A Synthesis of Tulipalin A and B and the Acylglucoside, Tuliposide A, Fungitoxic Agents from *Tulipa gesneriana*. Carbon-13 Nuclear Magnetic Resonance Analysis of Anomeric Configuration in Acylglucosides[1]

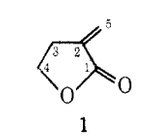
Charles R. Hutchinson

Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268

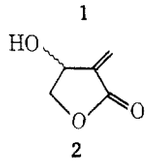
Received December 6, 1973

A synthesis of the plant antifungal agents, tulipalin A (1), tulipalin B (2), and pentaacetyl tuliposide A (5), the 1-acylglucoside of γ-hydroxy-α-methylenebutyric acid, is presented. The key steps of the syntheses involve the reductive amination of α-formyl-γ-butyrolactone (8) with dimethylamine and sodium cyanohydridoborate, indicative of a general route to α-methylenelactones. A C-13 nuclear magnetic resonance analysis of 1, 5, pentaacetyl α- and β-D-glucose, and the carbohydrate moiety of secologanin tetraacetate also is discussed. The results are indicative of a diagnostic carbon chemical shift for the anomeric carbon of peracetylated glucosides.

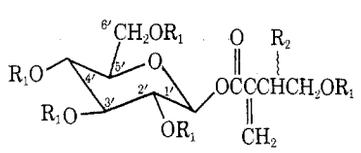
Among the many secondary natural products with biological activity that have been isolated from higher plants, there has been considerable interest recently in compounds that contain an α-methylene-γ- or -δ-lactone functional unit owing to their demonstrated cytotoxicity and tumor-inhibitory properties.[2] The simplest examples of naturally occurring α-methylene-γ-lactones are represented by tulipalin A (1) and B (*S*-2),[3] which occur



1



2



3, $R_1 = R_2 = H$
4, $R_1 = H$; $R_2 = OH$
5, $R_1 = Ac$; $R_2 = H$
6, $R_1 = R_2 = Ac$

in the common tulip *Tulipa gesneriana* L. as the 1-acylglucoside of their analogous γ-hydroxy acids, tuliposide A (3) and B (*S*-4).[4] These two lactones and perhaps also the glucosides appear to function as defensive agents against infection of the tulip plant by common pathogenic soil fungi, such as *Fusarium oxysporum*[5] and species of *Botrytis*.[6]

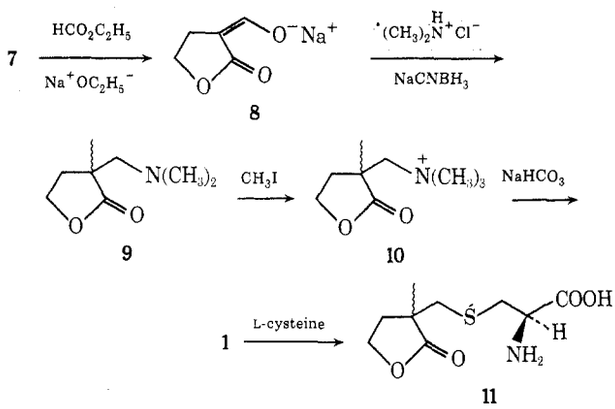
In view of the structural novelty of these glucosides[7] and a need for quantities of them for biological testing and for completion of a study of their biogenesis,[8] their synthesis was undertaken, arising out of our recently developed method for the conversion of γ- and δ-lactones to their α-methylene analogs.[1b] With the known instability of 3 and 4 to acid and base[3,4] in mind, it was decided at the outset to synthesize the glucosides as their acetates (*e.g.*, 5), which would satisfy our requirements and avoid the problem of acylglucosylating an unprotected γ-hydroxy acid with some form of D-glucose.[16]

It also was considered of interest to examine the ^{13}C nmr spectra of these novel compounds (a) to see if ^{13}C nmr assignments could allow the distinction of anomeric configuration in acylated glucosides, and (b) to establish the carbon chemical shifts of the α-methylene-γ-lactone unit.

Results and Discussion

Two syntheses of 1 had been reported at the outset of this work.[9] Jones, *et al.*,[10a] had prepared 1 in moderate yield from the reaction of but-3-yn-1-ol with nickel carbonyl in ethanol–acetic acid–water at 80°; McGraw[10b] had prepared α-hydroxymethyl-γ-butyrolactone from α-formyl-γ-butyrolactone (8) by high-pressure hydrogenation

Scheme I



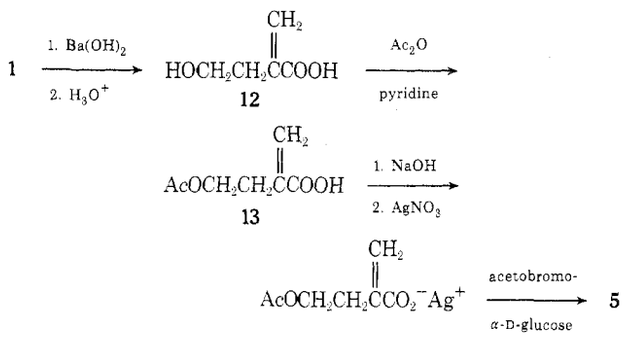
over Raney Ni, whence 1 was obtained in moderate yield by passage of the hydroxymethyl lactone over activated alumina at 340–350° to effect dehydration.

