Conversions of α-Methyl to α-Methylene γ-Lactones. Synthesis of Two Allergenic Sesquiterpene Lactones, (−)-Frullanolide and (+)-Arbusculin B[1]

Andrew E. Greene, Jean-Claude Muller, and Guy Ourisson*

Laboratoire Associé au Centre National de la Recherche Scientifique, Institut de Chimie, Université Louis Pasteur, 67008 Strasbourg, France

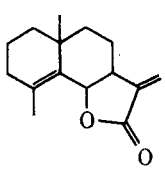
Received June 18, 1973

Two new routes to α-methylene-γ-butyrolactones starting from the corresponding α-methyl lactones are outlined. In the case of cis lactones, the conversion of α-methyl → α-methylene lactone has been realized by stereospecific introduction of bromine, α to the lactone carbonyl, followed by antidehydrobromination. In the case of trans lactones the conversion has been realized by stereospecific introduction of the benzoyloxy group, α to the lactone carbonyl, followed by pyrolytic syn elimination of benzoic acid. These conversions have been studied on appropriate lactone models and their generality has been illustrated by the syntheses of (−)-frullanolide (1) and (+)-arbusculin B (2).

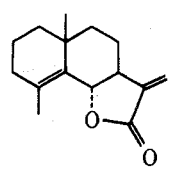
The α-methylene-γ-butyrolactone moiety characterizes a rapidly expanding group of sesquiterpenes, comprising to date more than 400 lactones fused on various skeletons.[2] These unsaturated lactones are very often biologically active, showing strong allergenic activity,[3] exhibiting growth-inhibitory activity *in vivo* against animal tumor systems and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB),[4] and/or effecting regulation of plant growth and antimitotic activity.[5] Very recently some α-methylene-γ-lactone sesquiterpenes have been shown to have antischistosomal activity.[6] α-Methylene-γ-butyrolactone itself, isolated from tulips, is not only an allergenic agent but also a fungicide in the white tulip bulb.[7] In all these cases, the presence of an α-methylene-γ-butyrolactone is essential for significant activity.

Efficient construction of the α-methylene-γ-butyrolactone moiety is a synthetic challenge which has received much attention during the past few years.[8] Many ingenious synthetic schemes have resulted but none permits access to this grouping *via* the corresponding α-methyl lactone. This transformation is of definite interest since appropriate α-methyl lactones are often readily available from synthetic procedures[9] and/or natural sources.[2]

We now report the synthesis of (−)-frullanolide (1), isolated from *Frullania tamarisci* (L.) Dum.,[3a,b] and (+)-arbusculin B (2), isolated from *Artemisia arbuscula*[10a]



1



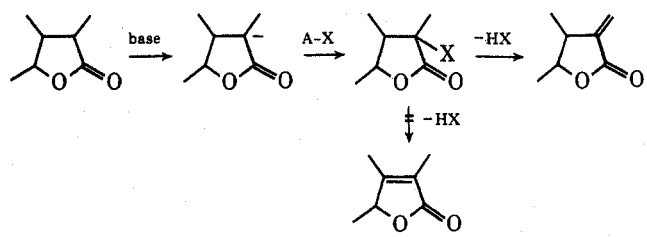
2

and from *Artemisia tridentata*,[10b] and thereby demonstrate the utility of two potentially general techniques for achieving the α-methyl → α-methylene conversion for cis- and trans-fused lactones.

We envisioned an approach which consisted of introducing a group X α to the carbonyl of the methyl lactone, and then eliminating HX to afford the α-methylene lactone (Scheme I). We had shown earlier that α-methyl lactones can be readily converted to the corresponding enolates using triphenylmethyllithium and subsequently methylated (X = CH_3).[11]

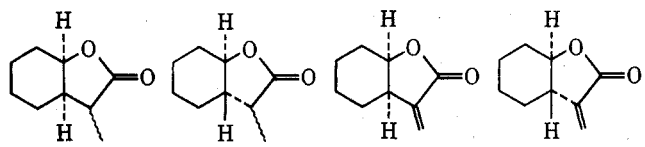
The method of introduction of X had to be compatible with the presence of at least a double bond in the molecule and the elimination of HX had to lead to the exocyclic olefin in preference to the isomeric endocyclic olefin. Therefore X had to be introduced stereospecifically since

Scheme I



it was anticipated that the direction of elimination for a given X group would be governed by the stereochemical outcome.

The viability of Scheme I was demonstrated by the conversion of the α-methyl lactones[12] 3 and 4 to the corresponding unsaturated lactones 5 and 6, which constitute structural prototypes of naturally occurring cis- and trans-fused sesquiterpene lactones.

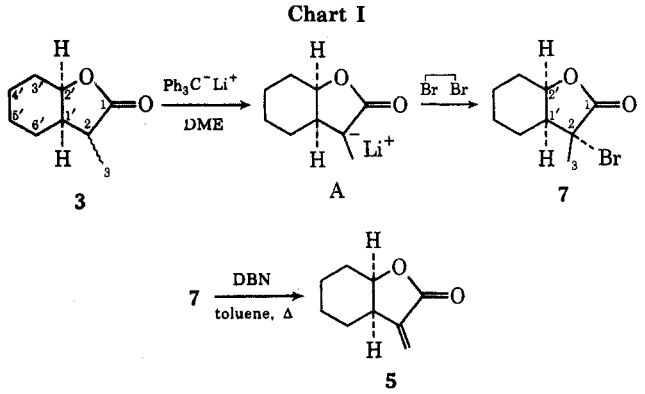


3 4 5 6

Bromine was first selected for the X group and could be introduced by treatment of the α-methyl lactone enolates with 1,2-dibromoethane. This reagent, which had been used for the formation of cyclopropanes,[13,14] in coupling reactions,[15] as an alkylating agent,[16] as a protonating agent,[17] and as a brominating agent of 1-propenyllithium,[18] had never been previously used for the formation of isolable α-bromocarbonyl compounds.

