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THE SYNTHESIS OF (-)-ANAMARINE

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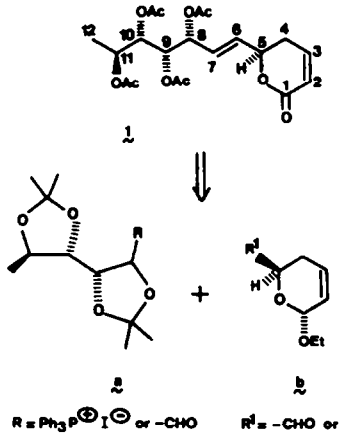
Abstract – The enantiospecific total synthesis of (-)-anamarine, starting from D-glucose, has been carried out.

Anamarine[1] (**1**), is an α,β-unsaturated δ-lactone isolated in our laboratory from an unclassified Hyptis species collected at Peru.

Its synthesis[2] can be envisaged (Scheme 1) as the reaction of two fragments (**a** and **b**) that could be derived from an appropriate hexose. Unfortunately, the stereochemistry of the natural compounds would require the use of sugars of the L-series. Consequently, we decided to prepare the enantiomers of **a** and **b** starting from D-glucose as indicated in Schemes 2 and 3.

1,2-O-Isopropylidene-α-D-glucofuranose (**2**), prepared according to literature procedures[3], was our starting material (see Scheme 2). Monotosylation of **2** was easily achieved (TsCl/pyr), and the 6-desoxyglucose derivative (**4**) was readily obtained (80 %) by treatment of **3** with $LiAlH_4$ in anhydrous ethyl ether. Compound **4** was a solid, m.p. 90-91°C, the NMR spectrum of which showed a C-Me doublet at δ 1.45. Treatment of **4** with ethyl thiol and concentrated hydrochloric acid, at the usual manner[4], afforded the dithiane derivative **5** [signals due to two SEt groupings at δ 1.21 (t) and 2.82 (q)], that was

Scheme 1

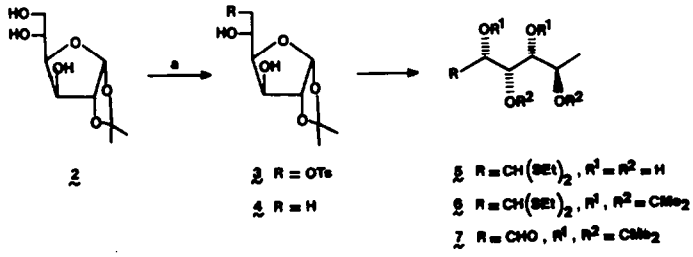


1

a R = $Ph_3P^{\oplus}I^{\ominus}$ or -CHO

b R^1 = -CHO or $Ph_3P^{\oplus}I^{\ominus}$

Scheme 2



2

3 R = OTs

4 R = H

5 R = $CH(SEt)_2$, $R^1 = R^2 = H$

6 R = $CH(SEt)_2$, R^1, $R^2 = CMe_2$

7 R = CHO, R^1, $R^2 = CMe_2$

a) TsCl, pyr; $LiAlH_4$, Et_2O. b) EtSH, HCl; CH_3COCH_3, $HClO_4$; $HgCl_2$, HgO, CH_3COCH_3

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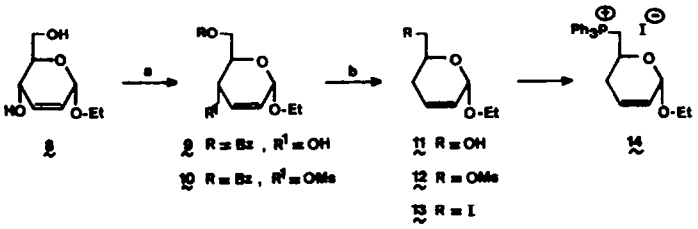
Scheme 3