One synthesis of 1 was developed, analogous to that of McGraw.[11] However, the capricious nature of the high-pressure Raney Ni reduction and the only moderate overall yield of 1 led me to consider an alternative route that would be compatible with the instability of 1 to mineral acids and heat.[10,11] The recent discovery of the unique reductive properties of sodium cyanohydridoborate by Borch, *et al.*,[12] in particular its rapid reduction of imines and enamines at mildly acidic pH's thereby permitting a technically easy reductive amination of β-keto esters, prompted me to investigate a synthesis of 1 as shown in Scheme I.

γ-Butyrolactone (7) was formylated by standard techniques to give the sodium salt of α-formyl-γ-butyrolactone (8).[13] The dried sodium salt of 8 was reductively aminated with dimethylamine–dimethylamine hydrochloride and sodium cyanohydridoborate in dimethoxyethane at *ca.* pH 6 to give α-dimethylaminomethyl-γ-butyrolactone (9) in good yield. Quaternization of 9 with methyl iodide gave 10, which readily eliminated trimethylamine on treatment with aqueous sodium bicarbonate at room temperature to give 1 in an overall yield of 70% from 7. The nmr and ir spectral values of 1 were in complete agreement with those reported by Bergman, *et al.*[14] Although the Michael adduct (11) of 1 with L-cysteine was readily prepared as a stable, crystalline solid, an analogous reaction with 4-bromothiophenol gave a crystalline solid (mp 89–91°) that reverted to the starting materials on attempted drying *in vacuo*.

The most direct route to 2 appeared to be *via* selenium dioxide oxidation of 1 in view of the recent work of Bhal-

Scheme II



erao and Rapoport[15] on the allylic oxidation of trisubstituted olefins. A modest yield of **2** was obtained by oxidation of **1** with 1 equiv of selenium dioxide in refluxing dioxane, whereas 0.5 equiv of selenium dioxide led to considerable recovery of unreacted **1** and 2.0 equiv gave less than a 5% yield of **2** plus many other products. No reaction of **1** with selenium dioxide was seen after 24 hr in refluxing ethanol, in contrast to the greater reactivity of the *gem*-dimethyl olefins investigated by Bhalerao and Rapoport. The physical constants of **2**, purified by preparative gas chromatography, were in excellent agreement with those reported by Tschesche, *et al.*,[4] for tulipalin B, except that the C-3 and C-4 protons of **2** were seen as an AA′BB′XX′ system ($J_{AA'} = J_{BB'} = J_{XX'} \leq 0.4$ Hz) due to the racemic center at C-3.

Because of the low yield of **2** obtained by oxidation with selenium dioxide, other synthetic routes to it have been investigated. Attempted allylic bromination of **1** with *N*-bromosuccinimide gave a white, bromine-containing solid whose properties were suggestive of a polymer, in accord with the reported ease of free radical induced polymerization of **1**.[10] A similar attempted oxidation of the methyl ester of **13** (Scheme II) gave in low yield several products, none of which appeared to be the desired secondary allylic bromide.

The synthesis of **5** was achieved analogously to the recent general glycoside synthesis of Wulff, *et al.*,[16] as shown in Scheme II. Hydrolysis of **1** with barium hydroxide followed by careful acidification to pH 4 and extraction with diethyl ether gave γ-hydroxy-α-methylenebutyric acid (**12**). Acetylation of **12** with pyridine–acetic anhydride gave the γ-*O*-acetate **13**, the silver salt of which (**14**) was allowed to react with α-acetobromo-D-glucose in dry benzene at room temperature to give **5** in an excellent yield. The nmr spectral values (60 MHz) of **5** agreed well with those given for the pentaacetate of tuliposide A by Tschesche, *et al.*;[17] additional physical constants (melting point, ir, accurate mass, $[\alpha]^{26}D$) were obtained, as well as ^{13}C nmr data (*vide infra*), to fully confirm the structure of **5** and, consequently, the presence of the 1-acylglucosidic bond in naturally occurring tuliposide A. An analogous sequence of reactions aimed at obtaining **6** from **2** has not been successfully carried out thus far with the limited amount of **2** available. Apparently, the presence of traces of selenium and/or selenium oxides in samples of **2** have led to its complete, rapid decomposition on attempted acetylation, *p*-bromobenzoate derivatization, or basic hydrolysis.

