(B) From Loganin Aglucone 6-Acetate (5). To an ice-cold solution of 105 mg of optically active aglucone **5**, 408 mg of 2,3,4,6-tetra-*O*-acetyl-β-D-glucose,[52] and 500 mg of Drierite in 3 ml of 1,2-dichloroethane was added dropwise 0.10 ml of boron trifluoride etherate. The mixture was stirred at 0° for 2 hr and at room temperature for 36 hr. After neutralization with pyridine, the mixture was poured into water and the product (550 mg) was isolated with ethyl acetate. The viscous oil was fractionated by thick layer chromatography to give 165 mg of a glucoside mixture. Further purification by tlc yielded 50 mg of an oil, $[\alpha]^{25}D$ −60° (*c* 1.05, $CHCl_3$), which crystallized on standing. The solid was recrystallized twice from ethanol to give 40 mg (17%) of fine white needles: mp 139–140° (lit.[2] mp 140–141°); $[\alpha]^{25}D$ −79.1° (*c* 0.35, $CHCl_3$) {lit.[2] $[\alpha]^{22}D$ −79.6° (*c* 0.39, $CHCl_3$)}; ir ($CHCl_3$) 1740 (CO, broad), 1710 (CO), 1645 (C=C), 1255, 1085, 1070, and 1045 cm^{-1}; uv (C_2H_5OH) 233 nm (ε 10,600); nmr ($CDCl_3$) δ 7.31 (s, 1, —CH=), 3.70 (s, 3, OCH_3), 3.02 (m, 1, H-4a), 2.09 (s, 3, CH_3CO), 2.03 (s, 6, CH_3CO), 2.00 (s, 3, CH_3CO), 1.81 (s, 3, CH_3CO), and 1.02 (d, 3, J = 7 Hz, CH_3); mass spectrum *m/e* (rel intensity) 600 (M^+, 0.1), 5.69 (0.1), 540 (0.3), 331 (70), 271 (5), 253 (4), 193 (35), 169 (100), 109 (40). A 1:1 mixture of this material and authentic loganin pentaacetate exhibited mmp 139–140°.

Anal. Calcd for $C_{27}H_{36}O_{15}$: C, 54.00; H, 6.04. Found: C, 53.90; H, 6.00.

Acknowledgment. We express our gratitude to the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for their assistance in this work.

Total Synthesis of Loganin

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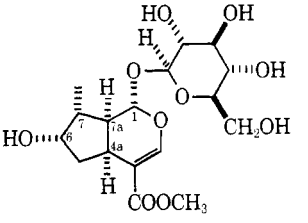
Abstract: A synthesis of loganin, a monoterpene glucoside occupying a central position in the biosynthesis of secoiridoids and alkaloids, is described. The photochemical cycloaddition of 2-formylmalonaldehydic acid methyl ester to the tetrahydropyranyl ether of 3-cyclopentenol is the key step in the synthesis, allowing the construction of the tetrahydrocoumalate unit typical of iridoids in a single operation. Methanolysis followed by oxidation with chromium trioxide afforded the crystalline ketoacetal **7**. The methyl group was introduced regioselectively *via* the *n*-butylthiomethylene ketone and the resulting product **12** epimerized to the more stable epimer **13**. Reduction of the carbonyl group and treatment of the corresponding mesylate with tetraethylammonium acetate followed by hydrolysis with aqueous acetic acid–perchloric acid gave loganol 5-acetate (**21**). Glucosidation of racemic **21** using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**23**) yielded optically active loganin pentaacetate which had previously been converted to loganin.

The glucoside loganin, first isolated from *Strychnos nux vomica*,[3] is a widely distributed product of secondary plant metabolism[4] and a key intermediate in the biosynthesis of *Corynanthe*, *Aspidosperma*, *Iboga*, *Ipecacuanha*, and structurally simpler monoterpene alkaloids.[5] Its detailed structure was established by chemical means[6–8] and confirmed by X-ray analysis of the methoxybromide.[9] In this paper we present details on the total synthesis of loganin (**1**),[10] which represents the first synthesis of an iridoid glucoside.[11]



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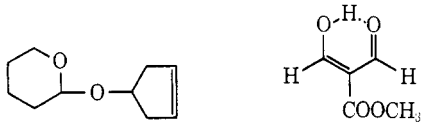
Our synthetic plan called for photochemical addition of 2-formylmalonaldehydic acid methyl ester (**3**) to a symmetrical cyclopentene[12] already containing the secondary hydroxyl group of loganin (**1**), followed by introduction of the *C*-methyl group and glucosidation. 2-Formylmalonaldehydic acid methyl ester (**3**) was formed after aqueous work-up when methyl 3,3-dimethoxypropionate, available from the condensation of ketene with trimethyl orthoformate,[13] was acylated with methyl formate in the presence of sodium.[14] Photochemical cycloaddition of the tricarbonyl compound **3** to 3-cyclopentenol[15,16] led to a multitude of products. Irradiation of a mixture of **3** and the tetrahydropyranyl

(1) National Institutes of Health Predoctoral Fellow 1966–1969.
(2) National Institutes of Health Predoctoral Fellow 1967–1969.
(3) W. R. Dunstan and F. W. Short, *Pharm. J. Trans.*, **14**, 1025 (1884).
(4) An up-to-date list of its occurrence in nature is presented in the accompanying paper: J. J. Partridge, N. K. Chadha, and M. R. Uskoković, *J. Amer. Chem. Soc.*, **95**, 532 (1973).
(5) Extensive researches on loganin as biointermediate in the laboratories of Arigoni, Battersby, and elsewhere have been summarized: A. R. Battersby, *Chem. Soc. Spec. Period. Rep.*, **1**, 31 (1971); A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970); D. Gross, *Fortschr. Chem. Org. Naturst.*, **28**, 140 (1970); E. Leete, *Accounts Chem. Res.*, **2**, 59 (1969).
(6) S. Brechbühler-Bader, C. J. Coscia, P. Loew, C. v. Szczepanski, and D. Arigoni, *Chem. Commun.*, 136 (1968).
(7) A. R. Battersby, E. S. Hall, and R. Southgate, *J. Chem. Soc. C*, 721 (1969).
(8) H. Inouye, T. Yoshida, and S. Tobita, *Tetrahedron Lett.*, 2945 (1968).
(9) P. L. Lentz, Jr., and M. G. Rossmann, *Chem. Commun.*, 1269 (1969).
(10) Announced previously in a communication: G. Büchi, J. A. Carlson, J. E. Powell, Jr., and L.-F. Tietze, *J. Amer. Chem. Soc.*, **92**, 2165 (1970).
(11) J. M. Bobbitt and K.-P. Segebarth in "Cyclopentanoid Terpene Derivatives," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1969, p 1.
(12) This photochemical addition of a β-tricarbonyl compound is an extension of that discovered by de Mayo for the synthesis of δ-diketones through cycloaddition of enolized β-diketones to olefins: P. de Mayo, *Accounts Chem. Res.*, **4**, 41 (1971).
(13) *Cf.* D. J. Crosby and R. V. Berthold, *J. Org. Chem.*, **27**, 3083 (1962).
(14) Method of L. Panizzi, *Gazz. Chim. Ital.*, **76**, 56 (1946).
(15) E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960).
(16) H. M. Hess and H. C. Brown, *ibid.*, **32**, 4138 (1967).

