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Total Synthesis of (±)-Citreoviridin

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Investigations of iodine-induced cyclizations of γ,δ-olefinic benzyl ethers have led to highly substituted tetrahydrofurans from acyclic precursors with excellent stereochemical control. Our studies have afforded total syntheses of two fungal metabolites, (±)-citreoviral (**7**) and (±)-citreoviridin (**1**), which itself, is a potent, specific inhibitor of mitochondrial F_1-ATP synthetase.

Studies on the toxicity of "yellowed rice" led to the isolation of a yellow substance produced by a variety of *Penicillium* fungi.[1] Toxic symptoms of ascending nerve paralysis, lowering of body temperature, tremorgenic effects, and respiratory arrest characterized the epidemic occurrence of cardiac beri-beri in parts of East Asia. In 1964, Hirata and co-workers were able to provide the structural elucidation for citreoviridin (**1**).[2] The acute toxicity of this potent mycotoxin has been recognized as comparable to that of the aflatoxins. Functioning as a specific inhibitor of mitochondrial F_1-ATP synthetase, it has been an important tool for studies on the mechanism of oxidative phosphorylation.[3] More recently, it has been shown that a series of the mycotoxins, citreoviridins B, C, D, E, and F, is produced in high yields by strains of *Aspergillus terreus*, one of the most common of soil organisms.[4] Related fungal neurotoxins include verrucosidin (**2**),[5] aurovertin B (**3**),[6] citreoviridinol (**4a**) and isocitreoviridinol (**4b**),[7] neocitreoviridinol and epineocitreoviridinol (**5a**,**b**),[8] and asteltoxin (**6**) (Chart I).[9] These substances share the same general properties and biological activity as found in citreoviridin. Other structurally related natural products including citreomontanin,[10] pectinatone,[11] diemensin A and B,[12] and citreoviral (**7**).[13] Biosynthesis studies for several of the polyene mycotoxins, including citreoviridin, have been recently reported.[14]

There has been considerable interest in the synthesis of this family of compounds. In 1984 Schreiber and Satake reported the first total synthesis of (±)-asteltoxin (**6**).[15] Several groups have communicated successful syntheses of the metabolite, citreoviral (**7**).[16-19] Although details have remained unpublished, the absolute configuration of (−)-citreoviridin was apparently established several years ago.[20] However, Yamamura and co-workers have described a low-yielding conversion of citreoviral to citreoviridin which has unambiguously established the absolute configurations of both of these natural products.[21,22] In

(1) Hirata, Y. *J. Chem. Soc. Jpn.* **1947**, *65*, 63, 74, 104.
(2) Hirata, Y.; Goto, T.; Sakabe, N. *Tetrahedron Lett.* **1964**, 1825. Hirata, Y.; Sakabe, N.; Goto, T. *Tetrahedron* **1977**, *33*, 3077.
(3) Gause, E. M.; Buck, M. A.; Douglas, M. G. *J. Biol. Chem.* **1981**, *256*, 557. Satre, M.; Bof, M.; Vignais, P. V. *J. Bacteriol.* **1980**, *142*, 768. Datta, S. C.; Ghosh, J. J. *Toxicon* **1981**, *19*, 217, 555. Cataldi deFlombaum, M. A.; Stoppani, A. O. M. *Mol. Biochem. Parasitol.* **1981**, *3*, 143. Boyer, P. D.; Chance, B.; Ernster, L.; Mitchell, P.; Racker, E.; Slater, E. C. *Annu. Rev. Biochem.* **1977**, *46*, 955.
(4) Franck, B.; Gehrken, H.-P. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 461.
(5) Burka, L. T.; Ganguli, M.; Wilson, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 544.
(6) Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Osselton, M. D. *J. Chem. Soc., Chem. Commun.* **1974**, 874. Steyn, P. S.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1979**, 1041.
(7) Nishiyama, S.; Shizuri, Y.; Imai, D.; Yamamura, S.; Terada, Y.; Niwa, M.; Kawai, K.; Furukawa, H. *Tetrahedron Lett.* **1985**, *26*, 3243.
(8) Nishiyama, S.; Shizuri, Y.; Yamamura, S.; Terada, Y.; Kawai, K.; Furukawa, H. *Tetrahedron Lett.* **1985**, *26*, 6239.
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(11) Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.* **1983**, *24*, 3055.
(12) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1983**, *24*, 1917.
(13) Shizuri, Y.; Nishiyama, S.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 4771.
(14) Steyn, P. S.; Vleggaar, R.; Wessels, P. L.; Woudenberg, M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2175. Vleggaar, R. *Pure Appl. Chem.* **1986**, *58*, 239. Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1984**, 977.
(15) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1983**, *105*, 6723.
(16) Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1986**, *27*, 2195.
(17) Shizuri, Y.; Nishiyama, S.; Shigemori, H.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1985**, 292.
(18) Bowden, M. C.; Patel, P.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4793.
(19) Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485.
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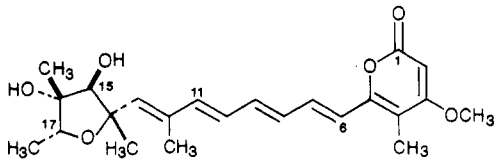
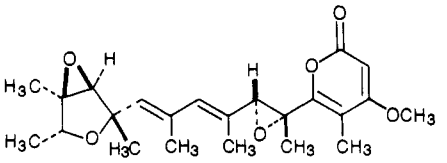
(21) Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231.

0022-3263/87/1952-5067$01.50/0

Chart I



1



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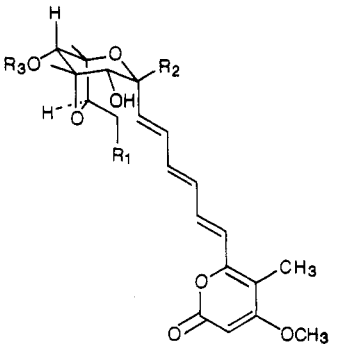
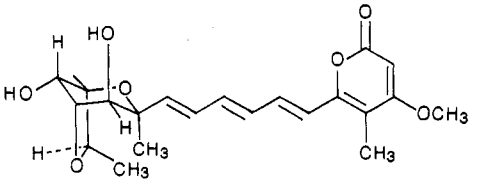
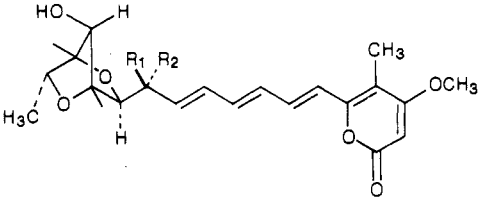


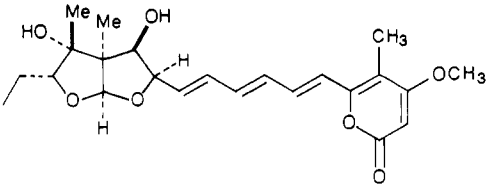
3, $R_1 = CH_3$; $R_2 = H$; $R_3 = Ac$
4a, $R_1 = H$; $R_2 = CH_3$; $R_3 = H$



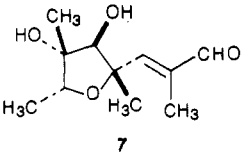
4b



5a, $R_1 = OH$; $R_2 = H$
5b, $R_1 = H$; $R_2 = OH$



6



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addition, studies directed toward these polyene mycotoxins have also been reported.[23] This account provides full details of our investigations for the preparation of tetrasubstituted tetrahydrofurans and the synthesis of (±)-citreoviral with subsequent completion of the total synthesis of (±)-citreoviridin.

Our previous efforts, exploring the formation of highly substituted terahydrofurans, prompted our interest in citreoviral and citreoviridin. We have investigated various strategies and the stereochemical elements which lead to C–O bond formation in these ring-closure processes[24-27] and have reported on a nucleophilic C–C bond formation as a route toward four-, five-, and six-membered oxacycles.[28] In this case, the highly substituted nature at C-14 of citreoviridin suggested that a cyclization induced by electrophilic attack on an acyclic γ,δ-unsaturated alcohol would effect C–O bond formation. Questions remained concerning the participation of competing nucleophilic elements at C-15 and C-16 in the cyclization process, and doubts about the regio- and stereochemical consequences were unanswered. However, Bartlett and Rychnovsky had reported the significant development of iodoetherifications as a stereocontrolled route to cis-2,5-disubstituted tetrahydrofurans.[29]

A retrosynthetic analysis of citreoviridin clearly identifies three subunits for sequential construction. A tetrahydrofuran with quaternary carbons at position 2 and position 4 can be linked to a polyene chain through a Wittig-type coupling, and subsequently the attachment of the 5-methyl-4-methoxy-2-pyrone will serve to complete the total synthesis. Our studies for preparation of the tetrahydrofuranyl component of these natural products is summarized in Scheme I, beginning with the readily available racemic ketone 3-(benzyloxy)-2-butanone.[30] Addition of freshly prepared vinylmagnesium bromide to ketone **8** at −30 °C in anhydrous tetrahydrofuran resulted in formation of a single tertiary alcohol **9** without detection of an additional isomer. On a larger scale, it was more appropriate to conduct reactions at 0 °C with distillation at reduced pressure, affording a colorless liquid; bp 118–120 °C (2.5 mmHg). This procedure also led to isolation of pure diastereomeric alcohol **9** in 78% yield as the product of an α-chelation-controlled addition.[31] Protection proceeded in excellent yield giving the β-methoxyethoxymethyl ether **10**, which clearly displayed a distinctive AB pattern in the proton NMR arising from the diastereotopic hydrogens of its isolated methylene unit. Ozonolysis of

(22) A total synthesis of (−)-citreoviridin has recently been completed by Professor Craig Wilcox and co-workers at the University of Texas (Austin). We thank Dr. Wilcox for informing us of their successful studies.

(23) Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395. See also: Bowden, M. D.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4797. Nishiyama, S.; Shizuri, Y.; Shigemori, H.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 723. Trost, B. M.; Lynch, J. K.; Angle, S. R. *Tetrahedron Lett.* **1987**, *28*, 375.

(24) Williams, D. R.; Phillips, J. G. *Tetrahedron* **1986**, *42*, 3013.

(25) Williams, D. R.; Grote, J.; Harigaya, Y. *Tetrahedron Lett.* **1984**, *25*, 5231.

(26) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'Sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641.

(27) Williams, D. R.; Moore, J. L.; Yamada, M. *J. Org. Chem.* **1986**, *51*, 3916.

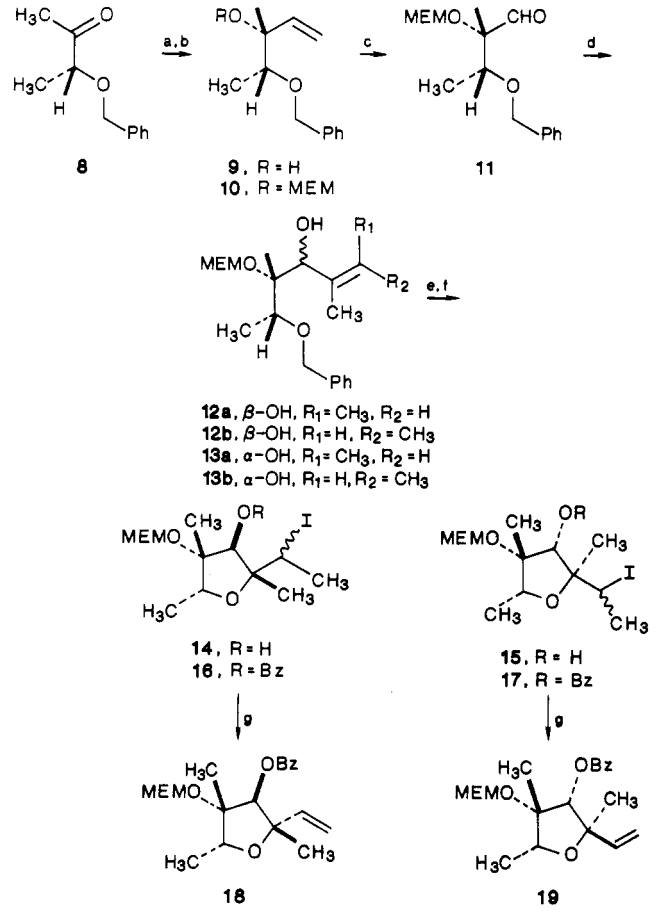
(28) Williams, D. R.; Grote, J. *J. Org. Chem.* **1983**, *48*, 134.

(29) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(30) Guillerm-Drom, D.; Capman, M. L.; Chodkiewicz, W. *Bull. Chim. Soc. Fr.* **1973**, *4*, 1417.

(31) Still, W. C.; MacDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. See also data in ref 30.

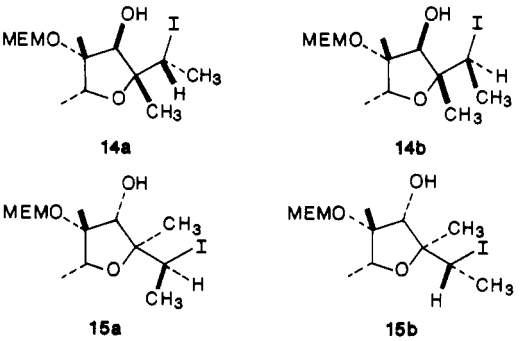
Scheme I[a]



[a] (a) H_2C=CHMgBr, THF, 0 °C (78%); (b) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 10 h (98%); (c) O_3, CH_2Cl_2, pyr, −78 °C; then Me_2S, −78 → 22 °C (82%); (d) Mg^0, 2-bromo-2-butene, THF; then add 11, −30 °C (85%); (e) I_2, $NaHCO_3$, CH_3CN, 0 °C, 3 h (79%); (f) Et_3N, BzCl, 4-DMAP, THF, 22 °C (83%); (g) DBU, *o*-dichlorobenzene, 180 °C (93%).

10 in dry methylene chloride containing 1.7 equiv of pyridine at −78 °C with subsequent reduction of the intermediate ozonide via addition of dimethyl sulfide gave 82% yield of the pure nonenolizable aldehyde **11**. The presence of pyridine in the ozonolysis prevented oxidation of the benzylic ether to its corresponding benzoate.

Incorporation of the electrophilic component for cyclization studies began with (*Z*)-2-bromo-2-butene, as prepared in a two-step sequence from *cis*-2-butene by bromination of the olefin and dehydrohalogenation as described by Landis and Bordwell.[32] Purification by fractional distillation gave an 8:1 ratio of *Z*/*E* isomers as determined by proton NMR (360 MHz) integration. Likewise the (*E*)-2-bromo-2-butene was prepared from *trans*-olefin in analogous fashion (1:8 *Z*/*E* ratio). Fortunately the double bond geometry was not significant in effecting the stereochemical results for our reaction scheme.[33] Grignard formation using predominantly (*Z*)-2-bromo-2-butene, and addition to aldehyde **11** in tetrahydrofuran at −30 °C proceeded in 85% yield affording a pair of allylic alcohols **12a,b** and **13a,b**, in which **12a** and **13a** were major isomers in a 3:2 ratio, respectively. The use of our freshy distilled (*E*)-2-bromo-2-butene led predominantly to **12b** and **13b** with the same efficiency and product ratios.[34] Since separation of the mixture of allylic alcohols was not feasible, cyclization by addition of iodine to a buffered ($NaHCO_3$) solution of **12a,b** and **13a,b** in acetonitrile was attempted, producing the two tetrahydrofuran-3-ols **14** and **15** in a 3:2 ratio.[29] Each tetrahydrofuran was produced as a mixture of epimers at the carbon bearing iodide in a ratio roughly proportional to the double bond geometries prior to cyclization. Thus, in the case of (*Z*)-2-bromo-2-butene, iodoetherification led to tetrahydrofurans **14** and **15**, which were separated by column chromatography on silica gel using a methylene chloride–tetrahydrofuran gradient to provide a net 79% yield of purified products. Further preparative thin-layer chromatography using 10% ethyl acetate in hexanes gave a separation of the major product **14a** and its minor epimer **14b**. The major tetrahydrofuran



15a crystallized on standing. The minor diastereoisomer **15b** was not obtained as a pure substance uncontaminated by **15a**. Further characterization of these diastereomers was obtained by conversion to the benzoates **16** and **17** in methylene chloride at room temperature with benzoyl chloride and 1 equiv of (dimethylamino)pyridine (83% yield). Benzoylations were sluggish, requiring 48 h to a week or more depending on the scale of the reaction. An acceleration of these reactions by heating was not appropriate as the starting alcohols were thermally labile. Proton NMR signals displayed the distinctive methine singlets at δ 5.52 and 5.73 for the tetrahydrofuran benzoates **16** and δ 5.53 and 5.44 for the pair of diastereomers **17**. In each case, elimination of hydrogen iodide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *o*-dichlorobenzene at reflux cleanly afforded a single alkene **18** and **19**, respectively, in excellent yields. Attempts to effect dehydrohalogenation with sublimed potassium *tert*-butoxide led to decomposition of the starting material, and treatment with sodium or potassium hydride in refluxing tetrahydrofuran gave no reaction.

