Chapter 5
Total Synthesis of (+)-5-*Epi*-Citreoviral Using Ruthenium-Catalyzed Asymmetric Ring-Closing Metathesis

If carbonyl compounds have been said to be 'virtually the backbone of organic synthesis,' the epoxides correspond to at least 'one of the main muscles.'[1]

Introduction

(+)-Citreoviral (**1**) was first isolated from *Penicillium citreoviride* in 1984,[2] and a year later its absolute configuration was determined (Figure 5.1).[3] Other structurally similar metabolites have been isolated from the same fungus (**3** and **4**),[4] and most have been found to be potent inhibitors of mitochondrial ATPase and oxidative phosphorylation.[5] The 2,6-dioxabicyclo[3.2.1]octane core of citreoviridinol (**4**) is also found in the aurovertin family of compounds, which exhibit a similar biological profile to the *P. citreoviride* metabolites.[6]

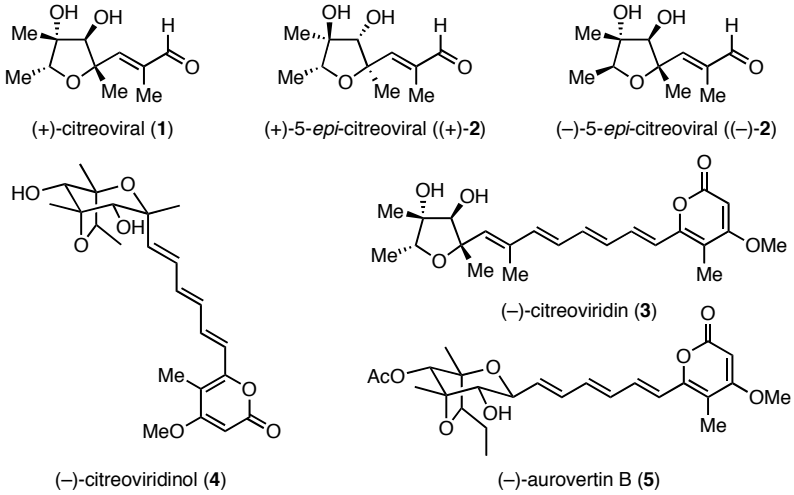
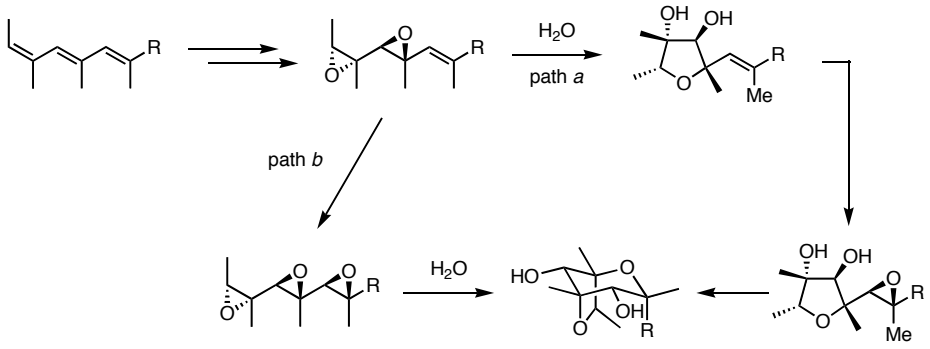


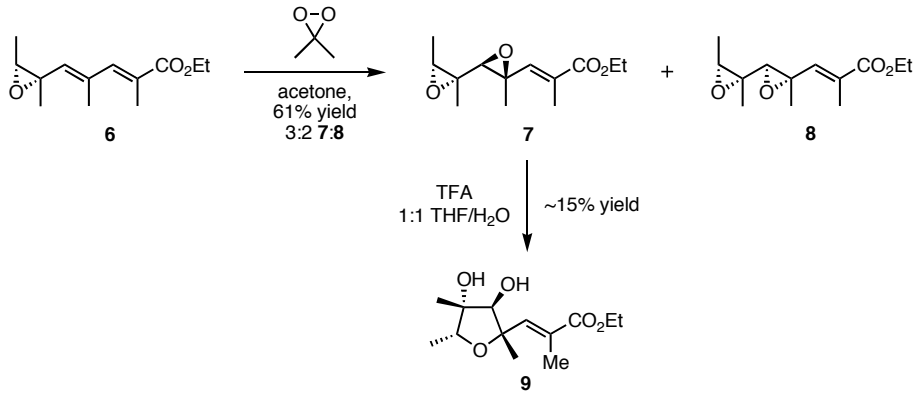
Figure 5.1. Members of a family of structurally related compounds.

The biosynthesis of **1** and **3** has been postulated to occur through a bis-epoxide that is attacked by water to yield the substituted tetrahydrofuran found in the natural product (Scheme 5.1, path *a*).[7,8] Epoxidation of the vinyl-substituted product followed by an intramolecular epoxide opening would lead to the 2,6-dioxabicyclo[3.2.1]octane core found in citreoviridinol and the aurovertins.[9] Alternatively, a tris-epoxide could be opened under aqueous conditions to yield the 2,6-dioxabicyclo[3.2.1]octane core in one biosynthetic operation (path *b*).[10]



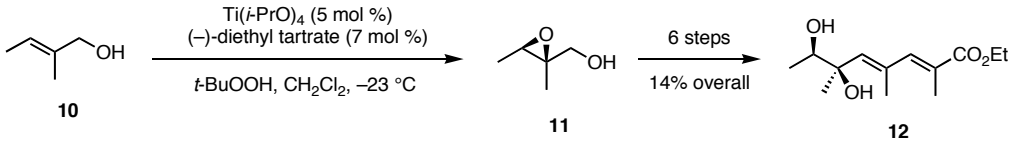
Scheme 5.1. Proposed biosynthesis of citreoviral, citreoviridin, and related structures.

Support for the proposed biosyntheses of these molecules has been provided through various syntheses of citreoviral, citreoviridin, and citreoviridinol.[11] In these cases, bis-epoxides or 1,2-diols with adjacent epoxides have reacted under acidic conditions to yield substituted tetrahydrofurans (Scheme 5.2). Further manipulation of the product by epoxidation and intramolecular ring opening (as illustrated in Scheme 5.1, path *a*) formed the desired 2,6-dioxabicyclo[3.2.1]octane core. These syntheses support the stepwise formation of citreoviridinol from citreoviral or citreoviridin. There have been no examples where a linear bis- or tris-epoxide has led to the 2,6-dioxabicyclo[3.2.1]octane core in one step.



Scheme 5.2. An example of a biomimetic synthesis of the tetrahydrofuran core (ref 10).

In addition to the biomimetic syntheses mentioned above, racemic and enantioenriched citreoviral has been made a number of other ways as well.[12] Of the asymmetric syntheses, all but one method use either a chiral auxiliary,[13] chiral reagents,[14] or a chiral, non-racemic starting material.[15] The only catalytic asymmetric report was a formal total synthesis, where a Sharpless asymmetric epoxidation was used to ultimately yield **12**, which is a known intermediate en route to citreoviral (Scheme 5.3).[16] Racemic forms of unnatural 3-*epi*-citreoviral[17] and 5-*epi*-citreoviral[18] have also been synthesized.

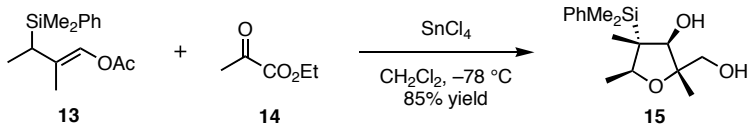


Scheme 5.3. Formal synthesis of (+)-citreoviral using asymmetric catalysis.

The interest in the synthesis of this class of compounds is due to their biological activity and the complexity of the tetrahydrofuran and 2,6-dioxabicyclo[3.2.1]octane cores. The formation of the desired cyclic structures with complete control over the stereochemistry is challenging, and the key step in many of the known syntheses is the generation of the ring system. Achieving not only diastereocontrol but also control of the

absolute stereochemistry is more challenging still, and it has been accomplished using asymmetric catalysis only once.

The previous chapter contains a study on ruthenium-catalyzed asymmetric ring-closing metathesis (ARCM), and the present chapter illustrates how ARCM was used to complete the first asymmetric total synthesis of (+)-5-*epi*-citreoviral ((+)-**2**). 5-*Epi*-citreoviral has only been synthesized once previously as a racemate, and the approach that was used to generate the tetrahydrofuran ring was a [3 + 2] annulation reaction between an allyl silane and a ketone (Scheme 5.4).[18] The synthesis described in the current chapter utilizes ARCM and an acid-catalyzed cascade epoxide opening as key steps. Additionally, the high-yield, single-step preparation of a diastereomer of the 2,6-dioxabicyclo[3.2.1]octane core found in citreoviridinol (**4**) from an intramolecular cascade epoxide-opening reaction will be discussed.