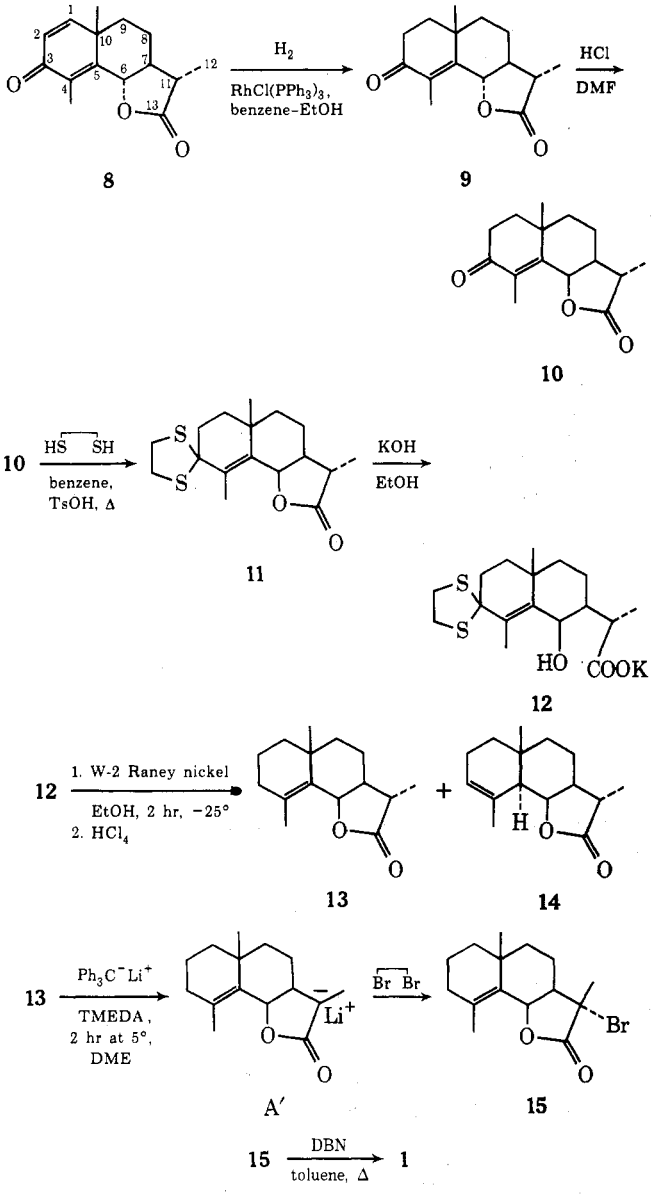
The carbanion A (Chart I), obtained by treatment of lactone 3 in 1,2-dimethoxyethane (DME) with a slight ex-

Chart I



3 A 7 5

Chart II



cess of triphenylmethyllithium, attacked bromine[19] rather than carbon to afford a single isolable α-bromo lactone, **7**, in 85% yield.

The (*r*-2′,*c*-2)[20] configuration assigned to the C–Br bond in lactone **7** is based on the following evidence: (a) this configuration corresponds to the introduction of bromine from the less hindered side; (b) the H-2′ proton is deshielded by 0.6 ppm with respect to starting material **3**; this deshielding is explained by a spatial proximity[21] between the H-2′ proton and bromine.

The α-bromo lactone **7** on treatment for a few minutes with 1,5-diazabicyclononene (DBN) in refluxing toluene afforded as the sole isolable product the known[8c] α-methylene lactone **5** in 80% yield (overall yield of conversion of α-methyl lactone → α-methylene lactone = 65%).

No endocyclic olefin could be detected from treatment of the α-bromo cis lactone **7** under these anti (or trans) dehydrobromination conditions, thus giving further evidence for the assignment of the (*r*-2′,*c*-2) configuration to the C–Br bond. [The relatively low reaction temperature should preclude a syn (or cis) elimination.][22]

For the synthesis of (−)-frullanolide (**1**), (−)-α-santonin (**8**)[23] was choosen as starting material because of its availability. 1,2-Dihydro-6-episantonin (**10**) was secured from α-santonin in 90% overall yield *via* 1,2-dihydro-α-santonin (**9**), by hydrogenation over tris(triphenylphosphine)chlororhodium(I)[24] followed by epimerization in DMF saturated with HCl gas[25] (Chart II).

Removal of the C-3 oxygen was effected using modifications of the general thioketalization–reduction procedure.[26] The known thioketal **11** was obtained in a much improved yield[27] (>90%) by heating **10** in benzene with excess ethanedithiol in the presence of a catalytic amount of *p*-toluenesulfonic acid. Initial attempts to reduce **11** with Raney nickel in absolute ethanol at room temperature led solely to acidic material by hydrogenolysis[28] of the axial C-6–O bond, in dramatic contrast to the trans system **16** (*vide infra*).

However, the hydroxy salt **12**, obtained by treatment of **11** with KOH in 95% EtOH, was much less prone to hydrogenolysis.[29] The salt **12** was stirred with W-2 Raney nickel (10 ml/g of **11**) in 95% EtOH (or MeOH) containing KOH at −25° and the mixture was then acidified and chromatographed to give 11β(H),11,12-dihydrofrullanolide (**13**)[30] in better than 40% overall yield. A second nonacidic product, tentatively identified as lactone **14**, was formed in about 10% yield. In the desulfurization reactions examined, higher yields were obtained by treatment of the thioketals with *active* W-2 Raney nickel at *low* temperatures than under the more often used desulfurization conditions[31] for sensitive systems (reflux for several hours with deactivated Raney nickel in acetone or ethanol). In the case of thioketal **11**, the desulfurization is complete in 2 hr at −25°.

The carbanion A′ (Chart II), unlike that of the model system **3**, is very unstable, and could only be obtained satisfactorily by treatment of **13** with excess triphenylmethyllithium in 1,2-dimethoxyethane in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). Carbanion A′, when quenched with 1,2-dibromoethane, afforded a single α-bromo lactone **15** in *ca.* 50% yield. The stereochemical assignment of an α configuration for the C–Br bond was made on the same basis as in the model experiment (steric considerations, deshielding by 0.6 ppm of the H-6 proton, and course of the subsequent elimination of HBr). The α-bromo lactone **18** on treatment with 1,5-diazabicyclononene in refluxing toluene afforded (−)-frullanolide (**1**) (mp 75–76°, $[\alpha]_D$ −112°) in 80% yield, identical in all respects with natural (−)-frullanolide[3a,b] (including skin tests).

Having found an efficient route for α-methyl → α-methylene conversion for cis-fused lactones, we attempted to utilize the same method in a synthesis of (+)-arbusculin B (**2**), an isomer of (−)-frullanolide with a trans-fused lactone junction (Chart III).

