Chemistry of F_1,F_0-ATPase Inhibitors. Stereoselective Total Syntheses of (+)-Citreoviral and (-)-Citreoviridin

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Abstract: The polyene pyrone mycotoxin (-)-citreoviridin is a light-sensitive inhibitor of the proton-translocating mitochondrial enzyme F_1,F_0-ATPase (EC 3.6.1.3) This paper describes total syntheses of (-)-citreoviridin and of (+)-citreoviral (a fungal metabolite structurally related to the mycotoxin). The syntheses are stereoselective, and excellent stereocontrol is achieved at each stage of the work. The strategies and reagents used are of general value in approaches to polyene pyrone mycotoxins. An investigation of the photoinstability of (-)-citreoviridin revealed that the synthesis must be completed in the dark or under red light in order to obtain pure material. The discovery of the photoisomerization of this enzyme inhibitor casts doubt on the previously reported enzyme inhibitory constants for (-)-citreoviridin.

Citreoviridin, the aurovertins, and asteltoxin are pyrone derivatives of fungal origin that are potent inhibitors of mitochondrial F_1,F_0-ATPase (EC 3.6.1.3) activity.[1,2] These molecules are known heptatotoxins and hepatocarcinogens. Biological energy transduction has been hypothesized to rely on F_1,F_0-ATPase (a ubiquitous membrane-bound protein), and citreoviridin and aurovertin B have found use in investigations into the mechanism of electron transport driven phosphorylation.[3-5] We have undertaken a broad investigation into the chemistry of these intriguing molecules. This paper presents a full report on the synthesis of (+)-citreoviral and (-)-citreoviridin and describes for the first time the instability of citreoviridin under ambient laboratory light.[6,7]

Synthetic Strategy

One objective of this project was to develop a synthesis of citreoviridin that would be efficient and would make available, with little additional effort, other similar mycotoxins. The structural features shared by citreoviral (**1**), citreoviridin (**2**), citreoviridinol (**3**),[8a] isocitreoviridinol (**4**),[8a] and aurovertin B (**6**)[8c] are illustrated in Figure 1. The similarity of these molecules suggested that a well-chosen advanced intermediate for the synthesis of citreoviridin could be useful in the preparation of any of these targets. The presence of the polyene pyrone moiety is the most obvious common denominator among these metabolites. More thoughtful consideration of these structures reveals that the molecules share quite similar spatial relationships among the elements of the saturated furanoid ring and the polyene pyrone moiety. In fact, the furanoid ring and its attached atoms are present as a substructure shared by each of the mycotoxins. The isosteric relationship between aurovertin B and citreoviridin suggests that aurovertin B may be considered as a conformationally restricted analogue of citreoviridin. It was concluded that citreoviral (**1**) would be an appropriate initial target, the synthesis of which would establish the practicality of synthetic approaches to citreoviridin (**2**), citreoviridinol (**3**), isocitreoviridinol (**4**), and aurovertin C (**5**).[8b] Citreoviral thus became our initial target.[9]

The general scheme for the syntheses is illustrated in Figure 2. On the basis of considerations put forward in the preceding paragraph, the furanoid intermediate A was conceived as an appropriate advanced intermediate for the synthesis of either (-)-citreoviridin (via (+)-citreoviral) or the aurovertins. Such furanoid systems may be prepared by cyclization of an acyclic precursor or by manipulation of one of many readily available furanoid starting materials. The interesting challenge of generating the four contiguous stereogenic centers in this molecule might therefore be confronted in the context of acyclic substrates and perceived as an exercise in acyclic stereocontrol and stereospecific cyclization. In the past few years a number of syntheses of citreoviral and one synthesis of citreoviridin have been completed, and these syntheses were all based on acyclic intermediates.[9]

We chose to eschew the use of acyclic intermediates and to confront the challenges inherent to the task of constructing citreoviridin from a furanoid starting material. The key intermediate A was to be prepared from 2,3-*O*-1-methylethylidene-D-ribonolactone (**7**). This lactone is a practical starting point for the synthesis in that it is readily available in quantity, is of known absolute configuration, and contains two of the stereogenic carbon atoms required for the preparation of the key intermediate. It was expected that intermediate A would be easily converted into citreoviral. Citreoviral, in turn (or some protected derivative of citreoviral), was envisioned as a necessary intermediate for the synthesis of (-)-citreoviridin. Finally, it was also expected that an analogue of the key intermediate A would serve as a reasonable starting point for the synthesis of aurovertin B and the citreoviridinols.

The preparation of the key intermediate (A, Figure 2) requires that two new stereogenic centers be created. Our expectation was that the bicyclic structure of lactone **7** would result in excellent stereocontrol during formation of the two new carbon-carbon bonds at C-5 (citreoviridin numbering scheme, Figure 1). The task of forming the tertiary alcohol at C-3 was to be confronted only after the introduction of the side chains at C-5. This order of events would allow the carboxylic acid (or some longer side

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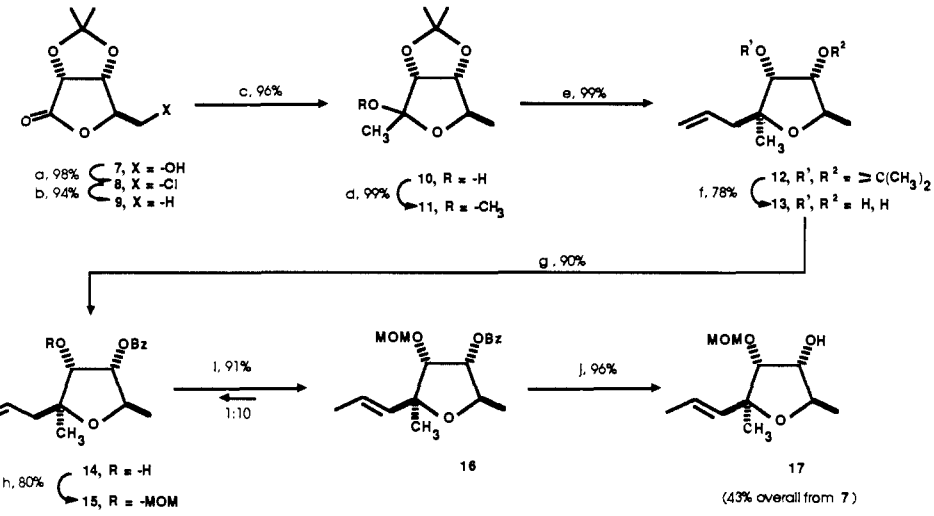
Scheme I[a]



[a](a) $(COCl)_2$-DMF, CH_2Cl_2; (b) *n*-Bu_3SnH, $C_6H_5CH_3$; (c) MeLi, Et_2O, -23 °C; (d) MeOH, *p*-TSA, $(CH_3)_2C(OCH_3)_2$; (e) CH_2=$CHCH_2$-$Si(CH_3)_3$, $ZnBr_2$, $ClCH_2CH_2Cl$; (f) MeOH-H_2O, HCl; (g) C_6H_5COCl, C_6H_5N, -47 °C; (h) CH_3OCH_2Cl, $C_6H_5N(CH_3)_2$, CH_2Cl_2; (i) $(PhCN)_2PdCl_2$, C_6H_6, 80 °C; (j) $NaOCH_3$, $HOCH_3$.

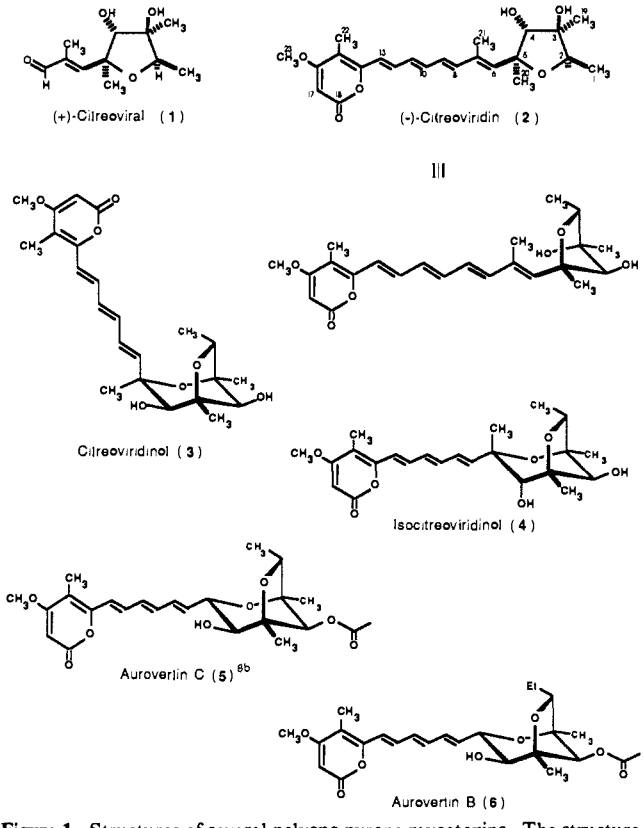


Figure 1. Structures of several polyene pyrone mycotoxins. The structure of aurovertin C has not been established.[8b]

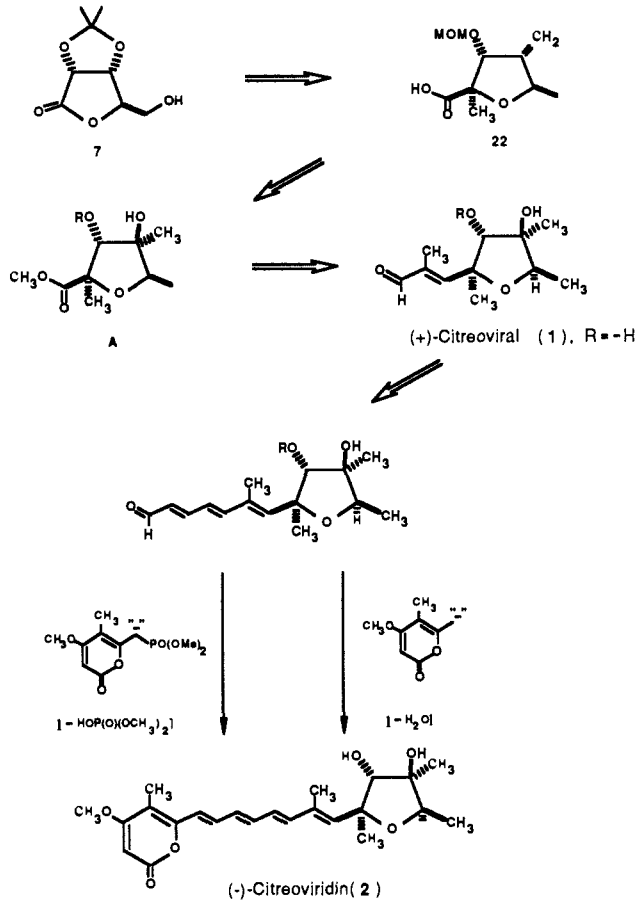


Figure 2. Overview of the synthetic strategy.

chain) in **22** (Figure 2) to play a role in directing the introduction of the tertiary hydroxyl group. The plan therefore begins with a furanoid starting material and maintains the furanoid ring throughout the synthesis. This strategy allows the compact functionality of the target system to be used to good advantage at each stage of the synthesis and ultimately has resulted in the first highly stereocontrolled synthesis of citreoviridin.

Results and Discussion

(1) Synthesis of Intermediate A. The transformation of lactone **7** into intermediate A (Figure 2) can be ordered in four distinct stages: (1) deoxygenation at C-5; (2) stereospecific dialkylation at C-1; (3) differentiation of the C-2 and C-3 hydroxyl groups; (4) construction of the tertiary alcohol at C-3 with the correct relative configuration. Preparation of intermediate A provides a key component for syntheses of (+)-citreoviral and (-)-citreoviridin and for the synthesis of aurovertin C and the citreoviridinols.

The starting material 2,3-*O*-1-methylethylidene-D-ribono-1,4-lactone (**7**)[10] was treated with oxalyl chloride in the presence of *N,N*-dimethylformamide to afford chloride **8** (Scheme I) in 98% yield.[11] An alternative transformation utilizing sulfuryl chloride

(10) Hough, L.; Jones, J. K. N.; Mitchell, D. L. *Can. J. Chem.* **1958**, *36*, 172.

in the presence of pyridine[12] gave the same chloride **8** but in slightly lower yield (88%). Reductive dehalogenation of the chloride **8** was effected with tri-*n*-butyltin hydride in the presence of AIBN to afford the 5-deoxyribose derivative **9** in 94% yield.[12d]

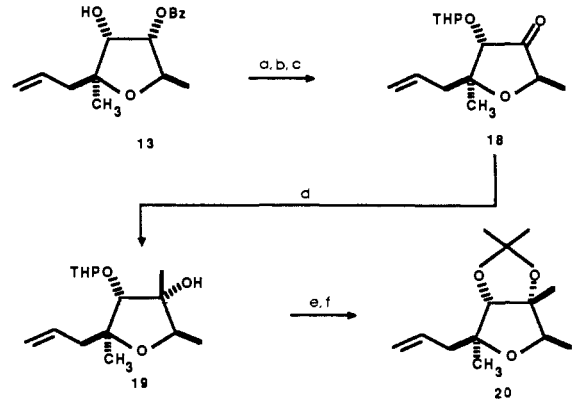
Citreoviral, citreoviridin, and aurovertin B can be considered as molecules in which two alkyl groups are attached at a carbon adjacent to the oxygen of a saturated furanoid or pyranoid ring. These molecules are thus related to the *C*-glycosides.[13] Whereas a number of methods are known for the preparation of *C*-glycosides wherein one carbon–carbon bond is present at the anomeric carbon, methods for stereospecific preparations of carbohydrate derivatives with two alkyl groups at the anomeric position have not been extensively explored.[11b,14]

The process used here for dialkylation at C-1 (ribose numbering) begins with an addition of methyllithium to lactone **9** at −23 ± 2 °C to afford hemiketal **10** in 96% yield.[15] Treatment of this hemiketal **10** with methyl alcohol and *p*-toluenesulfonic acid in the presence of 2,2-dimethoxypropane provided the ketal **11** in 99% yield and set the stage for the introduction of a second carbon–carbon bond at C-1. The ketal **11** was treated with trimethylallylsilane and zinc bromide in 1,2-dichloroethane to afford in 99% yield the allylated product **12** as a single isomer as judged by 360-MHz NMR spectral analyses.[16] The overall transformation is quite efficient. In three steps two carbon–carbon bonds are generated. That the new carbon–carbon bond is formed exocyclic to the trioxabicyclo[3.3.0]octane ring system was established in our previous work on a similar system and was verified by the further transformations of this intermediate.[15] The acetonide protecting group was removed by using aqueous 4 N hydrochloric acid in methyl alcohol to provide the corresponding diol **13**. The doubly alkylated and protected C-glycoside (**12**) is thus available in just six steps and 85% overall yield from D-ribono-1,4-lactone. With this success in hand, attention turned next to the possibility of differentiation of the C-2 and C-3 hydroxyl groups and introduction of the remaining stereogenic center.