The foregoing reaction sequence was anticipated to result in a β configuration at the anomeric carbon of the glucose moiety. Somewhat surprisingly, the optical rotation of **5** was negative at 589 nm, whereas the unacetylated tuliposides have positive rotations [A = +64° (*c* 1.0, H_2O); B = +56° (*c* 1.0, H_2O)][4] and most β-D-glycosides give plane positive ORD curves.[18] The ORD curve of **5** confirmed the negative rotation, and showed a negative Cotton effect with one maximum at 225 nm [$\Phi = -5.85 \times 10^3$°]. The nmr spectrum (100 MHz) of **5** revealed that the coupling constant of the anomeric proton at δ 5.78 was about 6 Hz, indicative of a β configuration;[4] however, clean resolution of its signal from that of the upfield vinyl proton was not possible at 100 MHz, thus making a definite decision impossible.

The power of ^{13}C nmr in assigning anomeric configuration among various sugars has been well documented.[19] In particular, the anomeric carbon of β-D-glucose resonates at 96.8 ppm downfield from TMS *vs.* 93.0 ppm for α-D-glucose.[20a] In both cases the resonances of the anomeric carbons fall downfield from all the other signals in the proton noise-decoupled ^{13}C nmr spectra. Hall and Johnson[20b] have shown that the anomeric center of several sugars (*e.g.*, D-glucose, D-galactose, and D-mannose) and their 1-*O*-methyl ethers has a diagnostic carbon chemical shift directly related to either the α or β anomer. The chemical shifts of the constituent carbons of **1**, **5**, α-D-glucose pentaacetate (**15**), and β-D-glucose pentaacetate (**16**) are shown in Table I. Carbons 1′–5′ of both **15** and **16** show a pronounced upfield shift, δ_c −2.5 to −4.9, which is in accord with the observed shielding of the β carbon in the alkyl group on acetylation of alcohols.[21] Carbon 6′ of **15** and **16** does not experience such a large upfield shift; the δ_c of −0.3 and −0.2, respectively, is probably indicative of some residual γ effect, however, for a small deshielding α effect (1.0–2.5 ppm) would have been anticipated.[21] If the assumption can be made that the relative δ_c of each carbon in **15** and **16** upon acetylation is of similar magnitude, then the assignments for carbons 2′, 3′, and 5′ follow as shown in Table I. Some small differences in the relative magnitude of δ_c for these carbons of **15** must occur, as two of the resonances were superimposed (tentatively, C-3′ and C-5′) at 69.9 ppm whereas in α-D-glucose they appear at 72.5 and 72.3 ppm, respectively.[22] Thus, the assignments for C-2′, C-3′, and C-5′ in **15** and **16** must be regarded as tentative. Analogous conclusions were reached by Dorman and Roberts.[20d] C-1′ of **15** has a 1.0 ppm smaller δ_c than C-1′ of **16**, which could be due to a diminished γ effect of its C-2′ acetoxyl group because of the latter's steric interaction with the axial acetoxyl at C-1′. Since the γ effect of an acetyl group has been attributed to through-space interaction, *i.e.*, shielding, of the carbonyl oxygens with the β carbon of the alkyl chain,[21] this is a reasonable explanation. Comparison of the chemical shifts for the carbohydrate moiety of **15**, **16**, and **5** shows that **5** has the anticipated β configuration at its anomeric center, for the chemical shifts of C-1′–C-6′ of **16** and **5** are within ±0.2 ppm of each other, whereas C-2′, C-3′, and C-5′ of **15** do not have such close similarity to the corresponding carbons of **5**, regardless of their relative assignments. Carbon 1′ of **5** appears at 0.5 ppm downfield of C-1′ of **16**. Although a direct explanation for this deshielding effect does not seem possible from available data,[21] some support for both the shift direction and magnitude is given by a comparison of the methyl ester carbon resonance of methyl acetate (51.0 ppm)[21] and methyl propionate (50.8 ppm)[21] to that of methyl methacrylate (51.5 ppm).[23] The downfield shift (0.5 ppm) of the latter compound from methyl acetate compares well that seen on going from the acetyl of **16** to the 4-acetoxy-2-pentenyl group of **5**.

The assignments for the carbon resonances of **1** were obtained directly from consideration of chemical shift theory and off-resonance decoupling data. They appear reasonable and are substantiated by the assignments given recently to the corresponding carbons of the trans-fused α-methylene-γ-lactone functionality of the germacranolide

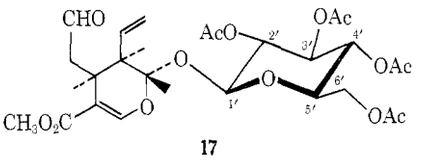
Table I

Compd	Chemical shifts, ppm[a] (δ_c)[b] C-1	C-2	C-3	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	CH_3
15						89.1 (−3.9)	69.3[c] (−2.6)	69.9[c] (−4.5)	68.0 (−2.6)	69.9[c] (−2.4)	61.5 (−0.3)	20.6
16						91.9 (−4.9)	70.5[c] (−4.7)	72.9[c] (−3.8)	68.1 (−2.5)	72.9[c] (−3.8)	61.6 (−0.2)	20.5
5	164.3	135.5	31.3	62.3	129.6	92.4	70.3[c]	72.8[c,d]	68.0	72.8[c,d]	61.5	20.5
1	170.7	134.3	27.4	65.5	121.4							
17						96.0	70.8[c]	72.6[c,e]	68.4	72.6[c,e]	61.8	20.6