The known[27] 11,12-dihydro-γ-cyclocostunolide (**17**) was secured in 70% overall yield from 1,2-dihydro-α-santonin (**9**) by thioketalization to give **16** followed by treatment with Raney nickel. Removal of the thioketal group in **16** with active W-2 Raney nickel was complete after 15 min at room temperature and led to more than 80% of the desired 11,12-dihydro-γ-cyclocostunolide (**17**).[32] The same thioketal **16**, when treated with W-2 Raney nickel in refluxing ethanol for 4 hr, led to only 33% of the deoxy compound **17**.[27] Dihydro-γ-cyclocostunolide (**17**), by successive treatment with triphenylmethyllithium followed by 1,2-dibromoethane, afforded a single α-bromo lactone **19** in 80% yield. The β configuration assigned to the C–Br bond in **19** is based on the following evidence: (a) this configuration corresponds to the introduction of bromine from the less hindered side; (b) the H-6 proton is deshielded by 0.3 ppm with respect to starting material **17**; this deshielding is explained by a 1,3-diaxial interaction[21]

Chart III

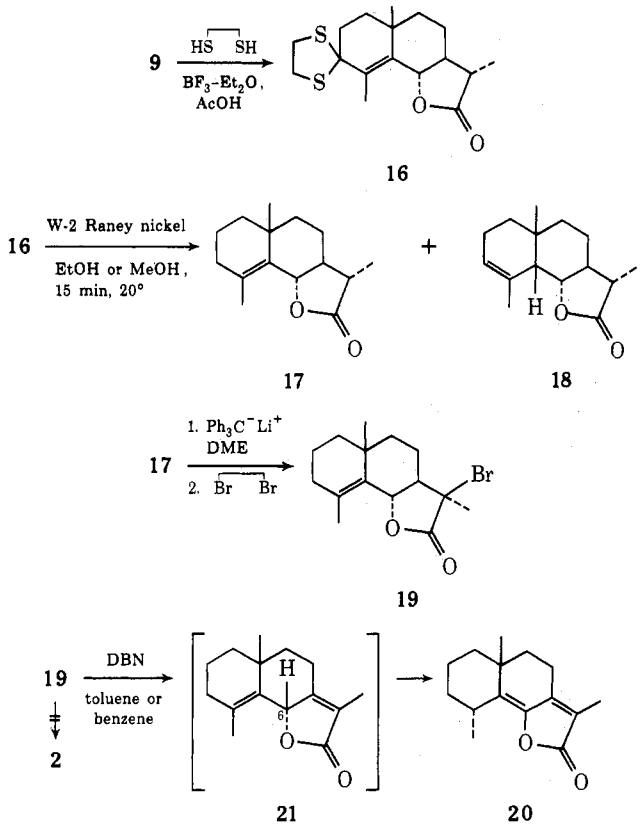
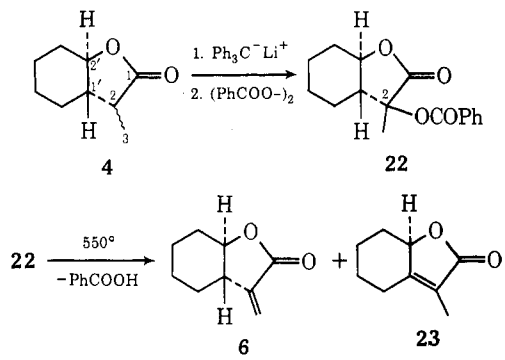
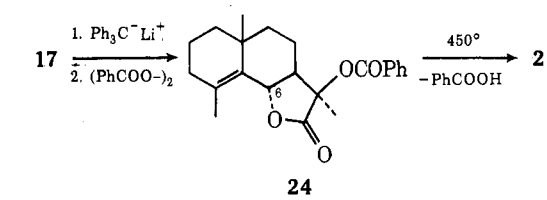


Chart IV



by 0.65 ppm with respect to starting material **17**. This deshielding is explained by a spatial 1,3-diaxial proximity between H-6 and the benzoyloxy group which involved a field effect[40] due to either the carbonyl or the phenyl group, and is only compatible with a β configuration for the C-OC(=O)Ph bond.

Chart V



between the axial H-6 proton and bromine, which is only compatible with a β configuration of the C-Br bond.

The α-bromo lactone **19** upon treatment with DBN does not afford (+)-arbusculin B (**2**) but the endocyclic unsaturated lactone **20** in 78% yield (λ_{max} 289 nm). Endocyclic lactone **20** probably arises from **21** (formed *via* trans elimination of HBr) through a facile enolization of the axial and doubly activated H-6 proton in the presence of excess DBN.

Since in the trans lactone series a trans elimination of HBr leading to the corresponding endocyclic unsaturated lactones[33] seemed to be the preferred pathway, a different approach was investigated for the synthesis of α-methylene-γ-butyrolactones from trans-fused α-methyl butyrolactone precursors. It appeared that an X group that possessed the same stereochemistry but could undergo an elimination in a syn manner (Scheme I) might give rise to the desired products, *e.g.*, *via* ester pyrolysis.[34]

A modification of the procedure of Larsen and Lawesson[35] was used to effect benzoyloxylation (X = $PhCO_2$). By treatment of the enolate of lactone **4**, formed as usual, with dibenzoyl peroxide[35,36] at 5°, the expected α-benzoyloxylactone **22**[37] could be isolated in 50% yield.[38] Pyrolysis at 600° of α-benzoyloxy lactone **22** gave after silica gel chromatography a readily separated 3:1 mixture of the known α-methylene-γ-butyrolactone[8c] **6** and the known[39] endocyclic unsaturated lactone **23** in 60% yield (Chart IV).

For the synthesis of (+)-arbusculin B (**2**) the enolate of 11,12-dihydro-γ-cyclocostunolide (**17**) was added to a cooled solution of dibenzoyl peroxide, the excess peroxide was destroyed, and the product was chromatographed on silica gel, affording the benzoyloxy lactone **24** (Chart V) in 50% yield (70% based on consumed **17**). The β configuration assigned to the C-OC(=O)Ph bond in lactone **24** was based on the following evidence: (a) this configuration corresponds to the introduction of the benzoyloxy group from the less hindered side; (b) the axial H-6 proton is deshielded

Pyrolysis at 450° of α-benzoyloxylactone **24** gave, after silica gel chromatography, (+)-arbusculin B (**2**), mp 86–88°, $[\alpha]_D$ +46° ($CHCl_3$), in 35% yield.[41] Spectroscopic[10] and chromatographic[42] properties of the synthetic compound were in full agreement with those of authentic material.

Since the pyrolysis of carboxylic esters is a unimolecular syn elimination[34] (which may proceed in two steps[22b,43]) the stereospecificity in which (+)-arbusculin B was obtained (no trace of the endocyclic isomer could be detected) from pyrolysis of benzoyloxylactone **24** gives further evidence for the assignment of a α configuration to the C-OC(=O)Ph bond.

In summary, both cis- and trans-fused α-methylene-γ-butyrolactones have been synthesized from the corresponding α-methyl lactones by procedures which should be capable of application to cis and trans α-methyl-γ-butyrolactones in general. A high-yield synthesis of endocyclic unsaturated methyl lactones is also available.