A number of methods were tested in an effort to selectively oxidize the diol **13** to afford a hydroxy ketone appropriate for the synthesis of the C-3 tertiary alcohol. Swern's method was applied to the oxidation of diol **13**, but no selectivity was achieved and the yields were low.[17] In another system, Fuchs explored with some success the problem of selective diol oxidation.[18] We found no effective means for oxidation of diol **13** to a single hydroxy ketone, and therefore a sequence involving selective hydroxyl protection was evaluated.

Selective protection of diol **13** was achieved through benzoylation using benzoyl chloride and pyridine at −35 ± 2 °C to give **14** in 90% yield. A plan to protect the resulting hydroxybenzoate **14** with 2-(methoxyethoxy)methyl chloride (MEM-Cl) could not be reduced to practice, as protection was not obtained with up to 5 equiv of MEM-Cl[19] in the presence of *N,N*-diisopropylethylamine and potassium iodide. A successful alkylation with bromomethyl methyl ether in the presence of dimethylaniline afforded the protected olefinic benzoate **15** in 80% yield. The choice of base for this alkylation was critical: diisopropylethylamine in methylene chloride catalyzed a rapid (incomplete) migration of the benzoate from the C-3 hydroxyl to the C-2 hydroxyl. Under similar conditions, no migration was observed with pyridine or with dimethylaniline. Isomerization of olefin **15** was accomplished with bis(benzonitrile)dichloropalladium in benzene to provide a mixture of **16** and **15** (10:1) in 91% yield.[20] The benzoyl group was removed by using sodium methoxide in methyl alcohol to prepare alcohol **17** in 43% overall yield from **7**.

Scheme II[a]



[a] (a) DHP, PPTS, CH_2Cl_2, 25 °C; (b) $NaOCH_3$–$HOCH_3$, 25 °C; (c) DMSO–$(COCl)_2$, −60 °C; (d) CH_3Li, CH_3MgBr or $(CH_3)_3Al$; (e) $(CH_3)_2(OCH_3)_2$, $CH_3(CO)CH_3$, HCl, 25 °C.

The challenge of introducing the tertiary alcohol at C-3 was now at hand. In preliminary experiments we examined nucleophilic additions to ketone **18** (Scheme II), which was obtained from hydroxybenzoate **14** by conventional procedures. Given the fact that of the many nucleophilic additions to furanoid ketoses, almost all proceed by addition of the nucleophile anti to an adjacent alkoxy substituent, this approach was thought unlikely to succeed.[21] Indeed, it was observed that additions of trimethylaluminum, methyllithium, or methylmagnesium bromide to ketone **18** gave only tertiary alcohol **19**, the undesired isomer. The fact that this tertiary alcohol was of the wrong configuration for the synthesis of the target mycotoxins was proven by the fact that acetonide formation to provided ketal **20** was easily accomplished following removal of the THP protecting group.

Thus faced with evidence that a construction of the tertiary alcohol via the ketone was unlikely to succeed, we turned our attention to an approach based on lactone formation via cyclization. The introduction of the desired tertiary alcohol might have been achieved through reaction of an exocyclic methylene group with an oxirane-forming reagent and ring opening of the oxirane with a hydridic reagent. This process has been frequently employed in the preparation of branched-chain carbohydrates. An attractive alternative was made feasible by the possibility that at this stage of the synthesis a carboxylic acid can be conveniently unmasked in close proximity to the ketone or methylene group at C-3. An oxidative cyclization process using either halonium ions or mercurinium ions might lead to the stereocontrolled introduction of the C-3 oxygen atom through an intramolecular process.

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(20) Sakurai, H.; Hosomi, A. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

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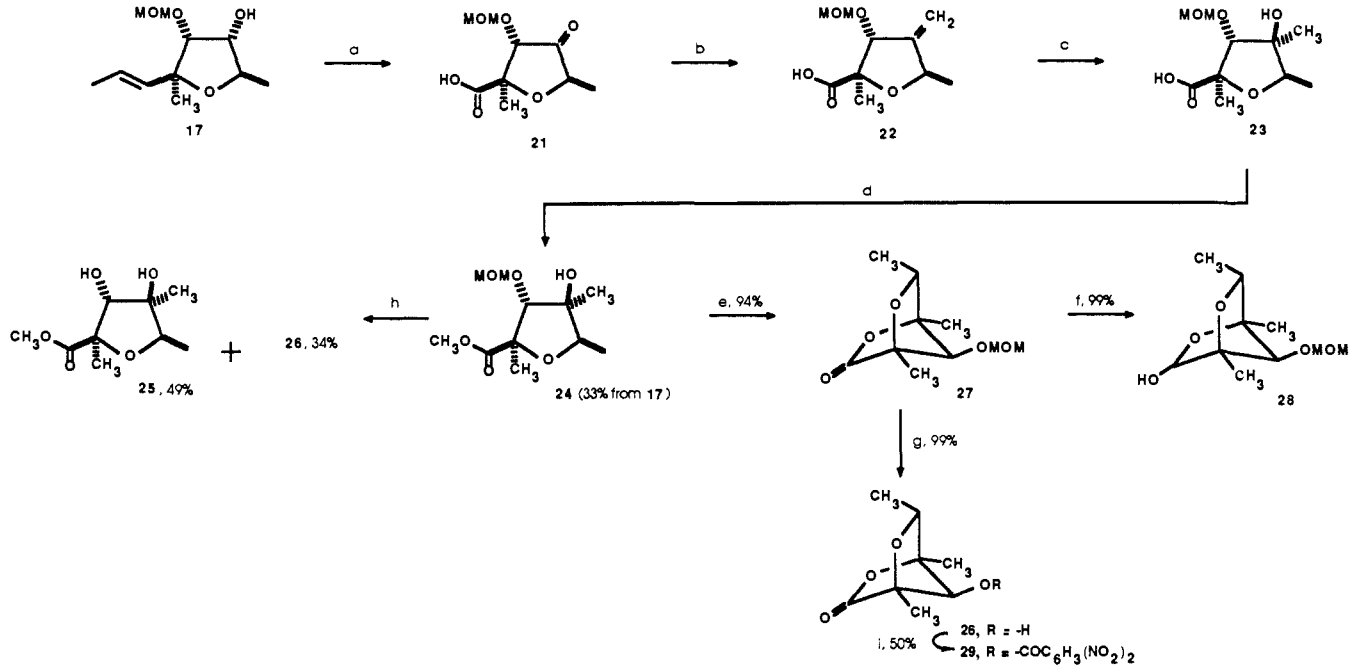
Scheme III[a]



[a] (a) $RuCl_3$–$NaIO_4$, H_2O–CH_3CN–CCl_4; (b) $Ph_3P{=}CH_2$, THF; (c) $Hg(OAc)_2$, THF–H_2O, then $NaBH_4$–OH^-; (d) CH_2N_2; (e) DBU, C_6H_6; (f) DIBAL–hexane, CH_2Cl_2, −78 °C; (g) $BF_3{\cdot}Et_2O$, $HSCH_2CH_2SH$, CH_2Cl_2, 0 °C; (h) THF, 10% HCl–H_2O; (i) $C_6H_3(NO_2)_2COCl$, C_6H_5N, DMAP.

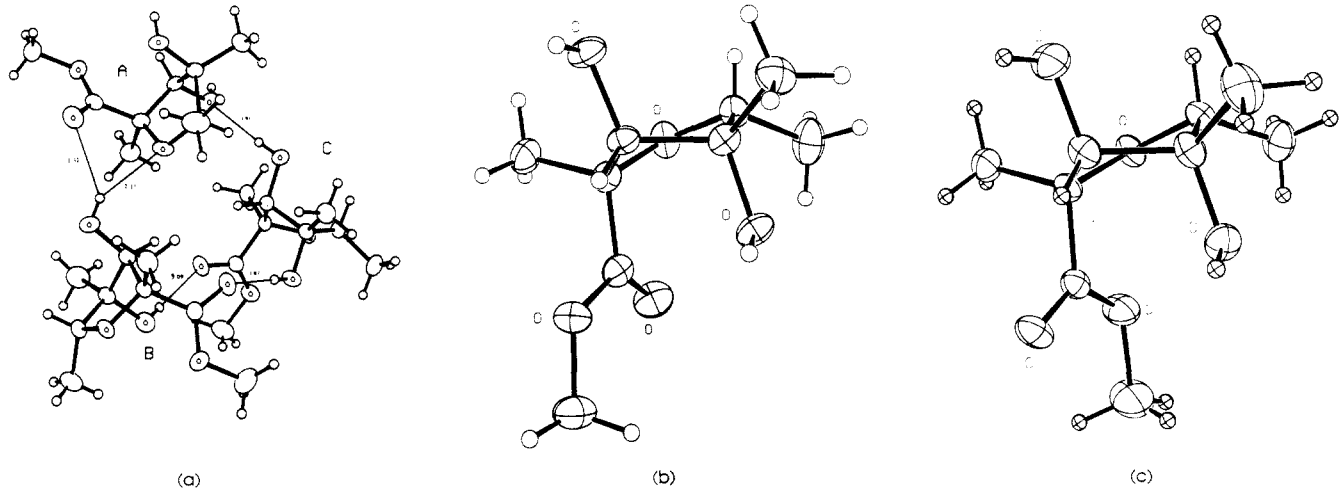


Figure 3. Structures for diol **25** as determined by X-ray crystallography. Three distinct molecules form a hydrogen-bonded triad (a). Molecule A of the triad (b) and molecule B of the triad (c) are shown separately.[23]

It was perceived that the two oxidations that would be necessary in order to arrive at the desired intermediate might be easily carried out in a single process. This potential was realized in a key step in which hydroxy olefin **17** (Scheme III) was oxidized to **21** by using sodium periodate and ruthenium chloride trihydrate in 3:2:2 ratio of water, carbon tetrachloride, and acetonitrile in 86% yield.[22] The keto acid **21** was converted to alkene **22** in 87% yield by a Wittig reaction using methyltriphenylphosphonium bromide and *n*-butyllithium. The synthesis of the olefinic acid (**22**) was in this way readily accomplished.

Finally, the required tertiary alcohol was constructed from this olefinic acid. Acid **22** was treated with mercuric acetate in water and THF followed by sodium hydroxide solutions and sodium borohydride to afford compound **23** in 63% yield. Carboxylic acid **23** was converted to methyl ester **24** in 70% yield. The methoxymethyl group was removed from **24** by using 10% aqueous hydrochloric acid in THF to afford a mixture of dihydroxy ester **25** (49% yield) and hydroxy lactone **26** (34% yield).

The key furanoid component (A, Figure 2) was thus prepared in 13% overall yield from D-ribono-1,4-lactone. The result of an X-ray diffraction analysis for diol **25** is shown in Figure 3.[23] There are a few interesting features of this structure that are worth further discussion. It was found that the unit cell contained three distinct molecules of the diol. Each of the crystallographically nonequivalent molecules had the same relative and absolute configurations. The three molecules formed a trimer (Figure 3a), and a packing diagram (not shown, but see ref 23) reveals that the trimer units are hydrogen bonded along both the A and B axes. Molecules A–C of the trimer have been labeled. In Figure 3b and 3c two of these molecules (A and B) are depicted. The conformation of molecule C is very similar to that of molecule B, and in both B and C the ester carbon–oxygen double bond is nearly antiperiplanar to the endocyclic carbon–oxygen bond. In contrast, the corresponding dihedral angle in molecule A is quite different, and the carbonyl double bond nearly eclipses the adjacent endocyclic carbon–oxygen bond. This eclipsed conformation is

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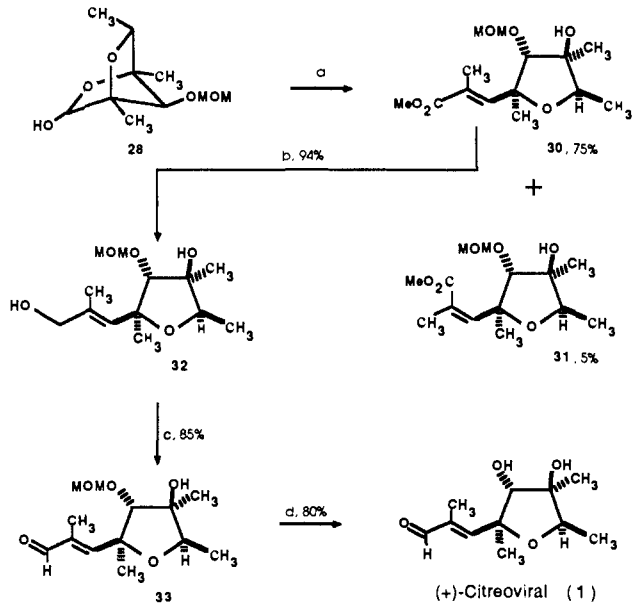
(23) Larson, S. B.; Suh, H.; Wilcox, C. S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C41*, 1095–1097.

Scheme IV[a]



[a](a) $Ph_3P{=}C(CH_3)CO_2CH_3$, C_6H_6; (b) DIBAL–hexane, CH_2Cl_2, −78 °C; (c) PDC, DMF; (d) THF, 10% HCl–H_2O.