ether **2**, on the other hand, gave a product which according to its spectral properties contained mostly stereoisomers of structure **5**. Treatment of the crude photoadducts with Amberlite IR-120 cation-exchange resin in methanol solution caused transformation to the much more stable hydroxyacetals **6**. The primary photoproduct **4** which presumably had undergone retroaldol cleavage and recyclization to the tetrahydrocoumalate **5** could not be detected. We consequently only assume that it has structure **4**, and the cis stereochemistry assigned is based on results from other photoadditions generating 4,5-fused ring systems.[17] The ring fusion in the photoadduct **4** is of no further consequence though, because epimerization within the corresponding dialdehyde will lead to the hemiacetal **5** with the more stable ring fusion. Inspection of scale models clearly indicates a preference for cis fusion and this agrees with an experiment performed on the structurally related verbenalin.[18] Oxidation of the alcohols **6** with Collins' reagent[19] gave a 3:1 mixture of ketones differing in configuration at the acetal carbon atom from which the major isomer could be isolated by crystallization. Nuclear magnetic resonance spectroscopy was used to assign configuration to the two epimers **7** and **8**. Comparison of chemical shifts and coupling constants of the acetal protons with those of closely related iridoids such as the epimeric *O*-methylloganols[7] suggest that major **7** (δ 4.74, J = 4.5 Hz) and minor epimer **8** (δ 4.96, J = 3 Hz) have the α- and β-methoxy configurations, respectively. The small coupling constants in **7** demand a pseudoaxially oriented methoxy group, a situation attributed to an "anomeric effect."[20]



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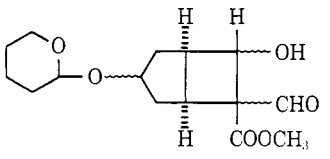

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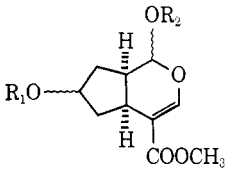
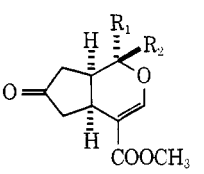




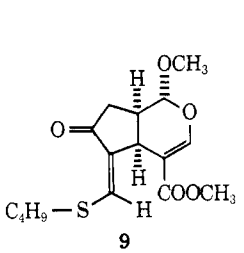
5, R_1 = tetrahydropyranyl; R_2 = H
6, R_1 = H; R_2 = CH_3
7, R_1 = OCH_3; R_2 = H
8, R_1 = H; R_2 = OCH_3

Following the synthetic scheme outlined at the beginning of this paper, we next had to introduce the requisite methyl at C-7. Not unexpectedly, efforts to do this by direct methylation of the cyclopentanone **7** led to inseparable mixtures of mono- and dimethylated products. Condensation of **7** with methyl formate and sodium *tert*-amyloxide afforded a mixture of hydroxymethylene ketones which was difficult to manipulate and consequently was transformed to the *n*-butylthiomethylene ketones by consecutive treatments with *p*-toluenesulfonyl chloride and 1-butanethiol.[21] Chromatographic separation furnished three aliquots. The two less polar fractions contained the undesired products **9** (11%) and **10** (8%) easily distinguished from the desired structural isomer **11** (58%), contained in the third fraction, by the presence in the nmr spectrum of a low-field signal at δ 3.8 caused by the doubly allylic protons at C-4a. The well-known difference in chemical shift of β protons with either *E* or *Z* relationship to the carbonyl group of cisoid α,β-unsaturated ketones served to distinguish the two geometrical isomers **9** and **10**. Similar analysis of the most polar fraction established the presence of an inseparable mixture of **11** and approximately 30% of its geometrical isomer. Hydrogenolysis of the major *n*-butylthiomethylene ketone **11** with Raney nickel[21] produced a mixture of methylated ketones in which the epimer **12** usually predominated as a result of kinetically controlled hydrogen addition from the less crowded α side of the molecule. Base treatment generated the thermodynamically preferred epimer **13** exclusively. Conspicuous spectral changes accompanied this epimerization, and infrared, mass, and nmr spectra of the synthetic, racemic ketone **13** were identical with those of its optically active modification produced by degradation of natural loganin (**1**) as follows. Treatment of loganin pentaacetate (**22**) with acetic anhydride in the presence of sulfuric acid gave 1-*O*,6-*O*-diacetylloganol (**15**),[22] which on methanolysis in the presence of boron trifluoride was converted to optically active hydroxyacetal **16**[23] and thence to optically active ketone **13**[23] by oxidation with chromium trioxide. In agreement with the configuration assigned to C-7, this ketone was stable to sodium methoxide in methanol solution, yet when the experiment was performed in deuteriomethanol a trideuterioketone resulted, demonstrating that the enol necessary for epimerization had indeed been formed.

Returning to the total synthesis, it should be mentioned that occasionally minor amounts of alcohol **14** with incorrect configurations at both C-6 and C-7 were formed in the desulfurization by kinetically controlled, further reduction of the unstable ketone **12**. To prepare the isomer with loganin configuration at these two centers the synthetic, racemic ketone **13** was reduced with sodium borohydride and the resulting alcohol **17** transformed to the mesylate **18**. Tetraethylammonium acetate[7,18] in acetone solution caused inversion and led to the desired acetate **19** accompanied by traces of olefin **20** resulting from elimination of methanesulfonic acid. Hydrolysis of the acetoxyacetal **19** to a noncrystalline anomeric mixture of racemic loganol 6-acetate **21** was accomplished in aqueous acetic acid containing perchloric acid.