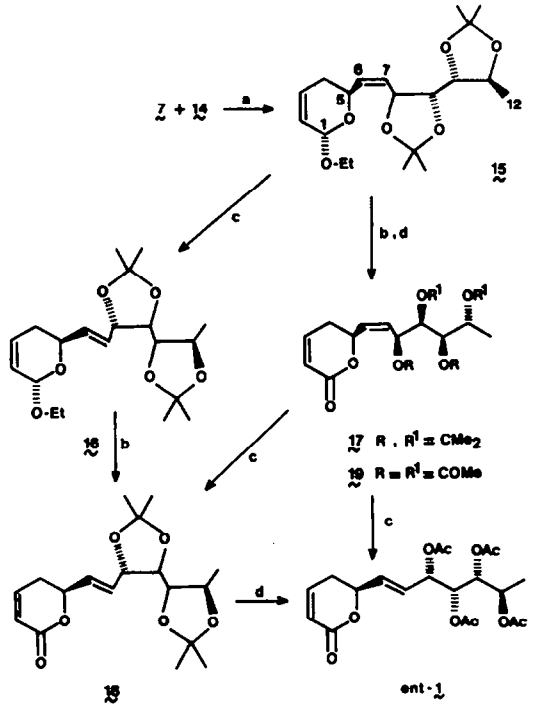
a) BzCl, pyr ; MsCl, pyr . b) $LiAlH_4$, THF ; MsCl, pyr ; $(n\text{-}Bu)_4NI$, $PhCH_3$. c) Ph_3P.

transformed into the diacetonide **6** (two acetalic carbon atom signal at δ 108.23 and 109.64), by reaction with acetone in the presence of catalytic amounts of perchloric acid at room temperature. Finally, aldehyde **7** was prepared by elimination of the dithiane protecting group[5] through the action of $HgCl_2$: HgO. A signal at δ 9.85 of its ^1H NMR spectrum, integrating for less than 1H, suggested the presence of hydrated forms[6,7].

Diol **8** (Scheme 3) was obtained from triacetyl-D-glucal following literature procedures[8]. The 6-monobenzoyl derivative **9** was readily prepared by selective benzoylation of **8** (BzCl/pyr) at low temperature (0°C) (85 % yield). Further mesylation of **9** (MsCl/pyr, 0°C) gave the 6-O-benzoyl, 4-O-mesyl derivative **10** (94 %) which was treated with $LiAlH_4$/THF at room temperature. The product of this reaction was the 4-deoxy derivative **11**, $|\alpha|_D^{20}$ -58°. The ^1H and ^{13}C NMR spectra showed signals due to the new C-4 methylene group at δ 2.0 (m) and 26.3 (t) respectively. A new mesylation of **11** at 0°C gave the mesyl derivative **12** (91 %), and further treatment of **12** with tetra-n-butylammonium iodide in toluene at reflux temperature gave the iodide **13** (95 %) which was purified by flash chromatography. A signal at δ 8.7 (t) in its ^{13}C NMR spectrum confirmed the formation of this product. Finally, compound **13** was treated with an equimolar amount of triphenylphosphine at 90°C for 72 h to afford the required phosphonium salt **14**, m.p. 170-173°C, $|\alpha|_D^{20}$ +31°.

There are literature precedents[6] on the Wittig condensations with compound analogs[§] of synthons **7** and **14**. It was obvious that the ylide derived from the phosphonium salt **14** (with a β-alkoxy substituted) could undergo a competing β-elimination, frustrating thus the course of the normal Wittig condensation[9]. Switching of the aldehyde and phosphonium salt group, such as it is indicated in Scheme 1 would not solve this problem. Considerable experimentation was required to find the optimum conditions. Finally, the conditions used were those described by Secrist *et al.*[6] slightly modified. Thus, the phosphonium salt **14** was added to a 2 : 1 mixture of anhydrous THF/HMPTA cooled at -78°C and containing 1.1 moles/equivalent of n-butyl lithium. The formation of the corresponding ylide was allowed to proceed for one minute, and immediately a solution of the aldehyde **7**, in the same solvent, was added. The reaction mixture was then allowed to slowly raise its temperature up to -15°C; it was quenched by the addition of wet ethyl ether and elaborated in the usual manner. Short column chromatography of the crude product afforded the olefin **15**

Scheme 4



a) n-BuLi, THF:HMPTA(2:1). b) CrO_3, H_2SO_4, CH_3COCH_3. c) hν, d) HCl, THF ; Ac_2O, pyr.

§ The authors thank Prof. Lichtenthaler for helpful discussions. An account of his work on the synthesis of (-)-anamarine has recently appeared[10].

(Scheme 4).

Compound **15** was an oil, $|\alpha|_D^{20}$ -28°, (35 %)[11]. As it could be anticipated, the Z-isomer was isolated (H-6, δ 5.80; H-7, δ 5.46; J 10 Hz). The presence of a β-alkoxy group in **14** apparently also led to the inversion of the C-5 center, and a small amount (less than 10 %) of this epimer was detected during the chromatographic separation of **15**.