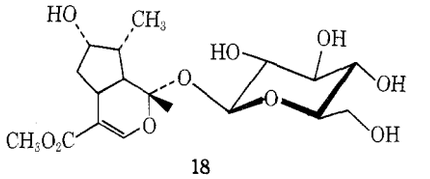
[a] In $CDCl_3$, relative to internal TMS = 0; 0.2–0.5 *M* solutions. [b] $\delta_c = \delta_{OAc} - \delta_{OH}$; δ_{OH} for α-D-glucose and β-D-glucose from ref 19, p 461. [c] Tentative assignments (see Results and Discussion). [d] Center of two resonances separated by *ca.* 0.1 ppm. [e] Center of two resonances separated by 0.16 ppm.

sesquiterpene, melampodin B.[24] The chemical shifts for the corresponding carbons of **5** were assigned from consideration of those for **1** and methyl methacrylate.[23]

In order to examine the generality of the carbon chemical shifts for anomeric configuration among acetylated glucosides, the ^{13}C nmr assignments for the glucose moiety of secologanin tetraacetate (**17**) are given in Table I.

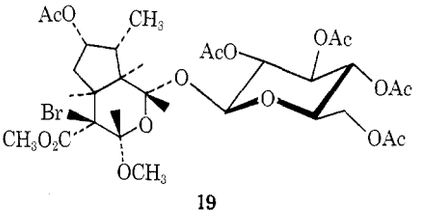


17

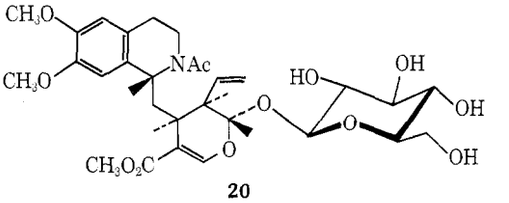


18

This compound has been shown to have the β configuration at its anomeric center by chemical means[25] and by correlation with loganin (**18**), whose absolute stereochemistry has been established by chemical[26] and X-ray[27] analysis. Since the chemical shifts for C-2′–C-6′ of **17** and **16** are within ±0.3 ppm, it appears that there is some generality among carbon chemical shifts for the carbohydrate moiety of acetylated β-D-glucosides. This is in complete agreement with the indications from work done in Hall's laboratory, particularly their recent INDOR study of several acetylated, anomeric *O*-methoxy pyranosides.[20c] Carbon 1′ of **17** has been shifted 0.8 ppm upfield from β-D-glucose. An upfield shift (0.2–0.3 ppm) of the anomeric carbon of α-D-glucose has been observed in the ^{13}C nmr spectra of sucrose, raffinose, and stachyose, wherein the glucose is linked α-1,2 to fructose.[28] The somewhat larger upfield shift for C-1′ of **17** most likely is due to the more pronounced γ effect of the dihydropyranyl oxygen. The X-ray crystallographic structures of loganin pentaacetate methoxybromide (**19**)[27] and *O,O*-dimethylipecoside (**20**)[29] both indicate that in the crystalline state conformation this oxygen would be close enough in **17** to sterically compress the carbon–proton bond at C-1′. The effect is similar to that of the axial hydroxyl in α-D-glucose on carbons 2, 3, and 5, which appear at higher fields than corresponding ones of β-D-glucose.[19] Obviously the conformation of **17** in solution may bear little similarity to that in the crystalline state, but the foregoing analysis seems reasonable in light of existing data. It also should be kept in mind that relative chemical shifts of such a small magnitude can be due to solvent-induced shifts.[30]



19



20

Experimental Section[31]

α-Formyl-γ-butyrolactone (8). Sodium hydride dispersion in mineral oil (57%, 44.0 g, 1.05 mol), contained in a dry 2-l. three-necked flask to which an addition funnel, condenser, and mechanical stirrer were attached, was washed three times with dry hexane and suspended in diethyl ether (1 l., freshly distilled from $LiAlH_4$) under nitrogen. A mixture of γ-butyrolactone (7, 86 g, 1 mol) and ethyl formate (74 g, 1 mol, dried over K_2CO_3 and distilled from P_2O_5) was slowly added to the stirred suspension, immediately following the addition of absolute ethanol (5 ml), at a rate that maintained a gentle reflux of the reaction solvent. After stirring overnight the reaction mixture was rapidly filtered by suction and the resulting solid material was washed well with dry diethyl ether and dried *in vacuo* to give the sodium salt of 8 as a light tan powder (136 g, 100%). Tlc analysis [silica gel, chloroform–methanol (9:1)] of an acidified (acetic acid) sample of this material showed only one spot (R_f 0.50).