Further studies of the cyclization process were undertaken by preparation of the allylic benzoates of **12** and **13** (Scheme I). The major isomers were cleanly separable by preparative TLC with multiple elutions of 10% ethyl acetate/hexanes, and saponification with lithium hydroxide in aqueous methanol at reflux led to the pure α- and β-alcohols **12a** and **13a**. Iodoetherification of **13a** yielded a single tetrahydrofuran isomer **15a**, and ring closure of **12a** afforded no less than a 9.5:1 ratio (by ^1H NMR integration) of tetrahydrofuran **14a** and a second isomer which may be a C-2 epimer or a small amount of **15a** contamination. Small quantities prevented an unambiguous structural assignment of this minor product.

(32) Landis, P. S.; Bordwell, F. G. *J. Am. Chem. Soc.* **1957**, *79*, 1593. Note that these authors refer to (*Z*)-2-bromo-2-butene as the trans isomer (methyls are trans). Material obtained from Aldrich was found to be a 5:1 ratio of *Z*/*E*-bromides after simple distillation.

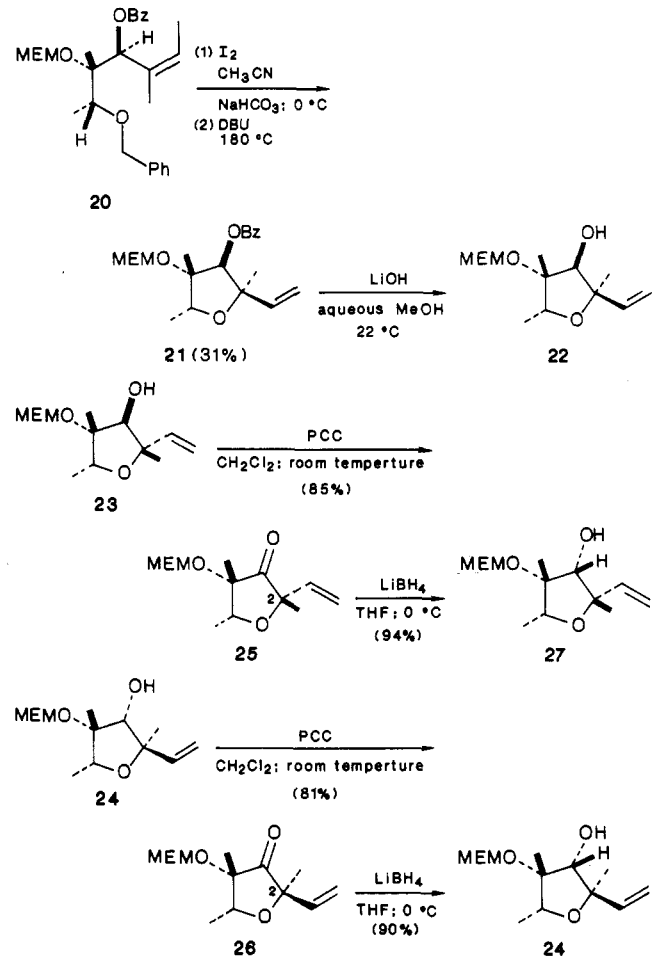
(33) Whitesides has noted approximately 7% loss of double bond geometry when preparing the alkenyllithiums of 2-bromo-2-butenes, apparently arising via isomerization of an intermediate vinyl radical. Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.

(34) The use of ethyl ether as solvent led to approximately 1:2 ratios of **12** to **13**.

The high degree of stereoselectivity obtained for these etherifications appeared to parallel results commonly observed in the iodolactonizations of 3-hydroxy-4-alkenoic acids and amides.[35] In such cases, the configuration of the secondary allylic alcohol has conferred facial selectivity for electrophilic attack at the neighboring olefin, thus providing a hydroxyl-directed, iodine-induced cyclization with syn (cis) orientations of the hydroxyl and α-iodoalkyl substituent. In fact, this methodology has recently been extended for the highly stereoselective formation of *cis*-2-(halomethyl)-3-hydroxypyrrolidines, as well as the analogous cis-2,3-disubstituted tetrahydrofurans.[36,37] Chamberlin and Hehre have reported calculations based on conformational analysis of the starting allylic alcohols with kinetically controlled iodocyclizations which predominantly support formation of syn (cis) orientations in the ring-closure process.[38] On the basis of these examples, we originally had reversed our assignments of the secondary alcohols in **12** and **13**.[39] Assuming that **12a** was of the α-configuration, we carried out an inversion of the secondary alcohol and proceeded along the synthetic pathway to a substance which was later identified as epicitreoviral. Subsequently, the stereochemical consequences of our cyclizations were unambiguously established by X-ray diffraction studies of the crystalline tetrahydrofuran **15a**.[40] The crystallographic data establish the result of an anti-periplanar addition of electrophilic iodine and the benzylic ether oxygen. However, the allylic alcohol has assumed a position which is anti (trans) with respect to the α-iodoethyl substituent in both tetrahydrofurans **14** and **15**. Revisions of our earlier stereochemical assignments and the preparation of racemic citreoviral have been communicated.[16] Reasons for the complete reversal of stereoselectivity remain unclear. The premature quenching of experiments showed the same product selectivity as seen in the complete reactions, and resubmission of either **14a** or **15a** to the buffered iodoetherification conditions with small amounts of acyclic benzyl ether failed to provide evidence of reversible processes. Rapid addition of iodine and/or exclusion of sodium bicarbonate allowed in situ formation of hydrogen iodide, apparently produced by decomposition of benzyl iodide. The stereoselectivity of these reactions remained unchanged with isolation of the corresponding diols of **14** and **15** resulting from cleavage of the acid-sensitive MEM ethers. Formation of the corresponding tetrahydropyranyl products were never detected in any of our cyclization attempts.[41]

Previously, we had demonstrated the preparation of 2,3-trans-disubstituted tetrahydrofurans as developed through an acyclic conformation which permitted C–O ring closure with strict adherence to an S_N2-like trajectory for backside opening of the initial iodonium intermediate, as well as a minimization of steric factors imposed by starting (*Z*)-olefin configurations.[25] However, our cyclizations of either *E* or *Z* trisubstituted alkenes **12a,b** and **13a,b** produced the same high selectivities for anti (trans) arrangements in the products. In addition, the iodoetherification–elimination sequence using benzoate **20** (Scheme II) afforded a separable mixture of **16** (41%) and the new isomer **21** (31%), which was converted to its corresponding alcohol **22** via standard saponification conditions (LiOH, aqueous methanol). On the other hand, similar treatment of the benzoate of **13** gave only tetrahydrofuran **17** (Scheme I). These general observations may suggest product development control with debenzylation of the oxonium intermediate as the slow, rate-determining step of the cyclization process.[29]

Scheme II



Further chemical transformations led to the important characterizations summarized in Scheme II. Saponifications of the benzoates **18** and **19** with lithium hydroxide in aqueous methanol gave the alcohols **23** and **24**, and oxidations of each tetrahydrofuran led to two distinct ketones **25** and **26**, demonstrating differing stereochemistry at C-2. These tetrahydrofuranones were more efficiently generated from the iodo alcohols **14a,b** and **15a,b**, respectively, by initial oxidation (PCC, CH_2Cl_2, 22 °C) and dehydrohalogenation of the resulting iodo ketones (DBU, 180 °C in *o*-dichlorobenzene). Subsequent reduction of **25** with lithium borohydride in anhydrous tetrahydrofuran at room temperature afforded exclusively the new diastereoisomer **27** in 85% yield, whereas ketone **26** gave back

(35) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079.

(36) Tamura, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063.

(37) Tamura, Y.; Kawamura, S.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 2885.

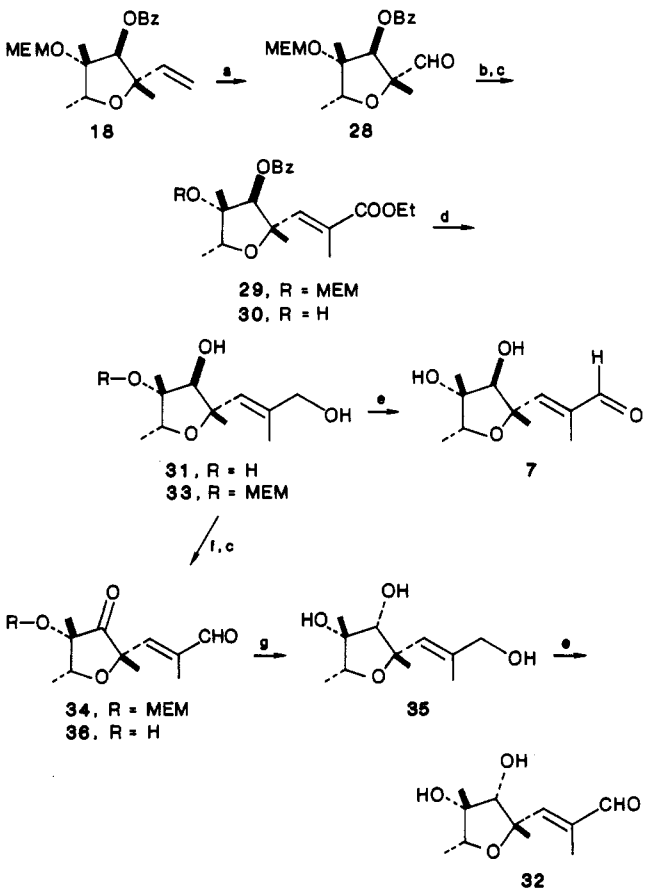
(38) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672. These authors also discuss situations where steric interactions account for formation of anti orientations.

(39) Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1985**, *26*, 2529.

(40) Structure **15a** was determined by single-crystal analysis (−154 °C). All atoms were located, including hydrogens, and refined by full-matrix techniques to final residuals of $R_F = 0.0369$ and $R_{wF} = 0.0386$. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 85091.

(41) Bartlett, P. A.; Ting, P. C. *J. Am. Chem. Soc.* **1984**, *106*, 2668. Chamberlin and co-workers have reported a case of high trans selectivity (9:1 ratio of trans/cis) for iodolactonization of 3-hydroxy-5-methyl-4-hexenoic acid to its butyrolactones. However, the major course of the reaction produces δ-lactones (90% yield), whereas the trans-butyrolactone was obtained in only 8% yield (see ref 35).

Scheme III[a]

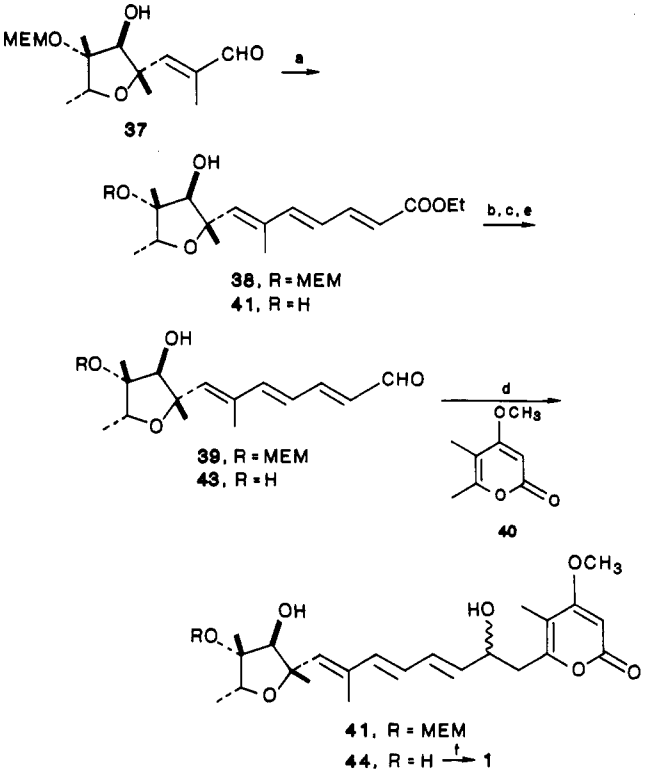


[a] (a) O_3, CH_2Cl_2, −78 °C; then Me_2S, −78 → 22 °C (89%); (b) $Ph_3P{=}CCH_3COOEt$, PhH, 80 °C, 72 h (93%); (c) $ZnBr_2$, CH_2Cl_2, 22 °C, 2 h (87%); (d) DIBAL, CH_2Cl_2, −78 °C (70%); (e) MnO_2, Et_2O, 22 °C, 1 h (68%); (f) PCC, CH_2Cl_2 22 °C, 24 h (43%); (g) $LiAlH_4$, Et_2O, 22 °C (72%).

its starting alcohol. Therefore, we had available pure samples of all four diastereoisomeric tetrahydrofuranyl alcohols **22**, **23**, **24**, and **27**, which might have been reasonably produced as a result of the cyclization process.

Completion of the total synthesis of (±)-citreoviral (**7**) is shown in Scheme III. Ozonolysis of olefin **18** at −78 °C provided the sterically hindered aldehyde **28** (^1H NMR singlet of δ 9.62) in 89% isolated yield. Wittig reaction with (carbethoxyethylidene)triphenylphosphorane in refluxing benzene produced only the *E*-α,β-unsaturated ester **29** in 93% yield. Removal of the β-methoxyethoxymethyl ether was performed in 87% yield by treatment of benzoate ester **29** with anhydrous zinc bromide in methylene chloride at 0 °C, affording a highly crystalline alcohol **30**; mp 106.5–108 °C. Reduction with excess diisobutylaluminum hydride in methylene chloride at −78 °C followed by selective oxidation of the resulting triol **31** with manganese dioxide gave racemic citreoviral **7** in 68% yield as white crystalline plates; mp 144.5–145 °C. The same reaction pathway was applied to the inverted C-3 alcohol **27**, yielding the unnatural (±)-epicitreoviral **32**. Proton chemical shift data for **32** were extremely similar to the literature values for citreoviral itself. Epicitreoviral was also available from **33** via oxidation with pyridinium chlorochromate in methylene chloride giving keto aldehyde **34**, and subsequent reduction and deprotection yielded the crystalline triol **35**; mp 82–84 °C. Manganese dioxide oxidation then gave pure racemic epicitreoviral **32**. The importance of the MEM unit for stereoselective hydride delivery was evident upon removal of the protecting group

Scheme IV[a]



[a] (a) $(EtO)_2POCHCH{=}CHCOOEt$, THF, −78 → 22 °C (75%); (b) DIBAL, CH_2Cl_2, −78 °C; (c) MnO_2, Et_2O, 22 °C, 0.5 h (65% from **36**); (d) LDA, THF, −78 °C, pyrone **40**; then add aldehyde (96%); (e) Me_2BBr, CH_2Cl_2, −78 °C (65%); (f) TsCl, 4-DMAP, Et_3N, CH_2Cl_2, 22 °C (35%).

from **34** ($ZnBr_2$, CH_2Cl_2 at 0 °C, 60%). Lithium borohydride reduction of this keto aldehyde **36** (THF at 0 °C) resulted in an inseparable mixture of C-3 diastereoisomers. Direct comparison of proton (360 MHz) spectra of our pure stereoisomeric aldehydes **7** and **32** with data we obtained from an authentic sample of (+)-citreoviral, as kindly supplied by Professor Yamamura, confirmed our structure assignments.[42] Subsequently data obtained from the ^{13}C NMR spectra for each compound in 5% DMSO-d_6/acetone-d_6 clearly characterized these isomers.