Experimental Section[44]

General Procedure for Preparation of Triphenylmethyllithium Solutions. In a flame-dried flask under N_2, triphenylmethane (distilled, recrystallized from anhydrous methanol, and dried under high vacuum for 24 hr) (1 mmol) was dissolved in dry THF or DME (1 ml). To the stirred solution, kept under a static atmosphere of dry nitrogen, was added dropwise through a serum cap a solution of *n*-butyllithium in hexane (0.95 mmol, Fluka or Merck). The solution, which became dark red immediately, was stirred for 1 hr at room temperature prior to further use.

c-2-Bromo-*r*-2′*H*,*c*-1′*H*,2(2′-hydroxycyclohexyl)propionic Acid Lactone (7). A solution of *cis*-α-methyl lactone **3**[12] (240 mg, 1.58 mmol) in dry THF (3 ml) was treated with excess triphenylmethyllithium (from 1 g of triphenylmethane, 1.7 ml of *n*-BuLi in hexane, and 6 ml of THF). The mixture was stirred for 2 hr at room temperature and treated with dry 1,2-dibromoethane (2 ml). After 2 hr of continued stirring the product was isolated with ether. The crude mixture was immediately chromatographed over 40 g of silica gel. Elution with benzene gave α-bromo lactone **7** (310 mg, 85%). Recrystallization from hexane gave an analytical sample: mp 107.5–109°; $M^{\cdot+}$ *m/e* 232–234; ν_{max} (CCl_4) 2940,

2860, 1785, 1204, 1178, 1117, and 968 cm^{-1}; δ_{TMS} (CCl_4) 4.85 (t, J = 4 Hz, 1 H), 2.38 (m, 2 H), and 1.80 ppm (s, 3 H). *Anal.* Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.29. Found: C, 46.6; H, 5.5; Br, 34.0.

***c*-1′*H*-*r*-2′*H*,2-(2′-Hydroxycyclohexyl)propenoic Acid Lactone (5).** A solution of 104 mg (0.445 mmol) of α-bromo lactone 7 in 2 ml of anhydrous toluene and 250 μl of 1,5-diazabicyclononene was refluxed under nitrogen for 45 min. The cooled solution was extracted with ether and washed with a cooled (~5°) 10% hydrochloric acid solution, which was back extracted with ether. The combined ether extracts were dried over potassium carbonate, evaporated, and short path distilled, affording 54 mg (78%) of the pure known[8c] methylene lactone 5: bp 70° (bath temperature, 0.05 mm); M·+ m/e 152; ν_{max} (film) 2920, 2860, 1767, 1449, 1367, 1342, 1161, 1125, 1012, 977, and 963 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.18 (d, J = 2, 5 Hz, 1 H), 5.52 (d, J = 2, 5 Hz, 1 H), 4.53 (q, J = 5, 5 Hz, 1 H), and 3.02 ppm (m, 1 H).

1,2-Dihydro-α-santonin[45] (9). Sims'[24] modified procedure was used in the preparation of 9. To a solution of 5 g of (−)-α-santonin (8) (20 mmol) in 250 ml of a 1:1 mixture of benzene and 95% ethanol was added 110 mg of tris(triphenylphosphine(chlororhodium(I) (Fluka). The mixture was flushed with hydrogen and then very efficiently stirred under hydrogen. After 12 hr the theoretical amount of hydrogen was absorbed. The solvents were evaporated and the mixture was filtered over 50 g of neutral alumina (grade II–III). Elution with 10% ethyl acetate in benzene afforded a brown oil (5 g) which was crystallized from a 1:1 mixture of hexane–carbon tetrachloride, affording 4.95 g (98%) of 1,2-dihydro-α-santonin (9): mp 102° after a phase change at 95°; λ_{max} (EtOH) 244 nm (ε 16,200); ν_{max} (KBr) 1782, 1667, and 1619 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.69 (d, J = 9 Hz, 1 H), 2.00 (d, J = 2 Hz, 3 H), 1.32 (s, 3 H), and 1.26 ppm (d, J = 7 Hz, 3 H). [lit.[45] mp 101–102°; λ_{max} 244 nm (ε 14,700); ν_{max} (CCl_4) 1795, 1680, and 1628 cm^{-1}].

1,2-Dihydro-6β-santonin[46] (10). A modified procedure of Piers and Cheng[25] was used for the preparation of 10. A solution of 2.48 g of 1,2-dihydro-α-santonin (9, 10 mmol, dried under vacuum for one night) in 15 ml of dry dimethylformamide was treated with 7.5 ml of a solution of dimethylformamide containing 1.5 g of hydrogen chloride and was heated under nitrogen for 30 min at 85°. The yellow solution was evaporated at 70° (20 mm), the residue was taken up in 50 ml of a 1:1 mixture of benzene and ether, and this solution was washed with ether. The residue of the organic layer (2.55 g) was chromatographed over 100 g of silica gel and the desired product was eluted with a 4:1 mixture of benzene and ethyl acetate. It was obtained as a yellow syrup (2.41 g) which crystallized from benzene–hexane as colorless, compact prisms: mp 125°; λ_{max} (EtOH) 245 nm (ε 14,600), 327 (44); ν_{max} (KBr) 1772, 1668, and 1614 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.49 (d, J = 6 Hz, 1 H), 1.96 (s, 3 H), 1.44 (d, J = 8 Hz, 3 H), and 1.33 ppm (s, 3 H) (lit.[46] mp 127°).

Thioketal of 1,2-Dihydro-6β-santonin (11). A solution of 5.28 g of 1,2-dihydro-6β-santonin (10, 2.12 mmol) in 450 ml of anhydrous benzene, 15 ml of ethanedithiol, and 400 mg of p-toluenesulfonic acid was heated at reflux under nitrogen for 10 hr. The cooled solution was extracted with chloroform, washed with a saturated solution of sodium bicarbonate, and dried under vacuum (0.01 mm) overnight. The crude mixture obtained was chromatographed over 100 g of silica gel and the thioketal 11 was eluted with chloroform and crystallized from hexane, affording 6.60 g (95%) of pure thioketal 11: mp 163–164°; M·+ m/e 324; [α]D −48° (c 0.11, $CHCl_3$); ν_{max} (KBr) 1772, 1615, 1455, 1277, 1236, 1212, 1200, 1185, 1165, 1012, 942, and 917 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.36 (d, J = 5 Hz, 1 H), 3.33 (m, 4 H), 2.05 (s, 3 H), 1.38 (d, J = 7.5 Hz, 3 H), and 1.10 ppm (s, 3 H). *Anal.* Calcd for $C_{17}H_{24}S_2O_2$: C, 62.95; h, 7.45; S, 19.75. Found: C, 63.0; H, 7.4; S, 19.7.