A portion of the sodium salt was added to a vigorously stirred mixture of ice-cold 0.5 *N* HCl and diethyl ether, the resulting two phases were separated, and the aqueous phase was extracted twice with more diethyl ether. The combined organic phases were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated *in vacuo* to a pale amber, viscous oil. Rapid distillation of this oil at reduced pressure gave 8, bp 83–85° (1 mm) (lit.[10b] bp 83–85°), as a colorless, viscous liquid in low yield, which slowly solidified on standing at 0–5°. Later distillation fractions contained γ-butyrolactone (boiling point) and the odor of formic acid could be detected in the distillation residue.

α-Dimethylaminomethyl-γ-butyrolactone (9). The sodium salt of 8 (275 mg, 2 mmol) and dimethylamine hydrochloride (325 mg, 4 mmol) were suspended in dry dimethoxyethane (20 ml, distilled from $LiAlH_4$) containing Linde 3A molecular sieves (*ca.* 0.25 g). $NaCNBH_3$ (130 mg, 2 mmol[32]) was added and the reaction mixture was stirred magnetically with protection from atmospheric moisture for 24 hr. The resulting brown slurry was filtered through a Celite pad, the solid material was washed with methanol (10 ml), and the combined filtrate and wash were acidified to pH *ca.* 2 with concentrated hydrochloric acid (hood!). The resulting acidic solution was concentrated *in vacuo* to a viscous oil containing some colorless, crystalline material. The total residue was partitioned between water (15 ml) and dichloromethane (2 × 20 ml). The remaining aqueous phase was basified with solid Na_2CO_3 (pH 8.5) and extracted with ethyl acetate (3 × 25 ml), then taken to pH 10 with solid KOH and reextracted with ethyl acetate (3 × 25 ml). The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo* to give 9 as a faintly yellow liquid:[33] 231 mg (81%); bp 72–73° (0.05 mm); $n^{25}D$ 1.4565; ir (neat) 1770 cm^{-1} (lactone); nmr (60 MHz) δ 2.24 (s, 6 H), 2.40–2.80 (m, 5 H), and 4.30 (m, 2 H); hydrochloride, recrystallized from methanol–diethyl ether, mp 190–190.5°.

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.80; H, 7.86; N, 7.80. Found: C, 46.91; H, 7.84; N, 7.87.

α-Trimethylaminomethyl-γ-butyrolactone iodide (10) was prepared quantitatively by allowing 9 to react with excess methyl iodide in methanol at 25° for 24 hr. The resulting colorless, shiny plates, obtained by filtration of the reaction mixture, were recrystallized from methanol. This caused a slow decomposition to give 1 (tlc analysis). The best melting point obtained was 206–206.5°; however, the melting point ranged from 200 to 207°, regardless of number of recrystallizations. Microanalysis was not attempted.

Tulipalin A (α-Methylene-γ-butyrolactone 1). The methiodide 10 (1.96 g, 7 mmol) was added to a separatory funnel containing a mixture of 5% aqueous $NaHCO_3$ (13 ml, 1.1 equiv) and dichloromethane (20 ml). The mixture was shaken until all the solid had dissolved and the organic layer was removed; the aqueous phase was extracted with more dichloromethane (5 × 20 ml), saturated with sodium chloride, and reextracted with dichloromethane (5 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* at *ca.* 5° to a yellowish liquid. Percolation of this crude product, dissolved in a small volume of dichloromethane, through a short silica gel column followed by evaporation of the effluent gave 1 as a faintly amber liquid: 0.66 g (97%): ir (neat) 1765 (lactone), 1668 (C=C), and 810 cm^{-1} (C=CH_2); nmr (60 MHz) δ 2.98 (m, 2 H), 4.37 (t, J = 7 Hz, 2 H), 5.64 (t, J = 3 Hz, 1 H), and 6.13 (t, J = 3 Hz, 1 H); mass spectrum m/e (rel intensity) 98 (M^+, 79), 68 (M − CH_2O, 100). An analytical sample was obtained by gas chromatography on SE-30 at 150°.

Anal. Calcd for $C_5H_6O_2$: C, 61.21; H, 6.17. Found: C, 61.24; H, 6.21.

The spectral values agreed quite well with those of the literature[4] for naturally occurring tulipalin A.

Michael Adduct of 1 with L-Cysteine (11). L-Cysteine (120.7 mg, 1 mmol) was dissolved in hot water (0.6 ml), 1 (100 mg, 1 mmol) dissolved in ethanol (0.7 ml) was added along with more water (0.3 ml), and the solution was stored at 0–5° until the formation of a white solid was complete (*ca.* 1 hr). The mixture was centrifuged and, after the supernatant was discarded, the solid was washed with acetone (2 ml); the mixture was recentrifuged, and the supernatant was again discarded; the yield was quantitative. Repeated recrystallization from water–ethanol–acetone, then water–ethanol–absolute ethanol and drying (1 mm, 61°) for several hours gave the pure L-cysteine adduct of 1 as short, colorless needles: mp 192–193°; ir (KBr) 1758 cm^{-1} (lactone).