The synthesis of (±)-citreoviridin required extension of the olefinic chain and introduction of the α-pyrone. Treatment of aldehyde **37** with the anion of ethyl 4-(diethoxyphosphinyl)crotonate in anhydrous tetrahydrofuran (−78 → 22 °C) gave only the (*E*,*E*,*E*)-triene ester **38** in 75% yield (Scheme IV). The Wittig extension was not successful using citreoviral itself. Reduction of **38** with diisobutylaluminum hydride in methylene chloride, and selective allylic oxidation (MnO_2 in ether) afforded a crystalline aldehyde **39** (mp 88–89 °C) in 65% yield for the two steps. Condensation of the extended enolate of the known pyrone **40**,[43] as described by Schreiber,[15] with our aldehyde **39** produced the allylic alcohol **41** in 96% yield. Unfortunately, we were unable to obtain (±)-citreoviridin from **41** because of serious side reactions observed in all attempts for MEM ether cleavage. However, treatment of ester **38** with dimethylboron bromide[44] in methylene chloride at −78 °C cleanly removed the MEM ether in

(42) We thank Professor S. Yamamura of Keio University for providing an authentic sample of (+)-citreoviral for our comparison studies.
(43) The pyrone **39** was prepared via the standard literature procedures. Harris, T. M.; Harris, C. M. *J. Org. Chem.* **1966**, *31*, 1032. Bu'Lock, J. D.; Smith, H. G. *J. Chem. Soc.* **1960**, 502.
(44) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969.

reproducible yields of 65% to give the crystalline diol **42**; mp 97–99 °C. Diol **42** retained its all trans double bond geometry as evident from the proton NMR data: δ 7.31 (dd, J = 15.4 and 11.1 Hz, 1 H), 6.51 (d, J = 15.4 Hz, 1 H), 6.30 (dd, J = 15.3 and 11.1 Hz, 1 H), and 5.88 (d, J = 15.2 Hz, 1 H). Reduction and oxidation as previously described gave aldehyde **43**, and condensation with the enolate derived from α-pyrone **40** produced the sensitive allylic alcohol **44** in 68% yield following silica gel chromatography. Final dehydration to the natural product proved to be troublesome. Attempts for acid-catalyzed eliminations failed completely, and other general elimination procedures gave only small amounts of **1**. However, treatment with *p*-toluenesulfonyl chloride and 1 equiv of (*N*,*N*-dimethylamino)pyridine in anhydrous methylene chloride–triethylamine at room temperature with rigorous exclusion of light minimized the observed side reactions. Purification by preparative TLC on silica gel in a photographic darkroom led to a 35% yield of crystalline, synthetic (±)-citreoviridin (**1**); mp 105–108 °C (chloroform/hexane). All spectral characterizations for our racemic material were identical with data obtained from an authentic sample of (–)-citreoviridin generously provided by Dr. Richard Cole of the U.S. Department of Agriculture.[45]

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Nicolet NT-360 (360 MHz) spectrometer using either deuteriochloroform ($CDCl_3$) or 5% DMSO-d_6/acetone-d_6 as solvents. Carbon-13 (^{13}C) nuclear magnetic resonance spectra were recorded at 75.4 MHz with proton decoupling on a Varian XL-300 (300 MHz) spectrometer. Chemical shifts are reported in δ (parts per million) downfield from tetramethylsilane (δ 0.00) as an internal standard. All coupling constants are reported in hertz. Data for proton NMR will be presented as follows: δ (multiplicity, coupling constants, number of protons). Infrared (IR) spectra were recorded on a Perkin-Elmer 298 spectrophotometer as a neat film or in a chloroform solution as indicated and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Ultraviolet (UV) spectra were recorded on a Perkin-Elmer 552 spectrophotometer using methanol as solvent. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Kratos MS-8 spectrometer using electron impact at 70 and 40 eV, respectively. Data for mass spectra are reported as follows: mass number (relative intensity with regard to base peak). Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Silica gel 60 (0.063–0.200 mm) and glass plates precoated with silica gel 60F-254 (0.25- and 0.5-mm thickness) were used for column and preparative thin-layer chromatography (TLC), respectively. Flash chromatography refers to purification on a column packed with Kieselgel 60H and eluted under pressure by using a hand ballast to develop the needed pressure. All silica products were obtained from E.M. Merck. All chromatography solvents were distilled prior to use. "Dry" solvents refer to solvents that have been purified as indicated. Tetrahydrofuran and diethyl ether (ether) were distilled from sodium benzophenone ketyl under argon. Methylene chloride, triethylamine, diisopropylamine, diisopropyletylamine, pyridine, benzene, acetonitrile, and *o*-dichlorobenzene were all distilled from calcium hydride prior to use.

All reactions were conducted in flame-dried flasks under an atmosphere of argon unless otherwise indicated. All reactions were monitored by using analytical TLC on silica gel (0.25-mm thickness). Components were visualized by UV light when possible, followed by application of ethanolic phosphomolybdic acid, cobalt chloride, or potassium permanganate and heating. Components were eluted from the adsorbents with tetrahydrofuran during preparative TLC. Removal of solvent from samples was accomplished on a rotary evaporator at aspirator pressure (~15–20 Torr). Samples were routinely dried under vacuum (~0.25 Torr) to a constant weight.

(±)-(3*R,4*R**)-4-(Benzyloxy)-3-methyl-1-penten-3-ol (9).** A solution of vinylmagnesium bromide was prepared in a 1-L flask by slow dropwise addition of vinyl bromide (41 mL, 0.582 mol) in 100 mL of dry tetrahydrofuran over 2 h to a rapidly stirred, flame-dried suspension of magnesium turnings (14.14 g, 0.582 mol). After addition was complete, the solution of vinyl magnesium bromide was diluted with an additional 300 mL of dry tetrahydrofuran to give a dark brown/black solution, which was then cooled to 0 °C in an ice bath. A solution of ketone **8** (34.42 g, 0.194 mol) in 50 mL of dry tetrahydrofuran was added dropwise over 20 min. The reaction was quenched by dropwise addition of 20 mL of saturated NH_4Cl solution, then diluted with 1 L of water, and extracted with ether (3 × 200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to an orange liquid. Purification by vacuum distillation using a short-path apparatus afforded 31.17 g (78%) of tertiary alcohol **9** as a single isomer: bp 118–120 °C (2.5 mmHg); R_f 0.43 (30% ethyl acetate/hexane); IR (neat) 3530, 3430, 3060, 3040, 3005, 2995, 2905, 2840, 1440, 1360, 1080, 905, 720 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.93 (m, 1 H), 5.23 (AB of ABX, J_{AB} = 1.3 Hz, J_{AX} = 17.4 Hz, J_{BX} = 10.8 Hz, $\Delta\nu$ = 68.9 Hz, 2 H), 4.54 (AB, $\Delta\nu$ = 69.4 Hz, J_{AB} = 11.6 Hz, 2 H), 3.40 (q, J = 6.3 Hz, 1 H), 1.23 (s, 3 H), 1.15 (d, J = 6.3 Hz, 3 H); MS (CI$^+$–NH_3), m/e (relative intensity) 206 (M^+, 1.8), 189 (72.4), 135 (48.1), 99 (12.6), 91 (100), 71 (62.3); HRMS, m/e calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1268. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.69; H, 8.84.

(±)-(3*R,4*R**)-4-(Benzyloxy)-3-[(2-methoxyethoxy)methoxy]-3-methyl-1-pentene (10).** Diisopropylethylamine (28.7 mL, 0.165 mol) was added to a magnetically stirred solution of alcohol **9** (6.76 g, 0.033 mol) in 15 mL of dry methylene chloride at 0 °C. Stirring was continued for 10 min followed by the dropwise addition of MEMCl (18.8 mL, 0.165 mol). The ice bath was removed and stirring continued for 10 h at the ambient temperature. The reaction mixture was poured into 500 mL of water and extracted with ether (3 × 200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a yellow liquid, which was purified on a Waters Prep 500 LC using 10% ethyl acetate/hexane to afford 10.01 g (98%) of olefin **10**: R_f 0.45 (30% ethyl acetate/hexane); IR (neat) 3060, 3040, 2960, 2905, 2850, 1445, 1360, 1090, 1010, 915, 840, 725, 690 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 5.88 (m, 1 H), 5.23 (m, 2 H), 4.79 (AB, $\Delta\nu$ = 36.6 Hz, J_{AB} = 7.3 Hz, 2 H), 4.61 (AB, $\Delta\nu$ = 24.8 Hz, J_{AB} = 11.9 Hz, 2H), 3.80 (m, 1 H), 3.63 (m, 1 H), 3.52 (m, 2 H), 3.46 (q, J = 6.5 Hz, 1 H), 3.37 (s, 3 H), 1.39 (s, 3 H), 1.14 (d, J = 6.5 Hz, 1 H); MS (20 eV), m/e (relative intensity) [no M^+] 205 (2.8), 189 (64.7), 135 (8.4), 99 (37.9), 91 (100), 89 (47.5); HRMS, m/e calcd for $C_{13}H_{17}O_2$ ($M^+ - CH_3OCH_2CH_2OCH_2$) 205.1229, found 205.1245. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.35; H, 8.90. Found: C, 69.28; H, 8.85.

(±)-(2*S,3*R**)-3-(Benzyloxy)-2-[(2-methoxyethoxy)methoxy]-2-methyl-1-butanal (11).** Ozone was bubbled through a solution of olefin **10** (10.06 g, 0.034 mol) in 250 mL of dry methylene chloride containing pyridine (4.69 mL, 0.058 mol) at –78 °C. When a bluish color was observed, ozone generation was stopped, and the system was flushed with oxygen for 5 min. The reaction was quenched by the addition of dimethyl sulfide (2.5 mL, 0.034 mol) and then allowed to warm to room temperature. The crude reaction mixture was concentrated in vacuo, diluted with 100 mL of ethyl acetate, and extracted with saturated aqueous $CuSO_4$ solution (5 × 75 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a pale yellow liquid, which was purified on a Waters Prep 500 LC using 15% ethyl acetate/hexane to afford 8.3 g (82%) of aldehyde **11**: R_f 0.27 (30% ethyl acetate/hexane); IR (neat) 3000, 2950, 2900, 2845, 1713, 1435, 1355, 1085, 1008, 720, 680 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 7.28 (m, 5 H), 4.93 (AB, $\Delta\nu$ = 18.7 Hz, J_{AB} = 7.5 Hz, 2 H), 4.52 (AB $\Delta\nu$ = 70.1 Hz, J_{AB} = 11.8 Hz, 2 H), 3.80 (m, 2 H), 3.71 (q, J = 6.3 Hz, 1 H), 3.52 (m, 2 H), 3.36 (s, 3 H), 1.31 (s, 3 H), 1.24 (d, J = 6.3 Hz, 3 H); MS (20 eV), m/e (relative intensity) [no M^+] 207 (1.2), 162 (1.1), 135 (1.7), 101 (11.2), 91 (96.0), 89 (100), HRMS m/e calcd for $C_{12}H_{15}O_3$

(45) We gratefully acknowledge Dr. Richard Cole of the National Peanut Research Laboratories, U.S. Department of Agriculture, Dawson, GA, for a generous sample of pure, natural (–)-citreoviridin.

($M^+ - CH_3OCH_2CH_2OCH_2$) 207.1021, found 207.1014.

(±)-(5S*,6R*)-6-(Benzyloxy)-3,5-dimethyl-5-[(2-methoxyethoxy)methoxy]-2-hepten-4-ol (12a,b and 13a,b). A 5 M solution of the Grignard reagent was prepared by adding 2-bromo-2-butene (13.1 mL, 0.129 mol) to a rapidly stirred suspension of magnesium turnings (3.13 g, 0.129 mol) in 26 mL of dry tetrahydrofuran. The magnesium had been flame-dried and activated with addition of 1,2-dibromoethane (100 μL). The Grignard solution was added dropwise over 5 min to a cooled solution (−30 °C) of the aldehyde **11** (11.7 g, 0.039 mol) in 100 mL of dry tetrahydrofuran. The resulting cloudy solution was stirred for 45 min with gradual warming to 0 °C. The reaction was quenched by the addition of 10 mL of saturated NH_4Cl, followed by addition of 500 mL of water and extraction with ether (2 × 150 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil, which was purified on a Waters Prep 500 LC using 20% ethyl acetate/hexane to afford 11.72 g (85%) of the allylic alcohols **12a,b** and **13a,b** as an inseparable mixture of isomers: R_f 0.60 (10% tetrahydrofuran/methylene chloride); IR (neat) 3450, 2895, 2850, 1433, 1355, 1183, 1005, 825, 720 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) [major isomer **12a**] δ 7.31 (s, 5 H), 5.53 (br q, 1 H), 5.09 (AB, Δν = 177.7 Hz, J_{AB} = 10.8 Hz, 2 H), 4.55 (br s, 1 H), 4.43 (AB, Δν = 136.0 Hz, J_{AB} = 14.4 Hz, 2 H), 3.74 (m, 3 H), 3.52 (m, 2 H), 3.37 (s, 3 H), 1.81 (br s, 3 H), 1.61 (br s, 3 H), 1.31 (d, J = 6.5 Hz, 3 H), 1.15 (s, 3 H), [minor isomer **13a**] δ 7.31 (s, 5 H), 5.43 (m, 1 H), 5.01 (AB, Δν = 44.3 Hz, J_{AB} = 7.3 Hz, 2 H), 4.75 (d, J = 5.6 Hz, 1 H), 4.51 (AB, Δν = 85.9 Hz, J_{Ab} = 11.6 Hz, 2 H), 3.74 (m, 3 H), 3.52 (m, 2 H), 3.37 (s, 3 H), 3.30 (br s, 1 H), 1.77 (s, 3 H), 1.58 (d, J = 5.6 Hz, 3 H), 1.29 (d, J = 6.3 Hz, 3 H), 1.18 (s, 3 H); MS (CI^+–NH_3), m/e (relative intensity) 337 ($M^+ - 15$, 0.1), 227 (3.96), 199 (1.90), 91 (100), 89 (95.8); HRMS m/e calcd for $C_{19}H_{29}O_5$ ($M^+ - CH_3$) 337.2014, found 337.2059, and m/e calcd for $C_{16}H_{23}O_3$ ($M^+ - CH_3OCH_2CH_2OCH_2$) 263.1647, found 263.1650.