For the transformation of **15** into the desired end product, (-)-anamarine, we had several alternatives depicted in Scheme 4. We decided to explore all these routes. Irradiation of **15**, in cyclohexane solution[6], in the presence of diphenyl disulfide afforded the E-isomer in 70 % yield. The transformation was about 6:4 after two hours. Some decomposition took place simultaneously making scarcely advisable longer reaction times. On the other hand, the starting material (**15**) could be recovered and recycled, raising the overall yield to ≃ 70 %. The ^{1}H NMR spectrum of **16** confirmed the isomerization of the double bond (H-6, δ 5.89; H-7, δ 5.68; J 15.5 Hz). The E-olefin (**16**) was subjected to Jones'oxidation[12] at 0-5°C during 15 minutes; lactone **18** (50 %) was thus obtained. Acid hydrolysis[13] of **18**, followed by acetylation afforded ent-**1** as expected (70 %). The IR, ^{1}H and ^{13}C NMR spectra of the synthetic material ($|\alpha|_D^{20}$ -15°) were identical with those obtained with an authentic sample (see Experimental).

Alternatively, compound **15** was subjected to Jones'oxidation (60 %) using the same conditions as in the previous case (see above). The lactone **17** was thus obtained. This compound was a solid, m.p. 150°C, $|\alpha|_D^{20}$ -65°. The ^{1}H NMR spectrum of **17** indicated that the oxidation had taken place as expected (H-2 and H-3 at δ 6.00 and 6.81, respectively).

Irradiation of **17** in cyclohexane solution[14], during nine hours afforded a mixture of **17** and **18** (≃ 2:8, 60 %) that could be separated by preparative tlc.

Finally, **17** was hydrolyzed[13] (HCl:THF), and acetylated to give the lactone **19** (70 % yield) (see Experimental). Direct irradiation of **19** during three hours yielded an approximately 6:4 mixture of **19** and ent-**1**, that could be chromatographycally separated. Recovered **19** was used in a new isomerization step, raising the overall yield to approximately 60 %.

We have made no attempt to optimize the yields of the last steps leading from **15** to ent-**1**, but this last route seemed to offer slightly better results.

EXPERIMENTAL

Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). T.l.c. was carried out on plates of silica gel $60F_{254}$ (Merck). ^{1}H NMR spectra were measured for $CDCl_3$ solutions with a Varian EM-390 (90 MHz) or XL-300 (300 MHz) and a Brücker WP-200 (200 MHz) as stated. ^{13}C NMR spectra were measured for $CDCl_3$ solutions with a Varian XL-300 (75 MHz) or a Brücker WP-80 (20 MHz). M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Preparation of **3**.- Compound **2**, prepared from glucose following literature procedures[3], (5.0 g, 22.7 mmol), was dissolved in pyridine (30 mL) and this solution was cooled at 0°C; p-toluensulfonic acid chloride (4.7 g, 24.6 mmol) was added portion-wise. This mixture was kept at 0°C for 2 h and then it was stirred at room temperature overnight. The reaction was poured on a cold aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. This extract was dried and evaporated, and the residue was chromatographed on a short column. **3** solidifies spontaneously, m.p. 100-101°C, (6.32 g, 81.4 %), $|\alpha|_D^{20}$ -6° (c 1.0, $CHCl_3$). ^{1}H NMR (90 MHz) data: δ 1.3 (3H, s, C-Me), 1.5 (3H, s, C-Me), 2.5 (3H, s, arom-CH_3). ^{13}C NMR (20 MHz) data: δ 67.77 (t,C-6), 72.37, 74.89, 79.40, 85.15 (4 d, C-2 to C-5), 105.14 (d, C-1), (plus signals due to the acetonide C-Me (26.83, 26.24) and aromatic C-Me (21.57).