The final phase of the synthesis was concerned with

(17) J. D. White and D. N. Gupta, *J. Amer. Chem. Soc.*, **90**, 6171 (1968); P. E. Eaton, *ibid.*, **84**, 2454 (1962).
(18) G. Büchi and R. E. Manning, *Tetrahedron*, **18**, 1049 (1962).
(19) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(20) R. V. Lemieux in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1964, p 733; R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968).
(21) Procedure of R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).
(22) Method of D. Arigoni and P. Loew, ETH (Zürich). We wish to express our sincere thanks to Professor D. Arigoni for this unpublished procedure and for a generous sample of "natural" loganin pentaacetate.
(23) During the course of our work this compound was independently prepared from natural loganin by Battersby.[7]



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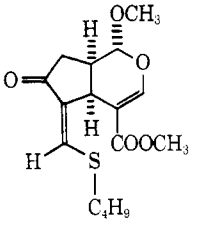

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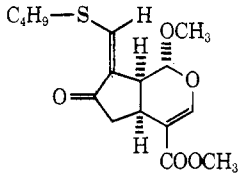

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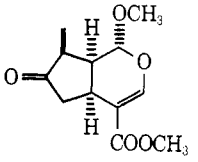

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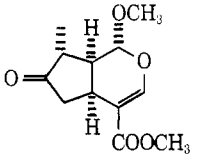

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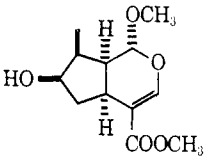

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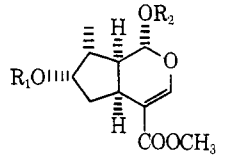
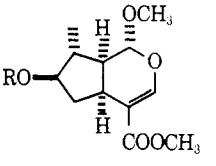
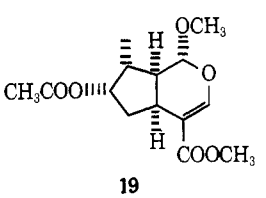


15, $R_1 = CH_3CO$; $R_2 = CH_3CO$
16, $R_1 = H$; $R_2 = CH_3$



17, R = H
18, $R = CH_3SO_2$



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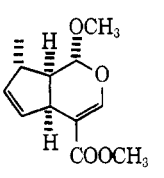

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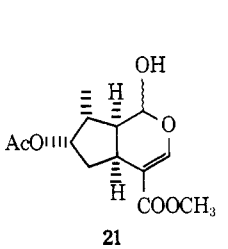

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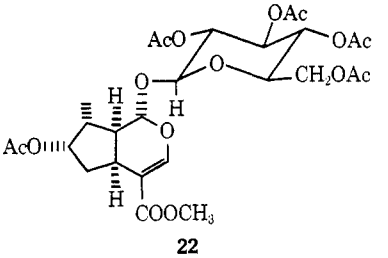

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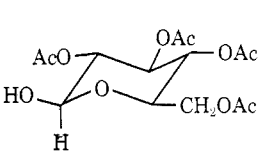
glucosidation. Rather than resolve loganol acetate **21** into optical isomers and combine the correct enantiomer with a suitable derivative of glucose, we decided to transform racemic loganol acetate **21** to a glucoside and separate the resulting mixture of diastereomers. Efforts to combine the hemiacetal **21** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide using either the original Koenigs–Knorr conditions or some more recent modifications[24] gave no trace of loganin pentaacetate (**22**). After these unsuccessful attempts we turned to a new method for the synthesis of β-glucopyranosides developed in the laboratories of Sandoz A.G.[25] It consists of treating the aglucone with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**23**) in the presence of boron trifluoride etherate at low temperature. The original β configuration in the glucose moiety is preserved in the glucoside, but the configuration at the aglucone hydroxyl group often is not because the reaction proceeds through a carbonium ion. Trying to utilize this method, a mixture of tetraacetylglucose **23** and the hemiacetal **21** were exposed to boron trifluoride etherate in 1,2-dichloroethane solution at −20°. After work-up, no loganin pentaacetate (**22**) was detectable, and we were able to account for most of the product in the form of starting materials. Since the conditions appeared to be too mild the reaction was performed at room temperature. Crystalline loganin pentaacetate (**22**) identified by ir spectrum and mixture melting point was now isolable after chromatographic purification, but in very low yield. The reasons for this are difficult to evaluate because there is no way to calculate the theoretical yield of the desired enantiomer. Several factors seem responsible. Tetraacetylglucose (**23**) is not stable under the reaction conditions used. As pointed out by its discoverers, this new glycoside synthesis gives satisfactory results when carbon–oxygen heterolysis in the aglucone yields a relatively stable carbonium ion. In the case of iridoids this ion **25** is unstable because of the electron-withdrawing effect of the α,β-unsaturated ester function, as pointed out many years ago by Schmid.[26] Carbonium ion **24**, originating from tetraacetylglucose (**23**), although capable of combining with the aglucone **21**, undoubtedly gives both α- and β-glucosides and, furthermore, is known to undergo a variety of neighboring group reactions leading to other products.[27] It will be of interest to ascertain



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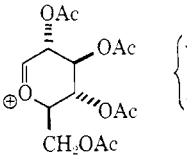

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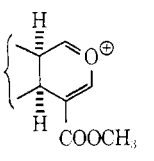

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whether the glucoside synthesis of Wulff[28] is applicable to the preparation of iridoid glucosides. The last step in the synthesis, the transformation of loganin pentaacetate (**22**) to loganin (**1**), has been accomplished previously.[7]

Experimental Section

Microanalyses were performed in the Massachusetts Institute of Technology microchemical laboratory. Melting points were determined on a hot-stage microscope and are uncorrected, as are boiling points. Reaction courses and product mixtures were routinely monitored by thin layer chromatography (tlc) or vapor phase chromatography (vpc) on a Varian Aerograph A-700 instrument. Thin layer separations were carried out on silica gel PF-254 or alumina PF-254, and visualization was by uv light or phosphomolybdic acid spray reagent. A particular mixture of silica gels for a column chromatography was selected primarily to control the flow rate of a given column. Infrared (ir) spectra were measured on Perkin-Elmer 237 and 237 B spectrometers. Ultraviolet (uv) spectra were recorded on Cary 14 and Perkin-Elmer 202 instruments. Nuclear magnetic resonance (nmr) spectra were obtained with Varian A-60, T-60, and HA-100 spectrometers and peak positions are given in parts per million downfield from tetra-

(24) R. J. Ferrier, *Fortschr. Chem. Forsch.*, **14**, 389 (1970); W. W. Zorbach and K. V. Bhat, *Advan. Carbohyd. Chem.*, **21**, 273 (1966).

(25) M. Kuhn and A. von Wartburg, *Helv. Chim. Acta*, **51**, 1631 (1968). We are indebted to Dr. A. von Wartburg for a generous supply of tetraacetylglucose.