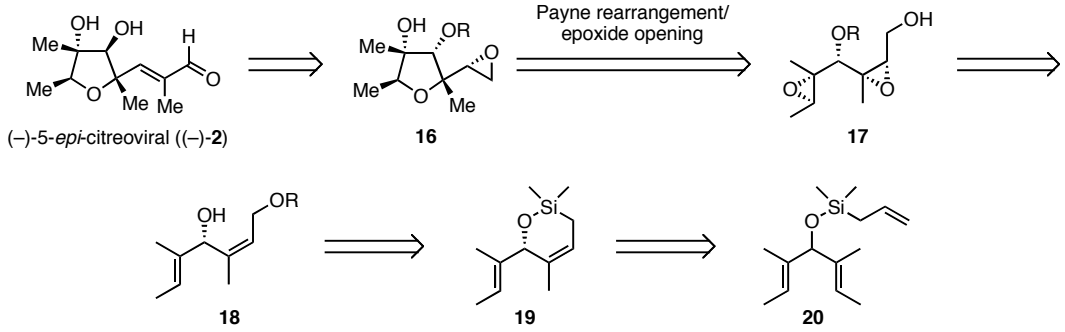


Scheme 5.4. [3 + 2] Annulation reaction to form an intermediate in the synthesis of (±)-5-*epi*-citreoviral.

Retrosynthetic Analysis

One of the most successful ARCM substrates used in the chiral, Ru-catalyzed reaction is **20**. Low catalyst loadings (≤1 mol %) can be used to obtain **19** in 92% *ee*, which makes **20** a practical starting material in the synthesis of 5-*epi*-citreoviral. It was envisioned that (–)-5-*epi*-citreoviral ((–)-**2**) could be made from tetrahydrofuran **16**, which could ultimately originate from **20** as illustrated in Scheme 5.5. The key steps in

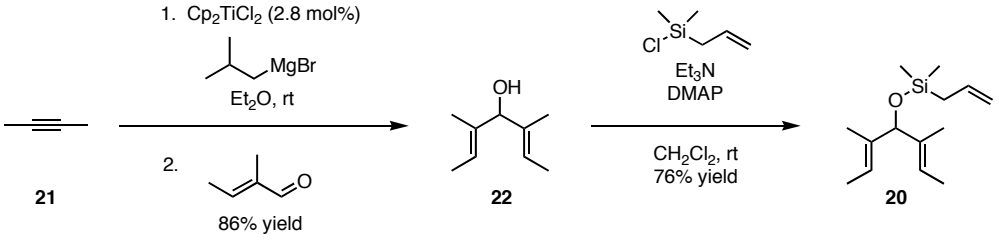
the proposed synthesis are the substrate-directed bis-epoxidation (**18** to **17**) and the Payne rearrangement/epoxide opening reaction (**17** to **16**).



Scheme 5.5. Retrosynthesis of (–)-5-*epi*-citreoviral to ARCM substrate **20**.

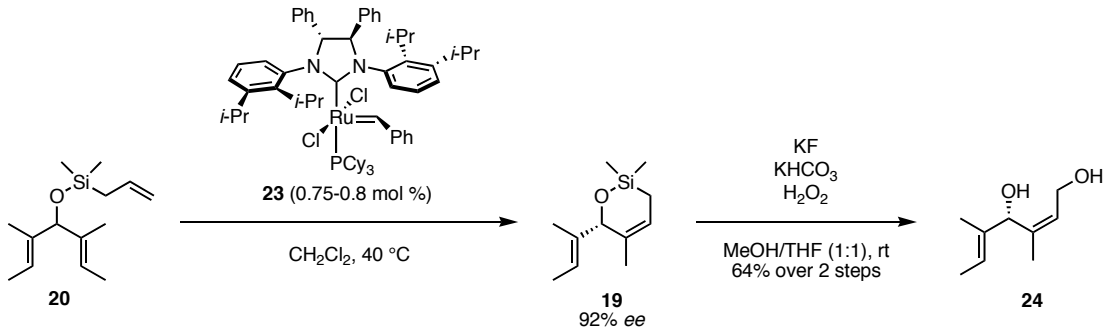
Results and Discussion

The ARCM substrate **20** was synthesized as described in the previous chapter (Scheme 5.6). The alcohol precursor **22** is available in multigram quantities in one step from 2-butyne (**21**) and tiglic aldehyde,[19] and the silyl ether **20** can be formed using standard conditions. Compound **20** is unstable to silica gel chromatography; within a minute of being applied to a silica gel column, the pale yellow oil becomes purple and an exothermic decomposition occurs. Attempts to distill the product gave impure material that would not undergo ARCM. Fortunately, the product is relatively stable to filtration through neutral alumina, and could be isolated in high purity in 76% yield.



Scheme 5.6. Synthesis of ARCM substrate **20**.

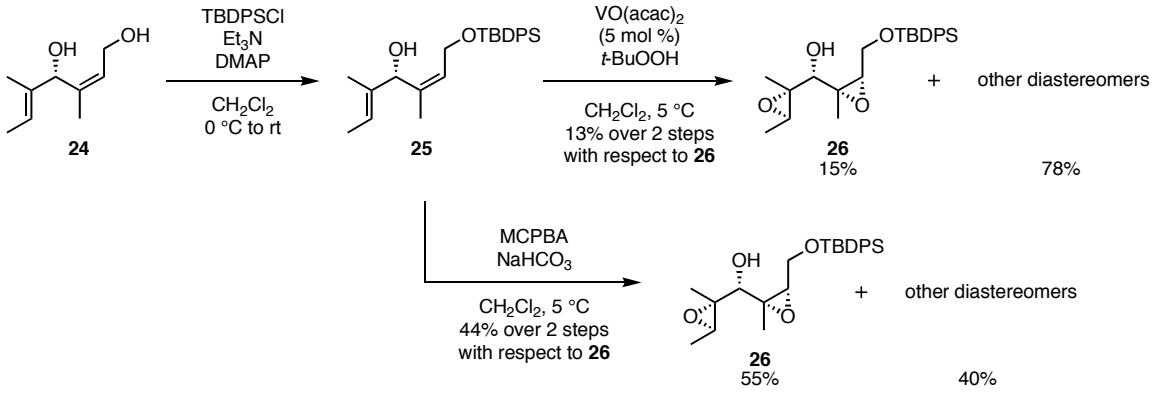
ARCM was preformed multiple times on approximately 1g of **20** using 0.75–0.8 mol % of catalyst **23**. None of the starting material was detected by TLC after 2 h (Scheme 5.7). The cyclic product **19** had an enantiomeric excess of 92%, and the absolute stereochemistry was determined as discussed in chapter 4 of this dissertation. After removal of the ruthenium-containing by-products via silica gel chromatography, **19** was subjected to a Tamao-Fleming oxidation to form diol **24** in 64% yield over two steps.[20] It has been reported that a sequential olefin metathesis/Tamao-Fleming oxidation process is possible without the need for purification,[21] but attempts to oxidize **19** to **24** without removing the ruthenium by-products resulted in an exothermic decomposition of hydrogen peroxide and no oxidation of **19**.



Scheme 5.7. Synthesis of enantioenriched diol **24** by ARCM.

Due to the different steric environments of the two hydroxyl groups in **24**, selective protection of the primary alcohol in the presence of a secondary alcohol was readily achieved. As illustrated in Scheme 5.8, installation of a *t*-butyldiphenylsilyl group occurred in high yield to afford compound **25**, which was isolated with a silicon-containing compound (most likely *t*-butyldiphenylsilanol) as a minor impurity (~7:1) that could not be removed by flash chromatography. At this point in the synthesis, only a single chiral center was present in the molecule, and its absolute stereochemistry was set

using ARCM. It was envisioned that all of the remaining chiral centers could be installed in a single, substrate-directed bis-epoxidation reaction.



Scheme 5.8. Acyclic substrate-directed epoxidation of secondary alcohol **25**.

Treatment of allyl alcohol **25** with catalytic $VO(acac)_2$ and *t*-butyl hydroperoxide as the stoichiometric oxidant resulted in a mixture of diastereomers, including the desired product **26** (Scheme 5.8, upper pathway). No starting material was present after 12 hours, and three products were isolated (separated by column chromatography) from the reaction mixture in an overall yield of approximately 93%. Due to the small amount of an impurity in alcohol **25**, the exact yield for the epoxidation reaction was not available. The ^{1}H NMR spectra of all three of the isolated products were consistent with epoxidation of both alkenes. Fortunately, the racemate of one of the diastereomers was a crystalline solid, and X-ray crystallography showed that it was the desired bis-epoxide **26** (Figure 5.2). Unfortunately, it was one of the minor products (15% of the recovered mass). The two other diastereomers were isolated in 74% and 4% yields, and the relative stereochemistry of the two products was not determined.

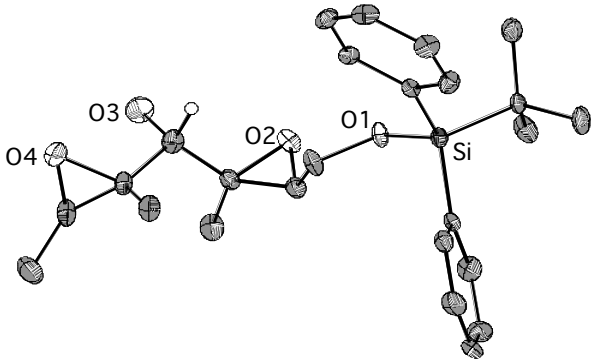


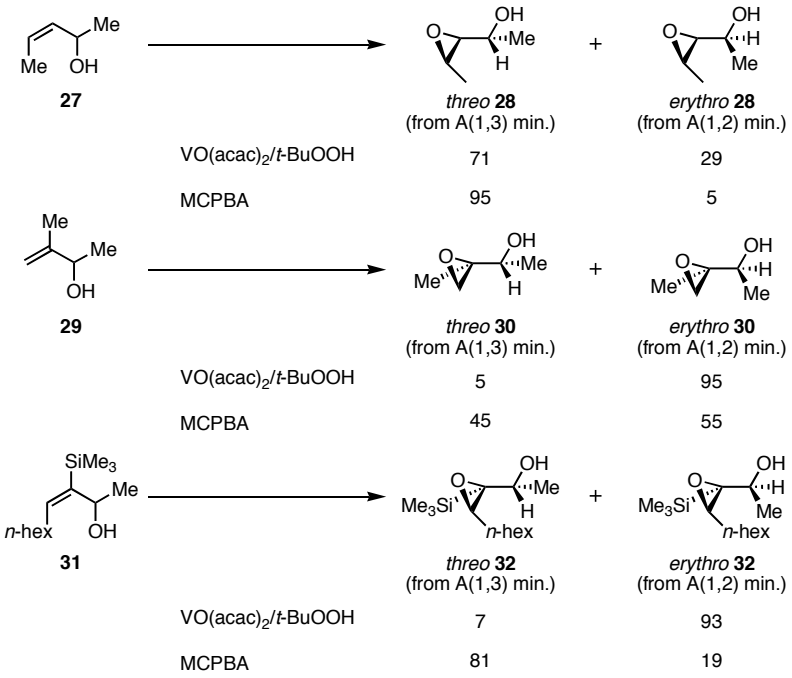
Figure 5.2. Structure of **26** with displacement ellipsoids drawn at 50% probability.