(−)-11,12-Dihydro-11βH-frullanolide (13). A solution of 2.00 g (6.17 mmol) of thioketal 11 in 95% ethanol was treated under nitrogen with 8.1 g of potassium hydroxide. After 90 min, the mixture was cooled to −40° and 20 ml (~12 g) of W-2 Raney nickel[47] in precooled 95% ethanol was rapidly added. The vigorously stirred mixture was kept for 2 hr between −25 and −30° under nitrogen. The cold mixture was filtered, washed with 95% ethanol, and acidified by slow addition of a 10% solution of hydrogen chloride. The green filtrate was extracted with a 1:1 mixture of benzene and ether, the organic phase was washed twice with a saturated solution of sodium bicarbonate, and the combined water phases were back extracted with ether. The combined organic phases were dried over magnesium sulfate and evaporated, affording 1.2 g of an oil which was chromatographed over 100 g of silica gel. Elution with benzene gave 590 mg (40%) of dihydrofrullanolide 13 and then 85 mg (6%) of its isomer 14. The analytical sample of 13 was prepared by recrystallization from hexane: mp 119–121°; M·+ m/e 234; [α]D −58° (c 0.12, $CHCl_3$); ν_{max} ($CHCl_3$) 1750, 1645, 1455, 1370, 1310, 1195, 1075, 1005, 940, and 910 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.43 (d, J = 5 Hz, 1 H), 2.42 (q, J = 8 Hz, 1 H), 1.77 (s, 3 H), 1.33 (d, J = 8 Hz, 3 H), and 1.07 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.9; H, 9.45. The analytical sample of **5α,6α,11βH-eudesm-3-en-6,13-olide (14)** was prepared by recrystallization from n-hexane: mp 102.5–103.5°; M·+ m/e 234; [α]D −108° (c 0.14, $CHCl_3$); ν_{max} ($CHCl_3$) 1762, 1450, 1382, 1340, 1208, 1170, 1082, 1000, and 975 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.42 (s, br, 1 H) 4.45 (dd, J = 6.5 Hz, 1 H), 1.82 (s, br, 3 H), 1.22 (d, J = 7 Hz, 3 H), and 0.91 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.9; H, 9.5.

11α-Bromo-11,12-dihydrofrullanolide (15). A cooled (0°) solution of 190 mg (0.82 mmol) of lactone 13 in anhydrous 1,2-dimethoxyethane (2 ml) was added to a cooled solution (0°) of triphenylmethyllithium (from 2.4 g of triphenylmethane, 6 ml of 1,2-dimethoxyethane, 1.5 ml of *N,N,N′,N′*-tetramethylenediamine, and 3.3 ml of n-butyllithium in hexane). The mixture, kept under nitrogen, was stirred for 3 hr, treated with 4 ml of 1,2-dibromoethane, and then stirred for an additional 75 min. The usual workup afforded a residue which was immediately chromatographed over 75 g of silica gel. Elution with benzene afforded 115 mg (48%) of bromide 15: M·+ m/e 312, 314; ν_{max} ($CHCl_3$) 1775 and 1650 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.68 (d, J = 4 Hz, 1 H), 1.92 (s, 3 H), 1.80 (s, 3 H), and 1.01 ppm (s, 3 H).

(−)-Frullanolide (1). A solution of 70 mg (0.22 mmol) of bromide 15 in 2 ml of anhydrous toluene and 150 μl of 1,5-diazabicyclononene was heated at reflux under nitrogen for 60 min. The cooled solution was extracted with ether and washed with a cold (~5°) 10% solution of hydrogen chloride and then with saturated brine. The combined water phases were back extracted with ether and the combined organic layers were dried over potassium carbonate and evaporated, affording a residue which was chromatographed over 10 g of silica gel. Elution with a 24:1 mixture of benzene–ethyl acetate afforded 41 mg (80%) of (−)-frullanolide. The analytical sample was recrystallized from n-hexane: mp 75.5–76° (no depression when mixed with authentic natural material); M·+ m/e 232; [α]D −112° (c 0.155, $CHCl_3$); ν_{max} (CCl_4) 1765, 1667, 1644, 1264, 1143, 1122, 1006, 940, and 915 cm^{-1}; ν_{TMS} ($CDCl_3$) 6.17 (d, J = 1.5 Hz, 1 H), 5.58 (d, J = 1.5 Hz, 1 H), 5.27 (d, J = 6 Hz, 1 H), 2.95 (m, 1 H), 1.75 (s, 3 H), and 1.08 ppm (s, 3H). *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.4; H, 8.8 (lit.[3a,b] mp 76°, [α]D −113°).

11,12-Dihydro-11βH-γ-cyclocostunolide (17). The procedure of Barton and coworkers[27] was modified affording lactone 17 *via* thioketal 16 in a substantially better yield. A solution of 2 g (6.17 mmol) of dihydrosantonin 9 in 20 ml of glacial acetic acid was cooled under nitrogen to ~5° and sirred with 4 ml of 1,2-ethanedithiol and 0.3 ml of freshly distilled boron trifluoride etherate. After 6 hr, an additional 0.3 ml of boron trifluoride was added and the mixture was stored at 5° for 15 hr. The product was isolated with ether and the residual ethanedithiol was removed under high vacuum, affording 2.57 g (98%) of thioketal 16: mp 166–168°; M·+ m/e 324; ν_{max} ($CHCl_3$) 1772, 1665, 1460, 1382, 1330, 1315, 1280, 1242, 1170, 1140, 1030, and 985 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.58 (d, br, 1 H), 3.30 (m, 4 H), 2.10 (d, J = 1.5 Hz, 3 H), 1.18 (d, J = 7 Hz, 3 H), and 1.14 ppm (s, 3 H).

A 2.50-g sample (7.72 mmol) of the above thioketal 16 in 250 ml of anhydrous methanol was stirred with 20 ml (*ca.* 12 g) of W-2 Raney nickel at room temperature for 15 min. The mixture was filtered through Celite, washed with methanol, and dried. The product was isolated with ether, affording 1.75 g of a clear oil. This oil was chromatographed over 150 g of silica gel. Elution with benzene gave 1.35 g (75%) of lactone 17 and 250 mg (14%) of an isomer 18.

The analytical sample of 17 was obtained by crystallization from n-hexane: mp 89–90°; M·+ m/e 234; ν_{max} ($CDCl_3$) 1762, 1455, 1380, 1330, 1312, 1240, 1185, 1165, 1140, 1112, 1080, 1030, and 980 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.55 (d, br, 1 H), 1.84 (s, br, 3 H), 1.22 (d, J = 6.5 Hz, 3 H), and 1.13 ppm (s, 3 H). The analytical sample of **11,12-dihydro-5β,11βH-α-cyclocostunolide (18)** was obtained by recrystallization from n-hexane: mp 119–121°; M·+ m/e 234; [α]D −65° (c 0.100, $CHCl_3$); ν_{max} ($CHCl_3$) 1769, 1455, 1385, 1271, 1245, and 1005 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.50 (m, 1 H), 4.34 (q, J = 5, 9 Hz, 1 H), 1.67 (s, br, 3 H), 1.19 (d, J = 7 Hz, 3 H), and 1.11 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.7; H, 9.4.