(26) O. Halpern and H. Schmid, *ibid.*, **41**, 1109 (1958).

(27) "Rodd's Chemistry of Carbon Compounds," Vol. I, 2nd ed, part F, Elsevier, Amsterdam, 1967, p 327.

(28) G. Wulff, G. Röhle, and U. Schmidt, *Chem. Ber.*, **105**, 1111 (1972), and earlier papers in this series.

methylsilane as an internal standard. The abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet; the coupling constant (J) is measured in hertz. Mass spectra were determined at 70 eV on a Hitachi RMU-6D spectrometer, and the abbreviation M^+ signifies the molecular ion.

Preparation of 3-Cyclopentenol Tetrahydropyranyl Ether (2). A mixture of 3-cyclopentenol[15,16] (14.70 g, 0.175 mol), excess freshly distilled dihydropyran (60.00 g), anhydrous ether (150 ml), and *p*-toluenesulfonic acid (75 mg) was stirred overnight at room temperature under argon. After the addition of solid potassium carbonate, filtration, and concentration *in vacuo*, the colorless oil was filtered through a plug of alumina (200 g; ether elution) and vacuum distilled from calcium carbonate to give 27.0 g (92%) of analytically pure **2** as a colorless liquid: bp 54–55° (1.2 mm); ir (CCl_4) 1605, 1460, 1445 cm^{-1}; nmr (CCl_4) δ 5.62 (2 H, s), 4.7–4.2 (2 H, m), 4.0–3.2 (2 H, m), 2.45 (4 H, m), 1.60 (6 H, m).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.36; H, 9.71.

Methyl 3,3-Dimethoxypropionate. The following procedure was adapted from that used in the preparation of the corresponding triethyl analog.[13] A 300-ml, three-necked flask fitted with a thermometer, a ketene inlet tube, and a nitrogen inlet was charged with freshly distilled methyl orthoformate (106 g, 1.0 mol) and cooled in an isopropyl alcohol–Dry Ice bath. Freshly distilled boron trifluoride etherate (8 g, 0.06 mol) was added, and with rapid magnetic stirring ketene gas was bubbled in at a rate sufficient to maintain a reaction temperature of −40 to −45°. A total of 29.8 g (0.71 mol) of ketene was introduced in 45 min. The red reaction mixture was then stirred at −70° for 1 hr before the addition of solid sodium bicarbonate (10 g) and removal of the cooling bath. Filtration of the black reaction mixture, concentration *in vacuo*, and fractional vacuum distillation through a 10-cm Vigreux column gave 19.5 g (19%)[29] of product as a colorless liquid: bp 61–62° (9 mm); $n^{25}D$ 1.4083 (lit.[30] bp 77° (20 mm); $n^{20}D$ 1.4095); ir (CCl_4) 1750 cm^{-1}; nmr (CCl_4) δ 4.75 (1 H, t, J = 6 Hz), 3.65 (3 H, s), 3.30 (6 H, s), 2.54 (2 H, d, J = 6 Hz).

2-Formylmalonaldehydic Acid Methyl Ester (3). Panizzi's formylation procedure[14] was employed. A solution of methyl 3,3-dimethoxypropionate (14.8 g; 0.1 mol) and methyl formate (48.4 g; 0.8 mol) in dry ether (50 ml) was introduced in a stream to a mixture of sodium sand (4.6 g, 0.2 mol) in dry ether (150 ml). The mixture was stirred for 24 hr under argon at room temperature. Additional methyl formate (48.4 g; 0.8 mol) was introduced and followed by 24 hr of further stirring. The reaction mixture was then diluted with water, and the aqueous phase was made basic with 10% aqueous NaOH. After thorough washing with ether, the aqueous phase was acidified with aqueous HCl and extracted with ether. This ether extract was washed three times with saturated salt solution, dried (Na_2SO_4), and concentrated *in vacuo* to provide 14.2 g of a dark liquid. Fractional vacuum distillation of this material gave 8.9 g (68%) of diformylacetate **3** as a colorless liquid: bp 54–55° (3.5 mm); ir (CCl_4) 3300–2500 (broad), 2960, 2880, 1730, 1660, 1585 cm^{-1}; uv max (absolute ethanol) 268 nm (ϵ 7940); uv max (absolute ethanol plus base) 270, 240 nm (ϵ 12,600, 12,600); uv max (95% ethanol) 274, 244 nm (ϵ 8640, 8020); uv max (95% ethanol plus base) 278, 241 nm (ϵ 12,800, 14,900); nmr (CCl_4) δ 14.6 (1 H, broad s, exchanges with D_2O), 8.95 (2 H, s), 3.74 (3 H, s).

Anal. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65. Found: C, 46.30; H, 4.90.

Photocycloaddition Reaction. Six 10% molar solutions of diformylacetate **3** (390 mg, 3.0 mmol) in tetrahydropyranyl ether **2** (5.04 g, 30 mmol) were prepared in Pyrex test tubes capped with no-air rubber stoppers. These solutions were deoxygenated by bubbling argon through for 20 min and then irradiated for 40 hr with a 450-W Hanovia lamp. The course of the irradiation was monitored by observing the change (270 → 240 nm; absolute ethanol) in the ultraviolet spectrum. Excess acetal was removed under high vacuum at 40° and recovered, leaving a residue of 6.59 g of crude adduct **5** still containing some acetal. Spectral data of this crude material indicated formation of the cyclic hemiacetal–enol ester system: ir (CCl_4) 3600, 3400, 1710, 1635 cm^{-1}; nmr (CCl_4) singlet at δ 7.4.

Conversion of Photoadducts 5 to Hydroxyacetals 6. The crude cycloadduct **5** (6.59 g) was stirred at room temperature under argon for 18 hr in 300 ml of methanol containing 5 g of IR-120 cation-exchange resin. Filtration followed by concentration *in vacuo* left 4.43 g of an orange oil which was chromatographed on 250 g of silica gel (2:1 silica gel PF-254, silica gel 0.05–0.2 mm, Merck). Elution with benzene–ethyl acetate (1:1) provided 2.40 g (59%) of a yellow oil which was vacuum distilled in a kugelrohr apparatus to give 1.8 g (45% overall yield from **3**) of pure hydroxy acetals **6** as a colorless gum homogeneous on tlc (silica gel; 1:1 benzene–ethyl acetate): 130° (bath) (0.02 mm); ir (CCl_4) 3625, 3490, 2950, 1712, 1635 cm^{-1}; uv max (95% ethanol) 238 nm (ϵ 10,600); nmr (CCl_4) δ 7.42 (1 H, s), 4.8 (1 H, m), 4.3 (1 H, m), 3.68 (3 H, s), 3.55–3.45 (4 H, four sharp singlets which collapse to three for 3 H on D_2O exchange), 3.1–1.5 (6 H, m); mass spectrum m/e 228 (M^+).