The overall yield for the formation of **26** from **24** using $VO(acac)_2$ and *t*-BuOOH was only 13%, so an alternative epoxidation procedure was examined. Treatment of **25** with buffered MCPBA at 5 °C generated all four of the possible bis-epoxide diastereomers in a different ratio than was obtained above (Scheme 5.8, lower pathway). In this case, the major product (55% of the recovered mass) was the desired compound **26**, resulting in a 44% yield over 2 steps. As with the metal-catalyzed epoxidation, no starting material was present after 12 hours, and only bis-epoxide products were isolated. Synthetically useful amounts of **26** could be produced using this procedure, with the stereochemistry at four chiral centers (three of which are present in the final product) being set in a single reaction.

A stereochemical rationale was sought in order to understand why the two epoxidation procedures led to different product distributions. In general, when there is a cis allylic olefin (**27**), MCPBA favors the product derived from A(1,3) strain minimization (*threo* **28**) to a greater extent than the vanadium conditions (Scheme 5.9).[22] On the other hand, $VO(acac)_2$/*t*-BuOOH favors the product derived from A(1,2) strain minimization more than MCPBA when the allylic alcohol has substitution at the internal position of the alkene (**29**). When there is substitution in both positions (**31**), the

vanadium-catalyzed reaction favors the product derived from A(1,2) strain minimization (*erythro* **32**), and MCPBA favors the product derived from A(1,3) strain minimization (*threo* **32**).

Sharpless proposed O=C–C=C dihedral angles for both the vanadium-catalyzed and MCPBA reactions based on the data shown in Scheme 5.9, and the preferred conformations are shown in Figure 5.3.[22b] The $VO(acac)_2$/*t*-BuOOH procedure has a favored dihedral angle of ~50 °; therefore if R_1 and R_2 are large groups, conformation **33** will higher in energy than **34**, and the *erythro* product will be preferred regardless of R_3. Due to the larger dihedral angle in the MCPBA reaction, R_1 interacts more with R_3 than R_2. Therefore, when R_1 and R_3 are large, conformation **35** (*threo* product) will be favored. These models are consistent with the products observed in the epoxidation of **31** shown in Scheme 5.9.



Scheme 5.9. Comparison of stereoselective epoxidation methods using substituted allylic alcohols (ref 22).

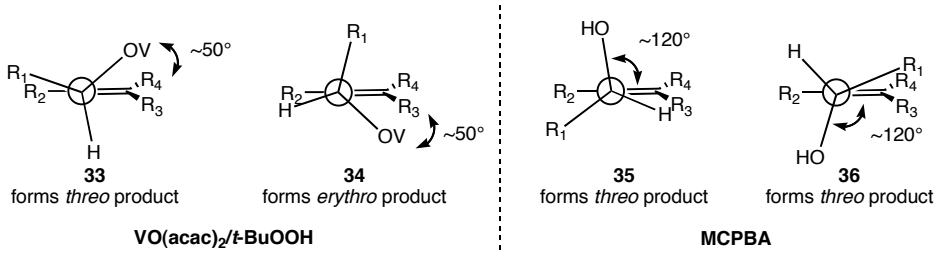
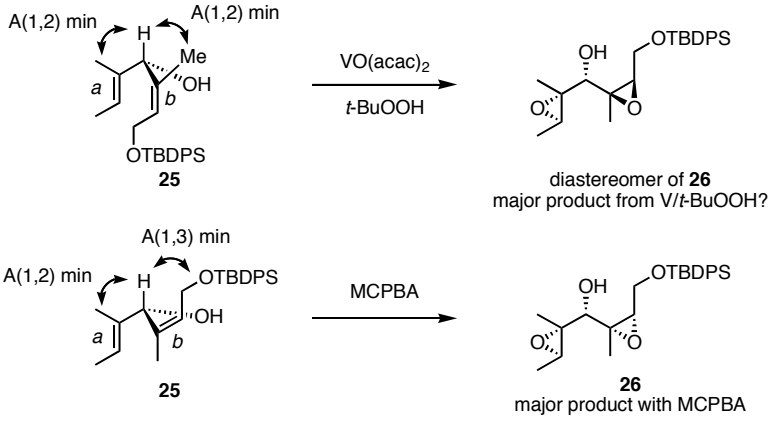


Figure 5.3. Proposed O=C–C=C dihedral angles for vanadium-catalyzed and MCPBA epoxidations.

It is possible to rationalize the difference in diastereoselectivity between the two epoxidations shown in Scheme 5.8 by looking at each olefin in 25 individually and comparing them to the model systems described above. In the desired product **26**, one epoxide needs to come from an A(1,2) strain-minimized configuration and one from an A(1,3) strain-minimized configuration (Scheme 5.10). Olefin *a* in substrate **25** does not have a cis methyl group, and therefore the A(1,2) interaction should minimized. Olefin *b* has substituents in the cis position and on the carbon adjacent to the alcohol, so both A(1,2) and A(1,3) strain is present.

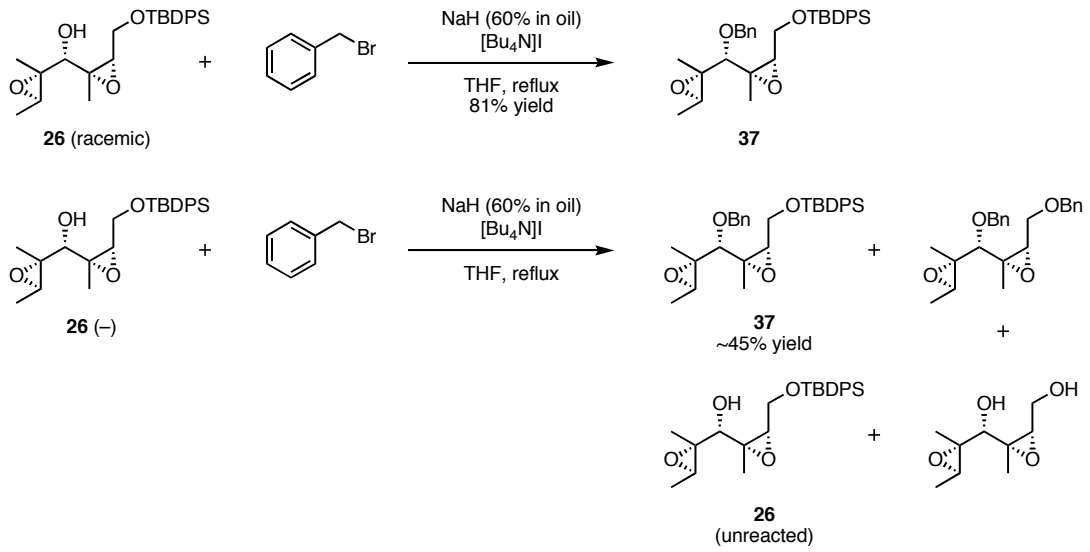


Scheme 5.10. Proposed configurations leading to bis-epoxides.

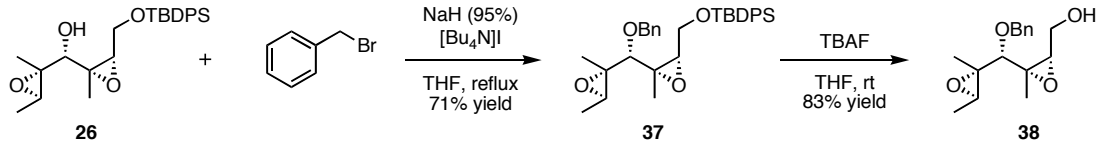
When $VO(acac)_2$/*t*-BuOOH is used as the oxidant, olefin *a* resembles model substrate **29**, and the desired epoxide (from A(1,2) minimization) should be strongly preferred. Compound **31** is most like olefin *b*, and the vanadium conditions are expected

to favor minimization of the A(1,2) strain to yield the diastereomer of **26** shown in Scheme 5.10. The MCPBA epoxidations would be expected to proceed with different levels of selectivity for each olefin oxidation relative to the vanadium reaction. The major oxirane from the epoxidation of olefin *a* should be the same as in the $VO(acac)_2$/*t*-BuOOH reaction, but the selectivity is expected to be lower based on the oxidation of model compound **29**. When olefin *b*, which resembles **31**, is treated with MCPBA, the opposite face of the alkene is expected to be epoxidized, because A(1,3) strain is preferentially minimized. Overall, the presence of **26** as the major product with MCPBA can be rationalized by treating each alkene as a separate allylic alcohol and predicting the relative stereochemistry using the proposed configurations discussed above.