11β-Bromo-11,12-dihydro-γ-cyclocostunolide (19). A solution of 54 mg (0.23 mmol) of dihydro-γ-cyclocostunolide **17** in 1 ml of anhydrous 1,2-dimethoxyethane kept under nitrogen was added dropwise to a solution of triphenylmethyllithium (from 300 mg of triphenylmethane and 0.45 ml of *n*-butyllithium in hexane in 1.2 ml of 1,2-dimethoxyethane) at room temperature. After 15 min the stirred solution was cooled to 0° and stirring was continued for 75 min. The mixture was then treated with 0.5 ml of 1,2-dibromethane and stirred for 45 min at 0°. Extraction with ether afforded a mixture which was immediately chromatographed over 15 g of silica gel. Elution with benzene gave 55 mg (77%) of α-bromo lactone **19**. The analytical sample was recrystallized from *n*-hexane: mp 139–141°; M·+ *m/e* 312–314; $[\alpha]_D$ −2° (*c* 0.12 $CHCl_3$); ν_{max} ($CHCl_3$) 1780, 1455, 1381, 1293, 1130, 1065, 1032, and 980 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.87 (d, br, 1 H), 1.89 (s, 3 H), 1.84 (d, J = 1.5 Hz, 3 H), and 1.15 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{21}BrO_2$: C, 57.56; H, 6.76; Br, 25.23. Found: C, 57.7; H, 6.6; Br, 25.4.

4β*H*-Eudesma-5,7(11)-dien-6,13-olide (20). A solution of 78 mg (0.27 mmol) of α-bromo lactone **19** in 1.5 ml of anhydrous toluene or benzene was treated under nitrogen at reflux with 150 μl of 1,5-diazabicyclononene for 30 min. The cooled mixture was extracted with ether, washed with a cooled (~5°) hydrogen chloride solution and then with saturated brine, dried over potassium carbonate, and evaporated. The crude oil was chromatographed over 10 g of silica gel. The product was eluted with a 98:2 mixture of benzene and ethyl acetate, affording 47 mg (78%) of diene lactone **20**. The analytical sample was recrystallised as long needles from *n*-hexane: mp 114–115° (with beginning of sublimation); M·+ *m/e* 232; $[\alpha]_D$ − 206° (*c* 0.14, $CHCl_3$); λ_{max} (EtOH) 289 nm (ε 14,500); ν_{max} ($CHCl_3$) 1738, 1650, 1283, 1108, 1070, 1025, 998, 943, and 905 cm^{-1}; δ_{TMS} ($CDCl_3$) 2.60 (m, 3 H), 1.84 (s, br, 3 H), 1.42 (d, J = 6.5 Hz, 3 H), and 1.18 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.6; H, 8.7.

2-Benzoyloxy-*r*-2′*H*,*t*-1′*H*,2-(2′-hydroxycyclohexyl)propionic Acid Lactone (22). A solution of 290 mg (0.019 mmol) of *trans*-α-methyllactone **4**[12] in 4 ml of anhydrous 1,2-dimethoxyethane was treated under nitrogen at room temperature for 2 hr with a solution of triphenylmethyllithium (from 1.2 g of triphenylmethane, 2.1 ml of *n*-butyllithium in hexane, and 10 ml of 1,2-dimethoxyethane). The enolate solution was added dropwise (behind a safety screen) with a hypodermic syringe to a cooled (~5°) solution of 2 g of recrystallized dibenzoyl peroxide in 10 ml of 1,2-dimethoxyethane. A white salt precipitated instantaneously. The stirring was maintained for 45 min. The excess peroxide was destroyed with a solution of 2 g of potassium iodide in 5 ml of water and 0.5 ml of acetic acid. Usual work-up afforded a residue which was immediately chromatographed over 50 g of silica gel. Elution with a 97:3 mixture of benzene and ethyl acetate afforded 330 mg (60%) of α-benzoyloxylactone **22** as an oil which could not be induced to crystallize, but was shown by tlc to be a single product: ν_{max} ($CHCl_3$) 1785, 1725, 1450, 1382, 1280, 1108, 1030, and 710 cm^{-1}; δ_{TMS} ($CDCl_3$) 8.01 (m, 2 H), 7.43 (m, 3 H), 4.25 (m, 1 H), and 1.74 ppm (s, 3 H).

***t*-1′*H*,*r*-2′*H*,2-(2′-Hydroxycyclohexyl)propenoic Acid Lactone (6).** The apparatus for vapor-phase pyrolysis used was almost identical with the one described by DePuy and King.[34]

A solution of 540 mg (2 mmol) of benzoyloxylactone **22** in 2 ml of anhydrous ether was introduced dropwise with a syringe on top of a vertical 30-cm Pyrex column, which was packed with 4-mm Pyrex beads, preequilibrated at 550° for 4 hr, and flushed with a 20 ml/min nitrogen stream. The products resulting from the pyrolysis were trapped in a flask at −78°, appearing after a contact time of about 20 sec. The cooled apparatus was washed with dry ether and the ether solution was washed with a 5% sodium hydroxide solution and then dried over potassium carbonate. Evaporation of the solvent led to 217 mg of an oil which was distilled and chromatographed over 15 g of silica gel. Elution with benzene afforded 125 mg (45%) of the known[8c] methylene lactone **6** and elution with a 4:1 mixture of benzene and ethyl acetate afforded 25 mg (~15%) of the known[39] α,β-unsaturated lactone **23**.

The methylene lactone **6** was distilled, bp 65° (0.01 mm), to give a sample identical in all respects with the one described by Marshall and Cohen.[8c]

Pure 2-(2′-hydroxycyclohexylidene)propionic acid lactone (23) was obtained by distillation and was identical with the previously prepared sample (*cf.* ref 33): bp 65–68° (bath temperature, 0.05 mm); mp ~20°; M·+ *m/e* 152; $n^{25}D$ 1.5069; λ_{max} (EtOH) 217 nm (ε 13,100); ν_{max} ($CHCl_3$) 1745, 1678, 1450, 1095, 1038, and 1027 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.58 (m, 1 H) and 1.78 ppm (s, br, 3 H) [lit.[39] bp 121–124° (3 mm); $n^{25}D$ 1.5060; λ_{max} (EtOH) 217 nm (ε 14,150)].