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.98; H, 7.01.

Further elution with the same solvent gave 7% of a product whose structure was not elucidated in detail.

Oxidation of Hydroxyacetals 6 to Ketoacetals 7 and 8. The Collins' oxidation procedure[19] was employed. A solution of hydroxyacetal **6** (3.20 g; 14.02 mmol) in methylene chloride (50 ml) was added in one batch to a solution of dipyridinechromium(VI) oxide (36.2 g; 140.2 mmol) in methylene chloride (900 ml). After 1 hr the dark reaction mixture was filtered through a plug of silica gel (200 g) with the aid of ethyl acetate. Removal of the solvents *in vacuo* left 3.46 g of a yellow oil which was vacuum distilled in a kugelrohr apparatus to give 3.00 g (95%) of ketoacetals **7** and **8** as a pale yellow gum homogeneous on tlc (silica gel; 1:1 benzene–ethyl acetate): 115° (bath) (0.02 mm); ir (CCl_4) 1752, 1712, 1640 cm^{-1}; nmr (CCl_4) δ 7.4 (1 H, s), 4.95 (d, J = 3 Hz) and 4.75 (d, J = 5 Hz) (together 1 H), 3.65 (3 H, s), 3.50 and 3.40 (3 H, two singlets in ratio 3:1), 3.25–1.40 (6 H, m).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.09; H, 6.18.

This mixture of epimers crystallized and repeated recrystallization from ether gave 1.4 g of pure epimer **7**: mp 90–91.5°; ir ($CHCl_3$) 1745, 1705, 1635 cm^{-1}; uv max (95% ethanol) 236 nm (ϵ 10,200); nmr ($CDCl_3$) δ 7.50 (1 H, d, J = 1.5 Hz), 4.80 (1 H, d, J = 4.5 Hz), 3.72 (3 H, s), 3.52 (3 H, s), 3.2 (1 H, m), 2.7–2.0 (5 H, m); mass spectrum m/e 226 (M^+).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.43; H, 6.32.

Formylation of Ketone 7. A benzene solution of sodium *tert*-amyloxide (6.0 ml of a 0.82 *N* solution, 4.92 mmol) was introduced dropwise into a solution of ketone **7** (1.01 g, 4.46 mmol) and methyl formate (2.0 ml) in dry benzene (30 ml). The solution was stirred for 2 hr at room temperature under argon, and then glacial acetic acid (0.5 ml) was added. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to produce 1.46 g of an orange oil. Distillation in a kugelrohr apparatus provided 845 mg (75%) of formyl ketone as a pale yellow gum: 145° (bath) (0.02 mm); two unresolved streaks on tlc (silica gel; 9:1 benezene–ether); ir ($CHCl_3$) 3300–2700 (broad), 1705, 1680, 1635, 1605 cm^{-1}; uv max (95% ethanol) 240, 270 nm (ϵ 9800, 6000); uv max (95% ethanol plus base) 238, 298 nm (ϵ 8600, 15,200); nmr ($CDCl_3$) δ 10.8 (1 H, broad s, exchanges with D_2O), 7.53 (1 H, s), 7.48 (1 H, s), 4.82 (0.25 H, d, J = 10 Hz), 4.48 (0.75 H, d, J = 8 Hz), 3.70 (3 H, s), 3.57 and 3.48 (3 H, two singlets in ratio 3:1), 3.2–2.1 (4 H, m); mass spectrum m/e 254 (M^+).

Formation of *n*-Butylthiomethylene Ketones 9, 10, and 11. The Ireland–Marshall procedure[21] was employed. *p*-Toluenesulfonyl chloride (780 mg, 4.06 mmol) was added to a solution of hydroxymethylene ketones (1.03 g, 4.06 mmol) in dry pyridine (13 ml) chilled in an ice–water bath. The cooled reaction mixture was stirred for 30 min under argon before the addition of 1-butanethiol (0.48 ml, 4.44 mmol). The reaction mixture was stirred for 4 hr and then poured into 1% aqueous NaOH and extracted four times with ether. The organic extract was washed with 25% aqueous KOH, water, and saturated salt solution. Drying ($MgSO_4$) and concentration *in vacuo* provided 1.41 g of an orange oil which was chromatographed on 140 g of silica gel (3:1 silica gel PF-254; silica gel 0.05–0.2 mm, Merck). Elution with 19:1 benzene–ether produced first 150 mg (11%) of pure *n*-butylthiomethylene ketone **9** as a pale yellow gum unstable to distillation at 0.01 mm: ir ($CHCl_3$) 1695, 1635, 1560 cm^{-1}; uv max (95% ethanol) 231, 325 nm (ϵ 11,100, 13,400); nmr ($CDCl_3$) δ 7.52 (1 H, d, J = 1 Hz), 7.25 (1 H, d, J = 1 Hz), 4.72 (1 H, d, J = 5 Hz), 3.73 (4 H, sharp singlet overlapping an additional absorption), 3.50 (3 H, s), 2.9–2.3 (5 H, m), 1.9–0.7 (7 H, m); mass spectrum m/e 326 (M^+).

(29) Dr. J. J. Partridge of Hoffmann-La Roche, Nutley, N. J., who will publish his findings elsewhere, found that the yield in this synthesis is tripled when excess ketene is used.

(30) J. Croxall and H. J. Schneider, *J. Amer. Chem. Soc.*, **71**, 1257 (1949).

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.89; H, 6.79. Found: C, 58.51; H, 6.92.

The same solvent system next eluted 110 mg (9%) of pure *n*-butylthiomethylene ketone **10** as a pale yellow oil which could be distilled in a kugelrohr apparatus: 200° (bath) (0.01 mm); ir ($CHCl_3$) 3000, 2960, 1700, 1630, 1575 cm^{-1}; uv max (95% ethanol) 232, 314 nm (ϵ 10,500 16,300); nmr ($CDCl_3$) δ 7.55 (2 H, two overlapping singlets), 4.75 (1 H, d, J = 4.5 Hz), 3.82 (1 H, m), 3.72 (3 H, s), 3.52 (3 H, s), 3.0–2.6 (2 H, m), 2.5–2.3 (3 H, m), 1.9–0.7 (7 H, m); mass spectrum *m/e* 326 (M^+).

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.89; H, 6.79. Found: C, 59.16; H, 6.86.