(±)-(2R*,3S*,4S*,5R*)-4-[(2-Methoxyethoxy)methoxy]-2-(1-iodoethyl)-2,4,5-trimethyl-3-tetrahydrofuranol (14) and (±)-(2S*,3R*,4S*,5R*)-4-[(2-Methoxyethoxy)methoxy]-2-(1-iodoethyl)-2,4,5-trimethyl-3-tetrahydrofuranol (15). A 1000-mL flask containing the alcohols **12a,b** and **13a,b** (21.2 g, 0.06 mol) in 250 mL of dry acetonitrile was charged with solid sodium bicarbonate (40 g, 0.48 mol) and cooled to 0 °C in an ice bath. A solution of iodine (33.6 g, 0.132 mol) in 250 mL of dry acetonitrile was added via cannula over 40 min to the rapidly stirred solution of the alcohols. After addition was complete, stirring was continued at 0 °C for 3 h. The reaction was quenched by the addition of 50 mL of saturated sodium bicarbonate and diluted with 150 mL of water. Solid sodium bisulfite was then added to the reaction solution until the red/brown color was discharged with vigorous foaming. The resultant pale yellow reaction mixture was extracted with ether (4 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to an orange oil. Purification by column chromatography on 2 kg of silica gel was accomplished by gradient elution with 4 L of methylene chloride followed by 2 L each of 2.5%, 5%, 7.5%, and 10% tetrahydrofuran/methylene chloride to afford separation of a total of 18.39 g (79%) of tetrahydrofuran **15** and tetrahydrofuran **14** in a 2:3 ratio. The less polar isomer **15a** was characterized as follows: R_f 0.43 (5% tetrahydrofuran/methylene chloride, two elutions); mp 54.5–56 °C (recrystallized from chloroform/hexane); IR (neat) 3420, 2985, 2910, 1445, 1375, 1065, 1030, 950, 905, 845, 725 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.88 (AB, Δν = 28.8 Hz, J_{AB} = 7.4 Hz, 2 H), 4.30 (q, J = 7.1 Hz, 1 H), 3.82 (m, 4 H), 3.56 (m, 2 H), 3.39 (s, 3 H), 1.91 (d, J = 7.1 Hz, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.17 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 91.13, 85.25, 83.16, 81.31, 78.83, 71.72, 68.29, 58.93, 40.50, 23.33, 19.51, 17.21, 13.49.

The more polar tetrahydrofuran **14** gave the following data: R_f 0.37 (5% tetrahydrofuran/methylene chloride, two elutions). The major isomer from Z-double bond, **14a**: IR (neat) 3450, 2990, 2940, 1452, 1385, 1100, 1035, 955, 920, 885, 850, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.81 (AB, Δν = 81.9 Hz, J_{AB} = 7.5 Hz, 2 H), 4.41 (q, J = 7.1 Hz, 1 H), 4.10 (d, J = 5.1 Hz, 1 H), 3.97 (m, 4 H), 3.60 (m, 2 H), 3.38 (s, 3 H), 1.90 (d, J = 7.1 Hz, 3 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.21 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 90.08, 86.05, 83.37, 80.67, 80.39, 71.49, 66.63, 58.88, 42.05, 23.68, 17.47, 17.20, 15.90. The minor isomer from Z-double bond, **14b**: IR (neat) 3440, 2980, 2930, 2870, 1450, 1375, 1285, 1247, 1155, 1100, 1035, 972, 940, 875, 845, 795, 730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$ δ 4.85 (AB, Δν = 46.5 Hz, J_{AB} = 7.5 Hz, 2 H), 4.34 (q, J = 6.9 Hz, 1 H), 4.21 (d, J = 4.8 Hz, 1 H), 3.87 (m, 1 H), 3.82 (q, J = 6.4 Hz, 1 H), 3.67 (m, 1 H), 3.60 (m, 2 H), 3.41 (s, 3 H), 2.96 (d, J = 4.8 Hz, 1 H), 1.94 (d, J = 7.0 Hz, 3 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 1.18 (d, J = 6.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 90.45, 85.09, 84.22, 83.59, 81.26, 71.67, 66.93, 59.06, 38.72, 23.18, 17.26, 15.12. (Note: This reaction is easily performed on a large scale; however, since benzyl iodide, a severe lachrymator, is produced as a byproduct extreme care should be exercised in the workup and chromatography of these compounds.)

(±)-(2S*,3R*,4S*,5R*)-4-[(2-Methoxyethoxy)methoxy]-2-(1-iodoethyl)-2,4,5-trimethyl-3-tetrahydrofuranyl Benzoate (17). Triethylamine (15.9 mL, 0.12 mol) and 4-(dimethylamino)pyridine (1.0 g, 8.24 mmol) were added to a stirred solution of tetrahydrofuran **15** (3.2 g, 8.24 mmol) in 75 mL dry methylene chloride at ambient temperature. Freshly distilled benzoyl chloride (15.9 mL, 0.12 mol) was added, and the reaction was stirred at the ambient temperature for 3 days to give an orange mixture. The reaction was quenched by the addition of 50 mL of water followed by dilution with 300 mL of ethyl acetate. The entire mixture was then poured into a 1000-mL Erlenmeyer flask and stirred with 500 mL of 10% NaOH for 1 h to remove excess benzoyl chloride (**caution**: the addition of water and mixing with 10% NaOH required the use of an ice bath). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to a thick orange oil, which was preadsorbed onto 6 g of silica gel and applied to a column of 35 g of Kieselgel 60H. Elution with hexane afforded 3.37 g (83%) of compound **17** as a mixture of two nonseparable iodo epimers: R_f 0.30 (30% ethyl acetate/hexane); IR (neat) 2970, 2920, 2865, 1720, 1600, 1585, 1445, 1375, 1265, 1110, 1030, 955, 905, 725, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) [major isomer **17a**] δ 8.06 (m, 2 H), 7.61 (m, 1 H), 7.48 (m, 2 H), 5.53 (s, 1 H), 4.94 (AB, Δν = 49.3 Hz, J_{AB} = 7.5 Hz, 2 H), 4.34 (q, J = 7.1 Hz, 1 H), 4.01 (q, J = 6.2 Hz, 1 H), 3.80 (m, 1 H), 3.63 (m, 1 H), 3.40 (m, 2 H), 3.31 (s, 3 H), 1.91 (d, J = 7.1 Hz, 3 H), 1.56 (s, 3 H), 1.42 (s, 3 H), 1.27 (d, J = 6.2 Hz, 3 H), [minor isomer **17b**] δ 8.06 (m, 2 H), 7.61 (m, 1 H), 7.48 (m, 2 H), 5.44 (s, 1 H), 4.88 (AB, Δν = 32.2 Hz, J_{AB} = 7.5 Hz, 2 H), 4.27 (q, J = 6.9 Hz, 1 H), 4.12 (q, J = 7.2 Hz, 1 H), 3.80 (m, 1 H), 3.63 (m, 1 H), 3.40 (m, 2 H), 3.28 (s, 3 H), 1.87 (d, J = 7.1 Hz, 3 H), 1.61 (s, 3 H), 1.42 (s, 3 H), 1.25 (d, J = 6.9 Hz, 3 H).

(±)-(2R*,3S*,4S*,5R*)-4-[(2-Methoxyethoxy)methoxy]-2-(1-iodoethyl)-2,4,5-trimethyl-3-tetrahydrofuranyl Benzoate (16). The same procedure as for the preparation of tetrahydrofuranyl benzoate **17** was followed except that longer reaction times were needed for approximately similar yields: R_f 0.40 (30% ethyl acetate/hexane); IR (neat) 2970, 2920, 2860, 1720, 1600, 1585, 1448, 1380, 1265, 1100, 1030, 950, 845, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) [major isomer **16a**] δ 8.05 (m, 2 H), 7.61 (m, 1 H), 7.48 (m, 2 H), 5.52 (s, 1 H), 5.00 (AB, Δν = 61.9 Hz, J_{AB} = 7.4 Hz, 2 H), 4.58 (q, J = 7.1 Hz, 1 H), 3.95 (q, J = 6.1 Hz, 1 H), 3.79 (m, 2 H), 3.59 (m, 2 H), 3.39 (s, 3 H), 1.91 (d, J = 7.2 Hz, 3 H), 1.40 (s, 3 H), 1.29 (d, J = 6.2 Hz, 3 H), 1.23 (s, 3 H), [minor isomer **16b**] δ 8.05 (m, 2 H), 7.61 (m, 1 H), 7.48 (m, 2 H), 5.73 (s, 1 H), 5.05 (AB, Δν = 81.3 Hz, J_{AB} = 7.4 Hz, 2 H) 4.52 (q, J = 6.9 Hz, 1 H), 3.93 (q, J = 6.2 Hz, 1 H), 3.79 (m, 2 H), 3.59 (m, 2 H), 3.40 (s, 3 H), 1.96 (d, J = 6.9 Hz, 3 H), 1.50 (s, 3 H), 1.24 (d, J = 6.6 Hz, 3 H), 1.21 (s, 3 H).

(±)-(2R*,3S*,4S*,5R*)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranyl Benzoate (19). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.93 mL, 6.2 mmol) was added to a stirred solution of tetrahydrofuranyl benzoate **17** (2.0 g, 4.1 mmol) in 3 mL of freshly distilled o-dichlorobenzene. The flask was equipped with a reflux condenser and lowered into a preheated oil bath at 200 °C. The reaction was heated for 20 min and allowed to cool to room temperature, and the entire reaction mixture was preadsorbed onto 7 g of silica gel. Flash chromatography on 40 g of Kieselgel 60 H eluted with hexane afforded 1.39 g (93%) of olefin **19** as a colorless viscous oil: R_f 0.33 (30% ethyl acetate/hexane); IR (neat) 3090, 3060, 2980, 2930, 2880, 1725, 1605, 1587, 1450, 1375, 1270, 1110, 1040, 915, 730, 710 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.07 (m, 2 H), 7.61 (m, 1 H), 7.48 (m, 2 H), 6.04 (m, 1 H), 5.26 (s, 1 H), 5.19 (AB of ABX, J_{AB} = 1.3 Hz, J_{AX} = 17.3 Hz, J_{BX} = 10.7 Hz, Δν = 100.1 Hz, 2 H), 5.03

(AB, $\Delta\nu$ = 72.3 Hz, J_{AB} = 7.5 Hz, 2 H), 3.88 (m, 1 H), 3.81 (q, J = 6.3 Hz, 1 H), 3.65 (m, 1 H), 3.48 (m, 2 H), 3.35 (s, 3 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.32 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.78, 142.61, 133.46, 129.68, 129.38, 128.63, 111.68, 91.56, 83.82, 82.55, 81.58, 79.61, 79.68, 66.92, 58.95, 22.71, 18.62, 13.25. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.89; H, 7.75. Found: C, 65.83; H, 8.06.

(±)-(2*S,3*S**,4*S**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranyl Benzoate (18).** The same procedure as for the preparation of tetrahydrofuran **19** was followed, beginning with iodo benzoate **16**. Yields were typically the same. The elimination reaction was easily scaled-up to produce large amounts of material; however, instead of purification by flash chromatography, it was much easier to use a large gravity column due to the amounts of *o*-dichlorobenzene required. Typically a column containing approximately 2 kg of silica gel is needed to purify 30–40 g of the pale yellow oil **18**: R_f 0.31 (30% ethyl acetate/hexane); IR (neat) 3070, 2990, 2940, 2880, 1725, 1605, 1455, 1383, 1273, 1110, 1040, 925, 710 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.05 (m, 2 H), 7.60 (m, 1 H), 7.48 (m, 2 H), 6.14 (m, 1 H), 5.45 (s, 1 H), 5.21 (AB of ABX, J_{AB} = 1.0 Hz, J_{AX} = 17.4 Hz, J_{BX} 10.8 Hz, $\Delta\nu$ = 86.4 Hz, 2 H), 4.90 (AB, $\Delta\nu$ = 54.1 Hz, J_{AB} = 7.5 Hz, 2 H), 4.01 (q, J = 6.3 Hz, 1 H), 3.79 (m, 1 H), 3.70 (m, 1 H), 3.54 (m, 2 H), 3.38 (s, 3 H), 1.31 (d, J = 6.3 Hz, 3 H), 1.30 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.07, 143.20, 133.20, 129.40, 129.32, 128.38, 112.46, 90.67, 85.19, 83.44, 82.55, 80.71, 71.50, 67.04, 58.74, 20.84, 15.92, 12.60; MS (70 eV), m/e (relative intensity) 289 (13), 138 (12), 137 (100), 105 (33), 89 (21); HRMS, m/e calcd for $C_{20}H_{29}O_6$ (M^+ + 1) 365.1964, found 365.1941.

(±)-(2*R,3*S**,4*S**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranyl Benzoate (21).** The allylic benzoate **20** (26.7 mg, 0.058 mmol) was submitted to the identical cyclization conditions as described for **12** and **13**. Purification of the products by preparative TLC on two silica gel plates (10 × 20 cm × 0.25 mm) eluted four times with 15% ethyl acetate/hexanes yielded 11.8 mg (41%) of the previously prepared compound **16a** and 8.9 mg (31%) of a second tetrahydrofuran iodide as slightly yellow oil: R_f 0.47 (50% ethyl acetate/hexane); IR (neat) 3070, 2990, 2935, 2880, 1750, 1455, 1385, 1272, 1180, 1075, 715 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.02 (m, 2 H), 7.63 (m, 1 H), 7.49 (m, 2 H), 5.67 (s, 1 H), 5.00 (AB, $\Delta\nu$= 67.6 Hz, J_{AB} = 7.4 Hz, 2 H), 4.81 (q, J = 6.3 Hz, 1 H), 4.03 (q, J = 6.3 Hz, 1 H), 3.81 (m, 1 H), 3.72 (m, 1 H), 3.57 (m, 2 H), 3.39 (s, 3 H), 1.74 (d, J = 6.8 Hz, 3 H), 1.61 (s, 3 H), 1.27 (d, J = 6.3 Hz, 3 H), 1.19 (s, 3 H).

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (22 μL, 0.145 mmol) was added to a stirred solution of the tetrahydrofuranyl benzoate (14.3 mg, 0.029 mmol) in 0.7 mL of *o*-dichlorobenzene. The flask was equipped with a reflux condenser and lowered into a preheated oil bath at 200 °C. The reaction was heated for 10 min and allowed to cool to room temperature, and the entire reaction mixture was applied directly to four TLC plates (10 × 20 cm × 0.5 mm). Elution once with 5% tetrahydrofuran/methylene chloride afforded 10.1 mg (95%) of tetrahydrofuran **21**: R_f 0.54 (10% tetrahydrofuran/methylene chloride; IR (neat) 3090, 3060, 2985, 2935, 2880, 1725, 1605, 1455, 1275, 1110, 1040, 930, 710 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.01 (m, 2 H), 7.61 (m, 1 H), 7.47 (m, 2 H, 5.82 (m, 1 H), 5.37 (s, 1 H), 5.21 (AB of ABX, J_{AB} = 1.6 Hz, J_{AX} = 17.5 Hz, J_{BX} = 10.1 Hz, $\Delta\nu$ = 110.7 Hz, 2 H), 4.99 (AB, $\Delta\nu$ = 43.9 Hz, J_{AB} = 7.9 Hz, 2 H), 3.97 (q, J = 6.5 Hz, 1 H), 3.83 (m, 1 H), 3.77 (m, 1 H), 3.58 (m, 2 H), 3.40 (s, 3 H), 1.55 (s, 3 H), 1.33 (d, J = 6.3 Hz, 3 H), 1.30 (s, 3 H).

