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Studies on the Stereostructure of Eudesmanolides from *Umbelliferae*: Synthesis of 11β-angeloyloxy-α-santonin

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Abstract: The first approach to the synthesis of decipienin A (1) having the stereostructure **b** (11β-angeloyloxy-α-santonin) have been performed following three different synthetic routes. The key step on the synthetic procedures is the stereoselective hydroxylation at C-11 position. An evaluation of the different used routes is discussed. Comparison of spectroscopic data of compound **1b** and those from the natural decipienin A suggests that a stereostructure type **a** could be assigned to the natural product.

INTRODUCTION

During the last two decades sesquiterpene lactones have emerged as one of the largest groups of plant products with over 4000[1] naturally occurring substances known. This group of natural products, belonging to *Compositae*[2] and *Umbelliferae*[3] families principally, shows interesting biological activities.[4]

Holub[3] found that practically all the sesquiterpene lactones from *Umbelliferae* have a different stereostructure from the analogous skeletal type of sesquiterpene lactones from *Compositae* species. He suggested that the biogenetic steps leading to the sesquiterpene lactones in this two plant families form two parallel series and proceed very probably in both families by similar reactions assuming a different conformation of the *trans,trans*-farnesyl diphosphate precursor.

Based on spectroscopic criteria, he proposed that decipienin A (**1**) and other eudesmanolides isolated from *Melanoselinum decipiens* (Schrader-Wendl.) Hoffm. (Umbelliferae, tribe *Laserpitieae*)[5] should have structures type (**a**) (5βH,6αH,7αH,10α,11β-Methyl-eudesman-6,12-olide) instead of structures (**b**) (5αH,6βH, 7αH,10β,11α-Methyl-eudesman-6,12-olide) (Figure 1).

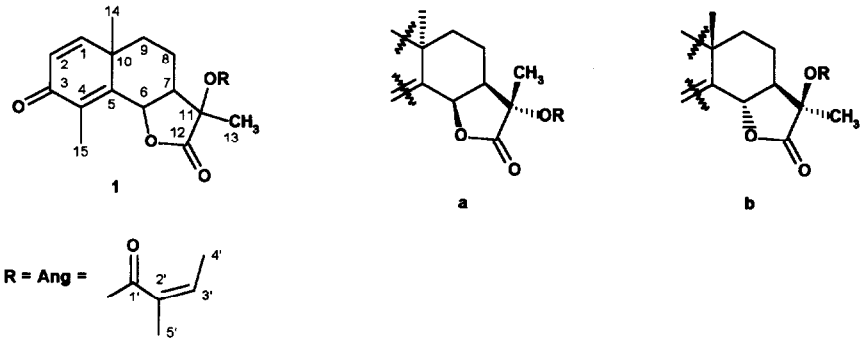


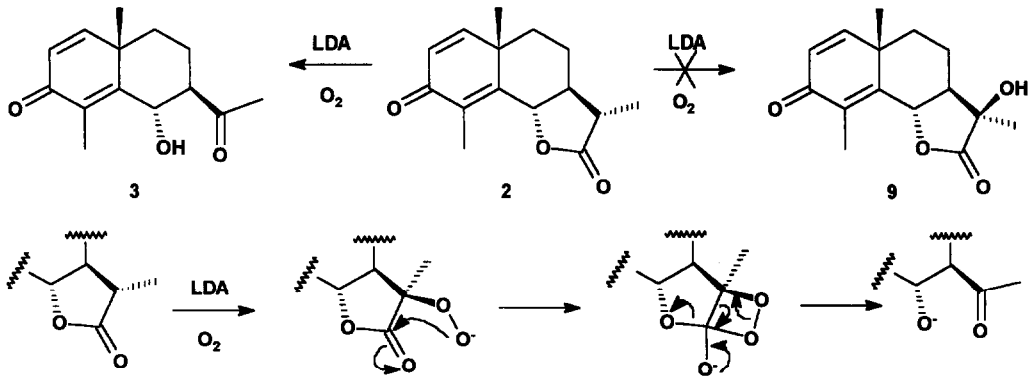
Figure 1

In this paper we report the first approach to the synthesis of decipienin A (**1**) having the stereostructure **b**. The differences between spectroscopic and physical data of this compound and those reported for the natural product led to the conclusion that the original proposed stereostructure is not correct. Consequently a stereostructure type **a** could be assigned to the natural product, but this is still an open question.

RESULTS AND DISCUSSION

In the course of our research program on the synthesis of bioactive sesquiterpene lactones, we reported a method for α-hydroxylation of the γ-lactones[6]. We thought that decipienin A (**1**) could be easily prepared by this hydroxylation procedure and further angeloylation of α-santonin (**2**), thus providing more information about the validity of the originally proposed stereostructure **b** for this natural product (H-$C_6\beta$; CH_3-$C_{11}\alpha$; CH_3-$C_{10}\beta$).

Surprisingly, direct hydroxylation with LDA at -70°C and trapping the resulting enolate with O_2 at 0°C, gave compound **3** in low yield as well as a complex mixture of byproducts, instead of the corresponding 11-hydroxy derivative. The IR spectrum of **3** shows absorptions at 3435 (OH) and 1696 (ketone) and 1640 (α,β-



Scheme 1

unsaturated ketone) cm^{-1} and the absence of the γ-lactone absorption at 1750 cm^{-1}. A molecular ion at m/z 234, additional peaks at 216 $[M-H_2O]^+$ and 173 $[M-H_2O-COCH_3]^+$(base peak) together with a clear singlet at δ 2.19 ($3H,H_{13}$) in the ^1H NMR spectrum are in accordance with a methyl ketone derivative at C-7. The formation of this compound can be rationalized as depicted in Scheme **I**.

The fact that other α-hydroxylation methods[7] resulted in the formation of intractable mixtures suggests that the presence of the dienone system is a serious problem for preparing 11-hydroxy-α-santonin. The unfavorable course of the direct introduction a hydroxyl group at C_{11}, prompted us to undertake other synthetic routes where the hydroxylation step is carried out on more convenient substrates. These procedures are outlined in Scheme II.

Dihydroderivative **4** was obtained by catalytic hydrogenation of commercial α-santonin **2** with Wilkinson's catalyst[8] (98%). Treatment of **4** with ethanedithiol in the presence of $BF_3{\cdot}Et_2O$ gave thioketal **5**[7] (99%).