With compound **26** in hand, the Payne rearrangement/epoxide-opening substrate **17** was the targeted intermediate. Attempts to protect the secondary alcohol as a *p*-methoxybenzyl (PMB) ether using a variety of conditions resulted in either no reaction or substrate decomposition. Alternatively, protection with benzyl bromide using NaH (60% in oil) as a base led to benzyl ether **37** (Scheme 5.11). These conditions were initially developed using racemic **26**; when the same conditions were used a few months later with enantioenriched **26**, a mixture of products was isolated. The ^{1}H NMR spectrum of enantioenriched **26** looked identical to that of the racemate, so it was expected that water or NaOH from the 60% NaH in oil may be contaminating the reaction and causing a hydroxide-mediated deprotection of the silyl ether. By using dry NaH in place of 60% NaH in oil, **37** was isolated in 71% yield (Scheme 5.12). Deprotection of the primary alcohol using tetrabutylammonium fluoride proceeded uneventfully to yield the Payne rearrangement/epoxide-opening substrate **38**.



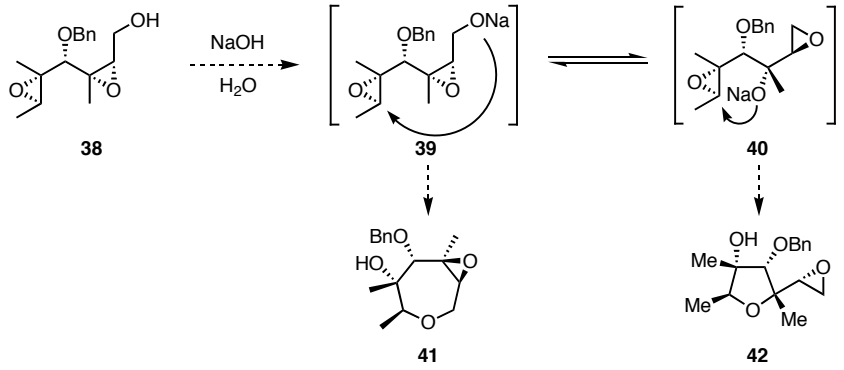
Scheme 5.11. Benzyl ether formation using fresh (upper) and aged (lower) NaH (60% in oil).



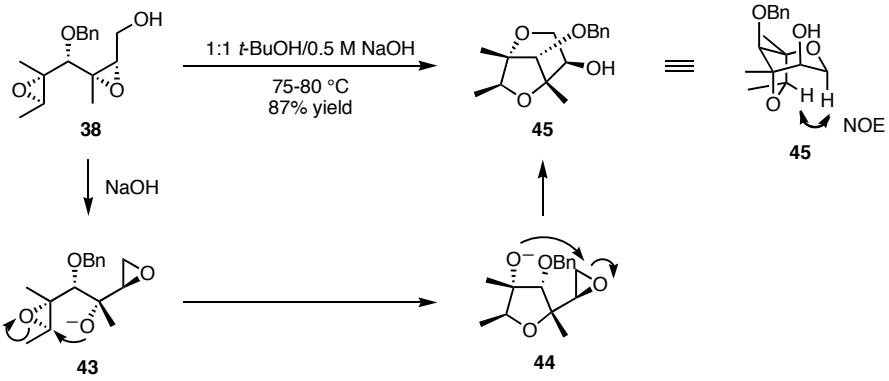
Scheme 5.12. Synthesis of bis-epoxide intermediate **38**.

It was envisioned that, upon exposure to aqueous base, compound **38** would undergo a Payne rearrangement.[23] An equilibrium of epoxy alcohols is typically formed, but internal trapping of alkoxide **40** could occur to form 5-membered ring **42** (5-endo-tet) that should be favored over a seven-membered ring derived from **39** (Scheme 5.13). When **38** was treated with aqueous NaOH at 80 °C, a single compound was isolated in 87% yield. The ^{1}H NMR spectrum contained no oxirane methylene hydrogens, and a secondary alcohol was present (based on the coupling of hydroxyl hydrogens in DMSO-d_6), indicating the desired product was not formed. Instead of **42**, the isolated product was **45**, and NOE experiments supported this structure. A proposed mechanism for the formation of **45** is shown in Scheme 5.14. The first two steps are consistent with the

mechanism in Scheme 5.13, but a second intramolecular epoxide-opening reaction occurs to give the bicyclic product.



Scheme 5.13. Proposed synthesis of **42** using a Payne-rearrangement/epoxide opening process.

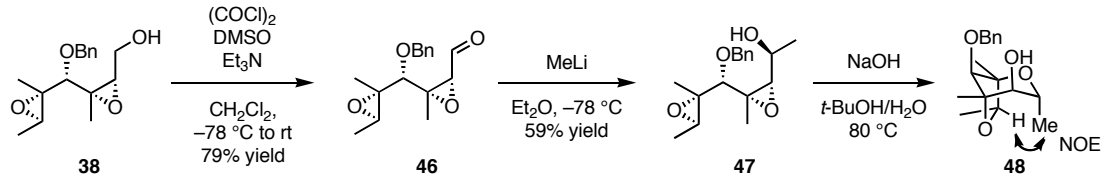


Scheme 5.14. Payne rearrangement/cascade epoxide opening sequence to form **45**.

Although compound **45** was not the desired product, it is a 2,6-dioxabicyclo[3.2.1]octane ring system and is a diastereomer of the core found in citreoviridinol and the aurovertins. Its formation here may provide insight into the biosynthesis of these families of natural products. Scheme 5.2 illustrates an epoxide opening sequence that is thought to mimic the biosynthesis of the substituted tetrahydrofuran found in citreoviral and citreoviridin. The same approach with a tris-epoxide has not been shown,[10,24] and all biomimetic synthetic approaches to compounds containing a 2,6-dioxabicyclo[3.2.1]octane core have gone through an isolated,

substituted tetrahydrofuran intermediate.[25] The high yield and stereospecificity (only one stereoisomer was observed) of the reaction in Scheme 5.14 suggest that the natural products with 2,6-dioxabicyclo[3.2.1]octane cores maybe be formed in a single step from a tris-epoxide (Scheme 5.1, path *b*).

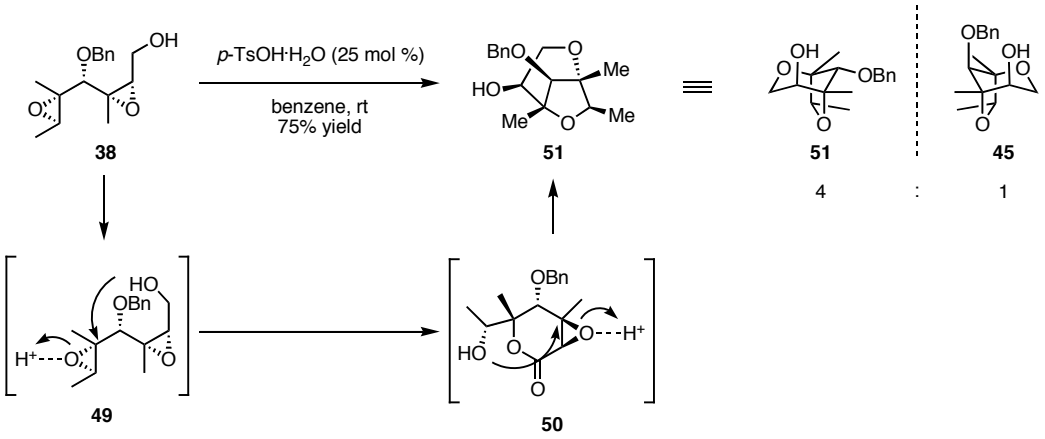
In an attempt to explore if the above route could be used to synthesize citreoviridinol, the aurovertins, or diastereomers of these natural products, substitution was introduced to **45** in the appropriate position. Primary alcohol **38** was transformed into an aldehyde with a Swern oxidation, and methyllithium was added to yield secondary alcohol **47** (Scheme 5.15). This reaction was done on 7.5 mg, and only one diastereomer was isolated. Compound **47** was treated under the same conditions as the formation of **45**, and a single product (**48**) was observed. This result illustrates that the Payne rearrangement/cascade epoxide opening sequence could be used to make citreoviral, the aurovertins, or stereoisomers of these biologically active natural products.



Scheme 5.15. Formation of a substituted 2,6-dioxabicyclo[3.2.1]octane ring system.

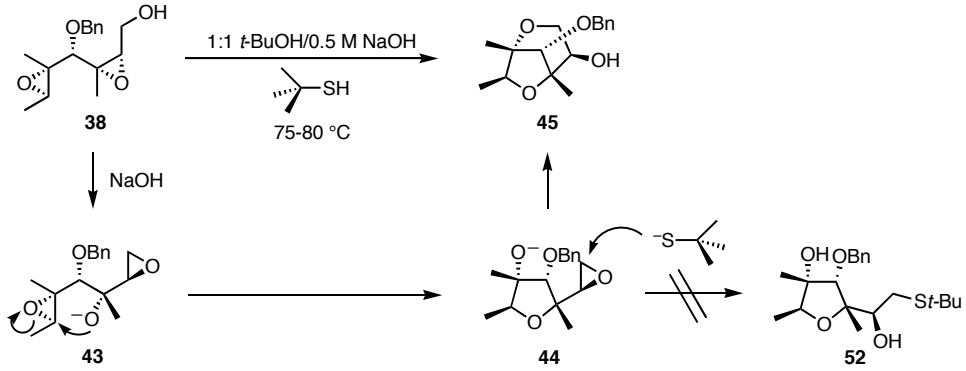
It was thought that if the formation of **45** occurred as illustrated in Scheme 5.14, treatment of **38** with acid could result in a reaction where the epoxides are opened at the more sterically hindered positions. Gratifyingly, a catalytic amount of *p*-toluenesulfonic acid caused **38** to undergo an intramolecular reaction to yield a mixture of **51** and **45** (Scheme 5.16). Compound **51** is derived from the expected epoxide opening at the more hindered position and is a pseudoenantiomer of **45**. This result suggests that both

enantiomers of compounds containing 2,6-dioxabicyclo[3.2.1]octane cores could be made from a single enantiomer.