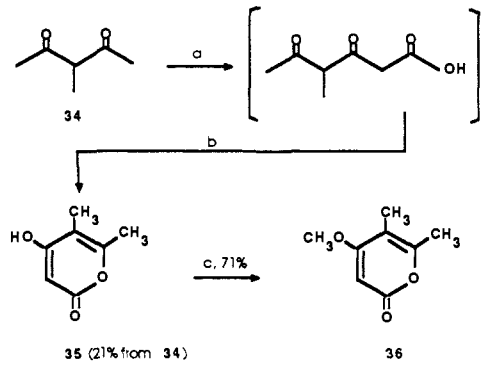
apparently stabilized by a bifurcated hydrogen bond. Critical distances are labeled in the figure.

Of relevance to this synthesis is the fact that the X-ray data also reveal that the tertiary hydroxyl group and the ester carbonyl carbon atom are quite close together. The oxygen to carbon distance is 2.693–2.730 Å. The significance of the enforced propinquity of these atoms was revealed during our attempts to attach the tetraene side chain to this tetrahydrofuranoid nucleus (vide infra).

(2) Preparation of (+)-Citreoviral. For the synthesis of (+)-citreoviral an efficient method of reducing ester **24** to provide an aldehyde or lactol was required. Through further experimentation it was therefore established that cyclization of ester **24** by a catalytic amount of diazabicyclo[5.4.0]undec-7-ene (**DBU**) in the presence of molecular sieves in benzene (Scheme III) and removal of the methoxymethyl protecting group provides hydroxy lactone **26** in 93% overall yield. Lactone **27** (still bearing the methoxymethyl protecting group) was reduced with diisobutylaluminum hydride to form lactol **28** in 99% yield. This lactol was soon to be converted to citreoviral, but before proceeding with this route, additional proof of the structural correspondence between these intermediates and the natural products was sought. For that purpose, the hydroxy lactone **26** was acylated with 3,5-dinitrobenzoyl chloride and pyridine in the presence of 4-(dimethylamino)pyridine to give dinitrobenzoate **29**. It was reassuring to find that data for these lactones **26** and **29** compared well with spectroscopic data obtained for two degradation products from citreoviridin.[2b]

Lactone **27** is a practical advanced intermediate that could be used for preparation of the citreoviridinols, citreoviral, or citreoviridin. The completion of the preparation of (+)-citreoviral is outlined in Scheme IV. Lactol **28** was treated with the stabilized ylide 2-(triphenylphosphoranylidene)propanoate to afford unsaturated esters **30** and **31** in 80% yield. The ratio of products obtained was 15:1 (*E* to *Z*). A differential nuclear Overhauser enhancement experiment established that the major product was **30**, the *E* isomer. Irradiation of the vinylic proton in **30**, the major isomer, resulted in pronounced enhancements of the signal due to the proton at C-4 (citreoviridin numbering scheme, Figure 1), a strong effect on the homoallylic group, and very little effect on the signal due to the allylic methyl group. Irradiation of the vinylic proton in **31**, the minor isomer, resulted in pronounced enhancements of the signal due to the proton at C-4, and in contrast to the result with **30**, the allylic methyl group resonance was enhanced.

Scheme V[a]



[a](a) $NaNH_2$, NH_3, then CO_2, Et_2O; (b) HF; (c) $(CH_3O)_2SO_2$, K_2CO_3, 2-butanone.

Ester **30** was converted to allylic alcohol **32** in 94% yield by using an excess of diisobutylaluminum hydride. Alcohol **32** was oxidized with pyridinium dichromate to afford the α,β-unsaturated aldehyde **33** in 85% yield. Finally, the penultimate intermediate was deprotected by using 10% aqueous hydrochloric acid to provide (+)-citreoviral (**1**) in 80% yield. Spectroscopic data for this synthetic (+)-citreoviral (**1**) are identical with that reported by Yamamura for the natural material.[24]

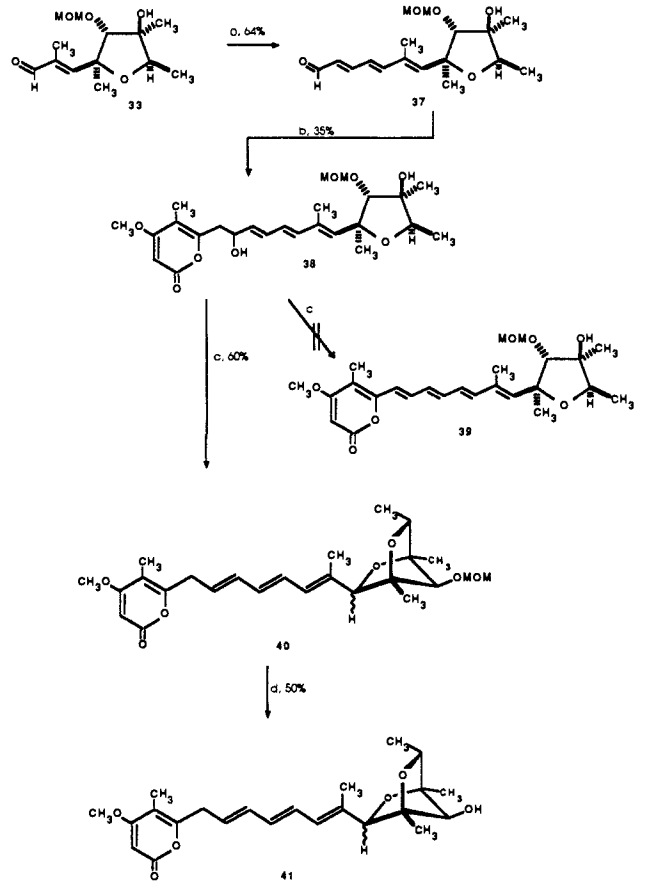
(3) Synthesis of (−)-Citreoviridin. Citreoviral has been converted by Yamamura et al. to citreoviridin in four steps and about 4% yield. An improved synthesis of citreoviridin was desired, and therefore two approaches to the polyene pyrone mycotoxin were examined. The first approach to be examined was based on the synthesis of asteltoxin reported by Schreiber and Sakate.[9g] These workers had observed that 5,6-dimethyl-4-methoxy-2-pyrone could be deprotonated at the C-6 methyl group and the resulting anion will react with an unsaturated aldehyde. Dehydration of the resultant secondary alcohol provided the desired 6-alkenylpyrone moiety of asteltoxin.[9g] For reasons soon to be revealed, this approach is not practical for the preparation of citreoviridin from citreoviral.

Before turning to the results of the first approach to attaching the side chain, the synthesis of the pyrone moiety must be described. There are several ways to prepare 5,6-dimethyl-4-methoxy-2-pyrone (**36**).[26-28] We adapted a general synthetic approach to polyketides that had been developed by Harris and Harris to the synthesis of 4-hydroxy-5,6-dimethyl-2-pyrone (**35**) (Scheme V). Readily available 3-methyl-2,4-pentanedione (**34**) was treated with sodium amide to afford the corresponding dicarbanion, to which carbon dioxide was added. The resulting carboxylic acid was treated directly with hydrogen fluoride to generate 4-hydroxy-5,6-dimethyl-2-pyrone (**35**) in 21% yield from the pentane dione. The hydroxypyrone **35** was methylated by dimethyl sulfate and potassium carbonate to afford 5,6-dimethyl-4-methoxy-2-pyrone (**36**) in 71% yield.[28]

As shown in Figure 2, selective anion formation at C-6 (of **36**) by the use of lithium diisopropylamide with hexamethylphosphoramide was envisioned to provide access to a crossed aldol condensation product and thus connect pyrone **36** with the target trienal.[29] To test this idea, methoxymethyl-protected citreoviral **33** was converted to trienaldehyde **37** (Scheme VI) and coupled with the activated pyrone to provide the diol **38**. Wollenberg's process employing 1-(tributylstannyl)-4-ethoxybutadiene and *n*-butyllithium was used to convert the methoxymethyl-protected citreoviral **33** to trienaldehyde **37** in 64% yield.[30] 4-Methoxy-

(24) Shizuri, H.; Nishiyama, S.; Imai, D.; Yamamura, S.; Furukawa, H.; Kawai, K.; Okada, N. *Tetrahedron Lett.* **1984**, *25*, 4771.
(25) Harris, T. M.; Harris, C. M. *J. Org. Chem.* **1966**, *31*, 1032.
(26) Suzuki, E.; Sekizaki, H.; Inoue, S. *J. Chem. Res. Synop.* **1977**, 200.
(27) Suzuki, E.; Katsuragawa, B.; Inoue, S. *J. Chem. Res., Synop.* **1982**, 224.
(28) Suzuki, E.; Hamajima, R.; Inoue, S. *Synthesis* **1975**, 192.
(29) Bloomer, J. L.; Zaidi, S. M. H.; Strupczewski, J. T.; Brosz, C. S.; Gudzyk, L. A. *J. Org. Chem.* **1974**, *39*, 3615.

Scheme VI[a]

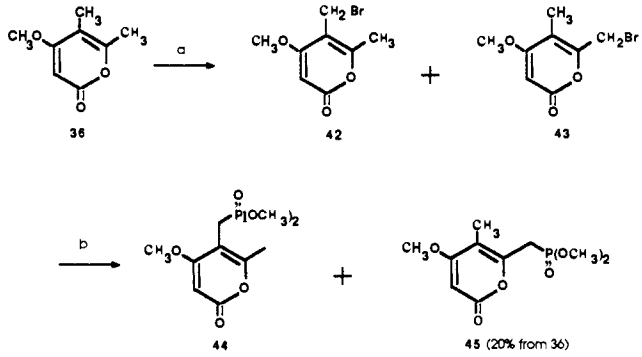


[a] (a) EtOCH=CHCH=C(H)Li, THF, −78 → −45 °C, then SiO_2; (b) **36**, LDA, THF–HMPA, −78 → +23 °C; (c) *p*-TsCl, TEA, DMAP, CH_2Cl_2, 23 °C; (d) THF, 10% HCl–H_2O.

5,6-dimethylpyrone (**36**) was treated with lithium diisopropylamide in the presence of hexamethylphosphoramide to form the required anion,[9g] and subsequent addition of trienaldehyde **37** provided diol **38** in 35% yield. In an attempt to dehydrate the allylic alcohol and generate the target tetraene, the alcohol **38** was treated with *p*-toluenesulfonyl chloride in the presence of 4-(dimethylamino)pyridine and triethylamine.[31] It was expected that the major product of dehydration would be **39**, a methoxymethylated derivative of citreoviridin. It was soon determined, however, that the product in hand was not **39** but instead an alternative dehydration product, the bicyclic system **40** (a mixture of two isomers in 6:4 ratio), had been obtained in 60% yield. The tertiary alcohol was apparently reacting with the adjacent olefin or a cationic intermediate. This result is consistent with the X-ray data for **25** (vide supra), which had revealed that the hydroxyl group and the side chain are likely to be quite close. The result of such an intramolecular reaction was the two isomeric [2.2.1]bicyclic products, **40**. The methoxymethyl group was removed from these isomers (the isomers were not separated) by using 10% aqueous hydrochloric acid in THF to provide major isomer **41** in 50% yield. Evaluation of the ^{13}C NMR and ^1H NMR data revealed that citreoviridin (**2**) was not formed in any amount. Under the conditions of dehydration the tertiary alcohol had formed a bond to the closeby (Figure 1) olefinic carbon. Attempts to convert the product **41** to (−)-citreoviridin gave no encouraging results, and this route to citreoviridin was therefore abandoned.

A solution to this problem of cyclization appeared to lie along a path requiring a modified pyrone synthon. The use of an anion derived from the pyrone *phosphonate* illustrated in Figure 2 promised to allow olefin formation under conditions not likely to result in cyclizations involving the tertiary hydroxyl group. To test this possibility, dimethyl phosphonate **45** was prepared from 5,6-dimethyl-4-methoxy-2-pyrone by bromination and treatment of the resulting mixture of 5-bromomethyl and 6-bromomethyl products (**42**, **43**) with trimethyl phosphite. The phosphonates (**44**, **45**) were separated, and the desired 6-phosphonic acid derivative (**45**) was isolated in 20% overall yield (Scheme VII).

Scheme VII[a]



[a] (a) NBS, $(C_6H_5CO)_2O_2$, CCl_4; (b) $(CH_3O)_3P$, $C_6H_5CH_3$.

With the crucial pieces now in hand, the completion of the synthesis of citreoviridin seemed imminent. Dimethyl phosphonate **45** was constructed so as to allow formation of the tetraene without generation of an intermediate likely to react (intramolecularly) with the tertiary alcohol. In this way formation of byproducts similar to **40** was to be avoided. In the event, dimethyl phosphonate **45** (Scheme VIII) was treated with lithium diisopropylamide in the presence of hexamethylphosphoramide, and to the resulting anion was added trialdehyde **37**. This sequence was indeed successful and provided **39**, methoxymethyl-protected (−)-citreoviridin, in 36% yield. Once again, however, we were to be frustrated on a close approach to our objective. Treatment of this methoxymethyl-protected citreoviridin **39** with 10% aqueous hydrochloric acid or under other conditions of deprotection gave a large number of unidentified products and none of the desired natural product.

This experiment revealed that it would be necessary to remove the methoxymethyl protecting group before coupling the two moieties. The synthesis would either be completed without protecting groups, or a protecting group removable under basic conditions would be required. To examine the first possibility, the deprotection of methoxymethyl ether **37** was attempted (Scheme VIII). The diol **46** was indeed obtained by deprotection of **37**, but in only 22% yield. It had already been shown that methoxymethyl-protected citreoviral **32** can be deprotected with a much better yield (80%). An attempt was therefore made to convert citreoviral (**1**) to trienaldehyde **46**. Synthetic citreoviral was treated with Wollenberg's reagent (vide supra) under a variety of conditions, but the yield of the trienaldehyde was unacceptably low. In addition to the desired product (25%), 23% of the starting material was recovered.