(±)-(2*R,3*S**,4*R**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranol (22).** The saponification procedure as described for the preparation of tetrahydrofuranol **24** was used. Yields averaged 70% for the alcohol **22**: R_f 0.22 (10% tetrahydrofuran/methylene chloride); IR (neat) 3460, 3095, 2980, 2935, 1445, 1375, 1105, 1045, 955, 930, 850 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 6.00 (m, 1 H), 5.26 (AB of ABX, J_{AB} = 1.9 Hz, J_{AX} = 17.6 Hz, J_{BX} = 10.9, $\Delta\nu$ = 65.5 Hz, 2 H), 4.82 (AB, $\Delta\nu$ = 50.5 Hz, J_{AB} = 7.4 Hz, 2 H), 3.96 (d, J = 4.7 Hz, 1 H), 3.90 (q, J = 6.5 Hz, 1 H), 3.84 (m, 1 H), 3.60 (m, 3 H), 3.41 (s, 3 H), 3.18 (d, J = 4.7 Hz, 1 H), 1.41 (s, 3 H), 1.22 (s, 3 H), 1.21 (d, J = 6.5 Hz, 3 H).

(±)-(2*R,3*R**,4*R**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranol (24).** Solid lithium hydroxide (5.0 mg) was added to a stirred solution of the tetrahydrofuranyl benzoate **19** (15.6 mg, 0.043 mmol) in 2 mL of tetrahydrofuran/1 mL of water/0.25 mL of methanol. The reaction was stirred at room temperature for 12 h. The mixture was poured into a separatory funnel and extracted with 3 mL of ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil. Purification on one preparative TLC plate (10 × 20 cm × 0.25 mm) eluted once with 7% tetrahydrofuran/methylene chloride afforded 7.6 mg (70%) of tetrahydrofuranol **24**: R_f 0.31 (10% tetrahydrofuran/methylene chloride); IR (neat) 3450, 3090, 2990, 2950, 1465, 1390, 1115, 1075, 1045, 960, 930, 855 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.96 (m, 1 H), 5.12 (AB of ABX, J_{AB} = 1.5 Hz, J_{AX} = 17.3 Hz, J_{BX} = 10.7 Hz, $\Delta\nu$ = 89.2 Hz, 2 H), 4.90 (AB, $\Delta\nu$ = 27.4 Hz, J_{AB} = 7.4 Hz, 2 H), 3.86 (m, 1 H), 3.73 (m, 2 H), 3.57 (m, 2 H), 3.40 (s, 3 H), 1.32 (s, 3 H), 1.28 (s, 3 H), 1.21 (d, J = 6.3 Hz, 3 H).

(±)-(2*S,3*S**,4*R**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranol (23).** The same procedure as described for the preparation of tetrahydrofuranol **24** was used, beginning with benzoate **18**. Yields were typically the same, affording **23** as a colorless oil: R_f 0.29 (5% tetrahydrofuran/methylene chloride); IR (neat) 3460, 3100, 2995, 2950, 1460, 1380, 1105, 1045, 925 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.06 (m, 1 H), 5.15 (AB of ABX, J_{AB} = 1.3 Hz, J_{AX} = 17.4 Hz, J_{BX} = 10.8 Hz, $\Delta\nu$ = 85.7 Hz, 2H), 4.81 (AB, $\Delta\nu$ = 67.5 Hz, J_{AB} = 7.5 Hz, 2 H), 4.10 (s, 1 H), 3.92 (q, J = 6.5 Hz, 1 H), 3.86 (m, 1 H), 3.57 (m, 3 H), 3.39 (s, 3 H), 1.34 (s, 3 H), 1.24 (s, 3 H), 1.20 (d, J = 6.5 Hz, 3 h).

(±)-(2*S,4*S**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranone (25).** Pyridinium chlorochromate (60 mg, 0.28 mmol) was added in one portion as a free-flowing powder to a stirred solution of tetrahydrofuranol **14** (21.6 mg, 0.055 mmol) in 3 mL of dry methylene chloride. The reaction was stirred for 16 h at room temperature and was filtered through a 2.5-cm bed of Florosil and washed with 50 mL of methylene chloride. The filtrate was concentrated to a pale orange oil, which was purified by preparative TLC on two silica gel plates (10 × 20 cm × 0.25 mm) eluted once with 2% tetrahydrofuran/methylene chloride to afford 20.4 mg (96%) of the corresponding iodotetrahydrofuranone: R_f 0.59 (5% tetrahydrofuran/methylene chloride); IR (neat) 2970, 2925, 2870, 1755, 1445, 1380, 1075, 1025, 970 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) [major iodo epimer] δ 4.78 (AB, $\Delta\nu$ = 57.8 Hz, J_{AB} = 7.3 Hz, 2 H), 5.52 (q, J = 7.1 Hz, 1 H), 3.86 (q, J = 6.3 Hz, 1 H), 3.70 (m, 2 H), 3.53 (m, 2 H), 336 (s, 3 H), 1.91 (d, J = 7.2 Hz, 3 H), 1.38 (d, J = 6.3 Hz, 3 H), 1.30 (s, 3 H), 1.25 (s, 3 H), [minor isomer] δ 4.78 (AB, $\Delta\nu$ = 144.6 Hz, J_{AB} = 7.4 Hz, 2 H), 4.32 (q, J = 6.9 Hz, 1 H), 3.91 (q, J = 6.2 Hz, 1 H), 3.70 (m, 2 H), 3.54 (m, 2 H), 3.36 (s, 3 H), 1.85 (d, J = 6.9 Hz, 3 H), 1.38 (d, J = 6.3 Hz, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H).

DBU (35 μL, 0.24 mmol) was added to a stirred solution of the α-(iodoethyl)tetrahydrofuranone (23 mg, 0.06 mmol) in 1.0 mL of *o*-dichlorobenzene. The flask was equipped with a reflux condenser and lowered into a preheated oil bath at 200 °C. The reaction was heated for 20 min, removed from the heat, and allowed to cool to room temperature. The crude mixture was applied directly to four preparative TLC plates (10 × 20 cm × 0.5 mm) and eluted once with 30% ethyl acetate/hexane to afford 13.4 mg (86%) of keto olefin **25** as a single isomer: R_f 0.49 (5% tetrahydrofuran/methylene chloride); IR (neat) 3090, 2980, 2930, 1760, 1640, 1450, 1380, 1070, 1030, 980, 925 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.89 (m, 1 H), 5.29 (AB of ABX, J_{AB} = 1.1 Hz, J_{AX} = 17.7 Hz, J_{BX} = 11.0 Hz, $\Delta\nu$ = 94.3 Hz, 2 H), 4.71 (AB, $\Delta\nu$ = 70.2 Hz, J_{AB} = 7.2 Hz, 2 H), 3.90 (q, J = 6.3 Hz, 1 H), 3.74 (m, 1 H), 3.59 (m, 1 H), 3.52 (m, 2 H), 3.37 (s, 3 H), 1.40 (d, J = 6.3 Hz, 3 H), 1.31 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 212.78, 138.04, 115.06, 90.95, 82.22, 78.73, 77.19, 71.56, 67.34, 58.95, 21.63, 15.60, 12.48.

(±)-(2*R,4*S**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranone (26).** The same procedure as that used for the oxidation of tetrahydrofuranol **14** was used on tetrahydrofuranol **15** to provide a colorless oil, which was characterized as the α-(iodoethyl)-3-tetrahydrofuranone: R_f 0.66 (5% tetrahydrofuran/methylene chloride); IR (neat) 2980, 2930, 1755, 1445, 1380, 1070, 1025, 980, 850 cm^{-1}; ^{1}H NMR (360

MHz, $CDCl_3$) δ 4.80 (AB, $\Delta\nu$ = 97.8 Hz, J_{AB} = 7.3 Hz, 2 H), 4.41 (q, J = 6.3 Hz, 1 H), 4.29 (q, J = 7.1 Hz, 1 H), 3.77 (m, 1 H), 3.62 (m, 1 H), 3.53 (m, 2 H), 3.38 (s, 3 H), 1.97 (d, J = 7.1 Hz, 3 H), 1.39 (s, 3 H), 1.38 (d, J = 7.1 Hz, 3 H), 1.35 (s, 3 H).

Dehydrohalogenation following the same procedure as described for preparation of **25** led to the purification of the isomeric tetrahydrofuranone **26** as a colorless oil: R_f 0.52 (5% tetrahydrofuran/methylene chloride); IR (neat) 3110, 2945, 2890, 1765, 1460, 1390, 1085, 1040, 995 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.72 (m, 1 H), 5.25 (AB of ABX, J_{AB} = 1.1 Hz, J_{AX} = 17.4 Hz, J_{BX} = 10.6 Hz, $\Delta\nu$ = 55.7 Hz, 2 H), 4.84 (AB, $\Delta\nu$ = 87.2 Hz, J_{AB} = 7.3 Hz, 2 H), 3.84 (q, J = 6.4 Hz, 1 H), 3.75 (m, 1 H), 3.64 (m, 1 H), 3.53 (m, 2 H), 3.38 (s, 3 H), 1.43 (s, 3 H), 1.39 (d, J = 6.4 Hz, 3 H), 1.24 (s, 3 H).

(±)-(2*S,3*R**,4*R**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranol (27).** Lithium borohydride (40 mg, 1.80 mmol) was added in one portion as a free-flowing powder to a magnetically stirred solution of ketone **25** (450 mg, 1.74 mmol) at 0 °C in 5 mL of anhydrous tetrahydrofuran. The reaction was stirred at 0 °C for 1 h. When the reaction was complete, quenching was carried out by the dropwise addition of 1 mL of methanol over 20 min. The reaction mixture was allowed to warm to room temperature and stirring continued for 3 h. The crude reaction mixture was preadsorbed directly onto 1 g of silica gel and purified by flash chromatography on a column packed with 6 g of Kieselgel 60H. Elution with 100 mL of hexane followed by elution with 300 mL of 10% ethyl acetate/hexane afforded 424 mg (94%) of tetrahydrofuranol **27**: R_f 0.11 (30% ethyl acetate/hexane); IR (neat) 3450, 3105, 2990, 2930, 1465, 1375, 1120, 1069, 940, 920, 850 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.99 (m, 1 H), 5.20 (AB of ABX, J_{AB} = 1.7 Hz, J_{AX} = 17.7 Hz, J_{BX} = 10.9 Hz, $\Delta\nu$ = 44.8 Hz, 2 H), 4.85 (AB, $\Delta\nu$ = 31.4 Hz, J_{AB} = 7.6 Hz, 2 H), 3.85 (m, 2 H), 3.72 (m, 1 H), 3.63 (d, J = 11.6 Hz, 1 H), 3.54 (m, 2 H), 3.38 (s, 3 H), 3.31 (d, J = 11.4 Hz, 1 H), 1.37 (s, 3 H), 1.31 (s, 3 H), 1.21 (d, J = 6.5 Hz, 3 H); MS (70 eV), m/e (relative intensity) 185 (16), 113 (13), 111 (10), 101 (23), 89 (100), 84 (26), 83 (21), 71 (30); HRMS, m/e calcd for $C_{13}H_{25}O_5$ (M^+ + 1) 261.1702, found 261.1697.

(±)-(2*S,3*R**,4*S**,5*R**)-4-[(2-Methoxyethoxy)methoxy]-2,4,5-trimethyl-2-vinyl-3-tetrahydrofuranyl Benzoate (Benzoylation of 27).** Triethylamine (3.0 mL, 22.7 mmol) and 4-(dimethylamino)pyridine (~50 mg) were added to a stirred solution of tetrahydrofuran **27** (596 mg, 2.2 mmol) in 10 mL of dry methylene chloride at ambient temperature. Freshly distilled benzoyl chloride (1.32 mL, 11.3 mmol) was added and the reaction stirred at ambient temperature for 48 h. The resulting orange reaction mixture was quenched by the addition of 5 mL of water followed by dilution with 100 mL of ethyl acetate. The entire mixture was then poured into a 500-mL Erlenmeyer flask and stirred with 100 mL of 10% NaOH for 30 min to remove the excess benzoyl chloride. The organic layer was then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to an orange oil, which was preadsorbed onto 1.5 g of silica gel. Purification by flash chromatography on a column packed with 10 g of Kieselgel 60 H and eluted with hexanes afforded 699 mg (87%) of the corresponding C-3 tetrahydrofuran benzoate of **27**: R_f 0.46 (5% tetrahydrofuran/methylene chloride); IR (neat) 3060, 3040, 2950, 2910, 2850, 1720, 1440, 1370, 1105, 1085, 1060, 1030, 995, 910, 720, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.01 (m, 2 H), 7.59 (m, 1 H), 7.54 (m, 2 H) 6.10 (m, 1 H), 5.19 (s, 1 H), 5.14 (AB of ABX, not resolved, 2 H), 5.02 (AB, $\Delta\nu$ = 80.3 Hz, J_{AB} = 7.4 Hz, 2 H), 3.96 (q, J = 6.2 Hz, 1 H), 3.86 (m, 1 H), 3.65 (m, 1 H), 3.49 (m, 2 H), 3.35 (s, 3 H), 1.50 (s, 3 H), 1.41 (s, 3 H), 1.32 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.50, 140.07, 133.12, 129.44 129.31, 128.34, 114.08, 91.25, 85.76, 81.78, 80.78, 79.41, 71.49, 66.66, 58.70, 24.45, 17.98, 13.19.

(±)-(2*S,3*S**,4*S**,5*R**)-2-Formyl-4-[(2-methoxyethoxy)methoxy]-2,4,5-trimethyl-3-tetrahydrofuranyl Benzoate (28).** Ozone was bubbled through a solution of olefin **18** (10.24 g, 0.028 mol) in 250 mL of dry methylene chloride at −78 °C. When a bluish color was observed after approximately 1 h, ozone generation was stopped, and the system was flushed with oxygen for 5 min. The reaction was quenched by the addition of dimethyl sulfide (2.2 mL, 0.03 mol) and then allowed to warm to room temperature. The crude reaction mixture was concentrated in vacuo to a pale yellow oil, which was purified on a Waters Prep LC/system 500A using one Prep PAK-500/silica gel cartridge (57 mm × 30 cm, 20% ethyl acetate/hexane, flow rate 250 mL/min, two injections) to afford 9.15 g (89% of tetrahydrofuranal **28**: R_f 0.39 (50% ethyl acetate/hexane); IR (neat) 2995, 2940, 2820, 1740, 1605, 1455, 1270, 1110, 1040, 1000, 850, 710 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.62 (s, 1 H) 8.06 (m, 2 H), 7.62 (m, 1 H), 7.48 (m, 2 H), 5.61 (s, 1 H), 4.77 (AB, $\Delta\nu$ = 85.6 Hz, J_{AB} = 7.7 Hz, 2 H), 4.22 (q, J = 6.3 Hz, 1 H), 3.78 (m, 1 H), 3.62 (m, 1 H), 3.55 (m, 2 H), 3.38 (s, 3 H), 1.31 (d, J = 6.2 Hz, 3 H), 1.30 (s, 3 H), 1.24 (s, 3 H).

(±)-(2*S,3*R**,4*S**,5*R**)-2-Formyl-4-[(2-methoxyethoxy)methoxy]-2,4,5-trimethyl-3-tetrahydrofuranyl Benzoate.** The corresponding C-3 α-epimeric benzoate was prepared as described above for **28**, giving the diastereomeric aldehyde as a clear, colorless oil: R_f 0.38 (50% ethyl acetate/hexane); IR (neat) 3070, 2980, 2930, 2880, 2820, 1730, 1455, 1270, 1120, 1040, 1010, 710 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 7.99 (m, 2 H), 7.60 (m, 1 H), 7.46 (m, 2 H), 5.39 (s, 1 H), 4.92 (AB, $\Delta\nu$ = 77.0 Hz, J_{AB} = 7.6 Hz, 2 H), 4.17 (q, J = 6.3 Hz, 1 H), 3.80 (m, 1 H), 3.63 (m, 1 H), 3.42 (m, 2 H), 3.32 (s, 3 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.36 (d, J = 6.1 Hz, 3 H). Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.17. Found: C, 62.42; H, 7.30.