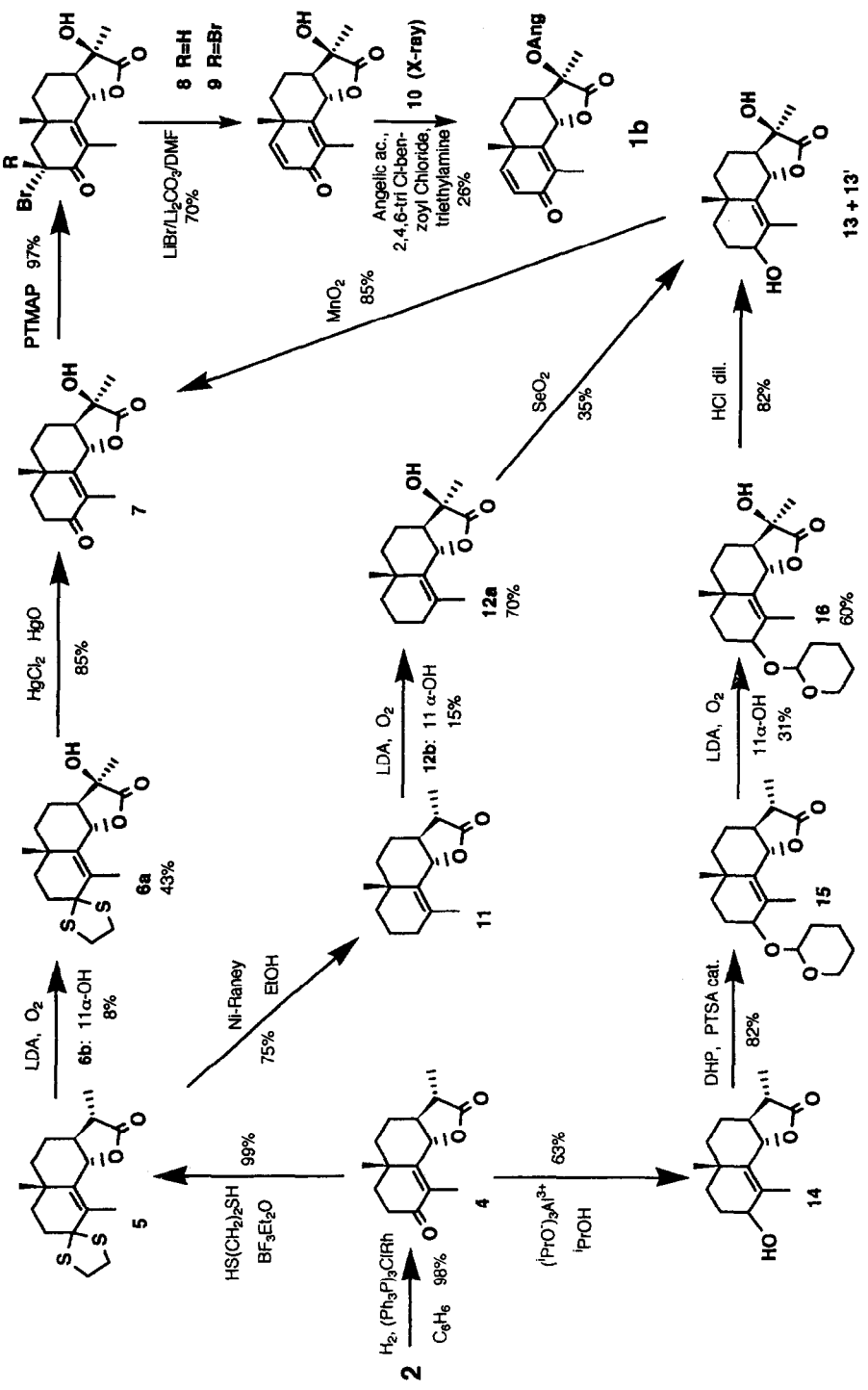
Desulfuration with Raney nickel (75%) and further C-11-hydroxylation yielded hydroxylactones **12a** and **12b** in 70 and 15% yield respectively. The β-orientation for the hydroxyl group in **12a** was inferred by the chemical shift of H_6 because a significant deshielding effect is produced upon the lactonic proton ($\Delta\delta$=0.38 ppm)[9]. This deshielding effect is due to an 1,3-interaction between H-6 and the hydroxyl group. Allylic oxidation of **12a** gave the diols **13** and **13'** in 35% yield, as a mixture of epimers at C-3. The preparation of **13** and **13'** starting from the thioketal **5** will be referred as route **A**. The same allylic alcohols were obtained from **4** through the following steps (route **B**): reduction of the α,β-unsaturated ketone **4** to give the alcohol **14** (63%); protection of the hydroxyl group (82%) and hydroxylation to give **16** (60%). Further deprotection gave compounds **13** and **13'** in 82% yield.

Oxidation of the mixture of allylic alcohols **13** and **13'** yielded the hydroxyketone **7**, which was characterized as 11β-hydroxy-1,2-dihydro-α-santonin. A deshielding effect of 0.21 ppm for H_6 signal in comparison with 1,2-dihydro-α-santonin (**4**) is in agreement with a β-orientation of the C_{11} hydroxyl group.

Compound **7** was prepared through a shorter and more efficient sequence starting from thioketal **5** (route **C**). The hydroxylation of **5**, as describe above, gave the C_{11} β-alcohol **6a** in 43% yield and the corresponding α-alcohol **6b** (8%). Deprotection of the carbonyl group was performed by treatment of the hydroxythioketal **6a** with $HgCl_2$ and HgO in acetonitrile[10] to give 11β-hydroxy-1,2-dihydro-α-santonin **7** (85%).

Comparison of the different described synthetic routes shows that route **C** lead to obtain compound **7** in three steps with the higher overall yield (36%) while routes **A** and **B** have 16% and 22% yield respectively in five steps. The key step on the whole synthetic design is the stereoselective hydroxylation of the different substrates at C_{11} position. While better total yield was found for this reaction in routes **A** (85%) and **B** (91%), the best stereoselectivity was found for routes **A** and **C** with a ratio 5:1 (11β-hydroxy:11α-hydroxy) in both cases. Consequently route **C** seems to be the more efficient although the C_{11} hydroxylation yield is the lowest.