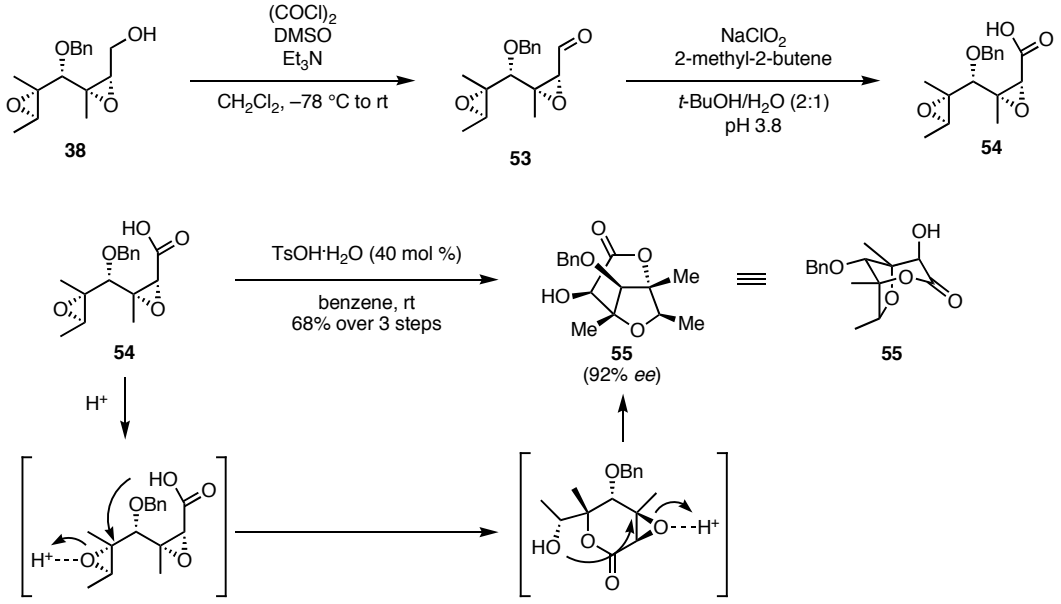
Scheme 5.16. Acid-catalyzed formation of 2,6-dioxabicyclo[3.2.1]octane ring system.

Although the formation of 2,6-dioxabicyclo[3.2.1]octane cores was exciting, it was not obvious how to synthetically transform **45** or **51** into (–)-5-*epi*-citreoviral. The six-membered ring ether needed to be opened to access a substituted tetrahydrofuran that was not part of a bicyclic system. Unfortunately, ethers are typically synthetically inert under all but extreme conditions. Attempts to intercept intermediate **44** with *t*-butyl thiolate so the six-membered ring could not form were unsuccessful (Scheme 5.17);[26] the cascade epoxide-opening reaction was too efficient.



Scheme 5.17. Failed attempt to intercept intermediate **44**.

It was finally decided that, because the cascade epoxide-opening reaction under both basic and acidic conditions was efficient and high yielding, the use of an alternative substrate could allow for further functionalization. The pyranyl rings in **45** and **51** would not be easily cleaved, but a lactone can be readily opened. Therefore, carboxylic acid **54** was made by a two-stage oxidation, and, upon treatment with acid, cyclized to cleanly form bicyclic lactone **55** in 68% yield over three steps (Scheme 5.18). No purification was needed until after the acid-catalyzed cascade epoxide-opening reaction, and no loss in optical purity was observed as determined by chiral HPLC analysis. Racemic **55** was a crystalline solid, and an X-ray crystal structure was obtained to prove the relative stereochemistry (Figure 5.4). Compound **55** resembles **51** (with a lactone in place of an ether) and is in the opposite absolute configuration relative to the initially targeted intermediate **42**. The original approach to 5-*epi*-citreoviral involved a base-induced cyclization, which would have led to the (–)-enantiomer. On the other hand compound **55** would lead to (+)-5-*epi*-citreoviral. Because both enantiomers of the chiral diamine used to make catalyst **23** are commercially available, both enantiomers of **55** should be accessible using the approach described here.



Scheme 5.18. Synthesis of lactone **55** using an acid-catalyzed cascade epoxide-opening reaction.

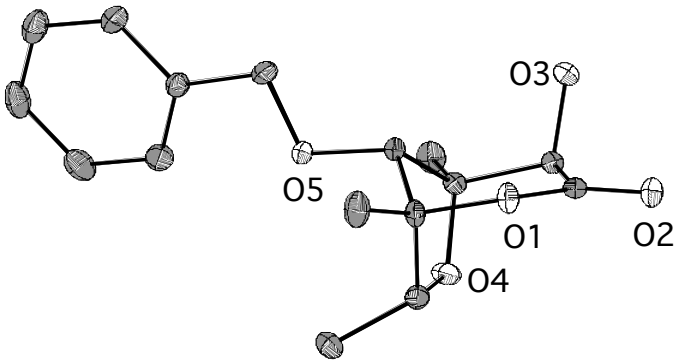
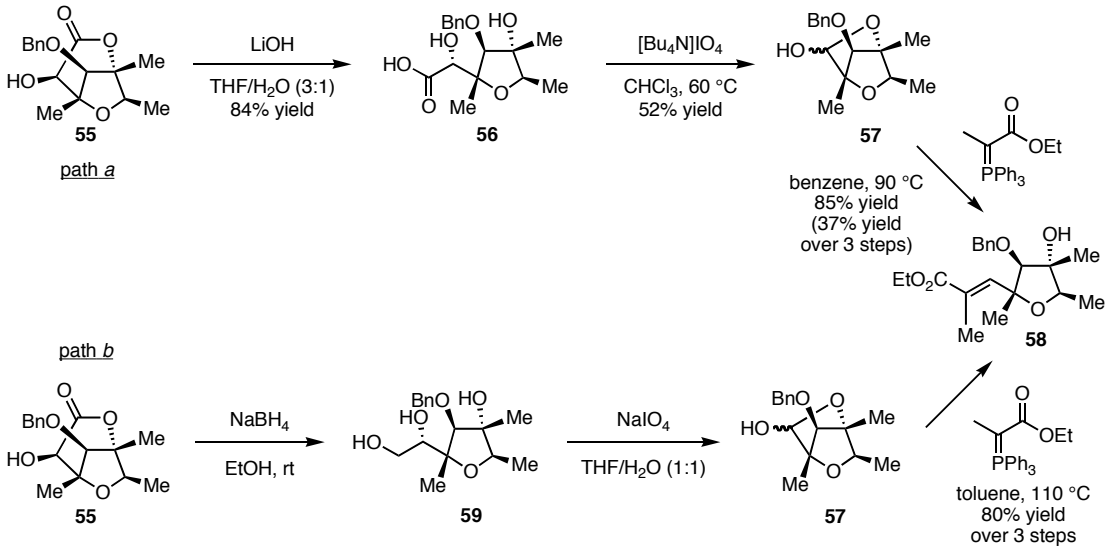


Figure 5.4. Structure of **55** with displacement ellipsoids drawn at 50% probability.

Lactone **55** contains the desired substituted tetrahydrofuran ring and can be further functionalized in a straightforward manner. The first route developed to unsaturated ester **58** is illustrated in path *a* of Scheme 5.19. The lactone was hydrolyzed with aqueous LiOH, and the resulting α-hydroxy acid was oxidatively cleaved with tetrabutylammonium periodate.[27] Treatment of **57** (which was a mixture of the hydroxy aldehyde and both diastereomers of the lactol in $CDCl_3$ and DMSO-d_6) with a stabilized

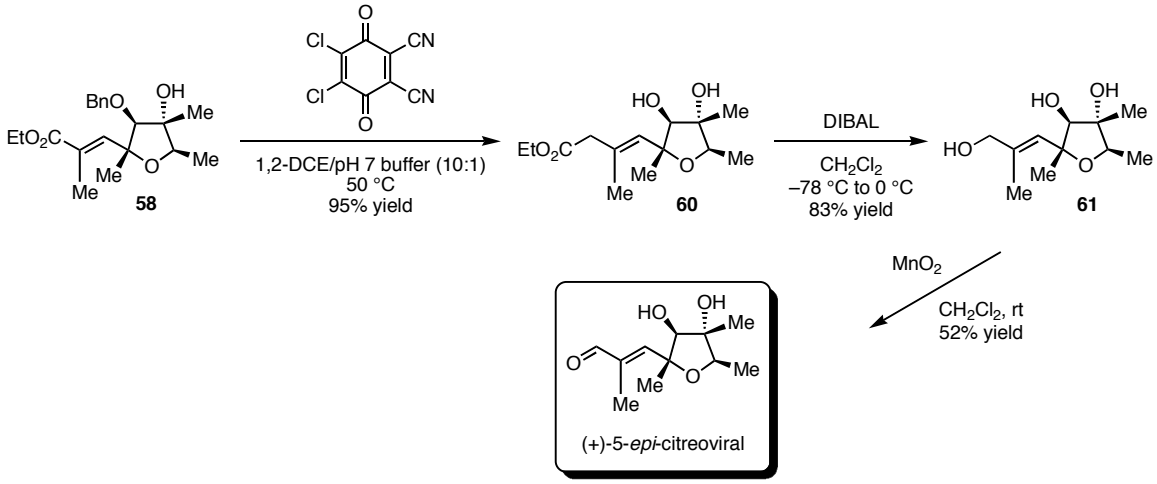
phosphorus ylide gave compound **58** in 37% yield over three steps. The oxidative cleavage reaction proceeded in 52% yield and column chromatography was needed after this step. An alternative route was developed (Scheme 5.19, path *b*) where unsaturated ester **58** was isolated as a 12:1 *E*/*Z* mixture in 80% yield over three steps with no chromatography until after the Wittig reaction.