11β-Benzoyloxy-11,12-dihydro-γ-cyclocostunolide (24). A solution of 700 mg (3 mmol) of dihydro-γ-cyclocostunolide **17** in 7 ml of 1,2-dimethoxyethane was rapidly added at room temperature to a solution of triphenylmethyllithium (from 4 g of triphenylmethane and 6 ml of *n*-butyllithium in hexane in 20 ml of 1,2-dimethoxyethane). After 15 min, the stirred solution was cooled to 0° for 2 hr and then added dropwise (behind a safety screen) with a hypodermic syringe to a cooled (5°) solution of 5 g of dibenzoyl peroxide in 20 ml of 1,2-dimethoxyethane. A white solid precipitated almost instantaneously. The stirring was maintained for 1 hr and then the excess peroxide was destroyed with a solution of 4 g of potassium iodide in 10 ml of water and 1 ml of acetic acid. Formation of iodine was immediate. The mixture was stirred for another 15 min at 0° followed by the usual work-up, which gave a residue which was chromatographed over 150 g of silica gel. Elution with benzene gave 550 mg of α-benzoyloxylactone **24** and 150 mg of starting material (yield 67%). The analytical sample of **24** was obtained by recrystallization from *n*-hexane: mp 139–140°; M·+ *m/e* 354; $[\alpha]_D$ +17° (*c* 0.29, $CHCl_3$); ν_{max} ($CHCl_3$) 1780, 1725, 1605, 1382, 1300, 1280, 1180, 1140, 1115, 1095, 1040, 985, and 705 cm^{-1}; δ_{TMS} ($CDCl_3$) 8.00 (m, 2 H), 7.50 (m, 3 H), 5.10 (d, J = 10 Hz, 1 H), 1.79 (s, br, 3 H), 1.68 (s, 3 H), and 1.01 ppm (s, 3 H). *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.6; H, 7.6.

(+)-Arbusculin B (2). A solution of 60 mg (0.17 mmol) of α-benzoyloxylactone **24** in 1 ml of anhydrous ether was added dropwise onto the pyrolysis apparatus described earlier preequilibrated at 450° and flushed with a nitrogen stream of 30 ml/min. The apparatus was washed with ether and the ethereal solution obtained was washed with a 5% sodium hydroxide solution, dried over potassium carbonate, and evaporated. The residue was chromatographed over 10 g of silica gel. Elution with benzene afforded 14 mg of (+)-arbusculin B and then 5 mg of starting material **24** (yield 35%, 40% based on consumed **24**). The analytical sample of (+)-arbusculin B was obtained by crystallization from *n*-pentane: mp 86–88°; M·+ *m/e* 232; $[\alpha]_D$ +46° (*c* 0.104, $CHCl_3$); ν_{max} ($CHCl_3$) 1763, 1665, 1452, 1290, 1254, 1146, 1133, 1034, 978, 941, and 907 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.12 (d, J = 3 Hz, 1 H), 5.44 (d, J = 3 Hz, 1 H), 4.52 (d, br, J = 12 Hz, 1 H), 2.53 (m, 1 H), 1.85 (s, 3 H), and 1.11 ppm (s, 3 H) [lit.[10a] mp 86.5–88°; $[\alpha]_D$ +47.3° ($CHCl_3$)]. *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.6; H, 8.75.

Acknowledgments. Partial support from Roure-Bertrand and Justin-Dupont (Grasse) and F. Hoffmann-La Roche (Basle) and a temporary fellowship from the CNRS awarded to one of us (A. E. G.) are gratefully acknowledged, as well as a continuing collaboration with Dr. J. Foussereau.

Registry No. **1**, 27579-97-1; **2**, 24164-19-0; **3**, 2205-25-6; **5**, 16822-06-3; **7**, 42807-10-3; **8**, 481-06-1; **9**, 42807-12-5; **10**, 25645-13-0; **11**, 37720-27-7; **13**, 37720-28-8; **14**, 42807-16-9; **15**, 37720-29-9; **16**, 20482-46-6; **17**, 42807-19-2; **18**, 42807-20-5; **19**, 42807-21-6; **20**, 42807-22-7; **22**, 38602-10-7; **23**, 15174-78-4; **24**, 38602-09-4; 1,2-dibromoethane, 106-93-4; 1,5-diazabicyclononene, 3001-72-7; 1,2-ethanedithiol, 540-03-6.

References and Notes

(1) For a preliminary account of this work see (a) A. E. Greene, J.-C. Muller, and G. Ourisson, *Tetrahedron Lett.*, 2489 (1972); (b) *ibid.*, 3375 (1972).
(2) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds," Vol. II, Terpenes, Academic Press, New York, N. Y., 1972, pp 79–175.
(3) (a) H. Knoche, G. Ourisson, G. W. Perold, J. Foussereau, and J. Maleville, *Science*, **166**, 239 (1969); (b) G. W. Perold, J.-C. Muller, and G. Ourisson, *Tetrahedron*, **28**, 5797 (1972), and references cited therein; (c) J. C. Mitchell, G. Dupuis, and T. A. Geissman, *Brit. J. Dermatol.*, **87**, 235 (1972), and references cited therein.
(4) (a) S. M. Kupchan, *Trans. N. Y. Acad. Sci.*, **32**, 85 (1970); (b) S. M. Kupchan, M. A. Eakin, and M. A. Thomas, *J. Med. Chem.*, **14**, 1147 (1971), and references cited therein.
(5) H. Shibaoka, M. Shimokariyama, S. I. Riuchijima, and S. Tamura, *Plant Cell Physiol.*, **8**, 297 (1967).
(6) P. M. Baker, C. C. Fortes, G. Gazzinelli, B. Gilbert, J. N. C. Lopes, J. Pelligrino, T. C. B. Tomassini, and W. Vichnewski, *J. Pharm. Pharmacol.*, **24**, 853 (1972).
(7) T. Tschesche, F.-J. Kämmerer, G. Wulff, and F. Schönbeck, *Tetrahedron Lett.*, 701 (1968).
(8) (a) E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 230 (1950); (b) E. E. van Tamelen and S. R. Bach, *J. Amer.*

Chem. Soc., **77**, 4683 (1955); **80**, 3079 (1958); (c) J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965); (d) H. Minato and I. Horibe, *J. Chem. Soc. C*, 1575 (1967); (e) A. Löffler, R. D. Pratt, J. Pucknat, and A. S. Dreiding, *Chimia*, **23**, 413 (1969); (f) E. Öhler, K. Reininger, and U. Schmidt, *Angew. Chem.*, **82**, 480 (1970); (g) J. Martin, P. C. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970); (h) E. S. Behare and R. B. Miller, *ibid.*, 402 (1970); (i) J. W. Patterson and J. E. McMurry, *ibid.*, 488 (1971); (j) L. K. Dalton and B. C. Elmes, *Aust. J. Chem.*, **25**, 625 (1972); (k) C. Alexandre and F. Rouessac, *C. R. Acad. Sci., Ser. C*, **274**, 1585 (1972); (l) P. A. Grieco and K. Hiroi, *Chem. Commun.*, 1317 (1972).

