, m, H-13), 1.88 and 1.42 (1 H, m ea, H-14), 1.83 (1 H, dd, *J* = 3.0, 15.2 Hz, $H_B$-17), 1.71 (3 H, s, Me-1), 1.57 (2 H, m, H-9), 1.56 (1 H, m, H-15), 1.33 and 1.09 (1 H, m ea, H-8), 1.35 and 1.23 (1 H, m ea, H-5), 1.28 and 1.21 (1 H, m ea, H-6), 0.97 (3 H, s, Me-25), 0.84 (3 H, d, *J* = 7.2 Hz, Me-24), 0.80 (3 H, s, Me-23); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 22.4 (C-1), 146.0 (C-2), 109.7 (C-3), 38.5 (C-4), 21.5 (C-5), 40.2 (C-6), 34.2 (C-7), 31.9 (C-8), 21.7 (C-9), 121.1 (C-10), 140.1 (C-11), 41.4 (C-12), 22.7 (C-13), 28.2 (C-14), 38.6 (C-15), 42.4 (C-16), 42.4 (C-17), 67.3 (C-18), 167.8 (C-19), 97.9 (C-20), 118.8 (C-21), 169.5 (C-22), 21.5 (C-23), 15.5 (C-24), 23.5 (C-25), 171.2 (-OOCMe), 21.0 (-OOCMe). Spectroscopic and physical data for the mixture of α- and β-epimers at $C_{20}$ in **2**: $R_f$ = 0.45 (hexane–EtOAc, 6:4, v/v); $[\alpha]_D$: +98.9 (*c* 0.64, $CHCl_3$); UV/Vis (EtOH): $\lambda_{max}$ = 205 nm (ε 8600); IR(film): $\nu_{max}$ 3378, 3074, 3052, 2938, 1753, 1649, 1451, 1377, 1263, 1136, 953, 885, 739 cm$^{-1}$; MS (FAB) *m/z* (%) = 403(6) [$M^+$ +1], 385(12), 367(16), 259(34), 154(100), 91(58); HRMS (FAB) *m/z* calcd for $[C_{25}H_{38}O_4 + H]^+$: 403.2848; found: 403.2823. Data for **major**: $^1$H NMR ($CDCl_3$, 400 MHz): δ = 6.06 (1 H, d, *J* = 6.8 Hz, H-20), 6.02 (1 H, br s, H-21), 5.66 (1 H, m, H-10), 4.80 (1 H, dd, *J* = 10.0, 1.8 Hz, H-18), 4.71 (1 H, s, $H_A$-3), 4.67 (1 H, s, $H_B$-3), 4.50 (1 H, d, *J* = 6.8 Hz, OH), 2.81 (1 H, d, *J* = 1.8 Hz, OH), 2.56 (1 H, dd, *J* = 10.0, 14.0 Hz, $H_A$-17), 2.16 (1 H, m, H-12), 2.06 (2 H, m, H-9), 1.97 (2 H, m, H-4), 1.71 (3 H, s, Me-1), 1.59 (2 H, m, H-13), 1.58 (1 H, m, H-15), 1.42 (2 H, m, H-5), 1.39 and 1.16 (1 H, m ea, H-8), 1.35 (2 H, m, H-14), 1.34 (1 H, d, *J* = 14.0 Hz, $H_B$-17), 1.23 and 1.18 (1 H, m ea, H-6), 1.11 (3 H, s, Me-25), 0.83 (3 H, d, *J* = 7.0 Hz, Me-24), 0.82 (3 H, s, Me-23); $^{13}$C ($CDCl_3$, 100 MHz): = δ 22.3 (C-1), 146.4 (C-2), 109.6 (C-3), 38.5 (C-4), 21.3 (C-5), 39.4 (C-6), 34.1 (C-7), 31.3 (C-8), 22.8 (C-9), 122.7 (C-10), 143.6 (C-11), 41.1 (C-12), 22.7 (C-13), 28.3 (C-14), 40.5 (C-15), 42.7 (C-16), 44.9 (C-17), 66.8 (C-18), 171.1 (C-19), 97.3 (C-20), 117.1 (C-21), 170.6 (C-22), 21.3 (C-23), 15.4 (C-24), 22.1 (C-25). Data for **minor**: $^1$H NMR ($CDCl_3$, 400 MHz): δ = 6.20 (1 H, d, *J* = 6.8 Hz, H-20), 5.96 (1 H, br s, H-21), 5.66 (1 H, m, H-10), 4.76 (1 H, dd, *J* = 10.0, 1.8 Hz, H-18), 4.69 (1 H, s, $H_A$-3), 4.65 (1 H, s, $H_B$-3), 4.50 (1 H, d, *J* = 6.8 Hz, OH), 2.86 (1 H, d, *J* = 1.8 Hz, OH), 2.56 (1 H, dd, *J* = 10.0, 14.0 Hz, $H_A$-17), 2.11 (1 H, m, H-12), 2.06 (2 H, m, H-9), 1.97 (2 H, m, H-4), 1.69 (3 H, s, Me-1), 1.59 (2 H, m, H-13), 1.58 (1 H, m, H-15),1.57 (1 H, d, *J* = 14.0 Hz, $H_B$-17), 1.42 (2 H, m, H-5), 1.46 and 1.23 (1 H, m ea, H-8), 1.40 (2 H, m, H-14), 1.23 and 1.18 (1 H, m ea, H-6), 1.09 (3 H, s, Me-25), 0.83 (3 H, d, *J* = 7.0 Hz, Me-24), 0.82 (3 H, s, Me-23); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 22.3 (C-1), 146.1 (C-2), 109.7 (C-3), 38.5 (C-4), 21.3 (C-5), 39.5 (C-6), 34.1 (C-7), 31.3 (C-8), 22.8 (C-9), 122.6 (C-10), 143.8 (C-11), 41.4 (C-12), 22.7 (C-13), 28.3 (C-14), 40.4 (C-15), 42.5 (C-16), 44.2 (C-17), 66.3 (C-18), 169.8 (C-19), 97.8 (C-20), 117.5 (C-21), 170.7 (C-22), 21.4 (C-23), 15.4 (C-24), 22.2 (C-25).