(±)-(2*S,3*S**,4*S**,5*R**)-3-(Benzoyloxy)-2-(2-carbethoxy-1(*E*)-propenyl)-4-[(2-methoxyethoxy)methoxy]-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran (29).** (Carbethoxyethylidene)triphenylphosphorane (23.9 g, 0.07 mol) was added as a free-flowing crystalline powder to a stirred solution of aldehyde **28** (8.25 g, 0.022 mol) in 100 mL of dry benzene. The flask was equipped with a reflux condenser and heated at reflux for 72 h, allowed to cool to room temperature, and concentrated to a yellow oil, which was purified by chromatography on a large gravity column packed with 1 kg of silica gel. Elution with 1 L of hexane followed by 2 L of 20% ethyl acetate/hexane afforded 9.24 g (93%) of unsaturated ester **29** as a clear colorless oil: R_f 0.47 (50% ethyl acetate/hexane); IR (neat) 3050, 2970, 2920, 2870, 1720, 1600, 1580, 1450, 1370, 1265, 1100, 1035, 945, 845, 740, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.06 (m, 2 H), 7.62 (m, 1 H), 7.49 (m, 2 H), 7.00 (m, 1 H), 5.61 (s, 1 H), 4.85 (AB, $\Delta\nu$ = 70.1 Hz, J_{AB} = 7.4 Hz, 2 H), 4.19 (m, 2 H), 4.01 (q, J = 6.3 Hz, 1 H), 3.76 (m, 1 H), 3.65 (m, 1 H), 3.52 (m, 2 H), 3.37 (s, 3 H), 1.98 (d, J = 1.3 Hz, 3 H), 1.39 (s, 3 H), 1.28 (m, 9 H). Anal. Calcd for $C_{24}H_{34}O_8$: C, 63.97; H, 7.61. Found: C, 63.70; H, 7.53.

(±)-(2*S,3*R**,4*S**,5*R**)-3-(Benzoyloxy)-2-(2-carbethoxy-1(*E*)-propenyl)-4-[(2-methoxyethoxy)methoxy]-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran.** (Carbethoxyethylidene)triphenylphosphorane (1.5 g, 4.09 mmol) was added to a stirred solution of the C-3 epimeric aldehyde of **28** (376 mg, 1.02 mmol) in 10 mL of dry benzene. The flask was equipped with a reflux condenser, heated at reflux for 36 h, and allowed to cool to room temperature and the entire reaction mixture preadsorbed onto 2.5 g of silica gel. Purification by flash chromatography on a column packed with 10 g of Kieselgel 60 H eluted with 200 mL of hexane followed by 400 mL of 10% ethyl acetate/hexane afforded 465 mg of (98%) of unsaturated ethyl ester of the C-3 epimeric series: R_f 0.52 (50% ethyl acetate/hexane); IR (neat) 3070, 2990, 2940, 2890, 1730, 1715, 1455, 1370, 1275, 1115, 1040, 960, 750, 710 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.05 (m, 2 H), 7.61 (m, 1 H), 7.47 (m, 2 H), 6.99 (br s, 2 H), 5.30 (s, 1 H), 4.92 (AB, $\Delta\nu$ = 94.7 Hz, J_{AB} = 7.3 Hz, 2 H), 4.17 (m, 2 H), 4.00 (q, J = 6.3 Hz, 1 H), 3.77 (m, 1 H), 3.58 (m, 1 H), 3.44 (m, 2 H), 3.33 (s, 3 H), 2.04 (d, J = 1.3 Hz, 3 H), 1.48 (s, 3 H), 1.40 (s, 3 H), 1.27 (d, J = 6.2 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H).

(±)-(2*S,3*S**,4*S**,5*R**)-3-(Benzoyloxy)-2-(2-carbethoxy-1(*E*)-propenyl)-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-4-ol (30).** Zinc bromide (405 mg, 1.8 mmol) was added in one portion as a free-flowing powder to a magnetically stirred solution of tetrahydrofuran **29** (164 mg, 0.365 mmol) in 7 mL of dry methylene chloride at room temperature. Rapid stirring was continued for 2 h, followed by quenching of the reaction with 1 mL of saturated NH_4Cl, followed by addition of 10 mL of saturated $NaHCO_3$. Removal of the cloudy white aqueous layer was followed by dilution of the organic layer with 30 mL of ethyl acetate and successive extractions with 20 mL of saturated NaCl and 20 mL of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a yellowish solid. Purification on four preparative TLC plates (10 × 20 cm × 0.5 mm)

eluted once with 30% ethyl acetate/hexane afforded 115 mg (87%) of alcohol **30** as a white crystalline powder: mp 106.5–108 °C (recrystallized from chloroform/hexane); R_f 0.40 (30% ethyl acetate/hexane, two elutions); IR ($CHCl_3$) 3535, 2990, 2925, 1720, 1650, 1605, 1455, 1380, 1310, 1270, 1105, 1030, 995, 910 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.08 (m, 2 H), 7.63 (m, 1 H), 7.49 (m, 2 H), 7.01 (s, 1 H), 5.45 (s, 1 H), 4.20 (m, 2 H), 4.03 (q, J = 6.2 Hz, 1 H), 2.04 (s, 3 H), 1.98 (br s, 1 H), 1.39 (s, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.26 (d, J = 6.3 Hz, 3 H), 1.21 (s, 3 H); MS (70 eV), m/e (relative intensity) 275 (6), 223 (13), 157 (18), 105 (100), 77 (52); HRMS, m/e calcd for $C_{20}H_{27}O_6$ (M^+ + 1) 363.1813, found 363.1808. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.32; H, 7.24. Found: C, 66.23; H, 7.35.

(±)-(2*S,3*R**,4*S**,5*R**)-3-(Benzoyloxy)-2-(2-carbethoxy-1(*E*)-propenyl)-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-4-ol.** The corresponding C-3 α-epimer of **30** was prepared as described above for compound **30**, affording 86% of the expected α-benzoate as a white crystalline solid: mp 82–83.5 °C (recrystallized from chloroform/hexane); R_f 0.48 (50% ethyl acetate/hexane); IR (neat, prior to crystallization) 3440, 3060, 2920, 2875, 1725, 1600, 1450, 1375, 1270, 1090, 1035, 845, 710 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.09 (m, 2 H), 7.61 (m, 1 H), 7.47 (m, 2 H), 6.94 (br s, 1 H), 5.27 (s, 1 H), 4.12 (m, 2 H), 3.98 (q, J = 6.1 Hz, 1 H), 2.07 (d, J = 1.4 Hz, 3 H), 1.51 (s, 3 H), 1.27 (d, J = 6.8 Hz, 3 H), 1.26 (s, 3 H), 1.21 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.46, 165.59, 140.46, 133.62, 129.82, 129.13, 129.02, 128.57, 84.66, 80.73, 78.85, 77.71, 60.66, 25.97, 21.51, 14.07, 13.31, 12.89. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.27; H, 7.23. Found: C, 66.37; H, 7.16.

(±)-(2*S,3*S**,4*S**,5*R**)-2-(3-Hydroxy-2-methyl-1(*E*)-propenyl)-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3,4-diol (31).** A solution of DIBAL-H (1.64 mmol, 1.64 mL of 1 M in methylene chloride) was added dropwise over 5 min to a magnetically stirred solution of alcohol **30** in 10 mL of dry methylene chloride at −78 °C. Stirring was continued for 20 min followed by quenching with 0.5 mL of saturated NH_4Cl solution. The reaction mixture was allowed to warm to room temperature followed by addition of 2 g of anhydrous $MgSO_4$. After all water had been absorbed, the reaction mixture was filtered through a 2-cm pad of Celite and washed with 20 mL of ethyl acetate and 20 mL of tetrahydrofuran. The filtrate was concentrated in vacuo to a yellowish oil, which was purified by preparative TLC on four plates (10 × 20 cm × 0.5 mm) eluted once with 40% tetrahydrofuran/methylene chloride to afford 50.4 mg (70%) of triol **31** as a very viscous, colorless oil: R_f 0.17 (40% tetrahydrofuran/methylene chloride); IR (neat) 3400, 2990, 2945, 2880, 1455, 1385, 1065, 1020, 945, 920, 815, 760 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.73 (br s, 1 H), 3.94 (br s, 2 H), 3.91 (br d, J = 4.5 Hz, 1 H), 3.78 (q, J = 6.3 Hz, 1 H), 3.67 (s, 1 H), 3.25 (d, J = 4.9 Hz, 1 H), 3.23 (br s, 1 H), 1.77 (s, 3 H), 1.31 (s, 3 H), 1.19 (s, 3 H), 1.16 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 135.27, 132.21, 85.52, 83.87, 81.07, 77.56, 68.19, 21.03, 17.79, 14.70, 12.37.

(±)-Citreoviral (7). Manganese dioxide (approximately 75 mg) was added in one portion to a magnetically stirred solution of triol **31** (37 mg, 0.17 mmol) in 3 mL of dry ether at room temperature. After being stirred for 1 h, the entire reaction mixture was filtered through a pipet containing a 3-cm pad of Celite and washed with 10 mL of ether and 20 mL of tetrahydrofuran. The filtrate was concentrated in vacuo to yield an off-white crystalline solid. Purification on two preparative TLC plates (10 × 20 cm × 0.25 mm) eluted once with 40% tetrahydrofuran/methylene chloride afforded 25 mg (68%) of synthetic citreoviral (**7**) as a white crystalline solid: mp 144.5–145 °C (recrystallized from chloroform/hexane); R_f 0.44 (40% tetrahydrofuran/methylene chloride); IR ($CHCl_3$) 3620, 2940, 1695, 1460, 1380, 1100, 1060, 1025, 715 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.36 (s, 1 H), 6.68 (br s, 1 H), 3.98 (br s, 1 H), 3.88 (q, J = 6.3 Hz, 1 H), 1.87 (d, J = 1.0 Hz, 3 H), 1.41 (s, 3 H), 1.25 (s, 3 H), 1.21 (d, J = 6.3 Hz, 3 H); ^1H NMR (360 MHz, 5% DMSO-d_6/acetone-d_6) δ 9.35 (s, 1 H), 6.79 (br s, 1 H), 5.19 (d, J = 5.7 Hz, 1 H), 3.94 (d, J = 5.4 Hz, 1 H), 3.85 (s, 1 H), 3.82 (q, J = 7.2 Hz, 1 H), 1.81 (d, J = 2.1 Hz, 3 H), 1.35 (s, 3 H), 1.20 (s, 3 H), 1.14 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, 5% DMSO-d_6/acetone-d_6) δ 195.93, 163.81, 135.90, 85.42, 85.23, 80.24, 79.35, 21.01, 19.63, 13.15, 10.08; MS (70 eV) m/e (relative intensity) 214 (2), 179 (6), 125 (41), 123 (17), 114 (45), 96 (43), 87 (56), 84 (49), 69 (100); HRMS, m/e calcd for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1213. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.70; H, 8.47. Found: C, 61.67; H, 8.51.

(±)-(2*S,3*S**,4*S**,5*R**)-2-(3-Hydroxy-2-methyl-1(*E*)-propenyl)-4-[(2-methoxyethoxy)methoxy]-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3-ol (33).** A solution of DIBAL-H (0.066 mol, 66 mL of 1 M in methylene chloride) was added via cannula over 20 min to a stirred solution of unsaturated ester **29** (6.0 g, 13.34 mmol) in 200 mL of dry methylene chloride at −78 °C. The reaction was stirred at −78 °C for 1.5 h followed by quenching with 2 mL of water at −78 °C. Upon warming to room temperature, the reaction mixture became gelatinous, but was diluted with 500 mL of ethyl acetate and treated with approximately 75 g of powdered sodium fluoride added in small quantities with rapid stirring. The mixture produced a solid, which settled rapidly, giving a clear solution when stirring was stopped (approximately 15 min). The solids were filtered off and washed with ethyl acetate (200 mL). The organic layer was concentrated in vacuo to a pale yellow oil, which was preadsorbed onto 7 g of silica gel. Purification by flash chromatography on a column packed with 35 g of Kieselgel 60 H eluted with 250 mL of methylene chloride followed by 700 mL of 10% tetrahydrofuran/methylene chloride yielded 4.02 g (13.2 mmol, 99%) of diol **33** as a colorless oil: R_f 0.11 (2% ethanol/18% tetrahydrofuran/80% methylene chloride, two elutions); IR (neat) 3435, 2990, 2945, 1445, 1390, 1110, 1045, 850, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.74 (m, 1 H), 4.80 (AB, $\Delta\nu$ = 69.9 Hz, J_{AB} = 7.3 Hz, 2 H), 4.23 (s, 1 H), 3.97 (s, 2 H), 3.84 (m, 3 H), 3.55 (m, 4 H), 3.39 (s, 3 H), 1.83 (d, J = 0.9 Hz, 3 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.19 (d, J = 6.5 Hz, 3 H). Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.17; H, 9.28. Found: C, 59.02; H, 9.34.

(±)-(2*S,4*S**,5*R**)-2-(2-Formyl-1(*E*)-propenyl)-4-[(2-methoxyethoxy)methoxy]-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3-one (34).** Pyridinium chlorochromate (1.3 g, 6.18 mmol) was added in one portion as a free-flowing powder to a stirred solution of diol tetrahydrofuran **33** (316.7 mg, 1.03 mmol) in 10 mL of dry methylene chloride. The reaction was stirred at room temperature for 24 h. The entire reaction mixture was filtered through a 3.5-cm pad of Celite/Florisil mixture and washed with 50 mL of ethyl acetate. The filtrate was concentrated in vacuo to a dark orange oil, which was preadsorbed onto 1 g of silica gel. Purification by flash chromatography on a column packed with 7 g of Kieselgel 60 H and eluted with 100 mL of methylene chloride followed by 100 mL of 5% tetrahydrofuran/methylene chloride afforded 135 mg (43%) of keto aldehyde **34**: R_f 0.72 (20% tetrahydrofuran/methylene chloride); IR (neat) 2860, 2700, 1758, 1685, 1455, 1200, 1160, 1135, 980, 955 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.37 (s, 1 H), 6.40 (br s, 1 H), 4.72 (AB, $\Delta\nu$ = 59.8 Hz, J_{AB} = 7.3 Hz, 2 H), 3.93 (q, J = 6.3 Hz, 1 H), 3.64 (m, 1 H), 3.52 (m, 1 H), 3.44 (m, 2 H), 3.34 (s, 3 H), 2.00 (d, J = 1.3 Hz, 3 H), 1.45 (s, 3 H), 1.40 (d, J = 6.3 Hz, 3 H), 1.32 (s, 3 H); MS (70 eV), m/e (relative intensity) 195 (9), 183 (19), 167 (14), 125 (19), 113 (40), 109 (15), 96 (14), 89 (100); HRMS, m/e calcd for $C_{15}H_{24}O_6$ (M^+) 300.1573, found, 300.1569.

(±)-(2*S,4*S**,5*R**)-2-(2-Formyl-1(*E*)-propenyl)-4-hydroxy-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3-one (36).** Zinc bromide (approximately 20 mg) was added to a rapidly stirred solution of keto aldehyde **34** (7.8 mg, 0.026 mmol) in 1 mL of dry methylene chloride at room temperature. The reaction was stirred for 3 h followed by direct application onto one preparative TLC plate (10 × 20 cm × 0.25 mm). Elution with 5% tetrahydrofuran/methylene chloride provided 2.3 mg (60%) of alcohol **36** as a colorless oil: R_f 0.53 (10% tetrahydrofuran/methylene chloride); IR (neat) 3450, 2950, 2885, 1775, 1695, 1455, 1390, 1215, 975, 935, 900 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.37 (s, 1 H), 6.43 (br s, 1 H), 4.06 (q, J = 6.4 Hz, 1 H), 2.03 (s, 1 H), 2.09 (d, J = 1.3 Hz, 3 H), 1.47 (s, 3 H), 1.36 (s, 3 H), 1.32 (d, J = 6.3 Hz, 3 H).