Treatment of **7** with phenyltrimethylammonium perbromide in dioxane gave the bromoketone **8** (97%) and a small amount of the C_2-dibrominated compound **9**. The α-orientation of the bromine atom in **8** was inferred from the value of the coupling constants of H_2 ($J_{1,2}$=7; $J_{1',2}$=12 Hz) according with an axial disposition for H_2. Introduction of the C_1-C_2 double bond was accomplished by treatment of **8** with lithium carbonate and lithium bromide in dry DMF yielding 11β-hydroxy-α-santonin **10** (70%). This compound is a mammalian metabolite of


PTMAP 97%
LiBr/Li2CO3/DMF 70%
8 R=H
9 R=Br
Angelic ac., 2,4,6-tri Cl-benzoyl Chloride, triethylamine 26%
10 (X-ray)
MnO2 85%
1b
HgCl2 HgO 85%
LDA, O2
6b: 11α-OH 8%
6a 43%
Ni-Raney EtOH 75%
LDA, O2
12b: 11 α-OH 15%
12a 70%
SeO2 35%
HCl dil. 82%
13 + 13'
HS(CH2)2SH BF3Et2O 99%
H2, (Ph3P)3ClRh C6H6 98%
2
(iPrO-)3Al3+ iPrOH 63%
DHP, PTSA cat. 82%
LDA, O2 11α-OH 31%
16 60%
15
14
5
4
11
7

Scheme 2

the natural α-santonin which was first isolated in 1897[11]. Pinhey and Sternhell obtained this lactone from the urine of a dog fed with α-santonin and proposed for it structure **10** on the basis of ^{1}H NMR data[12]. The preparation of **10** from α-santonin, establishes its structure and the configuration of the chiral centers C_6 , C_7 and C_{10}. To confirm the total stereostructure of this compound an X-ray diffraction[13] analysis was carried out. This analysis establishes the C_{11} configuration unambiguously as (R) (Figure 2).

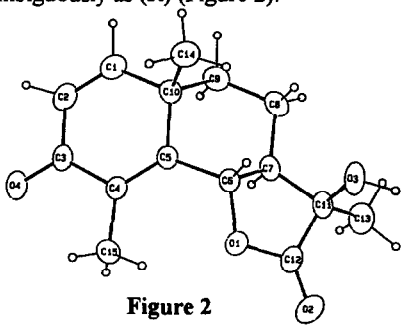


Figure 2

Esterification of C_{11} hydroxyl group by treatment of **10** with angeloyl chloride in pyridine afforded the tiglate derivative. When the reaction was carried out using the mixed anhydride obtained from angelic acid and 2,4,6-trichlorobenzoyl chloride[14], 11β-angeloyloxy-α-santonin (**1b**) was obtained in 26% yield.

Comparison of the ^{1}H NMR data of **1b** with those of natural decipienin **A**[5a], showed significant differences between chemical shift and coupling constants of H_6 and H_7 in both compounds. The H_6 and H_7 signals in decipienin A are shifted downfield (0.26 and 0.34 ppm respectively) respect to **1b**. Furthermore, the value of $J_{6,7}$ in decipienin **A** (9Hz) is lower than the observed in **1b** (11.3 Hz). The above differences suggest, that a stereostructure type **a** could be assigned to the natural product, but further synthetic studies directed to unambiguously establish its stereostructure need to be performed.

EXPERIMENTAL SECTION

Materials and General Procedures: Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer in film. ^{1}H NMR and ^{13}C NMR spectra were made on Varian Gemini-200 and Bruker AM-400 spectrometers, using $CDCl_3$ as internal standard. Mass spectra were recorded on a VG 12-250 spectrometer using 70 eV. Chromatographic separations were made on silica gel (Merck), employing hexane, ethyl acetate mixtures as eluent.

Direct hydroxylation of α-santonin.

A solution of **2** (1g) in dry THF (32 mL) was introduced dropwise with a syringe on a flask containing a mixture of diisopropylamine (1.7 mL), a 15% hexane solution of butyllithium (6.2 mL), and dry THF (4mL) and stirred continuously for 60 min at -73 °C under dry nitrogen atmosphere. After the mixture had been stirred for 40 min. it reached 0°C and then dry oxygen was bubbled through for 35 min. The mixture was carefully neutralized with HCl (aq) (1N) and extracted with EtOAc. The water layer was concentrated by distillation under

reduced pressure and the solid residue extracted with dichloromethane for several hours. Both EtOAc and dichloromethane fractions were concentrated and chromatographed (hexane/EtOAc, 7:3) to yield **3** (75 mg).

3: IR (KBr)^{neat} ν cm^{-1}: 3435 (hydroxyl group), 1696 (ketone), 1640 (α,β-unsaturated ketone). MS, m/z (relative intensity): 234 $[M]^+$ (2), 216 $[M-H_2O]^+$ (65), 201 $[M-H_2O-CH_3]^+$ (55), 173 $[M-H_2O-COCH_3]^+$ (100). ^1H NMR (200 MHz, $CDCl_3$) δ: 6.60 (d, $J_{1,2}$=10 Hz, H-1), 6.15 (d, $J_{1,2}$=10 Hz, H-2), 4.92 (ddq, $J_{6,7}$=10 Hz, $J_{6,OH}$=5 Hz, $J_{6,15}$=1.5 Hz, H-6), 3.16 (d, $J_{6,OH}$=5 Hz, OH), 2.70 (ddd, $J_{6,7}$=10 Hz, $J_{7,8\beta}$=12 Hz, $J_{7,8\alpha}$=5 Hz, H-7), 2.19 (s, 3H, H-13), 2.16 (d, $J_{6,15}$=1.5 Hz, 3H, H-15), 1.16 (s, 3H, H-14).

3 (15mg) were acetylated with Ac_2O/pyridine (3:1; 1 mL) for 24 h at room temperature. After purification by column chromatography (Hexane/EtOAc, 9:1), afforded the corresponding acetate (14 mg): IR (KBr)^{neat} ν cm^{-1}: 1740 (Ester), 1709 (ketone), 1655 (α,β-unsaturated ketone). MS, m/z (relative intensity): 276 $[M]^+$ (1), 261 $[M-CH_3]^+$ (10), 234 $[M-C_2H_2O]^+$ (15), 43 $[COCH_3]^+$ (100). ^1H NMR (200 MHz, $CDCl_3$) δ: 6.60 (d, $J_{1,2}$=10 Hz, H-1), 6.15 (d, $J_{1,2}$=10 Hz, H-2), 5.81 (dq, $J_{6,7}$=10 Hz, $J_{6,15}$=1.5 Hz, H-6), 2.88 (ddd, $J_{6,7}$=10 Hz, $J_{7,8\beta}$=11 Hz, $J_{7,8\alpha}$=3.5 Hz, H-7), 2.16 (s, 3H, H-13), 2.00 (s, 3H, H-2'), 1.91 (d,$J_{6,15}$=1.5 Hz, 3H, H-15), 1.33 (s, 3H, H-14).

1,2-Dihydro-α-santonin (4).