Anal. Calcd for $C_8H_{13}O_4NS$: C, 43.78; H, 5.99; N, 6.39. Found: C, 43.21; H, 5.85; N, 6.29.[34]

(*RS*)-Tulipalin B (α-Methylene-β-hydroxy-γ-butyrolactone 2). 1 (190 mg, 1.9 mmol) was dissolved in dry dioxane (25 ml, distilled from $LiAlH_4$), SeO_2 (225 mg, 2 mmol) was added, and the reaction mixture was heated at reflux for 2 hr. The warm reaction mixture was filtered through a Celite pad to remove precipitated Se and the filtrate was evaporated *in vacuo* to a dark reddish-brown gum. Plc of this crude product on silica gel in chloroform–methanol (95:5), two times, showed two major bands that turned yellow on spraying with 1% aqueous $KMnO_4$–$KHCO_3$: R_f 0.7–0.8 (starting material) and 0.3–0.4. Elution of the lower running band with chloroform–methanol (80:20) and evaporation of the solvents *in vacuo* gave a reddish-yellow, viscous oil (141 mg). Plc of this material on silica gel in chloroform–methanol (90:10) showed a major pale yellow band (R_f 0.4) contaminated with at least three minor absorbing bands. Elution of the major band as before gave crude 2 (95 mg) as a pale yellow, viscous oil. A portion of this material was purified by preparative gas chromatography on a 0.5 in × 5 ft glass column containing 15% OV-17 on Chromosorb A AW/DMCS, 45–60 mesh, at 175° and He flow of 100 ml/min; 2 was the major component (retention time 9.3 min) but four other peaks were seen, the most abundant of which was 1 (retention time 3.7 min). The spectral and analytical data were obtained on 15.9 mg of pure 2 thus obtained: ir ($CHCl_3$) 3410 (OH), 1760 (lactone), 1672 (C=C), and 830 cm^{-1} (C=CH_2, neat sample); nmr (100 MHz) δ 3.36 (br s, 1 H), 4.24 (δ_B, J_{AB} = −10, J_{BX} = 4.4 Hz, 1 H), 4.30 (δ_A, J_{AX} = 7.6 Hz, 1 H), 4.90 (δ_x, m, 1 H), 5.95 (d, J = 1.5 Hz, 1 H), and 6.34 (d, J = 2 Hz, 1 H); mass spectrum m/e (rel intensity) 114.0315 (calcd for $C_5H_6O_3$, 114.0327) (M^+, 1), 115 (M + 1, 4), 96 (M − H_2O, 15), and 84 (M − CH_2O, 100).

γ-Hydroxy-α-methylenebutyric acid (12) was prepared from 1 (150 mg, 1.5 mmol) by the procedure of Tschesche, *et al.*:[4] 80 mg (46%); colorless needles from chloroform; mp 66–66.5° (lit.[4] mp 65°).

γ-Acetoxy-α-methylenebutyric Acid (13). 12 (75 mg, 0.65 mmol) was acetylated with acetic anhydride (0.3 ml) and pyridine (0.3 ml) at 3° overnight. The reagents were removed by evaporation *in vacuo* (1 mm), the residue was reevaporated with water (5 ml) and then toluene (2 × 5 ml) to azeotropically remove the remaining traces of reagents, and the resulting gum was percolated through a short silica gel column as a chloroform solution. Evaporation of the column effluent *in vacuo* gave 13 as a colorless, viscous oil: 75 mg (73%); ir ($CHCl_3$) 1730 (CH_3COO), 1697 (COOH), and 1628 cm^{-1} (C=C); nmr (60 MHz) δ 2.03 (s, 3 H), 2.68 (t, J = 7 Hz, 2 H), 4.25 (t, J = 7 Hz, 2 H), 5.75 (d, $J \leq 1$ Hz, 1 H), and 6.39 (d, $J \leq 1$ Hz, 1 H); *p*-bromophenacyl ester, recrystallized from methanol–water, mp 76.5–77° (lit.[10a] mp 76°).

Silver Salt of 13 (14). 13 (75 mg, 0.47 mmol) was dissolved in a mixture of acetone (5 ml) and water (1 ml). The solution was adjusted to pH 7.0 (pH meter) with 0.1 *N* NaOH. Silver nitrate (87 mg, 0.5 mmol) dissolved in water (2 ml) was added to the magnetically stirred solution of the sodium salt of 13 in the dark. After 30 min the resulting suspension was cooled to ice-bath temperatures and 14 was removed by filtration, washed with ethanol (10 ml) and then diethyl ether (10 ml), and dried (25°, 0.5 mm): shiny, colorless plates; 86 mg (69%); mp 191–192° dec. An additional quantity (15 mg) of less pure 14 was obtained on concentration of the filtrate.