Scheme 5.19. Original (path *a*) and improved (path *b*) synthesis of unsaturated ester **58**.

Compound **58** is a late-stage intermediate in the synthesis of (±)-5-*epi*-citreoviral by the Woerpel group,[18] and the final three steps in the synthesis described here are the same as those used by Woerpel (Scheme 5.20). The benzyl ether was oxidatively deprotected with DDQ, and the ethyl ester was reduced to an allylic alcohol using diisobutylaluminum hydride. Finally, chemoselective oxidation of the primary allylic alcohol was achieved using activated manganese dioxide, and (+)-5-*epi*-citreoviral ((+)-**2**) was isolated in 2.4% yield over 17 steps (average of 80% yield per step). The ^{1}H and ^{13}C NMR spectra of the (+)-5-*epi*-citreoviral synthesized here match the spectra obtained by Woerpel.[18] Attempts to improve the yield of the final step using other procedures known to selectively oxidize a primary allylic alcohol over a secondary alcohol were not

successful.[28] Additionally, the final oxidation with MnO_2 only yielded (+)-5-*epi*-citreoviral when it was carried out in dry solvent under an atmosphere of argon.



Scheme 5.20. Completion of (+)-5-*epi*-citreoviral.

Conclusion

The total synthesis of (+)-5-*epi*-citreoviral has been accomplished using ruthenium-catalyzed asymmetric ring-closing metathesis (ARCM). Low catalyst loadings (<1 mol %), good yields, and high enantiomeric excesses made ARCM practical for use as a very early synthetic step. All of the stereocenters in the final product were set from the one chiral center generated in the ARCM step. In addition to ARCM, other key steps were the substrate-directed bis-epoxidation reaction, which set four chiral centers in one step, and the acid-catalyzed cascade epoxide-opening reaction, which generated the substituted tetrahydrofuran found in (+)-5-*epi*-citreoviral. A direct route to 2,6-dioxabicyclo[3.2.1]octane ring systems from hydroxy bis-epoxides using both acidic and basic conditions was also discovered. This synthesis illustrates how simple

compounds made using olefin metathesis can be readily transformed into biologically interesting molecules.

Experimental

General Information. NMR spectra were recorded on an Oxford 300 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent for ^{1}H NMR and ^{13}C NMR spectra. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). Optical rotations were taken on a Jasco P-1010 polarimeter with a wavelength of 589 nm. The concentration "c" has units of g/100 mL (or 10 mg/mL) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stain (10 g $KMnO_4$, 20 g Na_2CO_3, 1 L water), standard *p*-anisaldehyde stain (23 mL *p*-anisaldehyde in 500 mL 95% EtOH, cooled to 0 °C, added 9.4 mL cold glacial AcOH and 31.3 mL conc. H_2SO_4, diluted to 1 L with 95% EtOH) or UV light. Flash column chromatography of organic compounds was performed using silica gel 60 (230-400 mesh). All enantiomeric purities were determined by chiral GC (Chiraldex G-TA) or chiral SFC (supercritical CO_2, ADH column, 214 nm UV detection) and were compared to racemic samples. All glassware was flame dried, and reactions were done under an atmosphere of argon unless otherwise noted. All organic solvents were dried by passage through solvent purification columns containing activated alumina and activated

copper (for solvents with no heteroatoms). All commercial chemicals were used as obtained.

(2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (22). Titanocene dichloride (444 mg, 1.78 mmol) was added to a solution of 2-butyne (5.6 mL, 71 mmol) and isobutylmagnesium bromide (2.0 M in diethyl ether, 33 mL, 66 mmol) in 60 mL Et_2O, and the solution stirred at rt for 1 h. *Trans*-2-methyl-2-butenal (5.7 mL, 59 mmol) in 30 mL Et_2O was added slowly, and the mixture stirred at rt for 3 h. It was quenched with saturated aqueous NH_4Cl (100 mL), filtered through a pad of Celite, and the organic layer was removed from the filtrate. The aqueous layer was extracted with ether (3 × 75 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to a brown oil. The oil was purified by flash chromatography (10% ethyl acetate in hexanes) to a yellow oil, which was distilled (Kugelrohr, 1 torr, 120 °C) to afford 7.20 g (86% yield) of **22** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.56 (qquint, J = 6.6, 1.4 Hz, 2H), 4.34 (s, 1H), 1.63 (dt, J = 6.9, 1.1 Hz, 6H), 1.47 (t, J = 1.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.1, 120.4, 81.8, 13.3, 12.1. HRMS (EI) *m*/*z* calc. for $C_9H_{16}O$ (M^+) 140.1201, found 140.1203.

Allyl((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)dimethylsilane (20).

Allylchlorodimethylsilane (1.1 mL, 0.98 g, 7.5 mmol) was added to a solution of **22** (1.0 g, 7.1 mmol), triethylamine (1.2 mL, 0.87 g, 8.6 mmol), and *N*,*N*-dimethylaminopyridine (44 mg, 0.4 mmol) in 30 mL CH_2Cl_2 at rt. After 5 h the reaction was quenched with 50 mL water, the organic layer was removed, and the aqueous layer

was extracted with ether (3 × 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to an oil. The oil was redissolved in hexanes and was filtered through a pad of neutral alumina. The filtrate was condensed to give 1.30 g (76% yield) **20** as a colorless oil. Attempts to purify **20** by silica gel chromatography resulted in inconsistent yields and varying levels of purity due to product decomposition. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.70–5.85 (m, 1H), 5.52 (qquint, J = 6.9, 1.4 Hz, 2H), 4.80–4.90 (m, 2H), 4.30 (s, 1H), 1.61 (dt, J = 6.9, 1.1 Hz, 6H), 1.58–1.63 (m, 2H), 1.43 (t, J = 1.1 Hz, 6H), 0.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.4, 134.8, 119.9, 113.5, 82.4, 25.1, 13.3, 12.0, –1.9. HRMS (EI) *m/z* calc. for $C_{14}H_{26}OSi$ (M^+) 238.1753, found 238.1752.

(*S*,*E*)-6-(But-2-en-2-yl)-2,2,5-trimethyl-3,6-dihydro-2*H*-1,2-oxasiline (19). Triene **20** (0.95 g, 4.0 mmol) was added to a solution of **23** (35 mg, 0.032 mmol) in CH_2Cl_2 (72 mL), and the reaction stirred at 40 °C for 2 h. The solvent was evaporated, and the remaining residue was purified by flash chromatography (3% ethyl acetate in hexanes) to afford 0.70 g (89% yield) of **19** as a pale yellow oil in 92% *ee* (chiral GC, Chiraldex G-TA column, 60 °C for 60 min, 1 mL/min, 28.6 (minor) and 30.0 (major) min retention times for the two enantiomers). $[\alpha]_D^{25}$ = +195.4 ($CHCl_3$, *c* = 0.96). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.69 (dquint, J = 7.7, 1.4 Hz, 1H), 5.49 (q, J = 6.6 Hz, 1H), 4.54 (s, 1H), 1.63 (dd, J = 6.6, 1.1 Hz, 3H), 1.54 (t, J = 1.1 Hz, 3H), 1.51 (s, 3H), 1.29–1.39 (m, 1H), 1.12–1.21 (m, 1H), 0.19 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.9, 136.0, 122.9, 120.4, 83.4, 22.0, 13.5, 12.5, 10.7, 0.3, –0.6. HRMS (EI) *m/z* calc. for $C_{11}H_{20}OSi$ (M^+) 196.1284, found 196.1281.

(*S*,2*Z*,5*E*)-3,5-Dimethylhepta-2,5-diene-1,4-diol (24). KF (1.02 g, 17.6 mmol), $KHCO_3$ (0.88 g, 8.8 mmol), and 30% H_2O_2 (4.0 mL, 4.0 g, 35 mmol) were added to a solution of **19** (0.69 g, 3.5 mmol) in THF (35 mL) and MeOH (35 mL), and the reaction mixture stirred at rt for 12 h. The solvents were evaporated until only a small volume remained (~10 mL). Water (25 mL) was added, and the solution was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and evaporated to an oil. Purification by flash chromatography (1:1 ethyl acetate/hexanes) afforded 0.40 g (72% yield, 64% yield over two steps) of **24** as a thick, colorless oil. $[\alpha]_D^{25.3}$ = –54.7 (c = 0.93). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.56–5.64 (m, 2H), 4.83 (s, 1H), 4.27 (dd, J = 12.5, 7.7 Hz, 1H), 4.15 (dd, J = 12.5, 6.3 Hz, 1H), 2.32 (br s, 2H), 1.62–1.65 (m, 3H), 1.63 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 140.1, 135.4, 126.9, 119.7, 74.9, 58.4, 19.0, 13.3, 13.0. HRMS (EI) *m*/*z* calc. for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1145.