Finally, the same solvent system eluted 765 mg (58%) of *n*-butylthiomethylene ketone **11** as a pale yellow gum which would be distilled in a kugelrohr apparatus: 200° (bath) (0.01 mm); ir ($CHCl_3$) 1700, 1635, 1575 cm^{-1}; uv max (95% ethanol) 237, 318 nm (ϵ 10,900; 18,000); nmr ($CDCl_3$) δ 7.72 (0.7 H, d, J = 1.5 Hz) and 7.12 (0.3 H, s), 7.58 (1 H, s), 4.70 (1 H, d, J = 7 Hz), 3.75 (3 H, s), 3.55 (3 H, two overlapping singlets), 3.2–2.6 (5 H, m), 2.5–0.8 (8 H, m); mass spectrum *m/e* 326 (M^+).

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.89; H, 6.79. Found: C, 59.16; H, 6.94.

Desulfurization of *n*-Butylthiomethylene Ketone 11. The catalyst employed was No. 22 Raney nickel (W. R. Grace Co.) and was prepared for use by successively washing twice with distilled water, methanol, acetone, and ether and then drying under argon. A solution of *n*-butylthiomethylene ketone **11** (654 mg, 2.00 mmol) in methanol (20 ml) was added to a mixture of Raney nickel (10 g) in methanol (60 ml). The mixture was stirred at room temperature under argon until tlc (silica gel; 4:1 benzene–ether) indicated complete desulfurization (2–20 hr). The reaction mixture was then filtered through a bed of Celite, and the filtrate was concentrated *in vacuo* to give 440 mg of a yellow oil. Distillation of this material in a kugelrohr apparatus provided 411 mg (86%) of methylated ketone **12** as a colorless gum, bp 115° (bath) (0.02 mm), which solidified: mp 75–85° (after one recrystallization from ether; further recrystallizations effected essentially no change); ir ($CHCl_3$) 1740, 1700, 1640 cm^{-1}; uv max (95% ethanol) 238 nm (ϵ 13,000); nmr ($CDCl_3$) δ 7.50 (1 H, s), 4.9 (0.25 H, d, J = 3 Hz) and 4.55 (0.75 H, d, J = 8 Hz), 3.70 (3 H, s), 3.52 (3 H, s), 3.3–1.8 (5 H, m), 1.12 (3 H, d, J = 7 Hz); mass spectrum *m/e* 240 (M^+).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.01; H, 6.38.

This spectral evidence in conjunction with the epimerization experiment (see below) strongly suggests that this methylated ketone is a mixture of epimers at the *C*-methyl carbon consisting of 75% of the β-methyl epimer **12** and 25% of the α-methyl epimer **13**.

On occasion the desulfurization reaction also produced small amounts (10–15%) of a much more polar component which could be readily separated from the ketone by silica gel chromatography using 9:1 benzene–ether as eluent. This material appears to be the alcohol **14** derived from further reduction of the methylated ketone **13** on the basis of its spectral features: ir ($CHCl_3$) 3600, 1700, 1635 cm^{-1}; uv max (95% ethanol) 238 nm (ϵ 10,500); nmr ($CDCl_3$) δ 7.50 (1 H, s), 5.08 (1 H, d, J = 7.5 Hz), 4.2 (1 H, m), 3.73 (3 H, s), 3.56 (3 H, s), 2.9–1.8 (5 H, m), 2.05 (1 H, sharp singlet which exchanges with D_2O), 1.17 (3 H, d, J = 7 Hz).

Formation of α-*C*-Methyl Ketone 13 by Base Treatment of Ketone 12. The epimeric mixture of ketones containing mainly **12** (350 mg, 1.46 mmol) was dissolved in 50 ml of methanolic 0.13 *N* sodium methoxide and allowed to stand for 18 hr at 0° under argon. After neutralization with glacial acetic acid, the reaction solution was poured into water and extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution, water, and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to give 348 mg of a pale yellow oil which was chromatographed on 30 g of silica gel (2:1 silica gel PF-254–silica gel 0.05–0.2 mm, Merck). Elution with 9:1 benzene–ether provided 315 mg (90%) of pure α-*C*-methyl ketone **13** as a colorless gum. This material crystallized readily but even after repeated recrystallization from ether always exhibited mp 90–110°. Two sublimations of 275 mg (70°, 0.01 mm) produced 270 mg of material, mp 75–90°. The sublimed solid when recrystallized from hexane showed mp 90–105°. However, when the melt recrystallized and the melting point was determined a second time, the material exhibited mp 90–92° (this phenomenon could be duplicated).

The sublimed material exhibited spectral characteristics identical with those of the degradation product **13** prepared from loganin: ir ($CHCl_3$) 1740, 1700, 1630 cm^{-1}; uv max (95% ethanol) 235 nm (ϵ 10,500); nmr ($CDCl_3$) δ 7.46 (1 H, d, J = 1.5 Hz), 4.96 (1 H, d, J = 2.5 Hz), 3.72 (3 H, s), 3.52 (3 H, s), 3.18 (1 H, m), 2.58 (2 H, d, J = 6 Hz), 2.3–1.9 (2 H, m), 1.14 (3 H, d, J = 6.5 Hz); mass spectrum *m/e* 240 (M^+).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.88; H, 6.34.

Preparation of 1-*O*,6-*O*-Diacetylloganol 15.[22] A mixture of loganin pentaacetate[22] (1.2 g, 2.0 mmol), acetic anhydride (14 ml), acetic acid (6 ml), and sulfuric acid (0.4 ml) was heated at 100° for 30 min under nitrogen. After cooling, water was added carefully (very exothermic reaction) to hydrolyze excess anhydride. The dark reaction mixture was then diluted with more water and extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution, water, and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to leave 1.01 g of a dark semisolid mass which was chromatographed on 70 g of silica gel (4:1 silica gel PF-254–silica gel 0.05–0.2 mm, Merck). Development with 2:1 benzene–ethyl acetate eluted first 285 mg (48%) of the diacetate **15** as a yellow oil and the 510 mg of pure glucose pentaacetate. The diacetate was distilled in a kugelrohr apparatus to provide 276 mg (46%) of diacetate **15** as a yellow gum: 135° (bath) (0.02 mm); ir ($CHCl_3$) 1750, 1730, 1705, 1640 cm^{-1}; nmr ($CDCl_3$) δ 7.52 (1 H, d, J = 1.5 Hz), 6.25 (1 H, d, J = 3 Hz), 5.32 (1 H, t, J = 4 Hz), 3.82 (3 H, s), 3.22 (1 H, q, J = 7.5 Hz), 2.65–1.6 (10 H, m, two sharp singlets at 2.16 and 2.10), 1.10 (3 H, d, J = 6.5 Hz).