A solution of **2** (5 g) and $(Ph_3P)_3ClRh$ (350 mg) in a 1:1 mixture Benzene/EtOAc (250 mL) under hydrogen atmosphere was stirred for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexane/EtOAc, 7:3), to give **4** (4.93 g). IR (KBr)^{neat} ν cm^{-1}: 1750 (γ-lactone), 1640 (α,β-unsaturated ketone), 1600 (C-C double bond). MS, m/z (relative intensity): 248 $[M]^+$ (80), 233 $[M - CH_3]^+$ (30), 192 (100). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.66 (dd, $J_{6,15}$=1.5 Hz, $J_{6,7}$=11 Hz, H-6), 2.49 (ddd, $J_{2\alpha,2\beta}$=13 Hz, $J_{2\alpha,1\alpha}$=4.5 Hz, $J_{2\alpha,1\beta}$=6 Hz, H-2), 2.40 (m, obscured by other signals, H-11), 2.34 (ddd, $J_{2\alpha,2\beta}$=13 Hz, $J_{2\beta,1\alpha}$=11.5 Hz, $J_{2\beta,1\beta}$=6.5 Hz, H-2), 1.97 (d, $J_{6,15}$=1.5 Hz, H-15), 1.32 (s, 3H, H-13), 1.24 (d, $J_{11,13}$=6.5 Hz, 3H, H-14).

Thioketal of 1,2-dihydro-α-santonin (5).

A solution of **4** (2.7 g), ethanedithiol (5.4 mL) and freshly distilled boron trifluoride ethearate (0.4 mL) in 27 mL of glacial acetic acid was stirred under nitrogen atmosphere at 5-10°C. After 6 h, additional boron trifluoride ethearate (0.4 mL) was added and the mixture allowed to stand overnight at 5-10°C.

After neutralization with solid Na_2CO_3 and extraction with Et_2O, the organic layer was washed with 2N HCl, $NaHCO_3$ and water. The solvent was removed under reduced pressure and the residue chromatographed (Hexane/EtOAc, 9:1) to give **5** (3.5 g). IR (KBr)^{neat} ν cm^{-1}: 1765 (γ-lactone), 1600 (C-C double bond). MS, m/z (relative intensity): 324 $[M]^+$ (72), 296 $[M - C_2H_4]^+$ (25), 264 $[M - SC_2H_4]^+$ (100), 231 $[M-S_2C_2H_5]$ (72). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.54 (brd, $J_{6,7}$=10.5 Hz, H-6), 3.45-3.10 (m, 4H, S-C<u>H</u>$_2$-), 2.35-2.15 (m, 2H, H-7, H-11), 2.08 (s, 3H, H-13), 1.20 (d, $J_{11,13}$= 5.5 Hz, 3H, H-13), 1.15 (s, 3H, H-14).

Thioketal of 11β-hydroxy-1,2-dihydro-α-santonin (6a) and thioketal of 11α-hydroxy-1,2-dihydro-α-santonin (6b).

A solution of **5** (868 mg) in dry THF (22 mL) was added dropwise into a mixture containing 0.75 mL of diisopropylamine, a 15% hexane solution of butyllithium (2.94 mL), and THF (3 mL) and stirred continuously for 30 min at -70°C under dry nitrogen atmosphere. After 40 min the stirred solution reached 0°C and then dry

oxygen was bubbled through for 30 min. The reaction mixture was carefully neutralized with 1N HCl solution and extracted with EtOAc. The organic layer was concentrated and chromatographed (hexane/EtOAc, 7:3) to yield **6a** (390 mg) and **6b** (73 mg).

6a: IR (KBr)^{neat} ν cm^{-1}: 3583 (hydroxyl group), 1755 (γ-lactone). MS, m/z (relative intensity): 340 $[M]^+$ (14), 322 $[M-H_2O]^+$ (10), 280 $[M - SC_2H_4]^+$ (15), 69 (100). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.98 (dd, $J_{6,7}$=10 Hz, $J_{6,15}$=1.5 Hz, H-6), 3.45-3.20 (m, 4H, S-C<u>H</u>$_2$-), 2.35-2.15 (m, 2H, H-2α, H-2β), 2.06 (d, $J_{6,15}$=1.5 Hz, 3H, H-13), 1.42 (s, 3H, H-13), 1.11 (s, 3H, H-14).

6b: IR (KBr)^{neat} ν cm^{-1}: 3476 (hydroxyl group), 1755 (γ-lactone). MS, m/z (relative intensity): 340 $[M]^+$ (24), 322 $[M-H_2O]^+$ (31), 280 $[M - SC_2H_4]^+$ (16), 209 $[M-C_2H_4S_2-C_3H_3,]^+$ (25), 43 (100). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.60 (dd, $J_{6,7}$=11.5 Hz, $J_{6,15}$= 1.5 Hz, H-6), 3.40-3.20 (m, 4H, S-C<u>H</u>$_2$), 2.24 (ddd, $J_{2\alpha,2\beta}$=15 Hz, $J_{2\beta,1\beta}$=3.5 Hz, $J_{2\beta,1\alpha}$=11.5 Hz, H-2β), 2.17 (ddd, $J_{2\alpha,2\beta}$=15 Hz, $J_{2\alpha,1\beta}$=10 Hz, $J_{2\alpha,1\alpha}$=6 Hz, H-2α), 2.09 (d, $J_{6,15}$=1.5 Hz, 3H, H-15), 1.34 (s, 3H, H-13), 1.13 (s, 3H, H-14).

1,2-Dihydro-11β-hydroxy-α-santonin (7).

$HgCl_2$ (200 mg) and HgO (80 mg) were added to **6a** (114 mg) dissolved in a 4:1 mixture of acetonitrile/water at room temperature. The mixture was allowed to stand for 24 h, filtered over celite and the filter washed with hexane/CH_2Cl_2 (1:1). The organic layer was washed with ammonium acetate (5M), water and brain, dried over Na_2SO_4 and the solvent removed by distillation under reduced pressure. The residue was crystallized from EtOH to give **7** (75 mg). IR (KBr)^{neat} ν cm^{-1}: 3280 (hydroxyl group), 1765 (γ-lactone), 1680 (α,β-unsaturated ketone). MS, m/z (relative intensity): 264 $[M]^+$ (22), 246 $[M-H_2O]^+$ (100), 231 $[M- H_2O - CH_3]^+$ (28). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.87 (dd, $J_{6,7}$=11, $J_{6,15}$=2, H-6), 2.23 and 2.15 (m, H-2α and H-2β), 1.60 (m , H-7), 1.67 (d, $J_{6,15}$=2, 3H, H-15), 1.14 (s, 3H, H-13), 1.08 (s, 3H, H-14).

Compound **7** was also prepared by oxidation of the mixture **13** and **13'** (80 mg) dissolved in benzene (10 mL) with MnO_2 (1.5 mmol) and stirred continuously for 12 h at room temperature. The reaction mixture was filtered over celite and the filter washed with EtOAc. The organic layer was dried, concentrated and chromatographed using DCM:ether (4:1) as eluent to yield **7** (67 mg; 85%).