(±)-(2*S,3*S**,4*S**,5*R**)-2-(3-Hydroxy-2-methyl-1(*E*)-propenyl)-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3,4-diol (35).** Lithium aluminum hydride (14 mg, 0.37 mmol) was added in one portion to a magnetically stirred solution of ketone **36** (26.4 mg, 7.29 mmol) in 2 mL of dry ether at room temperature. Stirring was continued for 24 h followed by quenching with the successive addition of 10 drops of water, 10 drops of 10% NaOH solution, and finally with 25 drops of water. This mixture was stirred for 10 min and diluted with 10 mL of ether followed by addition of

2 g of anhydrous $MgSO_4$. When water had been removed from the mixture, the entire contents of the flask were filtered through a 2-cm plug of Celite and washed with 25 mL of tetrahydrofuran. The filtrate was concentrated in vacuo followed by application onto two silica gel preparative TLC plates (10 × 20 cm × 0.25 mm). Elution with 40% tetrahydrofuran/methylene chloride afforded 11.6 mg (72%) of triol **35**: mp 82–84 °C (recrystallized from chloroform/hexanes); R_f 0.44 (40% tetrahydrofuran/methylene chloride); IR (neat, prior to crystallization) 3360, 1450, 1380, 1320, 1265, 1220, 1160, 1120, 1105, 1065, 1015, 955, 930, 870, 845 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.63 (br s, 1 H), 3.99 (br s, 2 H), 3.80 (q, J = 6.1 Hz, 1 H), 3.66 (d, J = 9.8 Hz, 1 H), 2.93 (d, J = 10.0 Hz, 1 H), 1.86 (d, J = 1.0 Hz, 3 H), 1.41 (s, 3 H), 1.21 (d, J = 6.2 Hz, 3 H), 1.20 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.79, 126.04, 85.14, 81.78, 78.06, 77.58, 68.99, 26.81, 20.58, 15.09, 13.05.

The triol **35** was also prepared by deprotection of its corresponding MEM ether. Zinc bromide (9.0 mg, 0.4 mmol) was added in one portion to a rapidly stirred solution of the 3α-hydroxy isomer of **33** (30.0 mg, 0.098 mmol) in 2 mL of dry methylene chloride at 0 °C. Stirring was continued at 0 °C for 1 h followed by application directly onto two preparative TLC plates (10 × 20 cm × 0.25 mm) which were eluted once with 40% tetrahydrofuran/methylene chloride to afford 10.5 mg (49%) of triol **35** as white crystalline needles.

(±)-Epicitreoviral (32). Manganese dioxide (approximately 60 mg) was added in one portion to a magnetically stirred solution of triol **35** (22.1 mg, 0.1 mmol) in 2 mL of dry ether at room temperature. After being stirred for 45 min, the entire reaction mixture was filtered through a pipet containing a 3 cm thick pad of Celite and washed with 10 mL of ether and 10 mL of tetrahydrofuran. The filtrate was concentrated in vacuo to a pale yellow oil, which was purified by preparative TLC on a silica gel plate (10 × 20 cm × 0.25 mm) eluted once with 40% tetrahydrofuran/methylene chloride to yield 13.1 mg (61%) of epicitreoviral (**32**) as a colorless oil: R_f 0.47 (40% tetrahydrofuran/methylene chloride); IR (neat) 3460, 2980, 2930, 2880, 1680, 1450, 1375, 1210, 1105, 1045, 1070, 1015, 960, 930, 855, 795 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.40 (s, 1 H), 6.61 (br s, 1 H), 3.87 (q, J = 6.4 Hz, 1 H), 3.80 (d, J = 10.1 Hz, 1 H), 2.63 (br d, J = 7.0 Hz, 1 H), 1.95 (d, J = 1.2 Hz, 3 H), 1.48 (s, 3 H), 1.25 (s, 3 H), 1.23 (d, J = 6.4 Hz, 3 H); ^1H NMR (300 MHz, 5% DMSO-d_6/acetone-d_6) δ 9.37 (s, 1 H), 6.83 (s, 1 H), 5.10 (br s, 1 H), 3.88 (q, J = 6.1 Hz, 1 H), 3.79 (br s, 1 H), 2.53 (br s, 1 H), 1.89 (s, 3 H), 1.40 (s, 3 H), 1.18 (s, 3 H), 1.14 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75.4 MHz, 5% DMSO-d_6/acetone-d_6) δ 196.38, 158.03, 137.56, 85.65, 82.14, 79.51, 76.81, 26.02, 22.08, 13.92, 10.09.

(±)-(2*S,3*R**,4*S**,5*R**)-2-(2-Formyl-1(*E*)-propenyl)-4-[(2-methoxyethoxy)methoxy]-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3-ol (37).** Manganese dioxide (5.16 g, 0.059 mol) was added to a magnetically stirred solution of diol **33** (3.65 g, 0.012 mol) in 20 mL of dry ether at room temperature. The reaction was stirred for 3.5 h followed by filtration of the entire reaction mixture through a 60-mL fritted funnel containing a 3-cm bed of Celite. The manganese dioxide residues were washed with 100 mL of tetrahydrofuran. The filtrate was concentrated in vacuo to a yellow oil that was preadsorbed onto 4.5 g of silica gel. Purification by flash chromatography on a column packed with 15 g of Kieselgel 60 H eluted with 150 mL of methylene chloride followed by 150 mL of 5% tetrahydrofuran/methylene chloride provided 2.12 g (58%) of unsaturated aldehyde **37** as a colorless oil: R_f 0.47 (20% tetrahydrofuran/methylene chloride); IR (neat) 3450, 2930, 2880, 1685, 1640, 1455, 1380, 1045, 920, 850, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.37 (s, 1 H), 6.69 (br s, 1 H), 4.77 (AB, $\Delta\nu$ = 64.4 Hz, J_{AB} = 7.4 Hz, 2 H), 4.23 (d, J = 4.9 Hz, 1 H), 3.91 (q, J = 6.5 Hz, 1 H), 3.79 (m, 1 H), 3.53 (m, 4 H), 3.37 (s, 3 H), 1.90 (d, J = 1.2 Hz, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.19 (d, J = 6.5 Hz, 3 H). Anal. Calcd for $C_{15}H_{26}O_6$: C, 59.56; H, 8.67. Found: C, 59.69; H, 8.77.

Preparation of the 2(*E*),4(*E*),6(*E*)-Heptatrienoate 38. Lithium diisopropylamide (LDA) was prepared by the dropwise addition of *n*-butyllithium (14.5 mL of 2.55 *M* solution in hexane, 0.037 mol) to magnetically stirred diisopropylamine (6.0 mL, 0.043 mol) at 0 °C. After standing at 0 °C for 10 min followed by dilution with 75 mL of dry tetrahydrofuran, the solution was cooled to −78 °C and stirred for 10 min. Neat 4-(diethylphosphinyl)crotonate (8.86 mL, 0.04 mol) was added dropwise over 30 min, resulting in a deep yellow solution. Care must be taken not to add the phosphonate too rapidly as it will freeze and prevent stirring. The yellow phosphonate anion solution was allowed to stir for 1 h at −78 °C followed by the dropwise addition of a solution of aldehyde **37** (1.88 g, 6.15 mmol) in 3 mL of dry tetrahydrofuran over 10 min. The dry ice/acetone bath was left in place, and the reaction was allowed to gradually warm to room temperature with continued stirring for a total reaction time of 12 h. The reaction was quenched by the addition of 5 mL of saturated NH_4Cl solution and washed with 3 × 20 mL of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to an orange oil that was preadsorbed onto 4 g of silica gel. Purification by flash chromatography on a column packed with 15 g of Kieselgel 60 H eluted successively with 200 mL of hexane, 200 mL of 10% ethyl acetate/hexane, and 400 mL of 25% ethyl acetate/hexane afforded 1.85 g (75%) of triene ester **38** as a colorless oil: R_f 0.33 (65% ethyl acetate/hexane); IR (neat) 3460, 2980, 2940, 1710, 1612, 1450, 1370, 1330, 1240, 1035, 945, 855 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33 (dd, J = 15.2, 10.9 Hz, 1 H), 6.55 (d, J = 15.2 Hz, 1 H), 5.28 (dd, J = 15.1, 11.2 Hz, 1 H), 6.01 (br s, 1 H), 5.87 (d, J = 15.3 Hz, 1 H), 4.79 (AB, $\Delta\nu$ = 84.8 Hz, J_{AB} = 7.5 Hz, 2 H), 4.22 (s, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.86 (q, J = 6.5 Hz, 1 H), 3.82 (m, 1 H), 3.57 (m, 3 H), 3.40 (s, 1 H), 3.38 (s, 3 H), 1.96 (s, 3 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.18 (d, J = 6.6 Hz, 3 H); MS (70 eV), m/e (relative intensity) 309 (5), 221 (5), 163 (22), 135 (19), 127 (23), 107 (10), 89 (100). HRMS, m/e calcd for $C_{21}H_{34}O_7$ (M^+) 398.2295, found 398.2326.

Conversion to the Trienal 39. Diisobutylaluminum hydride (DIBAL-H) (0.17 mL of 1 M in methylene chloride, 0.17 mmol) was added dropwise to a solution of triene ester **38** (17.2 mg, 0.043 mmol) in 2 mL of dry methylene chloride at −78 °C. The reaction was stirred for 30 min followed by quenching with 15 drops of water. The mixture was allowed to warm to room temperature, diluted with 10 mL of tetrahydrofuran, and then dried with 1 g of anhydrous $MgSO_4$. Filtration of the reaction mixture and washing with 10 mL of tetrahydrofuran provided a filtrate which was concentrated in vacuo, affording crude trienol, which was used directly without purification. Addition of manganese dioxide (approximately 20 mg) to a stirred solution of the crude trienol in 1.5 mL of dry ether was followed by stirring at room temperature for 0.5 h. The entire reaction mixture was filtered through a 2 cm thick pad of Celite packed into a pipet and washed with 10 mL of tetrahydrofuran. Concentration of the filtrate in vacuo provided a pale yellow crystalline compound, which was purified by preparative TLC on silica gel. Elution with 60% ethyl acetate/hexane afforded 9.9 mg (65% overall for two steps) of white crystalline trienal **39**: mp 88–89 °C (recrystallized from ether/hexane); R_f 0.21 (60% ethyl acetate/hexane); IR ($CHCl_3$) 3410, 2990, 2930, 2880, 2815, 2720, 1670, 1600, 1450, 1440, 1290, 1155, 1120, 1040, 940, 850, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.55 (d, J = 7.9 Hz, 1 H), 7.16 (dd, J = 15.1, 11.0 Hz, 1 H), 6.66 (d, J = 15.2 Hz, 1 H), 6.41 (dd, J = 15.2, 11.0 Hz, 1 H), 6.17 (dd, J = 15.1, 8.0 Hz, 1 H), 6.10 (br s, 1 H), 4.79 (AB, $\Delta\nu$ = 75.3 Hz, J_{AB} = 7.4 Hz, 2 H), 4.24 (d, J = 4.9 Hz, 1 H), 3.87 (q, J = 6.5 Hz, 1 H), 3.82 (s, 1 H), 3.54 (m, 3 H), 3.40 (d, J = 5.0 Hz, 1 H), 3.38 (s, 3 H), 1.99 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.19 (d, J = 6.5 Hz, 3 H); MS (70 eV), m/e (relative intensity) 127 (8), 105 (11), 96 (12), 91 (28), 89 (100), 83 (13), 77 (14); HRMS, m/e calcd for $C_{19}H_{30}O_6$ (M^+) 354.2034, found 354.2085. Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.40; H, 8.37.

Aldol Condensation Product 41. Lithium diisopropylamide (LDA) was prepared by the dropwise addition of *n*-butyllithium (0.27 mL of 2.55 *M* solution in hexane, 0.68 mmol) to rapidly stirred, neat diisopropylamine (0.11 mL, 0.75 mmol) at 0 °C. The mixture was allowed to stand at 0 °C for 5 min followed by dilution with 3 mL of dry tetrahydrofuran, cooling to −78 °C, and continued stirring for 5 additional minutes. Freshly distilled hexamethylphosphoramide (HMPA) (0.13 mL, 0.75 mmol) was added to the solution as it was stirring at −78 °C. A solution of α-pyrone **40**[15] (101 mg, 0.66 mmol) in 1 mL of dry tetrahydrofuran was added dropwise over 1 min to the stirred LDA solution at −78 °C, resulting in a bright yellow solution. After the mixture was stirred for 5 min, a solution of aldehyde **39** (83 mg, 0.24 mmol) in 1 mL of dry tetrahydrofuran was added over a 1-min period.

The reaction was complete in approximately 5 min, followed by quenching with 0.5 mL of saturated NH_4Cl solution and warming to room temperature. The solution was then diluted with 20 mL of tetrahydrofuran and extracted with three 10-mL portions of saturated lithium chloride solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil that was preadsorbed onto 500 mg of silica gel. Purification by flash chromatography on a column packed with 5 g of Kieselgel 60 H eluted with ethyl acetate afforded 116.6 mg (96%) of the condensation product **41** as a colorless, thick oil: R_f 0.21 (ethyl acetate); IR (neat) 3420, 2980, 2930, 1690, 1640, 1560, 1450, 1405, 1245, 935, 810, 740 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.37–6.12 (m, 3 H), 5.84 (br s, 1 H), 5.72 (dd, J = 14.9, 6.8 Hz, 1 H), 5.46 (s, 1 H), 4.79 (AB, $\Delta\nu$ = 73.8 Hz, J_{AB} = 7.4 Hz, 2 H), 4.65 (br s, 1 H), 4.23 (d, J = 4.7 Hz, 1 H), 3.82 (s, 3 H), 3.74 (m, 3 H), 3.60–3.48 (m, 4 H), 3.38 (s, 3 H), 2.83 (dd, J = 14.2, 8.2 Hz, 1 H), 2.68 (dd, J = 14.2, 4.1 Hz, 1 H), 1.92 (s, 3 H), 1.91 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 3 H), 1.18 (d, J = 6.5 Hz, 3 H).

(±)-(2*S,3*S**,4*S**,5*R**)-2-(6-Carbethoxy-2-methyl-1(*E*),3-(*E*),5(*E*)-hexatrienyl)-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3,4-diol (42).** A solution of dimethylboron bromide (0.62 mL, 6.85 mmol) in 2 mL of freshly distilled ethylene dichloride was added dropwise over 5 min to a stirred solution of triene ester **38** (574 mg, 1.37 mmol) in 7 mL of dry methylene chloride at −78 °C. The reaction was stirred at −78 °C for 20 min, followed by quenching with 1 mL of saturated $NaHCO_3$ solution and warming to room temperature. Dilution of the reaction mixture with 10 mL of tetrahydrofuran and extraction with 5 mL of saturated $NaHCO_3$ solution was followed by drying of the organic layer with anhydrous $MgSO_4$ and filtering. The filtrate was concentrated in vacuo to a pale yellow viscous oil that was preadsorbed onto 1 g of silica gel. Purification by flash chromatography on a column packed with 5 g of Kieselgel 60H eluted with 100 mL of methylene chloride followed by 300 mL of 10% tetrahydrofuran/methylene chloride afforded 277 mg (65%) of a thick colorless oil (diol **42**), which crystallized upon standing: mp 97–99 °C (recrystallized from chloroform/hexane); R_f 0.22 (10% tetrahydrofuran/methylene chloride); IR (neat, prior to crystallization) 3460, 2990, 2940, 2880, 1705, 1618, 1450, 1385, 1335, 1245, 1140, 950, 930, 860, 800 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31 (dd, J = 15.4, 11.1 Hz, 1 H), 6.51 (d, J = 15.5 Hz, 1 H), 6.30 (dd, J = 15.3, 11.1 Hz, 1 H), 5.95 (br s, 1 H), 5.88 (d, J = 15.2 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 1 H), 3.95 (d, J = 4.7 Hz, 1 H), 3.81 (q, J = 6.3 Hz, 1 H), 1.93 (d, J = 1.0 Hz, 3 H), 1.91 (d, J = 5.0 Hz, 1 H), 1.71 (s, 1 H), 1.37 (s, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.21 (s, 3 H), 1.18 (d, J = 6.1 Hz, 3 H); MS (70 eV), m/e (relative intensity) 310 (12), 222 (25), 192 (25), 163 (94), 135 (100), 121 (66); HRMS, m/e calcd for $C_{17}H_{26}O_5$ (M^+) 310.1773, found 310.1794.