Compound **4**.- Powdered **3** (2.5 g, 7.3 mmol) was slowly added to a suspension of $LiAlH_4$ (720 mg, 20 mmol) in anhydrous ethyl ether while cooling in a water bath and stirring. This mixture was boiled under reflux for 2 h, cooled again and the excess hydride was destroyed by the cautions addition of H_2O (0.7 mL), aqueous 15 % NaOH (0.7 mL) and H_2O (2.2 mL). Solids were filtered off and the filtrates were dried and evaporated to yield 0.78 g of crude product. The solids were extracted in a Soxhlet apparatus to yield 0.56 g of material. Flash chromatography of the residues gave **4** (80 %), m.p. 90-91°C, $|\alpha|_D^{20}$ -25°

(c 0.4, $CHCl_3$) (1.15 g, 77 %). ^{1}H NMR (90 MHz) data: δ 1.4 (3H, s, C-Me), 1.45 (3H, d, J 6.0 Hz, H-6), 1.5 (3H, s, C-Me). ^{13}C NMR (20 MHz) data: δ 18.95 (q, C-6), 67.02, 75.43, 82.26, 85.39 (4d, C-2 to C-5), 104.91 (d, C-1) (plus signals due to the acetonide C-Me (26.80, 26.19).

Compound 5.- The monoacetonide **4** (370 mg, 3.7 mmol) was added to a cooled flask (0-5°C), containing ethylthiol (620 mg, 10 mmol). Concentrated HCl (0.75 mL) was added to this mixture that was kept at 0-5°C for 10 min and at r.t. for 40 min. Neutralization (NH_4OH) and extraction with CH_2Cl_2 provided crude **5**, that was purified by crystallization, m.p. 97-98°C, $|\alpha|_D^{20}$ -45° (c 0.7, H_2O) (430 mg, 42%). ^{1}H NMR (300 MHz, pyr-d_6) data: δ 1.21 (6H, t, J 7.5 Hz, S-CH_2CH_3), 1.70 (3H, d, J 6.2 Hz, H-6), 2.82 (4H, q, J 7.5 Hz, S-CH_2CH_3). ^{13}C NMR (20 MHz, pyr-d_6) data: δ 21.03 (q, C-6), 55.88 (d, C-1), 68.53, 71.20, 76.88, 77.95 (4d, C-2 to C-5), |plus two signals due to two S-CH_2 (25.42, 25.49) and S-CH_2CH_3 (14.80, 15.00)|. (Found: C, 44.72; H, 8.40; S, 23.67. Calcd. for $C_{10}H_{22}O_4S_2$: C, 44.44; H, 8.15; S, 23.70).

Compound 6.- Powdered **5** (450 mg, 1.67 mmol) was dissolved in anhydrous cooled acetone (10 mL, 0-5°C). A catalytic amount of $HClO_4$ was added to this solution. The solution was maintained at 0-5°C for 1 h and at r.t. for 20 h. Pyridine (a few drops) was added to this solution and the solvent was evaporated. The residue was purified in a short column, yielding **6** (90 %), m.p. 53°C, $|\alpha|_D^{20}$ -95° (c 0.4, $CHCl_3$). ^{13}C NMR (50 MHz) data: δ 15.13 (q, C-6), 52.60 (d, C-1), 72.91, 76.15, 78.02, 79.79 (4d, C-2 to C-5)|(plus signals due to S-CH_2CH_3, (14.27, 14.40), S-CH_2CH_3 (25.44, 25.44), and acetonides at 109.62 and 108.22 (acetalic carbon atoms) and C-Me at (25.36, 26.66, 27.17, 27.17)|.(Found: C, 55.0; H, 8.94; S, 18.0. Calcd. for $C_{16}H_{30}O_4S_2$: C, 54.70; H, 8.83; S, 18.23).

Compound 7.- $HgCl_2$ (652 mg, 2.4 mmol) and HgO (1,573 g, 7.2 mmol) were added to a solution of **6** (300 mg, 0.8 mmol) in aqueous acetone (90:10, 34 mL). This mixture was stirred at r.t. for 7 h; it was poured on aqueous saturated $NaHCO_3$ (11.0 mL). The solids were filtered off and washed with acetone. Most of the acetone was evaporated under reduced pressure and the resulting solution was extracted with CH_2Cl_2. This extract was washed with aqueous KI and brine. It was dried and evaporated to yield a sirupy oil (180 mg, 92 %), $|\alpha|_D^{20}$ -50° (c 0.7, $CHCl_3$). ^{1}H NMR (90 MHz) data: δ 9.85 (less than 1H, d, J 2 Hz). ^{13}C NMR (20 MHz) data: δ 201.6 (d, C-1).