2α-Bromo-2,3-dihydro-11β-hydroxy-α-santonin (8) and 2,2-dibromo-2,3-dihydro-11β-hydroxy-α-santonin (9).

To a solution of **7** (55 mg) in dioxane (25 mL) small portions of phenyltrimethylammomium perbromide were added. After the mixture was stirred for 1 h, ethyl ether was added and then filtered through celite with further addition of CH_2Cl_2/EtOAc (1:1). The solution was concentrated under reduced pressure and the residue was chromatographed, affording **8** (69 mg) and **9** (2 mg).

8: IR (KBr)^{neat} ν cm^{-1}: 3450 (hydroxyl group), 1760 (γ-lactone), 1690 (α,β-unsaturated ketone). MS, M/z (relative intensity): 342 $[M]^+$ (0.4), 344 $[M+2]^+$ (0.3), 235 $[M-Br-CO]^+$ (49), 43 (100). ^1H NMR (200 MHz, $CDCl_3$) δ: 5.01 (brd, $J_{6,7}$=10 Hz, H-6), 4.82 (dd, $J_{1,2}$=8 Hz, $J_{1',2}$=11 Hz, H-2), 2.33 (m, 2H, H-1 and H-1'), 2.00 (brs, 3H, H-15), 1.42 (s, 3H, H-13), 1.37 (s, 3H, H-14).

9: IR (KBr)^{neat} ν cm^{-1}: 3445 (hydroxyl group), 1760 (γ-lactone), 1685 (α,β-unsaturated ketone). MS, M/z (relative intensity): 396 $[M+2-CO]^+$ (3), 394 $[M-CO]^+$ (6), 392 $[M-2-CO]^+$ (3), 315 $[M-Br-CO]^+$ (40), 43 (100).

^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.15 (dd, $J_{6,7}$=10 Hz, $J_{6,15}$=1.5 Hz, H-6), 3.09 (d, $J_{1,1'}$=15 Hz, H-1), 3.01 (d, $J_{1,1'}$=15 Hz, H-1'), 2.16 (d, $J_{6,15}$=1.5 Hz, 3H, H-15), 1.50 (s, 3H, H-14), 1.48 (s, 3H, H-13).

Preparation of 11β-hydroxy-α-santonin (10).

To a suspension of dry LiBr (32 mg) and Li_2CO_3 (42 mg) in dry DMF (10 mL) at 120°C under nitrogen atmosphere was added 2-bromo-2,3-dihydro-11β-hydroxy-α-santonin (**8**) (60 mg). After the mixture was stirred for 75 min at 120-125°C, it was cooled and aq. acetic acid (5%) was added. The reaction mixture was extracted with EtOAc and the organic layer concentrated under reduced pressure. After chromatography, it yielded 32 mg (70%) of **10**.

10: IR (KBr)^{neat} ν cm^{-1}: 3300 (hydroxyl group), 1780 (γ-lactone), 1640 (α,β-unsaturated ketone). MS, m/z (relative intensity): 262 $[M]^+$ (15), 244 $[M-H_2O]^+$ (4), 173 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.63 (d, $J_{1,2}$=9.5 Hz, H-1), 6.36 (d, $J_{1,2}$=9.5 Hz, H-2), 5.36 (brd, $J_{6,7}$=11, H-6), 2.36 (s, 3H, H-15), 2.11 (dddd, $J_{8\alpha,8\beta}$=13, $J_{7,8\beta}$=12, $J_{8\beta,9\beta}$=3.5, $J_{8\beta,9\alpha}$=12, H-8β), 1.92 (ddd, $J_{6,7}$=11, $J_{7,8\alpha}$=3, $J_{7,8\beta}$=12, H-7), 1.76 (m, 2H, H-8α, H-9β), 1.65 (s, 3H, H-13), 1.38 (ddd, $J_{8\alpha,9\alpha}$=4, $J_{8\beta,9\alpha}$=12, $J_{9\alpha,9\beta}$=13.5, H-9α), 1.15 (s,3H, H-14)

11,13-Dihydro-11βH-arbusculin B (11).

5 (1.00 g) dissolved in ethanol (25 mL) was treated with a Raney nickel ethanol suspension (10 mL) and stirred for 3 h under hydrogen atmosphere (0.5 atm). The mixture was filtered through celite and chromatographed (hexane/EtOAc, 19:1) to yield **11** (543 mg). IR (KBr)^{neat} ν cm^{-1}: 1766 (γ-lactone), 1619 (C-C double bond). MS, m/z (relative intensity): 234 $[M]^+$ (11), 219 $[M-CH_3]^+$ (100). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.52 (dd, $J_{6,7}$=11 Hz, $J_{6,15}$=1.5 Hz, H-6), 2.22 (dq, $J_{7,11}$=12 Hz, $J_{11,13}$=7 Hz, H-11), 1.85 (m, 2H, H-3), 1.79 (s, 3H, H-15), 1.17 (d, $J_{11,13}$=7 Hz, H-13), 1.08 (s, 3H, H-14).

11,13-Dihydro-11β-hydroxyarbusculin B (12a) and 11,13-dihydro-11α-hydroxyarbusculin B (12b).

A solution of **11** (448 mg) in dry THF (18 mL) was added dropwise into a mixture containing diisopropylamine (1.71 mL), a 15% hexane solution of butyllithium (2.31 mL), and THF (3 mL) and stirred continuously for 30 min at -70°C under dry nitrogen atmosphere. After the mixture had been stirred for 15 min, it reached 0°C and then dry oxygen was bubbled through for 30 min. After careful neutralization with HCl (aq) (1N), the mixture was extracted with EtOAc, concentrated and chromatographed (hexane/EtOAc, 8:2) to yield **12a** (337 mg) and **12b** (70 mg).

12a: IR (KBr)^{neat} ν cm^{-1}: 3403 (hydroxyl group), 1754 (γ-lactone), 1601 (C-C double bond). MS, m/z (relative intensity): 250 $[M]^+$ (15), 232 $[M-H_2O]^+$ (25). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.99 (brdd, $J_{6,7}$=11 Hz, $J_{6,15}$=1.5 Hz, H-6), 1.95 (m, H-3), 1.90 (m, H-3'), 1.85 (ddd, $J_{6,7}$=11 Hz, $J_{7,8\alpha}$=4 Hz, $J_{7,8\beta}$=10 Hz, H-7) 1.81 (brs, 3H, H-15), 1.43 (s, H-13), 1.11 (s, 3H, H-14).^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8 (s, C-12), 130.2 (s, C-5), 126.3 (s, C-4), 81.9 (d, C-6), 73.0 (s, C-11), 55.6 (d, C-7), 41.0 (s, C-10), 40.7 (t, C-9), 37.1 (t, C-1), 34.5 (t, C-3), 26.0 (q, C-13), 21.5 (q, C-15), 20.0 (q, C-14), 18.8 (t, C-2), 18.5 (t, C-8).