(*S*,2*Z*,5*E*)-1-(*Tert*-butyldiphenylsilyloxy)-3,5-dimethylhepta-2,5-dien-4-ol (25). A solution of N,N-dimethylaminopyridine (DMAP) (16 mg, 0.13 mmol) and **24** (0.40 g, 2.5 mmol) in 25 mL CH_2Cl_2 was cooled to 0 °C. Triethylamine (0.53 mL, 0.38 g, 3.8 mmol) was added to the reaction solution followed by a slow addition of *t*-butyldiphenylsilyl chloride (0.73 mL, 0.77 g, 2.8 mmol) over 3 minutes. After 5 minutes at 0 °C, the solution was allowed to warm to rt and continued stirring for 5.5 h. The solution was quenched with 40 mL of water and was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated

to a pale yellow oil. Purification by flash chromatography (10% ethyl acetate in hexanes) afforded 0.86 g of **25** as a colorless oil contaminated with a small amount (~13%) of *t*-butyldiphenylsilanol (singlet at 1.08 ppm in the ^{1}H NMR spectrum). $[\alpha]_D^{26.2} = -38.9$ (c = 1.25). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.67–7.73 (m, 4H), 7.36–7.46 (m, 6H), 5.48–5.59 (m, 2H), 4.60 (br s, 1H), 4.33 (ddd, J = 12.8, 7.1, 0.8 Hz, 1H), 4.25 (ddd, J = 12.9, 6.0, 1.1 Hz, 1H), 1.69 (d, J = 3.3 Hz, 1H), 1.60 (d, J = 1.4 Hz, 3H), 1.58–1.59 (m, 3H), 1.44 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.89, 135.79, 135.00, 133.81, 129.90, 129.87, 127.93, 127.89, 127.84, 127.47, 119.15, 74.49, 60.23, 26.99, 19.33, 18.51, 13.21, 13.08. HRMS (FAB) *m/z* calc. for $C_{25}H_{33}O_2Si$ ($M^+ - H$) 393.2250, found 393.2280.

(*S*)-((2*R*,3*S*)-3-((*Tert*-butyldiphenylsilyloxy)methyl)-2-methyloxiran-2-yl)((2*R*,3*R*)-2,3-dimethyloxiran-2-yl)methanol (26). To a solution/suspension of **25** (0.86 g, 2.2 mmol) and $NaHCO_3$ (0.92 g, 11 mmol) in 22 mL of CH_2Cl_2 at 0 °C was added MCPBA (71.7 wt %, 2.10 g, 8.72 mmol). After stirring at 4 °C for 13 h, the mixture was diluted with CH_2Cl_2 (40 mL) and filtered through Celite. A solution of saturated aqueous Na_2CO_3 was added to the filtrate, and it was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and evaporated to a pale yellow oil. Purification by flash chromatography (20% ethyl acetate in hexanes) afforded 0.48 g (44% yield over two steps) of **26** as a colorless oil. The enantioenriched material was always an oil, but racemic **26** was a solid that was recrystallized from benzene/pentane vapor diffusion. $[\alpha]_D^{25.0} = -20.7$ (c = 0.90). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.67–7.70 (m, 4H), 7.37–7.45 (m, 6H), 3.88 (d, J = 5.5

Hz, 2H), 3.55 (br s, 1H), 3.33 (q, J = 5.8 Hz, 1H), 3.10 (t, J = 5.5 Hz, 1H), 2.20 (d, J = 2.2 Hz, 1H), 1.31 (d, J = 5.8 Hz, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.76, 135.70, 130.10, 128.01, 72.64, 64.69, 61.99, 61.96, 60.82, 54.86, 26.93, 19.35, 17.80, 14.49, 13.39. HRMS (FAB) *m/z* calc. for $C_{25}H_{35}O_4Si$ (M^+ + H) 427.2305, found 427.2299.

(((2*S*,3*S*)-3-((*S*)-Benzyloxy((2*S*,3*R*)-2,3-dimethyloxiran-2-yl)methyl)-3-methyloxiran-2-yl)methoxy)(*tert*-butyl)diphenylsilane (37). To a suspension of NaH (95%, 41 mg, 1.7 mmol) in THF (8.4 mL) was added **26** (dried by azeotroping from toluene, 0.36 g, 0.84 mmol) at rt. A small amount of bubbling occurred, and the reaction mixture stirred at 65–70 °C. After 10 minutes, the mixture was allowed to cool to rt and tetrabutylammonium iodide (16 mg, 0.042 mmol) and benzyl bromide (filtered through neutral alumina, 0.30 mL, 0.43 g, 2.5 mmol) were added. After 3 h at 65–70 °C, the mixture was carefully quenched with saturated aqueous NH_4Cl (20 mL) and was extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to a yellow oil. Purification by flash chromatography (8% ethyl acetate in hexanes) gave 309 mg (71% yield) of **37** as a colorless oil. $[\alpha]_D^{24.6}$ = –5.9 (c = 0.83). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.68–7.72 (m, 4H), 7.36–7.48 (m, 6H), 7.23–7.34 (m, 5H), 4.69 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 3.94 (dd, J = 11.8, 4.4 Hz, 1H), 3.73 (dd, J = 11.8, 6.1 Hz, 1H), 3.24 (s, 1H), 3.17 (q, J = 5.5 Hz, 1H), 3.05 (dd, J = 6.1, 4.4 Hz, 1H), 1.24 (d, J = 5.5 Hz, 3H), 1.34 (s, 3H), 1.23 (s, 3H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.80, 135.91, 135.78, 133.49, 133.21, 130.08, 130.06, 128.41, 128.03, 128.00, 127.87, 127.63, 81.07, 73.40, 63.57,

62.48, 62.20, 60.47, 55.89, 27.01, 19.44, 18.54, 14.95, 13.61. HRMS (FAB) *m/z* calc. for $C_{32}H_{41}O_4Si$ ($M^+ + H$) 517.2774, found 517.2764.

((2*S*,3*S*)-3-((*S*)-Benzyloxy((2*S*,3*R*)-2,3-dimethyloxiran-2-yl)methyl)-3-methyloxiran-2-yl)methanol (38). To a solution of **11** (0.30 g, 0.58 mmol) in THF (11mL) was added tetrabutylammonium fluoride (1M in THF, 1.2 mL, 1.2 mmol). After 2.5 h at rt, the solvent was removed by rotary evaporation, and the residue was dissolved in CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). It was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (40% ethyl acetate in hexanes) afforded 135 mg (83% yield) of **38** as a colorless oil. $[\alpha]_D^{24.4} = -28.0$ (c = 0.86). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.37 (m, 5H), 4.76 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 3.83 (dd, J = 12.4, 5.0 Hz, 1H), 3.42 (dd, J = 12.4, 8.0 Hz, 1H), 3.12 (br s, 1H), 3.04 (s, 1H), 3.01 (dd, J = 8.0, 5.0 Hz, 1H), 2.87 (q, J = 5.5 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.25 (d, J = 5.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.35, 128.57, 127.95, 127.91, 82.76, 72.47, 62.04, 61.73, 60.78, 60.69, 19.38, 13.77, 13.41. HRMS (FAB) *m/z* calc. for $C_{16}H_{23}O_4$ ($M^+ + H$) 279.1596, found 279.1586.

8-(Benzyloxy)-1,5,7-trimethyl-2,6-dioxabicyclo[3.2.1]octan-4-ol (45). To a solution of racemic **38** (50 mg, 0.18 mmol) in *t*-BuOH (0.9 mL) was added NaOH (0.5M in H_2O, 0.90 mL, 0.45 mmol). After stirring at 75–80 °C for 6 h, the solution was quenched with saturated aqueous NH_4Cl (1 mL) and was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layeres were dried over Na_2SO_4 and evaporated to an oil. Purification

by flash chromatography (45% ethyl acetate in hexanes) afforded 43.3 mg (87% yield) of **45** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.36 (m, 5H), 4.62 (d, J = 12.3 Hz, 1H), 4.47 (d, J = 12.4, 1H), 4.33 (s, 1H), 4.21 (dd, J = 13.2, 2.5 Hz, J = 1H), 3.85 (d, J = 13.2 Hz, 1H), 3.65 (br s, 1H), 3.49 (q, J = 6.6 Hz, 1H), 2.05 (br s, 1H), 1.43 (s, 3H), 1.23 (s, 3H), 1.00 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.30, 128.59, 127.82, 127.40, 89.11, 86.25, 80.17, 76.23, 75.67, 73.46, 72.23, 19.50, 18.56, 17.25. HRMS (FAB) *m/z* calc. for $C_{16}H_{21}O_4$ (M^+ – H) 277.1440, found 277.1432.