Compound 9.- Benzoyl chloride (1.64 g, 11.7 mmol) was added to a cooled (0°C) solution of **8** (1.74 g, 10 mmol) in pyridine (8 mL). The reaction was allowed to proceed at 0°C for 2.5 h. This mixture was poured on a cold saturated aqueous $NaHCO_3$ solution. The solution was extracted with CH_2Cl_2. Flash chromatography of the residue obtained by evaporation of the solvent, yielded the 6-monobenzoyl derivative **9**, thick oil, $|\alpha|_D^{20}$ -18° (c 0.5, $CHCl_3$) (2.4 g, 85%).

Compound 10.- A solution of **9** (3.5 g, 12.6 mmol) in pyridine (35 mL) was cooled at 0°C and then MsCl (1.6 g, 1.1 mL, 13.9 mmol) was added to this solution. The reaction mixture was maintained during 5 hours at 5°C and then poured on a cold aqueous $NaHCO_3$ solution. This mixture was extracted with ethyl ether and this solvent was dried and evaporated to yield almost pure **10**. Compound **10** slowly decomposed on standing (even when stored at low temperature); consequently, it was normally used in the following step, without further characterization. ^{1}H NMR (90 MHz) ($CDCl_3$): δ 6.0 (2H, m, H-2 and H-3).

Preparation of 11.- To a solution of **10** (5 g, 14 mmol) in dry THF (75 mL), under N_2 and with stirring at room temperature it was slowly added $LiAlH_4$ (1.5 g, 39.5 mmol). Stirring was continued for two hours and excess hydride was destroyed by the slow addition of a cold saturated aqueous Na_2SO_4 solution. The solids were filtered off and the aqueous solution was extracted with CH_2Cl_2. The residue obtained by evaporation of the CH_2Cl_2 extract was purified by flash chromatography yielding compound **11**, thick oil (80% yield). $|\alpha|_D^{20}$ -58° (c 0.74, $CHCl_3$). ^{1}H NMR (90 MHz) data: δ 1.2 (3H, t, J 6 Hz, CH_3), 2.0 (2H, m, H-4), 3.4-4.2 (complex signal, 5H, H-5, H-6, OCH_2), 5.0 (1H, H-1), 5.8 (2H, m, H-2, H-3). ^{13}C NMR data: δ 15.3 (q, -CH_3), 26.3 (t, C-4), 63.2 (t, OCH_2), 65.0 (t, C-6), 67.2 (d, C-5), 94.5 (d, C-1), 125.7 (d, C-3)*, 128.4 (d, C-2)*.

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* These signals can be exchanged.

Preparation of **12**.- To a solution of **11** (3 g, 19 mmol) in dry pyridine (10 mL) cooled at 0°C, it was added MsCl (2.36 g, 20.6 mmol). The reaction was kept during 90 min at 0°C. Finally, it was elaborated as above. Compound **12** was a thick oil (91 %), $|\alpha|_D^{20}$ -60° (c 0.4, $CHCl_3$). ^{13}C NMR (20 MHz) data: δ 15.1 (q, CH_3), 25.7 (t, C-4), 37.4 (q, SO_2CH_3), 63.4 (t, OCH_2), 64.2 (d, C-5), 71.2 (t, C-6), 94.2 (d, C-1), 125.5 (d, C-3)*, 127.3 (d, C-2)*.

Compound **13**.- To a solution of **12** (4.1 g, 17.4 mmol) in toluene (80 mL), it was added tetra-n-butylammonium iodide (9.25 g, 25 mmol) suspended in toluene (40 mL). The mixture was heated during 8 hours at 160°C. The solution was then filtered and the filtrate was concentrated to dryness. The residue was taken up in CH_2Cl_2 and this solution washed with water, dried and evaporated. Flash chromatography of this final residue afforded **13**, oil, (95 %), $|\alpha|_D^{20}$ +0.2° (c 1.0, $CHCl_3$). ^{13}C NMR (20 MHz) data: δ 8.7 (t, C-6), 15.1 (q, CH_3), 30.5 (t, C-4), 63.2 (t, OCH_2), 66.1 (d, C-5), 94.6 (d, C-1), 125.5 (d, C-3)*, 127.6 (d, C-2)*. (Found: C, 40.67; H, 5.94. Calcd. for $C_8H_{13}IO_2$: C, 40.42; H, 5.89).