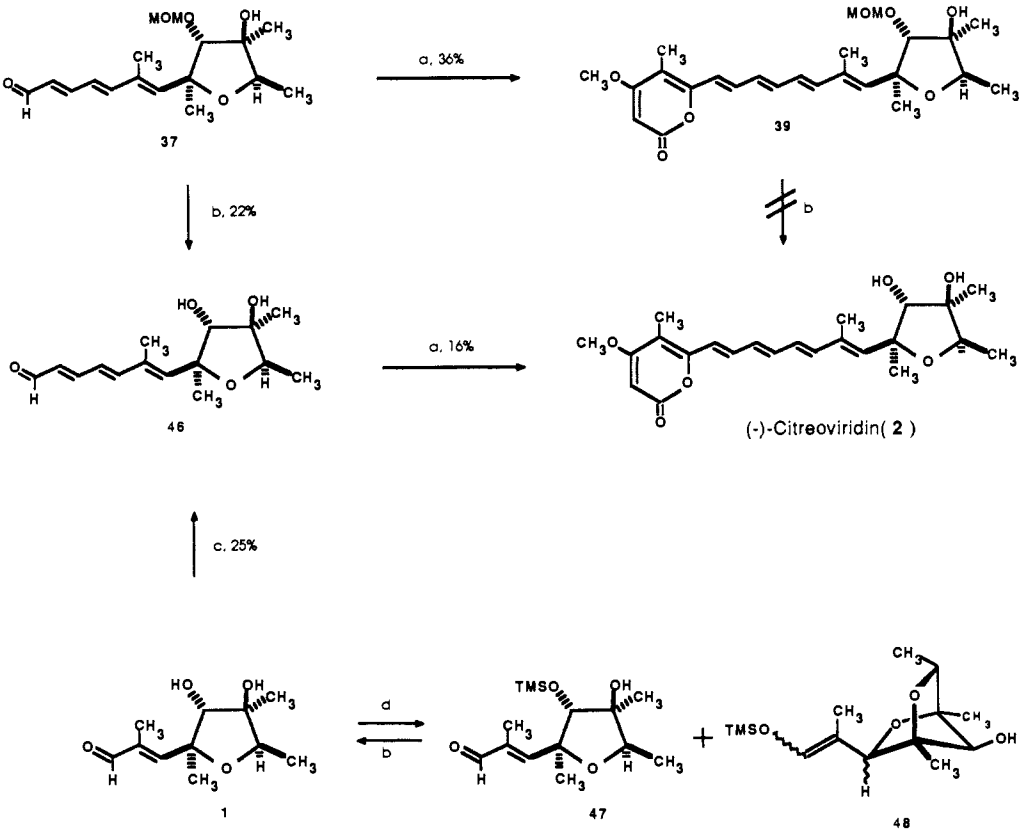
The low yields found in attempts to extend the side chain of unprotected citreoviral and the low yields found in attempts to remove the methoxymethyl protecting group from the chain-extended intermediate **37** required that other protecting groups be examined.

Several attempts were made to obtain a bis-silylated derivative of citreoviral appropriate for side-chain extension. The result illustrated in the bottom portion of Scheme VIII typifies the outcome of these attempts. Treatment of citreoviral with silylating agents provided a mixture of products **47** and **48**. The mixture of **47** and **48** was treated with a trace amount of acid in water and THF to recover citreoviral (**1**) in 75% yield. Once again, the close proximity of the tertiary alcohol and the first carbon of the side chain had led to an undesired result.

Although at this stage no improvement in the preparation of **46** had been achieved, it was deemed advisable to couple **45** and **46** to see whether these components would indeed afford (−)-

(30) Wollenberg, R. H. *Tetrahedron Lett.* **1978**, 717.
(31) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

Scheme VIII[a]



[a](a) **45**, LDA, THF–HMPA, −78 → +23 °C; (b) THF, 10% HCl–H_2O; (c) EtOCH=CHCH=C(H)Li, THF, then SiO_2; (d) $CH_3C[=NSi(CH_3)_3]OSi(CH_3)_3$, DMF.

citreoviridin. In hexamethylphosphoramide and THF, dimethyl phosphonate **45** was deprotonated by using lithium diisopropylamide and treated with trienaldehyde **46**. This reaction did indeed provide a small amount of (−)-citreoviridin, which was identifiable by comparison with published spectral data and by comparison with spectra generously provided by P. Steyn and R. Vleggaar (Pretoria, South Africa).

(4) Stability of Citreoviridin. The synthetic (−)-citreoviridin thus obtained was accompanied by an impurity that was at first quite difficult to remove. Successful separation followed the discovery that the impurity is a result of photoisomerization of the natural product. Samples of synthetic (−)-citreoviridin or natural (−)-citreoviridin that have been exposed to normal room illumination (fluorescent light or daylight or incandescent light) and analyzed by HPLC (see the Experimental Section) consist of two well-resolved major components, found in a ratio of 6:4 (NMR). Collection of material corresponding to either peak (normal fluorescent room illumination) and reinjection (citreoviridin corresponds to the first-eluted peak) results in a recreation of the original 6:4 mixture as determined by refractive index detection and NMR. In a critical experiment it was found that when only *red light* was allowed throughout the purification process no problems with the purification arose and NMR and HPLC analyses revealed that pure citreoviridin was in hand. This isomeric material is very likely the material discovered by Nagel and named isocitreoviridin.[32] It was proposed by Nagel to be a double-bond isomer of citreoviridin and to arise as an artifact of the isolation procedure, but the mechanism of its formation was not presented. We are continuing to examine the chemistry of this isomeric material.

The rate at which citreoviridin undergoes this isomerization and the effects of ambient light sources upon this reaction were examined. A sample of citreoviridin free of isocitreoviridin was prepared and dissolved in ethyl acetate under red light. This sample, handled only under red light and stored in the dark, remained free of isocitreoviridin or other impurities for several days. In contrast, exposure of a portion of this sample to a mixture of daylight and fluorescent light, or only fluorescent light, or only incandescent light (standard 90-W bulb) resulted in the formation of isocitreoviridin. The times required to reach the photostationary state under these typical laboratory ambient light conditions varied from 1 to 9 h and were dependent on the source of light (Figure 4). With fluorescent light, decomposition of citreoviridin is readily detectable by HPLC or by NMR after only 30 min. In the only previous report of a total synthesis of citreoviridin, no comment appears on this instability of the natural product.

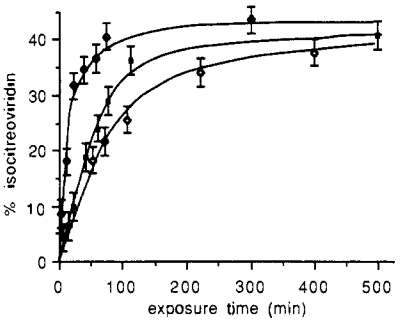


Figure 4. Effects of three light sources on a solution of citreoviridin. Pure citreoviridin (0.0005 M, EtOAc) was exposed to normal fluorescent light and daylight (◆), to only fluorescent light (■), or to a 90-W incandescent light at 0.7-m distance (◇).

The fact that citreoviridin is photolabile required that some changes be made in the plans for the final stages of this synthesis. In particular, it appeared that a route that delayed the formation of the tetraene was to be desired. Following the discovery that visible light catalyses the isomerization of citreoviridin, all purifications and ^1H or ^{13}C NMR were done only under red light. During spectroscopy, only NMR tubes made of amber-stained glass were used and only red light was allowed.

(32) Nagel, D. W.; Steyn, P. S.; Scott, D. B. *Phytochemistry* **1972**, *11*, 627.

Before seeking to refine this synthesis, a further test of the stability of citreoviridin (**2**) under the reaction conditions necessary to remove the methoxymethyl group was carried out. A small amount of synthetic citreoviridin in dichloromethane was treated with boron trifluoride etherate in the presence of ethanedithiol. After 2 h at 0 °C, HPLC analysis of the crude product revealed that these reaction conditions are too harsh for (−)-citreoviridin (**2**) and complex decomposition had occurred. Similar results followed from a test of the stability of (−)-citreoviridin with Brønsted acid.

To summarize, it may be stated that (−)-citreoviridin was found to be unstable to Lewis acids, unstable to Brønsted acids, and unstable to components of visible light. The molecule must be protected from even the mildest acids (NMR samples prepared in untreated deuteriochloroform decomposed within a few days) and can be handled indefinitely in the dark or under red-light illumination.

(5) Final Approach. The above results suggested that an optimized route to synthetic (−)-citreoviridin would require that a protecting group removable without the use of Brønsted acid or Lewis acid be used and also that, once the tetraene was prepared, all operations be conducted in the absence of fluorescent light, daylight, or incandescent light. Because, as mentioned earlier, the protection of the tertiary hydroxyl group of citreoviral (**1**) could not be efficiently accomplished, the intermediate lactone **26** was judged to be the best point at which to attach the new protecting group.

A silyl group was an attractive choice for the new protecting group. A prior investigation had indicated that citreoviridin could withstand base treatment.[2b] The *tert*-butyldimethylsilyl group was surmised to be stable enough with the reagents required to complete the synthesis. Alcohol **26** was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine to generate *tert*-butyldimethylsilyl (TBDMS) ether **49** in 91% yield (Scheme IX). This lactone was reduced by diisobutylaluminum hydride to provide lactol **50** in 99% yield. Methyl 2-(triphenylphosphoranylidene)propanoate was used to transform this lactol to α,β-unsaturated esters **51** and **52**. The major product was *trans*-α,β-unsaturated ester **51** and was obtained in 77% yield. The minor isomer was obtained in 9% yield.

The *trans*-α,β-unsaturated ester **51** was reduced to provide diol **53** in 82% yield. Diol **53** was oxidized with pyridinium dichromate to provide aldehyde **54** in 85% yield, and this aldehyde was converted in 31% yield to trienaldehyde **55**. Under red light, dimethyl phosphonate **45** in hexamethylphosphoramide and THF was treated with lithium diisopropylamide followed by trienaldehyde **55** to generate *tert*-butyldimethylsilyl-protected (−)-citreoviridin **56** in 56% yield. Deprotection of this product was also done under red light. In the final step, silyl ether **56** was treated with tetra-*n*-butylammonium fluoride in THF at 0 °C to give, after careful HPLC purification, in 35% yield, synthetic (−)-citreoviridin (**2**).

This synthetic (−)-citreoviridin (**2**) is identical with the natural product so far as may be judged by the published data. High-field (500/125 MHz $^1H/^{13}C$ NMR) data from P. Steyn and R. Vleggaar (Pretoria, South Africa) were compared with that obtained for this product (see the Experimental Section). Comparisons of the data confirm that the material prepared here is identical with the natural product.

The discovery of the photoisomerization of citreoviridin raised doubts concerning the olefin geometry for the major isomer in the photostationary mixture, i.e., whether the all-trans isomer was the major isomer. During the preparation of (+)-citreoviral an NOE experiment revealed that the first olefin next to the tetrahydrofuran moiety is of trans configuration. A proton NMR study (using a combination of COSY experiments and 2D-*J* data) established that the three remaining double bonds were of trans configuration. The coupling constants and chemical shifts determined by us for all the olefinic protons in both CD_2Cl_2 and $CDCl_3$ are presented in Table I.

The correctness of the assignments listed in Table I may be judged by comparing the olefinic regions of the real spectrum with that region as calculated based on the data from Table I. Such a comparison is illustrated in Figure 5. The match between the observed complex second-order spectrum and the calculated spectrum is very good indeed. With these values, the match between calculated and observed spectra is excellent for two solvents ($CDCl_3$ and CD_2Cl_2) and for both 500- and 360-MHz data.

Table I. Chemical Shifts and Coupling Constants Determined for Six Olefinic Protons (C8–C13) in (−)-Citreoviridin (Values for Two Solvents Shown)

$CDCl_3$	CD_2Cl_2
Shift, δ	
C12 H 7.208	C12 H 7.146
C10 H 6.523	C10 H 6.569
C11 H 6.384	C11 H 6.427
C8 H 6.337	C13 H 6.394
C13 H 6.332	C8 H 6.357
C9 H 6.303	C9 H 6.343
J, hertz	
$J_{12,13}$ 15.1	$J_{12,13}$ 15.0
$J_{11,12}$ 11.4	$J_{11,12}$ 11.2
$J_{10,11}$ 14.8	$J_{10,11}$ 14.7
$J_{9,10}$ 10.6	$J_{9,10}$ 9.7
$J_{8,9}$ 15.1	$J_{8,9}$ 15.6

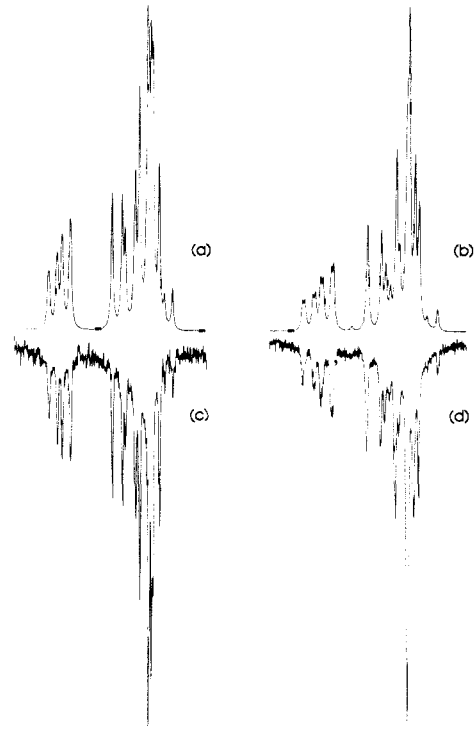
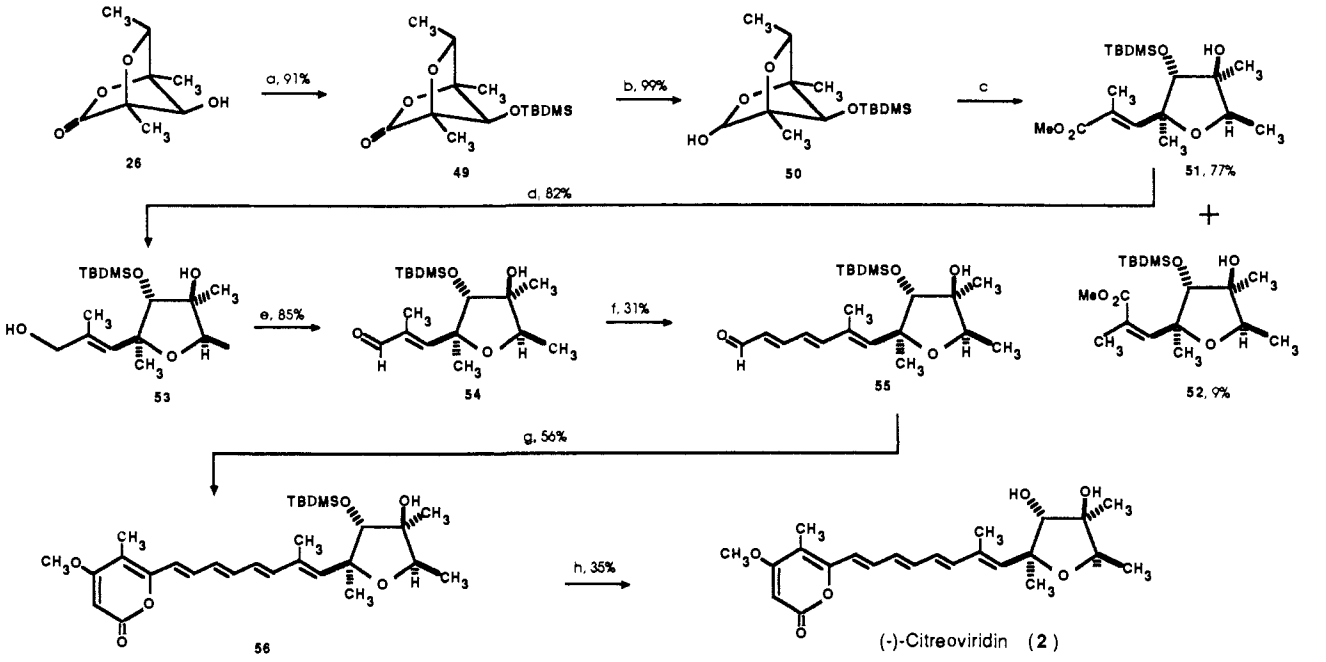