Tuliposide A Pentaacetate (5). 14 (47 mg, 0.18 mmol) was suspended in dry benzene (10 ml) by magnetic stirring. α-Acetobromo-D-glucose[35] (78 mg, 0.19 mmol) was added and the reaction mixture was stirred at 25° for 23 hr in the dark. The insoluble solids were removed by filtration and washed with chloroform (10 ml). Evaporation of the combined filtrates *in vacuo* gave crude 5 as a light amber oil. Plc of this oil on silica gel in chloroform–methanol (8:2) and elution of the major band (R_f 0.7) with chlo-

roform–methanol (3:1) resulted in **5** as a colorless gum: 45 mg (51%, yields of 80% were seen on larger scale runs); ir ($CHCl_3$) 1748 (ester) and 1628 cm^{-1} (C=C); nmr (60 MHz) δ 2.00 and 2.04 (s, 15 H), 2.64 (dd, J = 6 and ~1 Hz, 2 H), 4.19 (t + m, J = 7 Hz, 4 H), 5.19 (m, 3 H), 5.78 (broadened s + t, $J \cong 6$ Hz, 2H), and 6.34 (broadened s, 1 H); mass spectrum m/e 488.1504 (calcd for $C_{21}H_{27}O_{13}$, 488.1521); $[\alpha]^{26}D$ −120° (c 0.02, MeOH); ORD (c 0.0004, MeOH) [Φ] (26°) −366° (500 nm), −488° (400 nm), −732° (300 nm), −2318° (250 nm), −4392° (235 nm), −5856° (225 nm), and −5368° (220 nm).

Recrystallization of **5** from diethyl ether–hexane gave long, colorless needles, mp 97–97.5°.

Anal. Calcd for $C_{21}H_{27}O_{13}$: C, 51.62; H, 5.57. Found: C, 51.64; H, 5.59.

Acknowledgments. I would like to thank Mr. R. J. Kubarek for technical assistance and Mr. A. D. Harmon for certain experimental details. I am indebted to Professor J. A. Glasel, University of Connecticut Health Center, for his invaluable time in instruction on the use of the JEOL PFT-100 nmr spectrometer. Both of us are grateful to the NIH (RR 00639-01A2) and JEOL, Inc., for making this nmr facility available.

Registry No.—**1**, 547-65-9; 1 L-cysteine adduct, 51270-63-4; **2**, 51348-66-4; **5**, 20075-86-9; **7**, 96-48-0; **8**, 42023-16-5; 8 sodium salt, 51270-64-5; **9**, 42023-17-6; **10**, 42023-18-7; **12**, 24923-76-0; **13**, 51270-65-6; **14**, 51270-66-7; ethyl formate, 109-94-4; dimethylamine hydrochloride, 506-59-2; α-acetobromo-D-glucose, 572-09-8.