(9) (a) G. H. Posner and G. L. Loomis, *Chem. Commun.*, 892 (1972); (b) E. W. Colvin, R. A. Raphael, and J. S. Roberts, *ibid.*, 858 (1971); (c) E. I. Heiba and R. M. Dassau, *J. Amer. Chem. Soc.*, **93**, 995 (1971); (d) D. H. R. Barton and A. J. L. Beckwith, *Proc. Chem. Soc.*, 335 (1963); (e) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1354 (1952); (f) Y. Abe and M. Sumi, *J. Pharm. Soc. Jap.*, **72**, 652 (1952); (g) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972), and references cited therein.

(10) (a) M. A. Irwin and T. A. Geissman, *Phytochemistry*, **8**, 2411 (1969); (b) F. Shafizadeh, N. R. Bhadane, M. S. Morris, R. G. Kelsey, and S. N. Khanna, *ibid.*, **10**, 2745 (1971).

(11) A. E. Greene, J.-C. Muller, and G. Ourisson, *Tetrahedron Lett.*, 4147 (1971).

(12) E. H. Charlesworth, H. J. Campbell, and D. L. Stachiw, *Can. J. Chem.*, **37**, 877 (1959).

(13) C. Dupin and R. Fraisse-Jullien, *Bull. Soc. Chim. Fr.*, 1993 (1964).

(14) M. S. Newman, V. Devries, and R. Darlak, *J. Org. Chem.*, **31**, 2171 (1966).

(15) W. G. Kofron and C. R. Hauser, *J. Org. Chem.*, **35**, 2085 (1970).

(16) (a) A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957); (b) B. Angelo, *C. R. Acad. Sci., Ser. C*, **273**, 1767 (1971).

(17) L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **90**, 265 (1971).

(18) G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, **93**, 1379 (1971).

(19) Formation of isolable α-bromocarbonyl compounds, obtained by treatment of the corresponding enolates with 1,2-dibromoethane, is not a general reaction (see ref 14 and 16); appreciable yields have been obtained only in the case of α-methyl lactone enolates. The bromination in this case might proceed *via* a bromine–lithium interchange. *Cf.* D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963).

(20) Stereochemical designations of substituents in bicyclic compounds are indicated by *c* (cis) and *t* (trans) relative to a reference substituent *r* (hydrogen).

(21) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 189–190.

(22) (a) D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949); (b) A. Maccoll, *Advan. Phys. Org. Chem.*, **3**, 91 (1965).

(23) Purchased from Cooperative Pharmaceutique Francaise, S. A. Melun, $[\alpha]_D$ −176° ($CHCl_3$).

(24) J. J. Sims, V. K. Hønwed, and L. H. Selman, *Tetrahedron Lett.*, 87 (1969).

(25) E. Piers and K. F. Cheng, *Can. J. Chem.*, **46**, 377 (1968).

(26) *Cf.* C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, pp 20–30. See also ref 27.

(27) D. H. R. Barton, G. P. Moss, and J. A. Whittle, *J. Chem. Soc. C*, 1813 (1968).

(28) *Cf.* H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, pp 24–26.

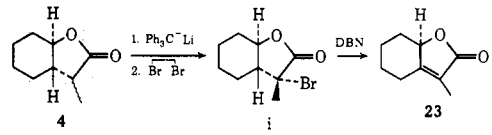
(29) P. Crabbé and A. Guzmán, *Tetrahedron Lett.*, 115 (1972).

(30) This compound has recently been isolated from *Frullania dilatata* (L.) Dum.: Y. Asakawa, J.-C. Muller, and G. Ourisson, unpublished results.

(31) G. R. Pettit and E. E. van Tamelen, *Org. React.*, **12**, 356 (1962).

(32) Under these conditions, a second product, tentatively identified as lactone **18**, was also formed in *ca.* 10% yield.

(33) In a preliminary model experiment, similar treatment of trans lactone **4** afforded the α-bromo lactone i, which underwent a trans



4 i 23

elimination of HBr to afford exclusively the endocyclic unsaturated lactone **23** (70% overall yield).

(34) C. H. De Puy and R. W. King, *Chem. Rev.*, **60**, 431 (1960), and references cited therein.

(35) E. H. Larsen and S. O. Lawesson, *Org. Syn.*, **45**, 37 (1965).

(36) D. J. Rawlinson and G. Sosnovsky, *Synthesis*, **1**, 1 (1972).

(37) Probably a mixture of epimers at C-2′.

(38) The low yield is probably due to difficulties in obtaining sufficiently pure dibenzoyl peroxide.

(39) W. G. Dauben and P. D. Hange, *J. Amer. Chem. Soc.*, **75**, 3352 (1953).

(40) C. R. Narayanan and M. S. Parkar, *Indian J. Chem.*, **9**, 1019 (1971).

(41) Changes in temperature and nitrogen flow greatly affect the yield of isolable arbusculin B, which is not stable under these conditions.

(42) We thank Dr. J. D. Connoly (Glasgow) for a sample of arbusculin B for chromatographic comparison.

(43) (a) E. L. Alexander and A. Mudrak, *J. Amer. Chem. Soc.*, **72**, 1810 (1950); (b) R. T. Arnold, G. G. Smith, and R. M. Dodson, *J. Org. Chem.*, **15**, 1256 (1950); (c) N. L. McNiven and J. Read, *J. Chem. Soc.*, 2067 (1952).

(44) The isolation procedure involved adding the reaction mixture to water or saturated brine followed by thorough extraction with the specified solvent. Anhydrous magnesium sulfate or potassium carbonate was used to dry the combined extracts and the solvent was subsequently removed on a rotary evaporator under reduced pressure. 1,2-Dibromoethane was distilled and filtered through neutral alumina (activity II–III) just before use. Dibenzoyl peroxide was purified by recrystallization from cold (−20°) chloroform–methanol and drying overnight under vacuum. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride. Boiling points are uncorrected. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Infrared spectra were recorded with a Beckman IR-8 spectrometer using sodium chloride cells or KBr disks. Nuclear magnetic resonance (nmr) spectra were determined with a Varian Associates Model A-60A equipment using tetramethylsilane as an internal standard. Mass spectra were determined on a Thomson-Houston THN 208 or a LKB 9000 mass spectrometers. Optical rotations $[\alpha]_D$ were determined at 20° on a Perkin-Elmer 141 polarimeter. Microanalyses were performed by the Strasbourg Division of the Service Central de Microanalyses of the CNRS. Gas chromatography (glc) was performed on a Varian 1200 instrument employing nitrogen as the carrier gas. The following columns were used: column A, a 5 ft × 0.12 in. column of 5% SE-30 on 100–120 mesh Gas-Chrom Q; column B, a 6 ft × 0.12 in. column of 3% OV 101 on 100–120 mesh Gas-Chrom Q.

(45) J. C. Banerji, D. H. R. Barton, and R. C. Cookson, *J. Chem. Soc.*, 5041 (1957).

(46) H. Ishikawa, *J. Pharm. Soc. Jap.*, **76**, 507 (1956).

(47) Prepared according to "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1900, p 181.