Figure 5. Experimental and calculated ^1H NMR spectra for the olefinic protons of citreoviridin (**2**) in CD_2Cl_2: (a) calculated, 500 MHz; (b) calculated, 361 MHz; (c) experimental, 500 MHz; (d) experimental, 361 MHz.

Conclusions

This paper describes the completion of the stereospecific total syntheses of (+)-citreoviral (**1**) and (−)-citreoviridin (**2**). (+)-Citreoviral (**1**) was prepared in 21 steps from D-ribono-1,4-lactone in 6.0% overall yield. (−)-Citreoviridin (**2**) was prepared in 25 steps from the same starting material in 0.4% overall yield. Importantly, we have shown for the first time that (−)-citreoviridin (**2**) in unstable under conditions of normal room illumination and that for optimum results (and if pure product is to be obtained for solution spectroscopy) the synthesis of this molecule must be completed in the dark or under red light. In addition, a careful examination of the NMR data has confirmed that citreoviridin is the major isomer in the photostationary mixture and that citreoviridin is the all-trans isomer.

Scheme IX[a]



[a] (a) TSBOTf, 2,6-lutidine, CH_2Cl_2; (b) DIBAL–hexane, CH_2Cl_2, −78 °C; (c) $Ph_3P{=}C(CH_3)CO_2CH_3$, C_6H_6; (d) DIBAL–hexane, CH_2Cl_2, −78 °C; (e) PDC, DMF; (f) EtOCH=CHCH=C(H)Li, THF, −78 → −45 °C, then SiO_2; (g) **43**, LDA, THF–HMPA, −78 → +23 °C; (h) n-$Bu_4N^+F^-$, THF, 0 °C.

The discovery that citreoviridin that has been exposed for even brief periods to room light contains significant amounts of another isomer casts doubt on the prior enzymological results for this inhibitor. In particular, the measured inhibitory constants for the molecule should be redetermined under carefully controlled conditions in order to accurately compare the potency of this molecule with the potency of aurovertin B and asteltoxin, two nonphotolabile inhibitors. In future work the structure of the photoisomerization product, its inhibitory activity, and the preparation of analogues of this natural product will be further explored.

Experimental Section[33]

Methyl (*E* and *Z*)-4,7-Anhydro-2,3,8-trideoxy-5-*O*-(methoxymethyl)-2-methyl-4,6-di-*C*-methyl-D-*gulo*-oct-2-enoate (30, 31). To a stirred solution of 233 mg (1.07 mmol) of lactol **28** in 11.1 mL of benzene at room temperature under nitrogen was added 579 mg (1.67 mmol) of methyl 2-(triphenylphosphoranylidene)propionate. After 10 h at reflux, the reaction mixture was diluted with 300 mL of ether and washed with 10 mL of a saturated aqueous sodium bicarbonate solution and 10 mL of a saturated aqueous sodium chloride solution. The organic phase was dried ($MgSO_4$), and after removal of the solvent under reduced pressure, flash chromatography (30 × 200 mm column, SiO_2, EtOAc–Skelly B) provided 234 mg (75%) of *trans*-α,β-unsaturated ester **30**, a yellow crystal, and 15 mg (5%) of *cis*-α,β-unsaturated ester **31**, a yellow oil. Trans isomer **30**: mp 69 °C; R_f 0.67 (SiO_2, 50% EtOAc–Skelly B); $[\alpha]^{23}_D$ −26.7° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3000, 1703, 1645, 1432, 1260, 1035 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.89 (d, 1 H, *J* = 1.1 Hz, $CH_3RC{=}CHR$), 4.73 (d, 1 H, *J* = 6.7 Hz, $OCHHOCH_3$), 4.68 (d, 1 H, *J* = 6.7 Hz, $OCHHOCH_3$), 3.85 (s, 1 H, H5), 3.78 (q, 1 H, *J* = 6.4 Hz, H7), 3.69 (s, 3 H, $COOCH_3$), 3.42 (s, 3 H, OCH_3), 1.99 (d, 3 H, *J* = 1.1 Hz, $CH_3RC{=}CHR'$), 1.86 (s, 1 H, OH), 1.32 (s, 3 H), 1.19 (s, 3 H), 1.13 (d, 3 H, *J* = 6.3 Hz, $CHCH_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.8, 146.6, 127.1, 97.7, 91.4, 83.6, 80.2, 78.6, 56.3, 51.8, 20.9, 18.6, 13.2, 12.4; MS, *m/e* calcd for $C_{13}H_{21}O_6$ ($M^+ - CH_3$) 273.13380, measured 273.13474. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.24; H, 8.29.

Cis isomer **31**: R_f 0.34 (SiO_2, 21% EtOAc–Skelly B); $[\alpha]^{23}_D$ −25.8° (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3430, 2990, 2940, 1711, 1672, 1450, 1357, 1207, 1143, 1040, 780–720, 665 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.48 (d, 1 H, *J* = 1.5 Hz, $CH_3RC{=}CHR'$), 4.69 (d, 1 H, *J* = 6.6 Hz, $OCHHOCH_3$), 4.64 (d, 1 H, *J* = 6.6 Hz, $OCHHOCH_3$), 3.82 (s, 1 H, H5), 3.75 (q, 1 H, *J* = 6.4 Hz, H7), 3.74 (s, 3 H, $COOCH_3$), 3.41 (s, 3 H, OCH_3), 1.88 (d, 3 H, *J* = 1.5 Hz, $CH_3RC{=}CHR'$), 1.66 (s, 1 H, OH), 1.25 (s, 3 H), 1.15 (s, 3 H), 1.13 (d, 3 H, *J* = 6.4 Hz, $CHCH_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.9, 135.4, 123.3, 97.7, 91.3, 83.0, 80.9, 79.3, 56.4, 51.9, 21.7, 21.0, 17.8, 11.1; MS, *m/e* calcd for $C_{13}H_{21}O_6$($M^+ - CH_3$) 273.13380, measured 273.13447.

(*E*)-2,5-Anhydro-1,6,7-trideoxy-4-*O*-(methoxymethyl)-7-methyl-3,5-di-*C*-methyl-L-*gluco*-oct-6-enitol (32). To a stirred solution of 74 mg (0.26 mmol) of ester **30** in 3.0 mL of dichloromethane at −78 °C under nitrogen was added 1.03 mL (1.03 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane. After 1.5 h at −78 °C, the reaction mixture was cautiously treated with 0.3 mL of methanol, warmed to room temperature, and diluted with 100 mL of ether. This solution was washed with 2 × 5 mL of 1 M saturated aqueous sodium tartrate solution and 5 mL of a saturated aqueous sodium chloride solution. The total aqueous extracts were washed with 2 × 50 mL of ether, and the combined organic extract was dried ($MgSO_4$) and concentrated. The oily residue was purified by flash chromatography (10 × 150 mm column, SiO_2, 75% EtOAc–Skelly B) to give 64 mg (94%) of diol **32**, a yellow oil: R_f 0.20 (SiO_2, 64% EtOAc–Skelly B); $[\alpha]^{23}_D$ −27.7° (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3500, 3020, 2405, 1530, 1425, 1230, 1042, 790–715, 665 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.67 (d, 1 H, *J* = 1.5 Hz, $CH_3CR{=}CHR'$), 4.73 (d, 1 H, *J* = 6.7 Hz, $OCHHOCH_3$), 4.68 (d, 1 H, *J* = 6.7 Hz, $OCHHOCH_3$), 3.92 ns, 2 H, CH_2OH), 3.84 (s, 1 H, H4), 3.78 (q, 1 H, *J* = 6.3 Hz, H2), 3.42 (s, 3 H, OCH_3), 1.81 (s, 3 H, $CH_3RC{=}CHR'$), 1.31 (s, 3 H), 1.18 (s, 3 H), 1.14 (d, 3 H, *J* = 6.3 Hz, $CHCH_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 136.1, 131.5, 97.7, 91.7, 83.5, 80.8, 78.5, 68.7, 56.3, 22.0, 18.2, 14.5, 12.5; MS, *m/e* calcd for $C_{13}H_{24}O_5$ 260.1624, measured 260.1608.

(*E*)-4,7-Anhydro-2,3,8-trideoxy-5-*O*-(methoxymethyl)-2-methyl-4,6-di-*C*-methyl-D-*gulo*-oct-2-enose (33). To a stirred solution of 64 mg (0.25 mmol) of the diol **32** in 0.83 mL of DMF at 0 °C under a nitrogen atmosphere was added 129 mg (0.34 mmol) of pyridinium dichromate. After 4 h at 0 °C, 2 mL of water was added, and the reaction mixture was diluted with 100 mL of ether. The solution was washed with 2 × 2 mL of water and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the solid residue was purified by flash chromatraphy (10 × 150 mm column, SiO_2, 33% EtOAc–Skelly B) to give 54.8 mg (85%) of aldehyde **33**, white crystals: mp 81 °C; R_f 0.39 (SiO_2, 40% EtOAc–Skelly B); $[\alpha]^{23}_D$ −11.4° (*c* 1.55, $CHCl_3$); IR ($CHCl_3$) 3500, 2999, 2932, 1687, 1638, 1445, 1373, 1145, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.36 (s, 1 H, CHO), 6.63 (s, 1 H, $CH_3RC{=}CHR'$), 4.79 (d, 1 H, *J* = 6.7 Hz, $OCHHOCH_3$), 4.73 (d, 1 H, *J* = 6.7 Hz, $OCHHOCH_3$), 3.91 (s, 1 H, H5), 3.87 (q, 1 H, *J* = 6.3 Hz, H7), 3.46 (s, 3 H, OCH_3), 1.91 (s, 3 H, $CH_3RC{=}CHR'$), 1.41 (s, 3 H), 1.25 (s, 3 H), 1.19 (d, 3 H, *J* = 6.3 Hz, $CDCH_3$); ^{13}C NMR (90 MHz, $CDCl_3$)

(33) Concentrations reported for optical rotation measurements (*c*) are grams/deciliter. Details of general experimental procedures, and complete details and analytical data for preparation of compounds **8–17**, **21–29**, **35**, and **36** are provided in the supplementary material.

δ 195.5, 159.5, 137.1, 97.8, 91.0, 83.9, 80.2, 78.8, 56.4, 20.8, 19.0, 12.4, 9.7; ME, *m/e* calcd for $C_{13}H_{22}O_5$ 258.14671, measured 258.14600. Anal. Calcd for $C_{13}H_{23}O_5$: C, 60.45; H, 8.58. Found: C, 60.67; H, 8.91.

(2*E*,4*E*,6*E*)-6-Methyl-7-[(2*S*,3*R*,4*S*,5*R*)-tetrahydro-4-hydroxy-3-(methoxymethoxy)-2,4,5-trimethyl-2-furyl]-2,4,6-heptatrienal (37). To a solution of 181 mL (0.51 mmol) 1-(tributylstannyl)-4-ethoxybutadiene in 0.7 mL of THF at −78 °C under nitrogen was added dropwise 0.27 mL (0.41 mmol) of a 1.61 M solution of *n*-butyllithium in hexane. After the reaction mixture was stirred for 2 h at −78 °C, 22 mg (0.085 mmol) of aldehyde **33** in 0.8 mL of THF was added. After 1 h at −78 °C, the temperature was raised to −45 ± 2 °C with acetonitrile and dry ice, and after 4 h, 0.5 mL of a saturated aqueous sodium bicarbonate solution was added. The reaction mixture was diluted with 100 mL of ether and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified twice by flash chromatography (15 × 150 mm column, SiO_2, 40% EtOAc–Skelly B) to give 16.8 mg (64%) of the extended aldehyde **37**, a yellow oil: R_f 0.29 (SiO_2, 40% EtOAc–Skelly B); $[\alpha]^{23}_D$ −81.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3500, 3020, 2405, 1671, 1602, 1225, 1040, 790–715, 665 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.55 (d, 1 H, *J* = 8.0 Hz, CHO), 7.13 (dd, 1 H, *J* = 10.8, 15.2 Hz, CHOCH=C*H*R), 6.62 (d, 1 H, *J* = 15.1 Hz, CHOCH=CHCH=C*H*R), 6.42 (dd, 1 H, *J* = 10.8, 15.2 Hz, CHOC*H*=CHCH=CHR), 6.00 (s, 1 H, CHOCH=CHCH=CHCCH$_3$=C*H*R), 4.77 (d, 1 H, *J* = 6.7 Hz, OC*H*HOCH$_3$), 4.71 (d, 1 H, *J* = 6.7 Hz, OC*H*HOCH$_3$), 3.88 (s, 1 H, H3), 3.81 (q, 1 H, *J* = 6.3 Hz, H5), 3.45 (s, 3 H, OC*H*$_3$), 2.00 (s, 3 H, CHOCH=CHCH=CHCC*H*$_3$=CHR), 1.37 (s, 3 H), 1.21 (s, 3 H), 1.16 (d, 3 H, *J* = 6.3 Hz, CHC*H*$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 193.4, 152.1, 147.9, 144.8, 133.8, 131.2, 125.1, 97.9, 91.9, 83.7, 80.5, 78.6, 56.4, 21.8, 18.5, 13.1, 12.5; MS, *m/e* calcd for $C_{17}H_{26}O_5$ 310.17801, measured 310.17738.