References and Notes

(1) (a) Part II in the series Reductive Amination of α-Formyl Lactones. (b) Part I: C. R. Hutchinson and A. D. Harmon, *Tetrahedron Lett.*, 1293 (1973). (c) Supported in part by the University of Connecticut Research Foundation, Grant 35-137.
(2) For leading references see (a) S. M. Kupchan, *Pure App. Chem.*, **21**, 227 (1970); (b) S. M. Kupchan, I. Ognyanov, and J. L. Moniot, *Bioorg. Chem.*, **1**, 13 (1971).
(3) J. C. M. Beijersbergen, *Recl. Trav. Chim. Pays-Bas*, **91**, 1193 (1972).
(4) R. Tschesche, F.-J. Kammerer, and G. Wulff, *Chem. Ber.*, **102**, 2057 (1969), and references cited therein.
(5) B. H. H. Bergman, *Neth. J. Pl. Path.*, **72**, 222 (1966).
(6) F. Schonbeck and C. Schroeder, *Physiol. Plant Pathol.*, **2**, 91 (1972).
(7) Acylglycosides are not commonly occurring natural products. For recent references see (a) F. R. Stermitz, W. T. Lowery, E. Ubben, and I. Sharifi, *Phytochemistry*, **11**, 3525 (1972); (b) G. Cooper-Driver and J. J. Corner-Zamodits, *Z. Naturforsch. B*, **27** 943 (1972); (c) R. Tschesche in "Pharmacognosy and Phytochemistry," H. Wagner and L. Horhammer, Ed., Springer-Verlag New York, N. Y., 1971.
(8) C. R. Hutchinson and E. Leete, *Chem. Commun.*, 1189 (1970).
(9) Another synthesis has been recently reported: P. F. Hurdlik, L. R. Rudnick, and S. R. Korzeniowski, *J. Amer. Chem. Soc.*, **95**, 6848 (1973).
(10) (a) E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 230 (1950); (b) W. J. McGraw, U. S. Patent 2,624,723 (1953); *Chem. Abstr.*, **47**, 11232 (1953).
(11) C. R. Hutchinson, Ph.D. Dissertation, University of Minnesota, Minneapolis, Minn., Dec. 1970.
(12) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93** 2897 (1971).
(13) In this case it was not possible to isolate the formylated lactone in acceptable yield by solvent extraction of its acidified aqueous solution (see Experimental Section).
(14) B. H. H. Bergman, J. C. M. Beijersbergen, J. C. Overeem, and A. K. Sijpesteijn, *Recl. Trav. Chim. Pays-Bas*, **86**, 709 (1967).
(15) U. T. Bhalerao and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 4835 (1971).
(16) G. Wulff, G. Rohle, and W. Kruger, *Chem. Ber.*, **104**, 1387 (1971); **105**, 1097 (1972).
(17) R. Tschesche, F.-J. Kammerer, and G. Wulff, *Tetrahedron Lett.*, 701 (1968), have reported the nmr chemical shifts of **5**, but no other constants.
(18) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill, New York, N. Y., 1960.
(19) J. B. Stothers, "Carbon-13 NMR Spectoscopy," Academic Press, New York, N. Y., 1972, pp 458–468.
(20) (a) D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1355 (1970); (b) L. D. Hall and L. F. Johnson, *Chem. Commun.*, 509 (1969); (c) R. Burton, L. D. Hall, and P. R. Steiner, *Can. J. Chem.*, **49**, 588 (1971); (d) D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 4463 (1971).
(21) E. Lippmaa and T. Pehk, *Eesti NSV Tead. Akad. Toim., Keem., Geol.*, **17**, 210 (1968); listed on p 150 of ref 19. This deshielding effect on the β carbon of the alkyl group of an acetate is analogous to the γ effect in hydrocarbons.
(22) H. J. Koch and A. S. Perlin, *Carbohyd. Res.*, **15**, 403 (1970).
(23) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," Wiley-Interscience, New York, N. Y., 1972, p 114.
(24) N. S. Bhacca, R. A. Wiley, N. H. Fischer, and F. W. Wehrli, *J. Chem. Soc., Chem. Commun.*, 615 (1973).
(25) A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc. C*, 1189 (1969).
(26) A. R. Battersby, E. S. Hall, and R. Southgate, *J. Chem. Soc. C*, 721 (1969).
(27) P. J. Lenz and M. G. Rossmann, *Chem. Commun.*, 1269 (1969).
(28) A. Allerhand and D. Doddrell, *J. Amer. Chem. Soc.*, **93**, 2777 (1971).
(29) O. Kennard, P. J. Roberts, N. W. Issacs, F. H. Allen, W. D. S. Motherwell, K. H. Gibson, and A. R. Battersby, *Chem. Commun.*, 899 (1971).
(30) H. H. Mantsch and Ian C. P. Smith, *Can. J. Chem.*, **51** 1384 (1973).
(31) Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Silica gel GF_{254} and PF_{254}, Merck, were used for tlc (0.25 mm) and plc (1.5 mm) chromatography. Evaporation *in vacuo* was done at <40° and at water aspirator pressures. Refractive indices were determined on a Bausch and Lomb Abbe 3L refractometer. Gas chromatography was done on a Varian 90-75 gas chromatograph. Ir spectra were determined on a Perkin-Elmer 21 double beam recording spectrophotometer or Beckman Acculab 3 infrared spectrometer. Uv spectra were determined on a Cary 14 recording spectrophotometer. Nmr spectra (60 MHz) were determined on a Perkin-Elmer R-24 spectrometer as solutions in $CDCl_3$ with TMS as internal standard; 100 MHz spectra were determined on a Jeol PFT-100 nmr spectrometer in the Fourier transform mode; carbon-13 spectra (25.1 MHz) were determined on the same instrument with a 90° pulse, pulse repetition 1.0 sec, trigger delay time 300 μsec, and 8192 data points (time domain) over a 5000-Hz sweep width downfield from an internal standard of TMS. Optical rotations were taken on a Cary 60 spectrophometer in the ORD mode or a von Rudoloph Model 80 polarimeter. Mass spectra were determined by Mr. Marv Thompson of the Chemistry Department, U-Conn, on an AEI MS-902 mass spectrometer. Microchemical analyses were determined at Baron Consulting Co., Orange, Conn.
(32) Used directly as obtained from Alfa Inorganics.
(33) Physical and spectral constants of **9** were obtained from larger scale runs.
(34) **11** as well as the L-cysteine adducts of other α-methylenelactones (A. D. Harmon and C. R. Hutchinson, unpublished observations) recrystallized as well-formed needles with melting ranges of 1°; however, tlc analysis [cellulose, 2-propanol–HCOOH–water (80:4:20)] frequently showed at least two spots, presumably due to sulfoxide formation. Consequently, microchemical analyses were not within the acceptable ±0.4% limits.
(35) Sigma Chemical Co., $[\alpha]^{26}D$ +186° (c 2, $CHCl_3$).