Compound **14**.- A mixture of compound **13** (2.0 g, 7.5 mmol) and triphenylphosphine (2.0 g, 7.6 mmol) was heated at 90°C for 72 h. The reaction mixture solidified on cooling. Compound **14**, solid, m.p. 170-173°C, $|\alpha|_D^{20}$ +31° (c 0.3, $CHCl_3$). ^1H NMR (300 MHz) data: δ 0.91 (t, J 7.5 Hz, CH_3); 2.41 (m, H_A -4); 2.69 (m, H_B -4 , overlapping with OCH_2); 2.75 and 2.95 (m, m, OCH_2), 3.67 (dd, J 16.0 and 10.5 Hz, H_A -6), 4.40 (m, H-5), 4.69 (dd, J 16.0 Hz, H_B -6), 4.75 (s, H-1), 5.59 (m, H-2), 6.00 (m, H-3). ^{13}C NMR (50 MHz) data: δ 15.01 (q, CH_3), 30.53 (t, C-6)§, 31.75 (t, C-4)§,62.75 (d, C-5)§, 63.79 (t, OCH_2), 94.83 (d, C-1), 124.40 (d, C-3)*, 128.35 (d, C-2)*.

Compound **15**.- A solution of n-butyllithium (2.71 mL, 4.34 mmol) was added *via* syringe to a flask containing tetrahydrofuran : hexamethylphosphoric triamide (THF : HMPTA) (2 : 1 v/v, 50 mL) under argon. This solution was cooled at -78°C. The phosphonium salt **14** (2.19 g, 4.13 mmol) was then added. This mixture was stirred for 1 m at -78°C. A solution of the aldehyde **7** (960 mg, 3.93 mmol) in THF : HMPTA (5 mL) was added and the new mixture was stirred at -78°C for 15 min. The bath temperature was allowed to slowly raise to -15°C (during ≃ 2.5 h). A t.l.c. analysis indicated that no aldehyde was present in the mixture. Wet ethyl ether was added to the reaction mixture and the ether layer was washed with brine. Flash chromatography of the crude product gave **15**, oil, $|\alpha|_D^{20}$ -28° (c 0.4, $CHCl_3$), (502 mg, 35 %). ^1H NMR (300 MHz) data: δ 1.37 (3H, d, J 6.4 Hz, 12-Me), 2.06 (2H, m, H-4), 3.83 (1H, dd, J 7.4 and 1.6 Hz, H-10), 3.88 (1H, dd, J 10.0 and 7.5 Hz, H-9), 4.36 (1H, quint., J 6.4 Hz, H-11), 4.72 (1H, dd, J 10.0 and 10.0 Hz, H-8), 4.85 (1H, m, H-5), 5.00 (1H, d, J 0.7 Hz, H-1), 5.46 (1H, dd, J 10.0 and 10.0 Hz, H-7), 5.80 (1H, m, overlapping H-2, H-6), 5.78 (1H, m, overlapping H-6, H-2), 6.00 (1H, m, H-3).

Compound **16**.- A cyclohexane solution of **15** (100 mg, 0.3 mmol) and diphenyl disulfide (59 mg, 0.3 mmol) was irradiated with a medium-pressure Hg-lamp for 2 hours. An approximately 6 : 4 mixture of **16** and **15** was obtained. Though irradiating for longer periods increased this ratio the overall yield was lowered through decomposition. Compounds **15** and **16** were separated by preparative t.l.c. (hexane : ethyl acetate 7 : 3 v/v). **16**, oil, (70 %), ^1H NMR (200 MHz) data: δ 1.29 (3H, d, J 6.1 Hz, 12-Me), 2.00 (2H, m, H-4), 3.55 (1H, dd, J 9.0 and 2.3 Hz, H-10), 3.89 (1H, dd, J 6.6 and 2.3 Hz, H-9), 4.27 (1H, m, overlapping H-8, H-11), 4.33 (1H, dd, J 6.6 and 1.5 Hz, H-8), 4.39 (1H, m, overlapping H-8, H-5), 4.95 (1H, m, H-1), 5.68 (1H, m, overlapping H-2, H-7), 5.72 (1H, m, overlapping H-7, H-2), 5.89 (1H, dd, J 15.5 and 4.6 Hz, H-6), 5.94 (1H, m, overlapping H-6, H-3).

Compounds **17** *and* **18**.- The same procedure (see below) was applied to prepare these two compounds. A large excess of Jones reagent (1.4 mL, 11.2 unequiv.) was added to **15** or **16** (200 mg, 0.54 mmol) dissolved in cold (0-5°C) purified acetone (14 mL). Solid $MgSO_4$ (996 mg) was added immediately after, and the reaction was stirred for 15 min in the ice-bath. Isopropanol (1 mL) and aqueous $NaHCO_3$ were

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§ These signals showed the following C-P couplings in the fully ^1H-decoupled spectra (J_{C-6} 51 Hz, J_{C-4} 15 Hz, J_{C-5} 6.5 Hz).