12b: IR (KBr)^{neat} ν cm^{-1}: 3448 (hydroxyl group), 1752 (γ-lactone), 1618 (C-C double bond). MS, m/z (relative intensity): 250 $[M]^+$ (8), 232 $[M-H_2O]^+$ (37). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.61 (brdd, $J_{6,7}$=11.5 Hz, $J_{6,15}$=1.5 Hz, H-6), 2.17 (ddd, $J_{6,7}$=11.5 Hz, $J_{7,8\alpha}$=3.5 Hz, $J_{7,8\beta}$=12 Hz, H-7), 1.99 (m, H-3), 1.92 (m, H-3'), 1.83 (brs, 3H, H-15), 1.35 (s, H-13), 1.10 (s, 3H, H-14).^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.5 (s, C-12), 129.5 (s, C-5), 127.0

(s, C-4), 80.8 (d, C-6), 74.1 (s, C-11), 55.3 (d, C-7), 40.9 (s, C-10), 40.6 (t, C-9), 37.1 (t, C-1), 34.6 (t, C-3), 26.1 (q, C-13), 20.1 (m, C-15, C-14), 18.8 (t, C-2), 18.4 (t, C-8).

11,13-Dihydro-3α,11β-dihydroxyarbusculin B (13) and 11,13-dihydro-3β,11β-dihydroxyarbusculin B (13′).

Reaction of **12a** (200 mg) with SeO_2 (1.0:2.0, molar) in dry CH_2Cl_2 under nitrogen atmosphere, after 3 h at 50°C, gave a mixture (75 mg) of **13** and **13′**.

13: IR $(KBr)^{neat}$ ν cm^{-1}: 3450 (hydroxyl group), 1750 (γ-lactone), 1630 (C-C double bond). MS, m/z (relative intensity): 266 $[M]^+$ (10), 248 $[M-H_2O]^+$ (8), 230 $[M-2xH_2O]^+$ (32). ^1H NMR (400 MHz, $CDCl_3$) δ: 5.03 (brd, $J_{6,7}$=10.5, H-6), 3.96 (brdd, $J_{2\alpha,3}=J_{2\beta,3}$=6, H-3), 1.95 (brs, 3H, H-15), 1.44 (s, H-13), 1.19 (s, 3H, H-14).^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.1 (s, C-12), 134.3 (s, C-5), 128.0 (s, C-4), 81.3 (d, C-6), 73.0 (s, C-11), 71.5 (d, C-3), 55.8 (d, C-7), 40.1 (t, C-9), 37.8 (s, C-10), 36.2 (t, C-1), 28.2 (q, C-13), 26.2 (t, C-2), 21.6 (q, C-15), 18.5 (q, C-14), 15.7 (t, C-8).

13′: IR $(KBr)^{neat}$ ν cm^{-1}: 3460 (hydroxyl group), 1752 (γ-lactone), 1630 (C-C double bond). MS, m/z (relative intensity): 266 $[M]^+$ (14), 248 $[M-H_2O]^+$ (6), 230 $[M-2xH_2O]^+$ (45). ^1H NMR (400 MHz, $CDCl_3$) δ: 4.98 (brdd, $J_{6,7}$=10.5, $J_{6,15}$=1.5, H-6), 3.89 (brs, H-3), 2.00 (d, $J_{6,15}$=1.5, 3H, H-15), 1.45 (s, H-13), 1.12 (s, 3H, H-14).^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.1 (s, C-12), 134.8 (s, C-5), 127.2 (s, C-4), 81.2 (d, C-6), 72.9 (s, C-11), 70.8 (d, C-3), 55.2 (d, C-7), 41.2 (t, C-9), 37.5 (s, C-10), 34.7 (t, C-1), 27.3 (q, C-13), 24.7 (t, C-2), 21.6 (q, C-15), 18.4 (q, C-14), 17.9 (t, C-8).

11,13-Dihydro-3α-hydroxyarbusculin B (14).

A solution of **4** (1.2 g) and aluminum isopropoxide (1.8 g) in dry 2-propanol (15 mL) and dry benzene (9 mL) was allowed to boil gently in an oil bath at 65°C until the acetone started to distill. The reflux ratio was adjusted so that the temperature in the column head was kept at about 55°C. After 2h ethanol (7.5 mL) was added and allowed to stand overnight. The solid was removed by centrifugation and the solvent by distillation under reduced pressure. **14** (760 mg, 63% yield) was isolated from the reaction mixture by column chromatography using CH_2Cl_2/Et_2O (9:1) as eluent.

14: IR $(KBr)^{neat}$ ν cm^{-1}: 3424 (hydroxyl group), 1759 (γ-lactone), 1630 (C-C double bond). MS, m/z (relative intensity): 250 $[M]^+$ (22), 235 $[M-CH_3]^+$ (53), 232 $[M-H_2O]^+$ (12), $[M-CH_3-OH]^+$ (30), 41 (100). ^1H NMR (200 MHz, $CDCl_3$) (some signals are double): 4.52 (dq, $J_{6,7}$=10 Hz, $J_{6,15}$=1.5 Hz, H-6), 4.46 (dq, $J_{6,7}$=9 Hz, $J_{6,15}$=1.5 Hz, H-6), 3.88 (brdd, $J_{3\alpha,2\alpha}=J_{3\alpha,2\beta}$=6 Hz, H-3α), 3.58 (brs, H-3β), 1.91, 1.87 (d, $J_{6,15}$=1,5 Hz, 3H, H-15), 1.14 (s, 3H, H-13), 1.09, 1.03 (s, 3H, H-14).

11,13-Dihydro-3-(tetrahydropyranyl)oxyarbusculin B (15).