4-Methoxy-5-methyl-6-[(1*E*,3*E*,5*E*,7*E*)-7-methyl-8-[(2*S*,3*R*,4*S*,5*R*)-tetrahydro-4-hydroxy-3-(methoxymethoxy)-2,4,5-trimethyl-2-furyl]-1,3,5,7-octatetraenyl]-2*H*-pyran-2-one (39). To 25.4 mg (0.095 mmol) of dimethyl phosphate **45** at −78 °C under nitrogen were added 0.26 mL of THF and 0.27 mL of HMPA followed by 0.43 mL (0.087 mmol) of a 0.2 M solution of LDA in THF. After 25 min at −78 °C, 12.5 mg (0.040 mmol) of aldehyde **37** in 0.4 mL of THF was added. After an additional 1 h at −78 °C, the mixture was warmed to room temperature, stirred for 30 min, and treated with 1.0 mL of water. The reaction mixture was diluted with 100 mL of ether, washed with 2 × 10 mL of water, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the oily residue was purified by HPLC (43% EtOAc–Skelly B) to give 6.4 mg (36%) of methoxymethyl-protected citreoviridin **39**, a bright yellow oil. Even after HPLC, there was some impurity. When this reaction was being done, the fact that room illumination causes isomerization of the product was not known: R_f 0.20 (SiO_2, 60% EtOAc–Skelly B); $[\alpha]^{23}_D$ −96.2° (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 3400, 2930, 1697, 1629, 1629, 1604, 1589, 1568, 1537, 1455, 1406, 1247, 1146, 1094, 1038 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.21 (dd, 1 H, $J_{12,13}$ = 15.3 Hz, $J'_{11,12}$ = 11.4 Hz, H12), 6.52 (1 H, $J_{10,11}$ = 14.4 Hz, $J'_{9,10}$ = 10.6 Hz, H10), 6.39 (1 H, $J_{11,12}$ = 11.4 Hz, $J'_{10,11}$ 14.4 Hz, H11), 6.34 (1 H, $J_{8,9}$ = 15.6 Hz, H8), 6.33 (1 H, $J_{12,13}$ = 15.3 Hz, H13), 6.31 (1 H, $J_{8,9}$ = 15.6 Hz, $J'_{9,10}$ = 10.6 Hz, H9), 5.83 (s, 1 H, H6), 5.49 (s, 1 H, H17), 4.77 (d, 1 H, *J* = 6.7 Hz, OC*H*HOCH$_3$), 4.71 (d, 1 H, *J* = 6.7 Hz, OC*H*HOCH$_3$), 3.88 (s, 1 H, H4), 3.83 (s, 3 H, H23), 3.82 (q, 1 H, *J* = 6.3 Hz, H2), 3.45 (s, 3 H, OCH$_2$OCH$_3$), 1.99 (s, 3 H, H22), 1.96 (s, 3 H, H21), 1.37 (s, 3 H, H20), 1.21 (s, 3 H, H19), 1.16 (d, 3 H, *J* = 6.3 Hz, H1); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.6, 163.5, 154.6, 141.0, 140.5, 138.5, 136.1, 134.7, 131.3, 127.4, 118.8, 107.7, 97.9, 92.1, 88.7, 83.8, 80.6, 78.6, 56.4, 56.1, 22.1, 18.3, 13.2, 12.6, 8.8; MS, *m/e* calcd for $C_{25}H_{34}O_7$ 446.23044, measured 446.22958.

4-Methoxy-6-[(2*E*,4*E*,6*E*)-7-[(1*S*,4*S*,6*R*,7*R*)-7-(methoxymethoxy)-1,4,6-trimethyl-2,5-dioxabicyclo[2.2.1]hept-3-yl]-2,4,6-octatrienyl]-5-methyl-2*H*-pyran-2-one (40). To a mixture of 3.7 mL (0.37 mmol) of a 0.1 M solution of LDA in THF and 1.1 mL of HMPA at −78 °C under nitrogen was added dropwise 91 mg (0.59 mmol) of pyrone **36** in 2 mL of THF. After 1 h at −78 °C was added dropwise 23.0 mg (0.074 mmol) of aldehyde **55** in 1.5 mL of THF. After 80 min, the mixture was quenched with 0.3 mL of a saturated aqueous ammonium chloride solution. The reaction mixture was diluted with 200 mL of ether, washed with 3 × 20 mL of water, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the oily residue was purified with flash chromatography (1.5 × 140 mm column, SiO_2, 80% EtOAc–Skelly B) to give 12.0 mg (35%) of **38**. To a stirred solution of 12.0 mg (0.026 mmol) of alcohol **38** in 2.0 mL of dichloromethane at room temperature under nitrogen was added 25.0 mg (0.129 mmol) of *p*-toluenesulfonyl chloride and 54 μL (0.039 mmol) of triethylamine followed by 4.7 mg (0.039 mmol) of 4-(dimethylamino)pyridine. After being stirred at room temperature for 4 h, the reaction mixture was diluted with 100 mL of ether and washed with 5 mL of a saturated aqueous sodium bicarbonate solution and 5 mL of a saturated aqueous sodium chloride solution. The aqueous phase was extracted with 30 mL of ether, and the total organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The oily residue was purified by flash chromatography (10 × 140 mm column, SiO_2, 70% EtOAc–Skelly B) to give 7.0 mg (60%) of **40**: R_f = 0.33 (SiO_2, 70% EtOAc–Skelly B); $[\alpha]^{23}_D$ −48.3° (*c* 0.886, $CHCl_3$); IR ($CHCl_3$) 2990, 1702, 1645, 1565, 1455, 1408, 1248, 1152, 1125, 1050 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (mixture of isomers) δ 6.60–6.10 (m, 4 H, H8–H11), 5.78–5.75 (m, 1 H, H12), 5.45, 5.46 (s, 1 H, H17), 4.79–4.70 (m, 2 H, OCH_2OCH$_3$), 4.32, 4.23 (s, 1 H, H6), 4.21, 4.15 (q, 1 H, *J* = 6.4 Hz, H2), 3.82, 3.82 (s, 3 H, H23), 3.74, 3.89 (s, 1 H, H4), 3.44, 3.41 (s, 3 H, H25), 3.32, 3.31 (d, 2 H, *J* = 6.5 Hz, H13), 1.89, 1.89 (s, 3 H, H22), 1.85, 1.77 (s, 3 H, H21), 1.33, 1.32, 1.26, 1.25, 1.21 (H20, H1, H19); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.9, 164.3, 158.5, 158.3, 135.5, 134.3, 133.7, 133.5, 132.5, 131.9, 128.5, 128.2, 128.0, 127.0, 126.5, 126.0, 107.2, 107.2, 96.7, 89.3, 88.0, 87.0, 86.5, 86.1, 84.4, 84.0, 83.2, 83.1, 80.4, 79.4, 56.1, 55.8, 34.6, 15.3, 15.2, 13.9, 13.6, 13.3, 13.2, 12.3, 9.1; MS, *m/e* calcd for $C_{25}H_{34}O_7$ 446.23044, measured 446.22976.

6-[(2*E*,4*E*,6*E*)-7-[(1*R*,4*R*,6*R*,7*R*)-7-hydroxy-1,4,6-trimethyl-2,5-dioxabicyclo[2.2.1]hept-3-yl]-2,4,6-octatrienyl]-4-methoxy-5-methyl-2*H*-pyran-2-one (41). To a stirred solution of 10.0 mg (0.022 mmol) of methoxymethyl ether **40** in 1.0 mL of THF at room temperature under nitrogen was added 1 mL of 10% aqueous hydrochloric acid. After being stirred at reflux for 12 h, the reaction mixture was diluted with 70 mL of ether and washed with 5 mL of a saturated aqueous sodium bicarbonate solution and 3 mL of a saturated aqueous sodium chloride solution. The aqueous phase was extracted with 30 mL of ether, and the total organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The oily residue was purified by HPLC (37% EtOAc–CH_2Cl_2) to give 4.5 mg (50%) of a single isomer **41**: R_f 0.32 (SiO_2, 70% EtOAc–ether); $[\alpha]^{23}_D$ −69.4° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3500, 2930, 1695, 1556, 1454, 1402, 1242, 1120, 1095, 1010, 985 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.42–6.10 (m, 4 H, H8–H11), 5.77–5.69 (m, 1 H, H12), 5.46 (s, 1 H, H17), 4.25 (s, 1 H, H6), 4.09 (q, 1 H, *J* = 6.4 Hz, H2), 3.82 (s, 3 H, H23), 3.74 (d, 1 H, *J* = 7.6 Hz, H4), 3.31 (d, 2 H, *J* = 6.5 Hz, H13), 1.89 (s, 3 H, H22), 1.76 (s, 3 H, H21), 1.33 (s, 3 H, CH$_3$), 1.28 (d, 3 H, *J* = 6.4 Hz, H1), 1.16 (s, 3 H, CH$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.6, 163.7, 159.3, 137.3, 134.4, 133.2, 129.2, 127.9, 127.8, 107.6, 90.7, 88.5, 87.0, 84.4, 79.3, 78.6, 56.9, 35.0, 15.5, 13.8, 13.6, 13.2, 9.3; MS, *m/e* calcd for $C_{25}H_{34}O_7$ 402.20422, measured 402.20368.

6-(Bromomethyl)-4-methoxy-5-methyl-2*H*-pyran-2-one (43) and 5-(Bromomethyl)-4-methoxy-6-methyl-2*H*-pyran-2-one (42). To a stirred solution of 479 mg (3.11 mmol) of 4-methoxy-5,6-dimethyl-2*H*-pyran-2-one (**36**) in 15.6 mL of CCl_4 at room temperature under nitrogen was added 642 mg (3.61 mmol) of *N*-bromosuccinimide followed by 20 mg (0.083 mmol) of benzoyl peroxide. The reaction mixture was stirred for 30 min. After filtration through cotton, the filtrate was concentrated under reduced pressure, and the yellow solid residue was purified by flash chromatography (52 × 150 mm column, SiO_2, 5% EtOAc–CH_2Cl_2 and 7% EtOAc–CH_2Cl_2) to give 787.7 mg (67%) of a mixture of 5-(bromomethyl)-4-methoxy-6-methyl-2*H*-pyran-2-one (**42**) and 6-(bromomethyl)-4-methoxy-5-methyl-2*H*-pyran-2-one (**43**) in a ratio of 2.4:1, as determined by ^1H NMR. **43** was not practically separable from **42**: mp (mixture) 117–118 °C; R_f 0.22 (SiO_2, 5% EtOAc–Skelly B); IR ($CHCl_3$) 3000, 1720, 1643, 1568, 1457, 1409, 1257 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ major isomer 5.49 (s, 1 H, RC*H*=C(OCH$_3$)R'), 4.32 (s, 2 H, RCH_2BrC=COR'CH$_3$), 3.91 (s, 3 H, OCH$_3$), 2.33 (s, 2 H, RCH$_2$BrC=COR'CH_3); ^1H NMR δ minor isomer 5.55 (s, 1 H, RC*H*=C(OCH$_3$)R'), 4.24 (s, 2 H, CH_2Br(RO)C=CCH$_3$R'), 3.86 (s, 3 H, OCH$_3$), 1.96 (s, 3 H, CH$_2$Br(RO)C=CCH_3R'); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.0, 168.6, 162.8, 162.0, 110.1, 109.1, 89.9, 87.9, 56.4, 56.3, 24.9, 22.7, 17.1, 19.1; MS, *m/e* calcd for $C_8H_9O_3Br$ 233.97146, measured 233.97215. Anal. Calcd for $C_8H_9O_3Br$: C, 41.23; H, 3.89. Found: C, 41.18; H, 3.96.

Dimethyl [(4-Methoxy-5-methyl-2-oxo-2*H*-pyran-6-yl)methyl]-phosphonate (45). To a stirred solution of 603 mg (2.59 mmol) of a mixture of 5-(bromomethyl)-4-methoxy-6-methyl-2*H*-pyran-2-one (**42**) and 6-(bromomethyl)-4-methoxy-5-methyl-2*H*-pyran-2-one (**43**) in a ratio of 2.4:1 in 26 mL of toluene at room temperature under nitrogen was added 6.1 mL (51.8 mmol) of trimethyl phosphite. After 6 h at reflux, solvent was removed under reduced pressure, and the residue was purified twice by flash chromatography (70 × 160 mm column, SiO_2, 3% MeOH–CH_2Cl_2 and 4% MeOH–CH_2Cl_2) to give 186 mg (27%) of dimethyl phosphonate **45**, yellow crystals: mp 131–133 °C; R_f 0.18 (SiO_2, 4% MeOH–CH_2Cl_2); IR ($CHCl_3$) 3000, 1710, 1650, 1565, 1250–1205, 1038 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.47 (d, 1 H, *J* = 5.4 Hz, RC*H*=C(OCH$_3$)R'), 3.81 (d, 6 H, *J* = 4.4 Hz, PO(OCH_3)$_2$), 3.77 (s, 3 H, CH$_3$O), 3.11 (d, 2 H, *J* = 22.2 Hz, RCH_2PO(OMe)$_2$), 1.93 (d, 3

H, J = 4.0 Hz, RCH_3C=COR'CH_2P); ^{13}C NMR (90 MHz, $CDCl_3$) δ 181.9, 170.5, 163.4, 161.2, 151.3, 151.2, 109.7, 109.6, 88.5, 56.1, 53.0, 53.0, 50.1, 30.2, 28.7, 9.6; MS, m/e calcd for $C_{10}H_{15}O_6P$ 262.06062, measured 262.06022. Anal. Calcd for $C_{10}H_{15}O_6P$: C, 45.81; H, 5.77. Found: C, 46.01; H, 5.93.