* These values can be interchanged.

added until the solution became neutral. The acetone was evaporated at reduced pressure and the aqueous solution was extracted with $CHCl_2$ to yield the corresponding lactones **17**[15] or **18**.

17, solidified spontaneously, m.p. 150°C, $|\alpha|_D^{20}$ -65° (c 0.4, $CHCl_3$). ^1H NMR (200 MHz) data: δ 1.34 (3H, d, J 6.5 Hz, 12-Me), 2.36 (2H, m, H-4), 3.47 (1H, dd, J 8.6 and 1.3 Hz, H-9), 3.73 (1H, dd, J 6.5 and 1.3 Hz, H-10), 4.33 (1H, quint., J 6.5 Hz, H-11), 4.55 (1H, ddd, J 8.6, 8.6 and 0.8 Hz, H-8), 5.39 (1H, quint., J 7.5 Hz, H-5), 5.53 (1H, ddd, J 11.3, 8.6 and 1.0 Hz, H-7), 5.81 (1H, ddd, J 11.3, 8.6 and 1.0 Hz, H-6), 6.00 (1H, dt, J 10.0 and 2.0 Hz, H-2), 6.81 (1H, dt, J 10.0 and 4.3 Hz, H-3).

18, oil, ^1H NMR (300 MHz) data: δ 2.43 (2H, m, H-4), 3.58 (1H, dd, J 6.6 and 1.3 Hz, H-10), 3.95 (1H, dd, J 6.6 and 1.3 Hz, H-9), 4.40 (2H, m, overlapping H-8, H-11), 4.94 (1H, m, H-5), 5.85 (1H, dd, J 15.2 and 7.5 Hz, H-7), 6.00 (1H, dd, J 15.2 and 6.0 Hz, H-6), 6.06 (1H, dt, J 10.0 and 2.0 Hz, H-2), 6.88 (1H, m, H-3).

Preparation of ent-**1**.- Three different routes have been followed.

1. **Acid hydrolysis of 18 followed by acetylation.**

A mixture of 10% aqueous HCl and THF (1:1, 1.3 mL) was added to a flask containing **18** (18.6 mg, 0.05 mmol). The mixture was heated at an oil bath at 65°C during 10 min. The solvent was evaporated at reduced pressure and the residue was acetylated (Py/Ac_2O) to afford ent-**1**, after purification by preparative t.l.c. (70%); $|\alpha|_D^{20}$ -15°C (c 0.02, $CHCl_3$). ^1H NMR (200 MHz) data: δ 1.12 (3H, d, J 6.4 Hz, 12-Me), 1.96, 2.01, 2.06 (3H, 6H, 3H, s,s,s, $COCH_3$), 2.38 (2H, m, H-4), 4.85 (1H, m, overlapping with H-5, H-11), 4.89 (1H, m, overlapping with H-11, H-5), 5.11 (1H, dd, J 7.0 and 3.0 Hz, H-10), 5.27 (2H, m, H-8, H-9), 5.76 (2H, m, H-6, H-7), 5.99 (1H, dt, J 10.0 and 1.9 Hz, H-2), 6.89 (1H, m, H-3). ^{13}C NMR and IR spectra were also identical with those obtained with an authentic specimen of the natural compound[1], isolated in this laboratory.

2. **Irradiation of 17 followed by acid hydrolysis and acetylation.**

A cyclohexane solution of **17** (8.2 mg, 0.02 mmol) and diphenyl disulfide (4.4 mg, 0.02 mmol) was irradiated with a medium-pressure Hg-lamp for 9 hours. Compound **18** was obtained by preparative t.l.c. (60%). This compound could be subjected to the same conditions as in route 1.

3. **Acid hydrolysis of 17, followed by acetylation and irradiation.**

The acid hydrolysis and acetylation of **17** (36 mg, 0.1 mmol) was carried out as in route 1 to obtain **19** (70%). Irradiation of **19** (45 mg, 0.1 mmol) using the same conditions as in route 2 gave a mixture of ent-**1** and **19** (≃ 4:6) which was separated by t.l.c. (18 mg, 40%).

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