14 (570 mg) was dissolved in 10 mL of freshly distilled dihydropyran, followed by a few crystals of *p*-toluenesulfonic acid. After 6 h, anhydrous potassium carbonate was added and the mixture allowed to stand overnight. The salts were removed by filtration and excess of dihydropyran was removed by distillation under reduced pressure. The reaction mixture was chromatographed (Hexane/AcOEt, 9:1) and 627 mg of **15** (82% yield) were isolated: IR $(KBr)^{neat}$ ν cm^{-1}: 1774 (γ-lactone). MS, m/z (relative intensity): 334 $[M]^+$ (0.5), 319 $[M-CH_3]^+$ (0.2), 250 $[M-C_5H_8O]^+$ (33), 85 $[C_5H_9O]^+$ (100). ^1H NMR (200 MHz, $CDCl_3$): 4.67, 4.61 (m, H-2'), 4.52,

4.47 (dq, $J_{6,7}$=10 Hz, $J_{6,15}$=1.5 Hz, H-6), 3.86, 3.42 (m, H-6'α and H-6'β), 3.74 (brdd, $J_{3\alpha,2\alpha}$=$J_{3\alpha,2\beta}$=6 Hz, H-3α), 3.59 (brs, H-3β), 1.91, 1.89, 1.81, 1.78 (d, $J_{6,15}$=1.5 Hz, H-15), 1.12 (d, $J_{11,13}$=7 Hz, H-13), 1.08, 1.07, 1.01, 1.00 (s, 3H, H-14).

Hydroxylation of 15.

A solution of **15** (385 mg) in dry THF (11 mL) was added dropwise into a mixture containing diisopropylamine (1.05 mL), a hexane solution of butyllithium (15%) (1.4 mL) and THF (2.0 mL) and stirred continuously for 30 min at -70°C under dry nitrogen atmosphere. After the mixture had been stirred for 15 min, it reached 0°C and then dry oxygen was bubbled through for 30 min. It was carefully neutralized with HCl (aq) (1N). The mixture was extracted with ethyl acetate. The organic layer was dried, concentrated and chromatographed (hexane/EtOAc, 8:2) and it yielded the diastereoisomeric mixture **16** (240 mg). IR $(KBr)^{neat}$ ν cm^{-1}: 3400 (hydroxyl group), 1774 (γ-lactone). MS, m/z (relative intensity): 266 $[M-C_5H_8O]^+$ (5), 248 $[M-C_5H_{10}O_2]^+$ (25), 230 $[M-C_5H_{10}O_2-H_2O]^+$ (30), 85 $[C_5H_9O]^+$ (100). ^1H NMR (200 MHz, $CDCl_3$): 5.25, 4.60-4.61 (m, H-2'), 5.05-4.90 (m, H-6), 1.94, 1.92, 1.84, 1.80 (d, $J_{6,15}$=1.5, H-15), 1.12 (s, 3H, H-13), 1.09, 1.03 (s, 3H, H-14).

Deprotection of 16.

16 (223 mg) was dissolved in methanol (20 mL) and HCl 1.75M (5.0 mL). After 1h the mixture was carefully neutralized with Na_2CO_3, filtered and concentrated. A mixture of **13** and **13'** (140 mg; 82% yield) was isolated by column chromatography.

11β-Angeloyloxy-α-santonin (1b).

To a stirred solution of angelic acid (0.5 mmol) in dry toluene (0.3 mL) under argon was added 2,4,6-trichlorobenzoyl chloride (0.5 mmol) and triethylamine (0.5 mmol). The resulting mixture was stirred for 2 h at 20°C and then treated with **10** (9 mg). The mixture was stirred for 4 days at room temperature and was then diluted with ether (2 mL) and filtered. The filtrate was concentrated under reduced pressure and the resulting crude mixture was purified by HPLC using silica gel column (Hexane/AcOEt, 13:7) to give **1b**: IR $(KBr)^{neat}$ ν cm^{-1}: 1745 (γ-lactone), 1718 (angeloyl ester). MS, m/z (relative intensity): 344 $[M]^+$ (2), 261 $[M-C_5H_7O]^+$ (10), 244 $[M-C_5H_8O_2]^+$ (5), 83 $[C_5H_7O]^+$ (100), 55 $[C_4H_7]^+$ (75). ^1H NMR (400 MHz, $CDCl_3$) δ: 6.66 (d, $J_{1,2}$=10 Hz, H-1), 6.25 (d, $J_{1,2}$=10 Hz, H-2), 6.21 (qq, $J_{3',4'}$=7.4, $J_{3',5'}$=1.4, H-3'), 5.36 (dd, $J_{6,15}$=1.4, $J_{6,7}$=11.3, H-6), 2.13 (d, $J_{6,15}$=1.4 H-15), 2.00 (dq, $J_{3',4'}$=7.4, $J_{4',5'}$=1.6, H-4'), 1.91 (dq, $J_{3',5'}$=1.4, $J_{4',5'}$=1.6, H-5'), 1.90 (m, H-7), 1.65 (s, 3H, H-13), 1.21 (s, 3H, H-14). ^1H-^1H correlations have been established using ^1H-COSY experiments.

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REFERENCES AND NOTES

1. (a) Vásquez, M. **1989** Public dissertation. Baton Rouge, Louisiana University.
   (b) Fraga, B.M. *Nat. Prod. Rep.* **1991**, *8*,.515.
   (c) Fraga, B.M. *Nat. Prod. Rep.* **1992**, *9*, 557
   (d) Fraga, B.M. *Nat. Prod. Rep.***1993**, *10*, 397

2. (a) Fischer, N.H., Oliver, E.J. and Fischer, H.D. *Fortschritte der Chemie Organischer Naturstoffe* **1979**, *38*, 47.
   (b) Seaman, F.C. *The Botanical Review* **1982**, *48*, 121.

3. (a) Holub, M. and Budesinsky, M. *Phytochemistry*, **1986**, *25*, 2015.
   (b) Holub, M., Budesinsky, M., Smitalová, Z., Saman, D and Rychlewska, U. *Collect. Czech. Chem. Commun.*, **1986**, *51*, 903.
   (c) Holub, M., Budesinsky, M., Smitalová, Z., Saman, D and Rychlewska, U. *Tetrahedron Lett..*, **1984**, 3755.
   (d) Holub, M., Budesinsky, M., Smitalová, Z., Saman, D and Rychlewska, U. *Collect. Czech. Chem. Commun.*, **1985**, *50*, 1878.

4. (a) Rodríguez,E. *Rev Latinoamer. Quím.* **1977**, 56.
   (b) Picman, A. *Biochem. Syst. Ecol.* **1986**, *14*, 255.
   (c) Duke, S.O. *Rev. Weed. Sci.* **1986**, *2*, 15.
   (d) Srivastava, R.P., Proksch, P. and Wray, V. *Phytochemistry* **1990**, *29*, 3445.
   (e) Macías, F.A., Galindo, J.C.G. and Massanet, G.M. *Phytochemistry* **1992**, *31*, 1969.