(2*E*,4*E*,6*E*)-6-Methyl-7-[(2*S*,3*R*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-2,4,5-trimethyl-2-furyl]-2,4,6-heptatrienal (46). To a solution of 147 mL (0.42 mmol) (tri-*n*-butylstannyl)-4-ethoxybutadiene in 0.5 mL of THF at −78 °C under nitrogen was added dropwise 0.18 mL (0.29 mmol) of a 1.61 M solution of *n*-butyllithium in hexane. After the resultant mixture was stirred for 2 h at −78 °C, 10.2 mg (0.047 mmol) of citreoviral **1** in 0.7 mL of THF was added dropwise. After 2 h at −78 °C, the temperature was raised to −23 °C, and after 6 h, 0.5 mL of a saturated aqueous sodium bicarbonate solution was added. The reaction mixture was diluted with 100 mL of ether and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the oily residue was purified twice by flash chromatography (15 × 120 mm column, SiO_2, 65% EtOAc–Skelly B) followed by HPLC (55% EtOAc–Skelly B) to give 3.1 mg (25%) of the extended aldehyde **46**, a yellow oil, and 2.3 mg (23%) of starting material **1**: R_f 0.25 (SiO_2, 70% EtOAc–Skelly B); $[\alpha]^{23}_D$ −58.2° (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 3690, 3020, 2403, 1673, 1610, 1520, 1427, 1230–1205, 795–720, 667 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.56 (d, 1 H, J = 8.0 Hz, CHO), 7.14 (dd, 1 H, J = 10.9, 15.2 Hz, CHOCH=C*H*R), 6.63 (d, 1 H, J = 15.2 Hz, CHOCH=CHC*H*=CHR), 6.43 (dd, 1 H, J = 10.9, 15.2 Hz, CHOCH=CHC*H*=CHR), 6.17 (dd, 1 H, J = 8.0, 15.2 Hz, CHOC*H*=CHCH=CHR), 6.05 (s, 1 H, CHOCH=CHCH=CHCCH$_3$=C*H*R), 3.96 (d, 1 H, J = 4.5 Hz, H3), 3.82 (q, 1 H, J = 6.3 Hz, H5), 1.96 (s, 3 H, CHOCH=CHCH=CHCCH_3=CHR), 1.38 (s, 3 H), 1.22 (s, 3 H), 1.18 (d, 3 H, J = 6.3 Hz, CHCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 193.4, 152.1, 147.5, 145.0, 133.7, 131.3, 125.1, 86.0, 84.0, 80.7, 77.7, 21.0, 17.5, 13.4, 12.2; MS, m/e calcd for $C_{15}H_{22}O_4$ 266.15180, measured 266.15121.

2,5-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-2,4-di-*C*-methyl-D-gulonic Acid, γ-Lactone (49). To a stirred solution of 53.0 mg (0.308 mmol) of alcohol **26** in 0.6 mL of dichloromethane at room temperature under nitrogen were added 143 μL (0.82 mmol) of 2,6-lutidine and 188 μL (1.23 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 2 h an additional 95 μL (0.55 mmol) of 2,6-lutidine and 125 μL (0.82 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate were added. After another 1 h, the reaction mixture was diluted with 150 mL of dichloromethane, washed with 5 mL of a saturated aqueous sodium chloride solution, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the solid residue was purified with HPLC (3% EtOAc–Skelly B) to give 80.0 mg (91%) of *tert*-butyldimethylsilyl ether **49**, white crystals: mp 63.5–64.0 °C; R_f 0.33 (SiO_2, 10% EtOAc–Skelly B); $[\alpha]^{23}_D$ +1.8° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2950, 2930, 2860, 1795, 1385, 1257, 1140, 1086, 1010, 877 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 429 (q, 1 H, J = 6.6 Hz, H2), 3.60 (s, 1 H, H7), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.1m (d, 3 H, J = 6.6 Hz, CHCH_3), 0.92 (s, 9 H, Si(CH_3)$_3$), 0.12 (s, 3 H, SiCH_3), 0.11 (s, 3 H, SiCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.3, 89.3, 82.5, 81.1, 76.7, 25.6, 17.9, 12.2, 12.1, 10.9, −4.4, −4.7; MS, m/e calcd for $C_{10}H_{17}O_4Si(M^+ - t\text{-Bu})$ 229.08960, measured 229.09008.

2,5-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-2,4-di-*C*-methyl-D-gulofuranose (50). To a stirred solution of 36.3 mg (0.127 mmol) of lactone **49** in 1.3 mL of dichloromethane at −78 °C under nitrogen was added 0.127 mL (0.127 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane. After 1.5 h at −78 °C, the reaction mixture was cautiously treated with 0.2 mL of methanol, warmed to room temperature, and diluted with 100 mL of ether. This solution was washed with 2 × 3 mL of a 1 M aqueous sodium tartrate solution and 5 mL of a saturated aqueous sodium chloride solution and dried ($MgSO_4$). After removal of solvent under reduced pressure, flash chromatography (10 × 200 cm column, SiO_2, 25% EtOAc–Skelly B) of the oily residue afforded 233 mg (99%) of lactol **50**, a yellow oil: R_f 0.58 (SiO_2, 50% EtOAc–Skelly B); R_f 0.56 (SiO_2, 45% EtOAc–Skelly B); IR ($CHCl_3$) 3600, 2930, 2860, 1446, 1380, 1255, 1132, 1068, 970, 842 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ major isomer 5.05 (d, 1 H, J = 12.8 Hz, C*H*(OH)OC), 4.22 (q, 1 H, J = 6.5 Hz, C*H*CH$_3$), 3.67 (s, 1 H, C*H*(OTBDMS)), 1.27 (d, 3 H, J = 6.5 Hz, CH$_3$CH), 1.15 (s, 3 H, CH$_3$), 1.14 (s, 3 H, CH$_3$); ^{1}H NMR δ minor isomer 4.10 (q, 1 H, J = 6.5 Hz, C*H*CH$_3$), 3.90 (d, 1 H, J = 12.8 Hz, C*H*(OH)OC), 3.82 (s, 1 H, C*H*(OTBDMS)), 1.21 (s, 3 H, CH$_3$), 1.19 (s, 3 H, CH$_3$), 1.13 (d, 3 H, J = 6.5 Hz, CH$_3$CH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 99.8, 99.3, 86.4, 84.4, 84.2, 83.6, 80.1, 79.2, 78.4, 77.9, 25.7, 25.7, 18.0, 13.1, 13.1, 12.9, 12.3, 12.2, 11.9, −4.4, −4.5; MS, m/e calcd for $C_{14}H_{27}O_3Si$ ($M^+ - CH_3$) 271.17294, measured 271.17366.

Methyl (*E* and *Z*)-4,7-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)-2,3,8-trideoxy-2-methyl-4,6-di-*C*-methyl-D-*gulo*-oct-2-enoate (51, 52). To a stirred solution of 36.1 mg (0.125 mmol) of lactol **50** in 1.26 mL of benzene at room temperature under nitrogen was added 65.4 mg (0.188 mmol) of methyl 2-(triphenylphosphoranylidene)propionate. After 10 h at reflux, an additional 32.7-mg (0.094 mmol) portion of methyl 2-(triphenylphosphoranylidene)propionate was added, and after an additional 6 h at reflux, the reaction mixture was diluted with 100 mL of ether and washed with 5 mL of a saturated aqueous sodium bicarbonate solution and 5 mL of a saturated aqueous sodium chloride solution. The organic phase was dried ($MgSO_4$), and after removal of solvent under reduced pressure, purification with HPLC (8% EtOAc-Skelly B) provided 34.4 mg (77%) of *trans*-α,β-unsaturated ester **51**, a colorless oil, and 4.0 mg (9%) of *cis*-α,β-unsaturated ester **52**, a colorless oil, *E* isomer **51**: R_f 0.32 (SiO_2, 20% EtOAc–Skelly B); $[\alpha]^{23}_D$ +3.67° (*c* 0.82, $CHCl_3$); IR ($CHCl_3$) 3600, 2956, 2860, 1712, 1640, 1433, 1260, 1090 cm^{-1}); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.83 (d, 1 H, J = 1.4 Hz, CH$_3$RC=C*H*R'), 3.87 (s, 1 H, H5), 3.87 (q, 1 H, J = 6.4 Hz, H7), 3.72 (s, 3 H, COOCH_3), 2.05 (d, 3 H, J = 1.4 Hz, CH_3RC=CHR'), 1.27 (s, 3 H), 1.14 (d, 3 H, J = 6.4 Hz, CHCH_3), 1.13 (s, 3 H), 0.92 (s, 9 H, Si(CH_3)$_3$), 0.12 (s, 3 H, SiCH_3), 0.10 (s, 3 H, SiCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.0, 145.5, 127.2, 86.2, 84.5, 80.8, 78.6, 51.9, 25.9, 21.1, 18.7, 18.1, 13.3, 12.3, −4.1, −4.2; MS, m/e calcd for $C_{17}H_{31}O_5Si$ ($M^+ - CH_3$) 343.19406, measured 343.19489.

Z isomer **52**: R_f 0.40 (SiO_2, 20% EtOAc–Skelly B); $[\alpha]^{23}_D$ +4.0° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3500, 2930, 1711, 1673, 1450, 1245, 1115, 1085, 864, 840 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.39 (d, 1 H, J = 1.5 Hz, CH$_3$RC=C*H*R'), 3.83 (s, 1 H, H5), 3.76 (q, 1 H, J = 6.3 Hz, H7), 3.75 (s, 3 H, COOCH_3), 3.57 (s, 1 H, OH), 1.89 (d, 3 H, J = 1.5 Hz, CH_3RC=CHR'), 1.17 (s, 3 H), 1.13 (d, 3 H, J = 6.3 Hz, CHCH_3), 1.07 (s, 3 H), 0.92 (s, 9 H, Si(CH_3)$_3$), 0.11 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.3, 134.3, 126.4, 86.2, 83.7, 81.4, 78.9, 51.9, 25.9, 21.9, 21.0, 18.1, 18.18 11.1, −4.3, −4.5; MS, m/e calcd for $C_{17}H_{31}O_5Si$ ($M^+ - CH_3$) 343.19406, measured 343.19505.

(*E*)-2,5-Anhydro-4-*O*-(*tert*-butyldimethylsilyl)-1,6,7-trideoxy-7-methyl-3,5-di-*C*-methyl-L-*gluco*-oct-6-enitol (53). To a stirred solution of 34.3 mg (0.096 mmol) of ester **51** in 1.0 mL of dichloromethane at −78 °C under nitrogen was added, drop by drop, 0.383 mL (0.383 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane. After 1 h at −78 °C, the reaction mixture was cautiously treated with 0.2 mL of methanol, warmed to room temperature, and diluted with 100 mL of ether. This solution was washed with 2 × 5 mL of a 1 M saturated aqueous sodium tartrate solution and 5 mL of a saturated aqueous sodium chloride solution. The total aqueous extracts were washed with 2 × 30 mL of ether, and the combined organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. The oily layer was purified by flash chromatography (10 × 150 mm column, SiO_2, 30% and 45% EtOAc–Skelly B) to give 25.8 mg (82%) of diol **53**, white crystals: mp 93.5 °C; R_f 0.30 (SiO_2, 45% EtOAc–Skelly B); $[\alpha]^{23}_D$ −8.03° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3600, 2930, 2860, 1500, 1380, 1265, 1095, 1005, 830 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.61 (m, 1 H, CH$_3$RC=C*H*R'), 3.94 (s, 2 H, CH_2OH), 3.85 (q, 1 H, J = 6.4 Hz, H2), 3.83 (s, 1 H, H4), 1.87 (d, 3 H, J = 1.8 Hz, CH_3RC=CHR'), 1.25 (s, 3 H), 1.14 (d, 3 H, J = 6.4 Hz, CHCH_3), 1.11 (s, 3 H), 0.92 (s, 9 H, Si(CH_3)$_3$), 0.11 (s, 3 H, SiCH_3), 0.08 (s, 3 H, SiCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 136.2, 130.6, 86.6, 84.4, 81.3, 87.4, 69.0, 26.0, 22.2, 18.3, 18.1, 14.6, 12.4, −4.1, −4.2; MS, m/e calcd for $C_{17}H_{32}Si(M^+ - H_2O)$ 312.2206, measured 312.21267.

(*E*)-4,7-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)-2,3,8-trideoxy-2-methyl-4,6-di-*C*-methyl-D-*gulo*-oct-2-enose (54). To a stirred solution of 18.4 mg (0.056 mmol) of the diol **53** in 0.5 mL of DMF at 0 °C under nitrogen was added 51.6 mg (0.134 mmol) of pyridinium dichromate. After 4 h at 0 °C, 2 mL of water was added, and the reaction was diluted with 100 mL of ether. The solution was washed with 2 × 3 mL of water and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the solid residue was purified by flash chromatography (10 × 150 mm column, SiO_2, 20% EtOAc–Skelly B) to give 15.6 mg (85%) of aldehyde **54**, a colorless oil: R_f 0.40 (SiO_2, 30% EtOAc–Skelly B); $[\alpha]^{23}_D$ +9.40° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3620, 2955, 2858, 1687, 1638, 1255, 1095, 1020 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.35 (s, 1 H, CHO), 6.51 (d, 1 H, J = 1.9 Hz, CH$_3$RC=C*H*R'), 3.91 (s, 1 H, H5), 3.91 (q, 1 H, J = 6.3 Hz, H7), 1.93 (d, 3 H, J = 1.9 Hz, CH_3RC=CHR'), 1.33 (s, 3 H), 1.17 (d, 3 H, J = 6.3 Hz, CHCH_3), 1.16 (s, 3 H), 0.94 (s, 9 H, Si(CH_3)$_3$), 0.14 (s, 3 H, SiCH_3), 0.12 (s, 3 H, SiCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 195.6, 158.2, 137.3, 85.9, 84.9, 81.0, 78.7, 25.9, 21.0, 19.1, 18.1, 12.3, 10.0, −4.0, −4.1; MS, m/e calcd for $C_{17}H_{32}O_4Si$ 328.20697, measured 328.20797.