Caution: Dimethylboron bromide is very volatile and corrosive. Extreme care should be exercised when using this reagent.

(±)-(2*S,3*S**,4*S**,5*R**)-2-(6-Formyl-2-methyl-1(*E*),3-(*E*),5(*E*)-hexatrienyl)-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran-3,4-diol (43).** Diisobutylaluminum hydride (DIBAL-H) (2.6 mL of a 1 M solution in methylene chloride, 2.6 mmol) was added dropwise over 5 min to a stirred solution of diol **42** (161 mg, 0.52 mmol) in 3 mL of dry methylene chloride at −78 °C. The reaction turned yellow upon the addition of the DIBAL-H. Stirring was continued at −78 °C for 45 min followed by quenching with 0.5 mL of water and warming to room temperature. The reaction mixture was diluted with 25 mL of ethyl acetate followed by the addition of solid sodium fluoride (approximately 3 g) in small portions with rapid stirring until the solution became clear. The mixture was filtered through a 2-cm pad of Celite and washed with 100 mL of ethyl acetate. The filtrate was concentrated in vacuo to a colorless oil that was applied to two preparative TLC plates (10 × 20 cm × 0.5 mm). Elution with 70% ethyl acetate/hexane afforded 8.61 mg (62%) of a triol as a thick colorless oil: R_f 0.17 (70% ethyl acetate/hexane); IR (neat) 3400, 2980, 2940, 1645, 1450, 1375, 1300, 830, 800, 730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.32–6.20 (m, 3 H), 5.87 (m, 1 H), 5.78 (s, 1 H), 4.20 (br t, J = 5.7 Hz, 2 H), 3.95 (d, J = 4.8 Hz, 1 H), 3.80 (q, J = 6.3 Hz, 1 H), 1.91 (d, J = 5.0 Hz, 1 H), 1.90 (s, 3 H), 1.36 (s, 3 H), 1.20 (s, 3 H), 1.17 (d, J = 6.3 Hz, 3 H).

Manganese dioxide (138 mg, 1.6 mmol) was added in one portion to a magnetically stirred solution of the triol (85 mg, 0.32 mmol) in 3 mL of dry ether at room temperature. The reaction was stirred for 3 h followed by filtration of the entire reaction mixture through a 1.5 cm thick pad of Celite and washing with 100 mL of tetrahydrofuran. The filtrate was concentrated in vacuo and applied directly to four preparative TLC plates (10 × 20 cm × 0.25 mm). Elution with 70% ethyl acetate/hexane afforded 58.5 mg (69%) of trienal **43** as a thick colorless oil: R_f 0.22 (70% ethyl acetate/hexane); IR (neat) 3430, 2980, 2930, 2740, 1660, 1600, 1445, 1375, 1295, 1010, 980, 940, 915, 845, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.56 (d, J = 8.0 Hz, 1 H), 7.14 (dd, J = 15.2, 10.9 Hz, 1 H), 6.63 (d, J = 15.3 Hz, 1 H), 6.42 (dd, J = 15.2, 10.9 Hz, 1 H), 6.18 (dd, J = 15.2, 7.9 Hz, 1 H), 6.06 (br s, 1 H), 3.96 (d, J = 4.7 Hz, 1 H), 3.82 (q, J = 5.8 Hz, 1 H), 2.04 (d, J = 5.0 Hz, 1 H), 1.96 (d, J = 1.1 Hz, 3 H), 1.70 (s, 1 H), 1.38 (s, 3 H), 1.22 (s, 3 H), 1.18 (d, J = 6.1 Hz, 3 H).

Formation of Pyrone 44. Lithium diisopropylamide (LDA) was prepared by the dropwise addition of *n*-butyllithium (0.22 mL of 2.55 M in hexane, 0.55 mmol) to rapidly stirred, neat diisopropylamine (0.079 mL, 0.57 mmol) at 0 °C. The mixture was allowed to stand at 0 °C for 5 min followed by dilution with 3 mL of dry tetrahydrofuran. To this solution was added freshly distilled hexamethylphosphoramide (HMPA) (0.1 mL, 0.57 mmol) followed by cooling to −78 °C and continued stirring for 10 min. A solution of pyrone **40** (88 mg, 0.57 mmol) in 1 mL of dry tetrahydrofuran was added dropwise over 1 min to a stirred LDA solution at −78 °C, resulting in a bright yellow solution. After the mixture was stirred for 5 min, a solution of aldehyde **43** (35.3 mg, 0.11 mmol) in 1 mL of dry tetrahydrofuran was added dropwise over 1 min. The reaction was quenched after 5 min by addition of 0.5 mL of saturated NH_4Cl solution and allowed to warm to room temperature. After dilution with 5 mL of tetrahydrofuran, the mixture was extracted with two 5-mL portions of saturated lithium chloride solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to a yellow oil, which was applied directly onto four preparative TLC plates (10 × 20 cm × 0.5 mm). Elution two times with ethyl acetate afforded 35 mg (68%) of the condensation product **44** as a thick, colorless oil: R_f 0.16 (ethyl acetate); IR (neat) 3400, 2980, 2930, 2860, 1700, 1630, 1560, 1450, 1410, 1245, 985, 930, 810, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.35–6.15 (m, 3 H), 5.81 (s, 1 H), 5.75 (dd, J = 14.9, 6.8 Hz, 1 H), 5.48 (s, 1 H), 4.65 (br s, 1 H), 3.97 (m, 1 H), 3.82 (s, 3 H), 3.81 (m, 2 H), 2.83 (dd, J = 14.2, 8.2 Hz, 1 H), 2.68 (dd, J = 14.2, 4.1 Hz, 1 H), 1.92 (s, 3 H), 1.91 (s, 3 H), 1.38 (s, 3 H), 1.22 (s, 3 H), 1.19 (d, J = 6.6 Hz, 3 H).

(±)-Citreoviridin (1). *p*-Toluenesulfonyl chloride (15.2 mg, 0.08 mmol) was added to a stirred solution of condensation product **44** (31 mg, 0.067 mmol), 4-(dimethylamino)pyridine (5.6 mg, 0.067 mmol), and triethylamine (27 μL, 0.2 mmol) in 3.0 mL of dry methylene chloride. It was important that the addition of reagents and actual reaction takes place in darkness. The reaction vessel was wrapped completely in aluminum foil and then covered with a thick black cloth. The reaction was stirred at room temperature for 12 h, after which addition of 3 mg of *p*-toluenesulfonyl chloride and continued stirring for 6 h accomplished complete conversion of starting material. The reaction flask was taken to a darkroom where chromatography was performed under a red "safe" light. Application of the entire reaction mixture onto four preparative TLC plates (10 × 20 cm × 0.5 mm) eluted twice with 20% hexane/ethyl acetate afforded crude (±)-citreoviridin (1). Once the compound was removed from silica gel it was not particularly light sensitive. Further purification by preparative TLC eluted three times with 25% hexane/ethyl acetate afforded 10.4 mg (35%) of (±)-citreoviridin as a bright yellow-orange oil, which crystallized upon standing at −20 °C in a freezer: mp 105–108 °C (recrystallized from chloroform/hexane); R_f 0.30 (ethyl acetate); IR ($CHCl_3$) 3420, 2995, 2970, 1695, 1630, 1590, 1540, 1455, 1410, 1250, 995, 810, 755 cm^{-1}; UV (MeOH) λ_{max} 386, 290, 282, 236 nm; ^1H NMR (360 MHz, $CDCl_3$) δ 7.19 (dd, J = 14.9, 11.2 Hz, 1 H), 6.54–6.23 (m, 5 H), 5.90 (s, 1 H), 5.49 (s, 1 H), 3.99 (br d, J = 3.9 Hz, 1 H), 3.83 (s, 3 H), 3.82 (q, J = 6.3 Hz, 1 H), 2.67 (br d, J = 3.9 Hz, 1 H), 1.96 (s, 3 H), 1.92 (s, 3 H), 1.82 (br s, 1 H), 1.38 (s, 3 H), 1.22 (s, 3 H), 1.18 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.70, 163.91, 154.56, 141.13, 140.70, 138.61, 136.04, 134.32, 131.13, 127.23, 118.61, 107.80, 88.57, 85.72, 84.06, 80.78, 77.00, 56.17, 21.32, 17.21, 13.41, 12.27, 8.87; MS (70 eV), m/e (relative intensity) 402 (6), 314 (38), 296 (29), 179 (11), 154 (23), 139 (100), 126 (28), 109 (22); HRMS, m/e calcd for $C_{23}H_{30}O_6$

(M^+) 402.2034, found 402.2048.

Our carbon-13 chemical shift data differed slightly from the data quoted in the literature.[4] However, a carbon spectrum of the natural product obtained at the same concentration in $CDCl_3$ as our racemic material gave the following data: ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.70, 163.93, 154.56, 141.25, 140.72, 138.64, 136.04, 134.26, 131.07, 127.18, 118.54, 107.80, 88.53, 85.68, 84.05, 80.80, 77.00, 56.16, 21.33, 17.20, 13.39, 12.26, 8.85.

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Registry No. **1**, 110549-63-8; **7**, 97514-85-7; **8**, 98168-70-8; **9**, 98095-59-1; **10**, 110510-53-7; **11**, 110510-54-8; **12a**, 107613-12-7; **12b**, 110549-54-7; **13a**, 107657-73-8; **13a** (benzoate), 110549-64-9; **13b**, 110549-55-8; **14a**, 107657-74-9; **14a** (3-one deriv), 110510-55-9; **14b**, 110549-56-9; **14b** (3-one deriv), 110549-61-6; **15a**, 107657-75-0; **15a** (3-one deriv), 110510-56-0; **15b**, 110549-57-0; **15b** (3-one deriv), 110549-62-7; **16a**, 107657-76-1; **16b**, 110549-59-2; **17a**, 107657-77-2; **17b**, 110549-58-1; **18**, 98168-77-5; **19**, 110549-60-5; **20**, 107613-13-8; **21**, 98168-73-1; **21** (iodide), 98095-65-9; **22**, 98168-74-2; **23**, 98168-76-4; **24**, 107657-78-3; **25**, 98095-68-2; **26**, 98168-75-3; **27**, 98095-67-1; **27** (benzoate), 98095-66-0; **28**, 110510-57-1; **28** (C-3 epimer), 110510-58-2; **29**, 110510-59-3; **29** (C-3 epimer), 110510-60-6; **30**, 110510-61-7; **30** (C-3 epimer), 110510-62-8; **31**, 102103-89-9; **32**, 110510-67-3; **33**, 110510-63-9; **33** (C-3 epimer), 110510-66-2; **34**, 110510-64-0; **35**, 110610-82-7; **36**, 110510-65-1; **37**, 110510-68-4; **38**, 110510-69-5; **39**, 110510-70-8; **40**, 64361-40-6; **41**, 110510-71-9; **42**, 110510-72-0; **42** (triol deriv), 110510-73-1; **43**, 110510-74-2; **44**, 110510-75-3; vinylmagnesium bromide, 1826-67-1; (*Z*)-2-bromo-2-butene, 3017-68-3; (*E*)-2-bromo-2-butene, 3017-71-8; (carbethoxyethylidene)triphenylphosphorane, 54356-04-6; ethyl 4-(diethylphosphinyl)crotonate, 10236-14-3.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles and stereoscopic views of the X-ray diffraction studies of tetrahydrofuran **15a** (10 pages). Ordering information is given on any current masthead page.

Lipase-Catalyzed Resolution of Chiral 2-Amino 1-Alcohols

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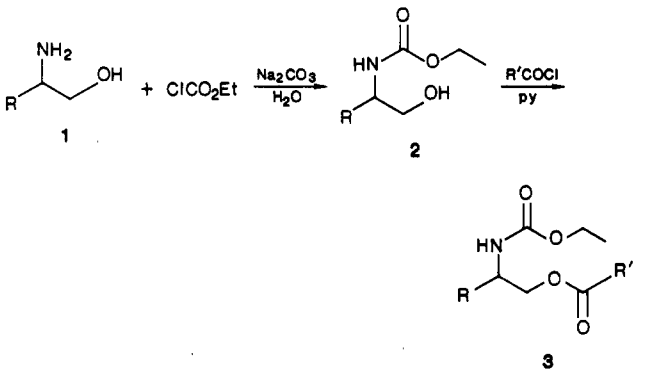
Lipase-catalyzed resolution of 2-amino 1-alcohols was readily accomplished provided that the amino group was protected as an *N*-alkoxycarbonyl derivative. Racemic 2-amino-1-butanol and 2-amino-1-propanol were chosen as model compounds, and the resolution was achieved both by hydrolysis of their ester derivatives and by transesterification in ethyl acetate. In either case the (*R*) enantiomers reacted faster, and at low conversion, the (*R*) form in high optical purity was obtained as alcohol by hydrolysis and as acetate by transesterification. The two procedures can therefore be considered as complementary with respect to the final product composition. By using commercially available lipase preparations both (*R*)-(−) and (*S*)-(+) enantiomers of 2-amino 1-alcohols were isolated in high enantiomeric excesses (≥95%).

Enzymatic catalysis has recently been successfully used for the optical resolution of several highly functionalized chiral molecules such as amino acids, diols, diesters, and hydroxy acids.[1] Surprisingly very little attention has been paid to the enzymatic resolution of chiral amino alcohols in spite of their importance both as chiral building blocks and as products of pharmaceutical interest. In particular (*S*)-(+)-2-amino-1-butanol, the chiral precursor in the synthesis of the antitubercular drug Ethambutol,[2] prepared by conventional chemical resolution is the subject of many patents[3] and papers,[4] while in only two cases was the enzymatic approach reported. The first is a Japanese patent,[5] where it is claimed that a culture of *Micrococcus* is able to selectively hydrolyze the (*R*) form of *N*-acetyl-2-amino-1-butanol, leaving the (*S*) form substantially unaffected. More recently, Klibanov and co-workers tried to resolve racemic 2-amino-1-butanol by phosphatase-catalyzed hydrolysis of its phosphate esters.[6] This approach allowed a simple, selective functionalization of the hydroxy group and an easy separation of reaction products, but reaction rate and optical purities were very poor.

Scheme I



a: R = C_2H_5, R' = CH_3
b: R = C_2H_5, R' = n-C_3H_7
c: R = CH_3, R' = CH_3

In this paper we report two strategies for enzymatic resolution of amino alcohols.

Our experiments showed that when 2-amino 1-alcohols were converted to their *N*-alkoxycarbonyl derivatives, optical resolution was easily achieved by lipase-catalyzed hydrolysis of carboxylic esters and by lipase-catalyzed transesterification in organic solvent. Racemic 2-amino-1-butanol and 2-amino-1-propanol were chosen as model

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