5. (a) González, A.G., Bretón-Funes, J.L., Galindo, A. and Rodríguez-Luis, F. *An. Quím.* **1973**, *69*, 1339.
   (b) González, A.G., Bretón-Funes, J.L., Galindo, A. and Rodríguez-Luis, F. *An. Quím.* **1974**, *70*, 1028.
   (c) González, A.G., Bretón-Funes, J.L., Galindo, A. and Cabrera, I. *Rev. Latinoamer. Quím.* **1976**, *7*, 37.

6. Collado, I.G., Macías, F.A., Massanet, G.M., Molinillo, J.M.G. and Rodríguez-Luis, F. *J. Org. Chem.* **1986**, *52*, 3323.

7. Vedejs, E., Engler, D.A. and Telschow, J.E. *J. Org. Chem.* **1978**, *43*, 188.

8. Greene, A.E., Muller, J.C. and Ourisson, G. *J. Org. Chem.* **1974**, 39, 186.

9. González, A.G., Bermejo, J., Bretón, J., Galindo, A. and Massanet, G.M. *Rev. Latinoamer. Quím.* **1978**, *9*, 78.

10. Corey E.J. and Erickson, B.W. *J. Org. Chem.* **1971**, *36*, 3553.

11. (a) Lo Monaco, D. *Gazz. Chim. Ital.* **1897**, *27*, 87.
    (b) Jaffe, R.H. *Hoppe-Seyl. Z.* **1897**, *22*, 538.

12. Pinhey, J.T. and Sternhell, S. *Aust. J. Chem* **1965**, *18*, 543.

13. X-ray data for compound **10**:

Bond distances (Angström) with e.s.d.'s in parentheses

O1-C6	1.448(2)	O1-C12	1.364(2)	O2-C12	1.199(2)
O3-C11	1.433(2)	O4-C3	1.234(2)	C1-C2	1.318(3)
C1-C10	1.494(2)	C2-C3	1.460(3)	C3-C4	1.472(2)
C4-C5	1.345(2)	C4-C15	1.501(3)	C5-C6	1.502(2)
C5-C10	1.526(2)	C6-C7	1.524(2)	C7-C8	1.513(2)
C7-C11	1.508(2)	C8-C9	1.522(3)	C9-C10	1.555(3)
C10-C14	1.554(2)	C11-C12	1.543(3)	C11-C13	1.505(3)

Bond angles (deg.) with e.s.d.'s in parentheses

C6-O1-C12	108.6(1)	C2-C1-C10	124.6(2)	C1-C2-C3	120.3(2)
O4-C3-C2	119.8(2)	O4-C3-C4	120.7(2)	C2-C3-C4	119.5(1)
C3-C4-C5	119.3(1)	C3-C4-C15	114.2(1)	C5-C4-C15	126.5(1)
C4-C5-C6	127.5(1)	C4-C5-C10	123.3(1)	C6-C5-C10	109.2(1)
O1-C6-C5	117.7(1)	O1-C6-C7	103.4(1)	C5-C6-C7	111.7(1)
C6-C7-C8	110.7(1)	C6-C7-C11	101.0(1)	C8-C7-C11	120.4(1)
C7-C8-C9	108.1(1)	C8-C9-C10	113.9(1)	C1-C10-C5	112.6(1)
C1-C10-C9	107.5(2)	C1-C10-C14	105.0(1)	C5-C10-C9	111.4(1)
C5-C10-C14	110.5(1)	C9-C10-C14	109.6(1)	O3-C11-C7	107.8(1)
O3-C11-C12	105.3(2)	O3-C11-C13	112.3(1)	C7-C11-C12	99.6(1)
C7-C11-C13	116.6(2)	C12-C11-C13	113.8(1)	O1-C12-O2	121.8(2)
O1-C12-C11	109.4(1)	O2-C12-C11	128.8(2)		

Torsion angles (deg.)

C12-O1-C6-C5	149.98(0.15)	C12-O1-C6-C7	26.28(0.16)	C6-O1-C12-O2	177.31(0.17)
C6-O1-C12-C11	-0.95(0.18)	C10-C1-C2-C3	0.12(0.36)	C2-C1-C10-C5	4.87(0.29)
C2-C1-C10-C9	128.01(0.22)	C2-C1-C10-C14	-115.37(0.23)	1-C2-C3-O4	178.71(0.21)
C1-C2-C3-C4	-3.34(0.32)	O4-C3-C4-C5	178.76(0.18)	O4-C3-C4-C15	-2.71(0.27)
C2-C3-C4-C5	0.83(0.27)	C2-C3-C4-C15	179.36(0.19)	C3-C4-C5-C6	-176.28(0.16)
C3-C4-C5-C10	4.78(0.26)	C15-C4-C5-C6	5.39(0.30)	C15-C4-C5-C10	-173.56(0.18)
C4-C5-C6-O1	2.97(0.25)	C4-C5-C6-C7	122.36(0.18)	C10-C5-C6-O1	-177.96(0.13)
C10-C5-C6-C7	-58.57(0.16)	C4-C5-C10-C1	-7.41(0.24)	C4-C5-C10-C9	-128.32(0.17)
C4-C5-C10-C14	109.63(0.18)	C6-C5-C10-C1	173.47(0.15)	C6-C5-C10-C9	52.57(0.17)
C6-C5-C10-C14	-69.49(0.17)	O1-C6-C7-C8	-169.70(0.12)	O1-C6-C7-C11	-41.02(0.13)
C5-C6-C7-C8	62.78(0.16)	C5-C6-C7-C11	-168.54(0.12)	C6-C7-C8-C9	-57.79(0.17)
C11-C7-C8-C9	-175.12(0.15)	C6-C7-C11-O3	-71.19(0.16)	C6-C7-C11-C12	38.47(0.14)
C6-C7-C11-C13	161.37(0.14)	C8-C7-C11-O3	50.98(0.21)	C8-C7-C11-C12	160.64(0.15)
C8-C7-C11-C13	-76.47(0.20)	C7-C8-C9-C10	53.76(0.18)	C8-C9-C10-C1	-176.27(0.14)
C8-C9-C10-C5	-52.40(0.18)	C8-C9-C10-C14	70.16(0.17)	O3-C11-C12-O1	86.95(0.15)
O3-C11-C12-O2	-91.15(0.22)	C7-C11-C12-O1	-24.69(0.18)	C7-C11-C12-O2	157.21(0.20)
C13-C11-C12-O1	-149.54(0.15)	C13-C11-C12-O2	32.36(0.28)		

Complete tables of distances, angles, torsion angles, least-squares planes, H-atom parametres, anisotropic thermal parametres and structure factors have been deposited with the British Library Document Supply Centre as Suplementary Publication. Copies may be obtained through the Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

14. Hartmann, B., Kanazawa, A.M., Deprés, J.P. and Greene, A.E. *Tetrahedron Lett.* **1991**, *32*, 5077.

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