Conversion of Diacetate 15 to Hydroxyacetal 16.[23] A solution of diacetate **15** (273 mg, 0.79 mmol) in methanol (30 ml) containing 0.5 ml of boron trifluoride etherate was stirred under argon at room temperature for 3 days. Then 10 ml of saturated sodium bicarbonate solution was added and the mixture concentrated *in vacuo*. The aqueous residue was diluted with water and extracted with ether. The ether extract was washed with water and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to leave 162 mg of a yellow oil. This material was distilled in a kugelrohr apparatus to provide 144 mg (76%) of a colorless gum which appeared as two incompletely resolved spots on tlc (silica gel; 2:1 benzene–ethyl acetate): 125° (bath) (0.02 mm); ir ($CHCl_3$) 3600, 1705, 1635 cm^{-1}; nmr ($CDCl_3$) δ 7.58 (1 H, d, J = 1.5 Hz), 5.04 and 4.75 (1 H, two doublets in ratio 15:85, J = 3 and 4 Hz, respectively), 4.20 (1 H, t, J = 4 Hz), 3.80 (3 H, s), 3.58 and 3.52 (3 H, two singlets in ratio 85:15), 3.1 (1 H, m), 2.75 (1 H, s), 2.6–1.5 (4 H, m), 1.14 (3 H, d, J = 6.5 Hz). The coupling constants for the acetal protons indicate a mixture containing 85% of the epimer with an α-methoxy group and 15% of the epimer with the β-methoxy group.

Oxidation of Natural Hydroxyacetal 16 to Ketoacetal 13.[23] A solution of natural hydroxyacetal **16** (140 mg, 0.58 mmol) in methylene chloride (2 ml) was added in one portion to a mixture of bipyridinechromium(VI) oxide (1.5 g, 5.8 mmol) in methylene chloride (20 ml). After stirring 15 min, the black reaction mixture was filtered through a plug of silica gel with the aid of ethyl acetate. The filtrate was concentrated *in vacuo*, leaving 125 mg of an off-white solid, mp 112–117°, which on recrystallization from ether provided 105 mg (75%) of analytically pure ketoacetal **13**: mp 118–120°; $[\alpha]^{25.5}D$ −141° (*c* 0.45, 95% ethanol); uv max (95% ethanol) 234 nm (ϵ 11,300) [lit.[7] mp 118–118.5°; $[\alpha]^{22}D$ −146° (0.33, $CHCl_3$); uv max (95% ethanol) 235 nm (log ϵ 4.06)]; ir ($CHCl_3$) 1740, 1700, 1630 cm^{-1}; nmr ($CDCl_3$) δ 7.46 (1 H, d, J = 1.5 Hz), 4.96 (1 H, d, J = 2.5 Hz), 3.72 (3 H, s), 3.52 (3 H, s), 3.18 (1 H, m), 2.58 (2 H, d, J = 6 Hz), 2.3–1.9 (2 H, m), 1.14 (3 H, d, J = 6.5 Hz); mass spectrum *m/e* 240 (M^+).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.28; H, 6.60.

Attempted Epimerization of Natural Ketone 13. A solution of natural ketone **13** (56 mg; 0.23 mmol) in methanol (25 ml) containing a small amount of sodium methoxide was stirred overnight at room temperature under argon. After neutralization with acetic acid and concentration *in vacuo*, the residue was partitioned between water and ether. The organic layer was washed with saturated sodium bicarbonate solution, water, and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo*, leaving 50 mg (95%) of an off-white solid, mp 90–112°. This material on tlc (silica gel; 3:1 hexane–ethyl acetate) showed the ketone **13** (R_f 0.25) as the principal component and lesser amounts of a more polar material (R_f 0.18). The major component obtained pure by preparative tlc exhibited mp 117–120° and spectral characteristics identical with those of the ketone **13** before base treatment. This observation agrees with that of Battersby.[7] The minor impurity obtained pure by preparative tlc was tentatively formulated as the

addition product of methanol to the enol-ester double bond from its spectral data: no uv max above 210 nm; ir ($CHCl_3$) 1740 cm^{-1}.

Deuterium Incorporation into Natural Ketone 13. A solution of sodium methoxide (0.01 mmol) in methanol-*O-d* was added to a solution of natural ketone **13** (16 mg, 0.066 mmol) in methanol-*O-d* (2 ml). The solution was stirred at room temperature for 24 hr under argon. Then an additional 0.01 mmol of sodium methoxide in methanol-*O-d* was added and stirring was continued for 24 hr. The solution was neutralized with glacial acetic acid and concentrated *in vacuo*. The residue was partitioned between ether and water, and the organic phase was washed with saturated sodium bicarbonate solution, water, and saturated salt solution. Drying ($MgSO_4$) and concentration *in vacuo* left 15 mg of a white solid, mp 112–118°, which appeared homogeneous on tlc (silica gel; 3:1 hexane–ethyl acetate). Two recrystallizations from ether gave 10 mg of small white crystals, mp 119–119.5°. The mass spectrum of this material confirmed the incorporation of three deuterium atoms, exhibiting major ions at *m/e* 243 (M^+) 212, 168, 124, 86, 85, 56, 45, 44, 40, 34, 29 [79% d_3, 19% d_2, 2% d_1 species].

Alcohol 17 from Sodium Borohydride Reduction of Ketone 13. Sodium borohydride (39 mg, 1.0 mmol) was added to a chilled (0°) solution of ketone **13** (240 mg, 1.0 mmol) in methanol (15 ml). After stirring for 30 min at 0°, the reaction mixture was neutralized with glacial acetic acid, poured into aqueous sodium bicarbonate and extracted with ether. The ether extract was washed with water and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to leave 242 mg of a yellow oil which was chromatographed on 12 g of silica gel (0.05–0.2 mm, Merck). Elution with 1:1 benzene–ether provided 235 mg which was distilled in a kugelrohr apparatus to give 212 mg (88%) of alcohol **17** as a colorless gum: 120° (bath) (0.02 mm); ir ($CHCl_3$) 3660, 3600, 1700, 1630 cm^{-1}; uv max (95% ethanol) 237 nm (ϵ 11,900); nmr ($CDCl_3$) δ 7.42 (1 H, d, J = 1 Hz), 4.74 (1 H, d, J = 5 Hz), 3.8–3.4 (1 H, m), 3.72 (3 H, s), 3.52 (3 H, s), 3.1 (1 H, sharp singlet which exchanges with D_2O), 2.95–2.3 (2 H, m), 1.9–1.25 (3 H, m), 1.12 (3 H, d, J = 7 Hz); mass spectrum *m/e* 242 (M^+).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.38; H, 7.56.