(2*E*,4*E*,6*E*)-7-[(2*S*,3*R*,4*S*,5*R*)-3-(*tert*-Butyldimethylsiloxy)tetrahydro-4-hydroxy-2,4,5-trimethyl-2-furyl]-6-methyl-2,4,6-heptatrienal (55). To a solution of 0.138 mL (0.39 mmol) of 1-(tri-*n*-butylstannyl)-4-ethoxybutadiene in 0.6 mL of THF at −78 °C under nitrogen was added dropwise 0.195 mL (0.31 mmol) of a 1.61 M solution of *n*-butyllithium in hexane. After the mixture was stirred for 2 h at −78 °C, 21.5 mg (0.066 mmol) of aldehyde **54** in 0.7 mL of THF was added. After 1 h

at −78 °C, the temperature was raised to −50 ± 2 °C, and after 4 h, 0.5 mL of a saturated aqueous sodium bicarbonate solution was added. The reaction mixture was diluted with 100 mL of ether and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the oil residue was purified by flash chromatography (15 × 150 mm column, SiO_2, 40% EtOAc–Skelly B) followed by HPLC (17% EtOAc–Skelly B) to give 7.9 mg (31%) of extended aldehyde **55**, a yellow oil: R_f 0.13 (SiO_2, 20% EtOAc–Skelly B); $[\alpha]^{23}_D$ −60.8° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3550, 2933, 2860, 1673, 1605, 1462, 1255, 1157, 1117, 1097 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.55 (d, 1 H, *J* = 8.0 Hz, CHO), 7.13 (dd, 1 H, *J* = 10.9, 15.2 Hz, CHOCH=C*H*R), 6.63 (d, 1 H, *J* = 15.3 Hz, CHOCH=CHCH=C*H*R), 6.44 (dd, 1 H, *J* = 10.9, 15.3 Hz, CHOCH=CHC*H*=CHR), 6.17 (dd, 1 H, *J* = 8.0, 15.2 Hz, CHOC*H*=CHCH=CHR), 5.90 (s, 1 H, CHOCH=CHCH=CHCCH$_3$=C*H*R), 3.87 (s, 1 H, H3), 3.87 (q, 1 H, *J* = 6.4 Hz, H5), 2.05 (s, 3 H, CHOCH=CHCH=CHCC*H*$_3$=CHR), 1.30 (s, 3 H), 1.15 (d, 3 H, *J* = 6.4 Hz, CHC*H*$_3$), 1.14 (s, 3 H), 0.94 (s, 9 H, Si(C*H*$_3$)$_3$), 0.13 (s, 3 H, SiC*H*$_3$), 0.10 (s, 3 H, SiC*H*$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 193.3, 152.1, 148.1, 143.7, 134.1, 131.2, 125.2, 86.9, 84.5, 81.1, 78.6, 26.0, 21.9, 18.8, 18.2, 13.2, 12.4, −4.1; MS, *m/e* calcd for $C_{21}H_{36}O_4Si$ 380.23827, measured 380.2390.

6-[(1*E*,3*E*,5*E*,7*E*)-8-[(2*S*,3*R*,4*S*,5*R*)-3-(*tert*-Butyldimethylsiloxy)-tetrahydro-4-hydroxy-2,4,5-trimethyl-2-furyl]-7-methyl-1,3,5,7-octatetraenyl]-4-methoxy-5-methyl-2*H*-pyran-2-one (56). To 13.1 mg (0.050 mmol) of dimethyl phosphate **45** at −78 °C under nitrogen were added 0.13 mL of THF and 0.14 mL of HMPA followed by 0.23 mL (0.046 mmol) of a 0.2 M solution of LDA in THF. After 25 min at −78 °C, room illumination was removed except for red light and 12.5 mg (0.040 mmol) of aldehyde **55** in 0.4 mL of THF was added. Only red light was used from this point all through the separation and $^1H/^{13}C$ NMR spectroscopy of the product. After an additional 1 h at −78 °C, the mixture was warmed to room temperature, stirred for 30 min, and treated with 0.5 mL of water. The reaction mixture was diluted with 100 mL of ether, washed with 2 × 5 mL of water, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the oily residue was purified with HPLC (32% EtOAc–Skelly B) to give 6.0 mg (56%) of *tert*-butyldimethylsilyl-protected citreoviridin **56**, a bright yellow oil: R_f 0.30 (SiO_2, 50% EtOAc–Skelly B); $[\alpha]^{23}_D$ −76.7° (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 2950, 2855, 1693, 1640, 1634, 1605, 1545, 1455, 1406, 1250, 1149, 660 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.21 (dd, 1 H, $J_{12,13}$ = 14.6 Hz, $J'_{11,12}$ = 11.4 Hz, H12), 6.52 (1 H, $J_{10,11}$ = 14.8 Hz, $J'_{9,10}$ = 10.6 Hz, H10), 6.38 (1 H, $J_{11,12}$ = 11.4 Hz, $J'_{10,11}$ = 14.8 Hz, H11), 6.34 (1 H, $J_{8,9}$ = 15.4 Hz, H8), 6.33 (1 H, $J_{12,13}$ = 14.6 Hz, H13), 6.31 (1 H, $J_{8,9}$ = 15.4 Hz, $J'_{9,10}$ = 10.6 Hz, H9), 5.74 (s, 1 H, H6), 5.48 (s, 1 H, H17), 3.87 (q, 1 H, *J* = 6.3 Hz, H2), 3.86 (s, 1 H, H4), 3.82 (s, 3 H, H23), 2.03 (s, 3 H, H22), 1.96 (s, 1 H, H21), 1.29 (s, 3 H, H20), 1.15 (d, 3 H, *J* = 6.3 Hz, H1)8 1.12 (s, 3 H, H19), 0.93 (s, 9 H, Si(CH$_3$)$_3$), 0.13 (s, 3 H, SiCH$_3$), 0.10 (s, 3 H, SiCH$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.6, 163.5, 154.7, 141.2, 139.5, 138.5, 136.1, 134.9, 131.3, 127.4, 118.7, 107.6, 88.7, 87.0, 84.6, 18.5, 18.1, 13.2, 12.5, 8.8, −4.0, −4.1; MS, *m/e* calcd for $C_{29}H_{44}H_6Si$ 516.2907, measured 516.2921.

Citreoviral (1). To a stirred solution of 10.3 mg (0.040 mmol) of methoxymethyl ether **33** in 1 mL of THF at room temperature under nitrogen was added 0.3 mL of 10% HCl. After 8 h at reflux, the reaction mixture was diluted with 70 mL of ether and washed with 5 mL of a saturated aqueous sodium bicarbonate solution and 3 mL of a saturated aqueous sodium chloride solution. The total aqueous solutions were washed with 2 × 40 mL of ether, and the combined organic phase was washed with 3 mL of a saturated aqueous sodium chloride solution, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (10 × 150 mm column, SiO_2, 60% EtOAc–Skelly B) to give 6.8 mg (80%) of citreoviral (**1**), a pale yellow oil: R_f 0.33 (SiO_2, 60% EtOAc–Skelly B); $[\alpha]^{23}_D$ = +18.7° (*c* 0.65, $CHCl_3$) [lit.[16] $[\alpha]^{23}_D$ +19.9° (*c* 1.8, $CHCl_3$)]; IR ($CHCl_3$) 3590, 2985, 2965, 1687, 1635, 1447, 1380, 1210, 1065, 1023 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.36 (s, 1 H, CHO), 6.68 (s, 1 H, CH$_3$RC=C*H*R'), 3.98 (d, 1 H, *J* = 3.8 Hz, C*H*CC(OH)), 3.88 (q, 1 H, *J* = 6.5 Hz, C*H*CH$_3$), 1.87 (s, 3 H, C*H*$_3$RC=CHR'), 1.41 (s, 3 H), 1.25 (s, 3 H), 1.20 (d, 3 H, *J* = 6.5 Hz, CHC*H*$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 195.3, 159.48 137.4, 85.3, 84.3, 80.5, 78.2, 20.0, 18.1, 12.2, 10.1; MS, *m/e* calcd for $C_{11}H_{18}O_4$ 214.12050, measured 214.12088.

Citreoviridin (2). To a stirred solution of 4.0 mg (7.8 μmol) of *tert*-butyldimethylsilyl-protected citreoviridin **56** in 0.5 mL of THF at 0 °C under nitrogen was added 23 μL (16.1 μmol) of a freshly made 0.7 M solution of tetra-*n*-butylammonium fluoride in THF. Only red light was used all through the reaction, the purification, and $^1H/^{13}C$ the spectroscopy.[34] After 30 min at 0 °C, the reaction mixture was diluted with 20 mL of dichloromethane, washed with 2 × 0.5 mL of a saturated aqueous sodium chloride solution, and dried ($MgSO_4$). The solvent was removed by concentration, and the residue was purified by using HPLC (43% EtOAc–CH_2Cl_2) to give 1.1 mg (35%) of citreoviridin (**2**), a yellow solid: mp 106 °C; R_f 0.25 (SiO_2, 70% ethyl acetate–CH_2Cl_2); $[\alpha]^{23}_D$ −77.0° (*c* 0.10, $CHCl_3$); UV (MeOH) λ_{max} 385, 294, 286, 233, 204 nm; IR ($CHCl_3$) 3610, 2912, 2855, 1695, 1623, 1602, 1587, 1565, 1535, 1453, 1405, 1245, 1145, 1095, 1050, 998, 810 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) (CH_2Cl_2, internal standard) δ 7.15 (dd, 1 H, $J_{12,13}$ = 15.0 Hz, $J'_{11,12}$ = 11.2 Hz, H12), 6.57 (1 H, $J_{10,11}$ = 14.7 Hz, $J'_{9,10}$ = 9.7 Hz, H10), 6.43 (1 H, $J_{11,12}$ = 11.2 Hz, $J'_{10,11}$ = 14.7 Hz, H11), 6.39 (1 H, $J_{12,13}$ = 15.0 Hz, H13), 6.36 (1 H, $J_{8,9}$ = 15.6 Hz, H8), 6.34 (1 H, $J_{8,9}$ = 15.6 Hz, $J'_{9,10}$ = 9.7 Hz, H9), 5.86 (d, 1 H, $J_{21,6}$ = 1.5 Hz, H6), 5.45 (s, 1 H, H17), 3.92 (d, 1 H, *J* = 4.9 Hz, H4), 3.82 (s, 3 H, H23), 3.77 (q, 1 H, *J* = 6.3 Hz, H2), 1.96 (s, 3 H, H22), 1.93 (d, 1 H, $J_{21,6}$ = 1.5 Hz, H21), 1.33 (s, 3 H, H20), 1.16 (s, 3 H, H19), 1.13 (d, 3 H, *J* = 6.3 Hz, H1); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.9, 163.4, 154.7, 141.6, 140.9, 138.6, 135.7, 134.6, 131.6, 127.6, 119.4, 108.3, 88.9, 86.3, 84.3, 80.9, 77.9, 56.6, 21.4, 17.5, 13.6, 12.4, 9.0; MS, *m/e* calcd for $C_{23}H_{30}O_6$ 402.20422, measured 402.20512.

Data for "natural citreoviridin":[2b,2c,32,35] mp 107–111 °C; R_f 0.25 (SiO_2, 70% ethyl acetate–CH_2Cl_2); $[\alpha]^{23}_D$ −68.9°; UV (MeOH) λ_{max} 383, 294, 285, 238, 206 nm; IR ($CHCl_3$) 3450, 3010, 2950, 1700, 1635, 1620, 1605, 1580, 1550, 1465, 1415, 1257, 1100, 1003 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) (CH_2Cl_2, internal standard) δ 7.14 (dd, 1 H, $J_{12,13}$ = 14.9 Hz, $J'_{11,12}$ = 11.2 Hz, H12), 6.54 ($J_{10,11}$ = 14.7 Hz, $J'_{9,10}$ = 9.4 Hz, H10), 6.41 (1 H, $J_{11,12}$ = 11.2 Hz, $J'_{10,11}$ = 14.7 Hz, H11), 6.38 (1 H, $J_{12,13}$ = 15.1 Hz, H13), 6.34 (1 H, $J_{8,9}$ = 15.2 Hz, H8), 6.31 (1 H, $J_{8,9}$ = 15.3 Hz, $J'_{9,10}$ = 9.3 Hz, H9), 5.89 (br s, 1 H, H6), 5.47 (s, 1 H, H17), 3.97 (br s, 1 H, H4), 3.82 (s, 3 H, H23), 3.79 (q, 1 H, *J* = 6.3 Hz, H2), 1.96 (s, 3 H, H22), 1.92 (br s, 1 H, H21), 1.34 (s, 3 H, H20), 1.18 (s, 3 H, H19), 1.14 (d, 3 H, *J* = 6.3 Hz, H1); ^{13}C NMR (125 MHz, CD_2Cl_2 δ 171.2, 163.9, 154.9, 142.2, 141.3, 139.0, 136.0, 134.4, 131.4, 127.5, 119.2, 108.4, 88.8, 86.2, 84.4, 81.1, 78.0, 56.7, 21.5, 17.8, 13.6, 12.6, 9.0.

Acknowledgment. This work was supported by a grant from the National Institute of General Medical Sciences. We thank Dr. R. Vleggaar and Dr. P. Steyn of the National Chemical Research Laboratory (Pretoria, South Africa) for providing NMR spectral data of natural (−)-citreoviridin.

Supplementary Material Available: General procedural details for the experimental work, detailed preparation procedures, and spectral data for **8–17**, **21–29**, **35**, and **36** (16 pages). Ordering information is given on any current masthead page.

(34) Melting point, specific rotation, UV, and IR measurements were done under normal laboratory light.

(35) Steyn, P. S.; Vleggaar, R.; Wessels, P. L.; Woudenberg, M. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2175–2178.