Acetate 19 from 17. Methanesulfonyl chloride (85 μl, 1.09 mmol) was added dropwise to an ice-water cooled solution of alcohol **17** (170 mg, 0.70 mmol) in dry pyridine (1 ml). Stirring was continued at 0° under argon for 1.5 hr. The reaction mixture was diluted with ether and filtered, and the filtrate concentrated *in vacuo*. The residue was extracted with ether and filtered through a plug of silica gel. Concentration of the filtrate *in vacuo* left 232 mg of a colorless gum which appeared homogeneous on tlc (silica gel, 1:1 benzene–ether) and exhibited ir ($CHCl_3$) absorptions expected for the mesylate **18**: 1700, 1635, 1440, 1360, 1340, 1290, 1175, 1085, 955 cm^{-1}.

The crude mesylate (232 mg, 0.70 mmol) was dissolved in acetone along with tetraethylammonium acetate (1.4 g, 7.4 mmol). This mixture was refluxed for 23 hr, cooled, and concentrated *in vacuo*. The residue was partitioned between ether and water. The ether extract was washed with saturated sodium bicarbonate solution, water, and saturated salt solution, dried ($MgSO_4$), and concentrated *in vacuo* to leave 195 mg of a pale yellow oil. This material was chromatographed on 18 g of silica gel (1:1 silica gel PF-254–silica gel 0.05–0.2 mm, Merck). Elution with 6:1 benzene–ether first gave 16 mg (10%) of a colorless gum which appears to be olefin **20** from its spectral characteristics: ir ($CHCl_3$) 1700, 1635 cm^{-1}; nmr ($CDCl_3$) δ 7.49 (1 H, d, J = 1.5 Hz), 5.9 (1 H, d, J = 6 Hz), 5.6 (1 H, d, J = 6 Hz), 4.58 (1 H, d, J = 6 Hz), 3.75 (3 H, s), 3.54 (3 H, s), 2.8 (1 H, m), 2.3–1.7 (2 H, m), 1.12 (3 H, d, J = 7 Hz). Further elution with the same solvent system produced 162 mg (82%) of an oil which was distilled in a kugelrohr apparatus to provide 160 mg (81%) of acetate **19** as a colorless oil, 115° (bath) (0.01 mm), which crystallized. Recrystallization of 135 mg from petroleum ether provided 126 mg of white crystals: mp 62.5–63.5°; ir ($CHCl_3$) 1730, 1700, 1630 cm^{-1}; uv max (95% ethanol) 236 nm (ϵ 11,100); nmr ($CDCl_3$) δ 7.40 (1 H, d, J = 1.5 Hz), 5.18 (1 H, m), 4.65 (1 H, d, J = 4 Hz), 3.70 (3 H, s), 3.50 (3 H, s), 3.1 (1 H, m), 2.5–1.5 (7 H, m with sharp s at 2.05), 1.05 (3 H, d, J = 6.5 Hz); mass spectrum *m/e* 284 (M^+).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.20; H, 7.42.

Methyl 6α-Acetoxy-7α-methyl-1-hydroxy-1,4aα,5,6,7,7aα-hexahydrocyclopenta[*c*]pyran-4-carboxylate (21). A mixture of 260 mg (0.92 mmol) of the acetal **19**, 40 ml of acetic acid, 20 ml of water, and 6 ml of 70% perchloric acid were heated at 50° under nitrogen for 3 hr. After cooling, 200 ml of cold saturated brine was added and the mixture was extracted with ether. The extract was washed (saturated $NaHCO_3$ solution and saturated brine), dried (Na_2SO_4), and evaporated to a yellow gum, which was purified by column chromatography (1:1 mixture of silica gel PF-254–silica gel 0.05–0.2 mm, Merck) using benzene–ether 1:1. The first fraction gave 125 mg (51%) of the hemiacetal **21** as a light yellow gum: uv max (95% ethanol) 237 nm (ϵ 9700); uv max (95% ethanol–NaOH) 274 nm (ϵ 10,800); ir ($CHCl_3$) 3400, 1740, 1710, 1640 cm^{-1}; nmr ($CDCl_3$) δ 7.40 (d, 1 H, J = 1 Hz), 5.20 (m, 1 H), 5.00 (d, ~1 H, J = 7 Hz), 3.73 (s, 3 H), 3.73 (s, 1 H, exchangeable with D_2O), 2.10 (s, 3 H), 1.07 (d, 3 H, J = 7 Hz), 1–3.5 (m, 5 H).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.75; H, 6.76.

(−)-Methyl 6α-Acetoxy-7α-methyl-1α-(2,3,4,6-tetraacetyl-β-D-glucopyranosyloxy)-4aα,5,6,7,7aα-hexahydrocyclopenta[*c*]pyran-4-carboxylate (22). To a solution of 62 mg (0.23 mmol) of the hemiacetal **21** and 174 mg (0.5 mmol) of 2,3,4,6-tetraacetyl-β-D-glucopyranose (**23**) in 5 ml of dry 1,2-dichloroethane was added under nitrogen at 0° boron trifluoride etherate (0.5 ml), freshly distilled from CaH_2. The mixture was stirred at room temperature for 4 hr, during which time 260 mg (0.75 mmol) of 2,3,4,6-tetraacetyl-β-D-glucopyranose (**23**) was added. The mixture was diluted with 50 ml of chloroform, neutralized with saturated $NaHCO_3$ solution, and extracted with chloroform. The extract was washed (water and saturated brine), dried (Na_2SO_4), and evaporated to 602 mg of a white foam, which was fractionated by thick layer chromatography (silica gel PF-254 in ethyl acetate–benzene 1:1). The second zone with R_f 0.40 was collected (96 mg) and purified further by repeated thick layer chromatography (aluminum oxide PF-254, Type E in chloroform–ether 1:1 (five times)). The first main zone was eluted giving 6 mg of an oil, which crystallized from ethanol giving 2.0 mg (1.4%) of the glucoside **22** as white needles: sample mp 137–139°; mixed with authentic sample, mp 137–139°; $[\alpha]^{22}D$ −77° (*c* 0.1, $CHCl_3$) [lit.[7] $[\alpha]^{22}D$ −79.6° (*c* 0.39, $CHCl_3$)]; ir ($CHCl_3$) 1765, 1645, 1090, 1070, 1040 cm^{-1}. The ir was identical with that of loganin pentaacetate derived from natural sources.

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