(1*R*,4*R*,5*R*,7*R*,8*R*)-8-(Benzyloxy)-4-hydroxy-1,5,7-trimethyl-2,6-dioxabicyclo[3.2.1]octan-3-one (55). To a solution of oxalyl chloride (0.19 mL, 0.28 g, 2.2 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added DMSO (0.25 mL, 0.28 g, 3.6 mmol). After 10 min at –78 °C, **38** (200 mg, 0.72 mmol) was added. After 20 min at –78 °C, triethylamine (0.70 mL, 0.51 g, 5.0 mmol) was added, and the solution stirred at –78 °C for 30 min before warming to rt. After 45 min at rt, the reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to a yellow oil (**53**), which was used directly in the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.38 (d, J = 3.8 Hz, 1H), 7.30–7.39 (m, 5H), 4.64 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 3.23 (d, J = 3.8 Hz, 1H), 3.15 (s, 1H), 2.81 (q, J = 5.5 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 1.23 (d, J = 5.5 Hz, 3H). To a solution of crude **53** in *t*-BuOH (5.8 mL) was added 2.9 mL of a pH = 3.8 buffer (NaH_2PO_4, 0.41M in H_2O), 2-methyl-2-butene (0.34 mL, 0.23 g, 3.2 mmol), and $NaClO_2$ (80%, 326 mg, 2.88 mmol). After stirring at rt for 1.5 h, the solution was diluted with pH = 3.8 buffer (10 mL) and was extracted with ethyl acetate (4 × 15

mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil (**54**) that was used directly in the next reaction. To a solution of crude **54** in 8 mL of benzene was added *p*-toluenesulfonic acid monohydrate (55 mg, 0.29 mmol). After 2 h at rt, the solution was diluted with water (10 mL) and was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (30% ethyl acetate in hexanes) afforded 157 mg (68% yield over three steps) of **55** as a colorless oil. The enantioenriched material never crystallized, or even became a solid, but the racemic material was a white solid that was recrystallized from benzene/pentane vapor diffusion. Chiral SFC (supercritical CO_2 with 5% MeOH, ADH column, 214 nm UV detection, 4.78 (minor) and 5.27 (major) min retention times of the enantiomers) showed a 92% *ee*. $[\alpha]_D^{24.9} = -20.0$ (c = 0.96). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.33–7.41 (m, 5H), 4.75 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.11 (q, J = 6.9 Hz, 1H), 4.07 (s, 1H), 3.81 (s, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.27 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 172.73, 137.41, 128.76, 128.33, 127.96, 91.23, 83.21, 83.17, 82.88, 75.81, 75.16, 18.68, 16.54, 16.08. HRMS (EI) *m*/*z* calc. for $C_{16}H_{20}O_5$ (M^+) 292.1311, found 292.1305.

(*E*)-Ethyl-3-(benzyloxy)-4-hydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylate (58) through 56 (Scheme 5.19, path *a*). To a solution of racemic **55** (160 mg, 0.55 mmol) in THF (6.8 mL) was added LiOH (0.72M in water, 2.3 mL, 1.6 mmol). After 2.5 h at rt, the solution was diluted with 7 mL of 1N HCl (aqueous) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (2% acetic acid

in ethyl acetate) afforded 142 mg (84% yield) of **56** as a colorless, sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.36 (m, 5H), 4.71 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.27 (s, 1H), 4.24 (s, 1H), 3.89 (q, J = 6.6 Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H). Tetrabutylammonium periodate (243 mg, 0.56 mmol) was added to a solution of **56** (142 mg, 0.51 mmol) in 3.5 mL of $CHCl_3$. After 12 h at 62 °C, the solution was diluted with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (40% ethyl acetate in hexanes) afforded 63 mg (52% yield) of **57** as a yellow oil. The ^{1}H NMR spectrum in $CDCl_3$ was unclean and showed no peak corresponding to an aldehyde hydrogen; it is presumably in the lactol form in $CDCl_3$. In DMSO-d_6 an aldehyde peak was present, and the spectrum showed multiple forms of **57** (both diastereomers of the lactol and the aldehyde). ^{1}H NMR (300 MHz, ppm) diagnostic signals: δ 4.70 (s, $CDCl_3$), 3.93 (q, J = 6.9 Hz, $CDCl_3$), 3.46 (s, $CDCl_3$); 9.53 (s, DMSO-d_6). The phosphorus ylide (carbethoxyethylidene)triphenylphosphorane (11 mg, 0.030 mmol) was added to a solution of **57** in benzene (0.3 mL) in a 1 dram vial, which was sealed. After 48 h at 90 °C, the reaction mixture was directly placed on a silica gel column and was purified by flash chromatography (20% ethyl acetate in hexanes) to afford 5.3 mg (85% yield, 37% over three steps) of **58** (12:1 *E*/*Z*, *Z* isomer has a peak in the ^{1}H NMR spectrum ($CDCl_3$) at δ 5.32 (d, J = 1.4 Hz, 1H)) as a very pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.28–7.40 (m, 5H), 6.87 (d, J = 1.4 Hz, 1H), 4.83 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.89 (s, 1H), 3.68 (q, J = 6.3 Hz, 1H), 1.94 (d, J = 1.1 Hz, 3H), 1.59 (br s, 1H), 1.32 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.24 (s,

3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 168.68, 148.59, 138.25, 128.64, 127.96, 127.79, 127.62, 92.22, 82.07, 80.57, 77.34, 72.95, 61.00, 21.99, 16.65, 14.47, 13.74, 12.71.

(*E*)-Ethyl-3-((2*R*,3*S*,4*R*,5*R*)-3-(benzyloxy)-4-hydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylate (58) through 59 (Scheme 5.19, path *b*). To a solution of $NaBH_4$ (91 mg, 2.4 mmol) in ethanol (7 mL) was added **55** (140 mg, 0.48 mmol) as a solution in 4 mL of ethanol. After 4.5 h at rt, the solvent was removed by rotary evaporation, and the remaining residue was dissolved/suspended in ethyl acetate and quenched with 1N aqueous HCl until the pH was <2. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a sticky oil (**59**) that was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.37 (m, 5H), 4.78 (d, J = 11.8 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.07 (s, 1H), 3.88 (q, J = 6.6 Hz, 1H), 3.77–3.82 (m, 1H), 3.56–3.64 (m, 2H), 1.26 (s, 3H), 1.15 (s, 3H), 1.14 (d, J = 6.6 Hz, 3H). To a solution of crude **59** in THF (3 mL) was slowly added $NaIO_4$ (113 mg, 0.53 mmol) as a solution in 3 mL of water. After 1 h at rt, the reaction solution was diluted with water (10 mL) and extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a pale yellow oil (**57**) that was used directly in the next step. The ^{1}H NMR spectrum in $CDCl_3$ was unclean and showed no peak corresponding to an aldehyde hydrogen; it is presumably in the lactol form in $CDCl_3$. In DMSO-d_6 an aldehyde peak was present, and the spectrum showed multiple forms of **57** (both diastereomers of the lactol and the aldehyde). ^{1}H NMR (300 MHz,

ppm) diagnostic signals: δ 4.70 (s, $CDCl_3$), 3.93 (q, J = 6.9 Hz, $CDCl_3$), 3.46 (s, $CDCl_3$); 9.53 (s, DMSO-d_6). The phosphorus ylide (carbethoxyethylidene)triphenylphosphorane (0.52 g, 1.4 mmol) was added to a solution of crude **57** in toluene (5 mL). After 18 h at 110 °C, the solvent was removed by rotary evaporation. The remaining residue was purified by flash chromatography (25% ethyl acetate in hexanes) to afford 136 mg (80% over three steps) of **58** (12:1 *E*/*Z*, *Z* isomer has a peak in the ^{1}H NMR spectrum ($CDCl_3$) at δ 5.32 (d, J = 1.4 Hz, 1H)) as a very pale yellow oil. $[\alpha]_D^{25.3}$ = +48.3 (c = 0.99). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.28–7.40 (m, 5H), 6.87 (d, J = 1.4 Hz, 1H), 4.83 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.89 (s, 1H), 3.68 (q, J = 6.3 Hz, 1H), 1.94 (d, J = 1.1 Hz, 3H), 1.59 (br s, 1H), 1.32 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 168.68, 148.59, 138.25, 128.64, 127.96, 127.79, 127.62, 92.22, 82.07, 80.57, 77.34, 72.95, 61.00, 21.99, 16.65, 14.47, 13.74, 12.71. HRMS (FAB) *m*/*z* calc. for $C_{20}H_{29}O_5$ (M^+ + H) 349.2015, found 349.2026.

(*E*)-Ethyl 4-((2*R*,3*S*,4*S*,5*R*)-3,4-dihydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-3-methylbut-3-enoate (60). To a solution of **58** (66 mg, 0.19 mmol) in 1,2-dichloroethane (3.1 mL) and pH 7 buffer (0.31 mL) was added DDQ. After 13 h at 50 °C, saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (10 mL) were added, and the mixture was filtered through Celite. The filtrate was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to an brown oil. Purification by flash chromatography (55% ethyl acetate in hexanes) afforded 47 mg (95% yield) of **60** as a very pale purple solid (mp = 94–96 °C). $[\alpha]_D^{24.6}$ = +20.2 (c =

0.86). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.87 (d, J = 1.7 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.06 (s, 1H), 3.68 (q, J = 6.3 Hz, 1H), 2.92 (br s, 2H), 1.97 (d, J = 1.4 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 1.15 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 169.13, 148.50, 127.75, 85.59, 82.34, 80.45, 61.22, 21.37, 16.32, 14.40, 14.34, 12.87. HRMS (EI) *m/z* calc. for $C_{13}H_{22}O_5$ (M^+) 258.1467, found 258.1463.

(2*R*,3*S*,4*S*,5*R*)-2-((*E*)-3-Hydroxy-2-methylprop-1-enyl)-2,4,5-trimethyltetrahydrofuran-3,4-diol (61). A solution of diisobutylaluminum hydride (1.5M in toluene, 0.93 mL, 1.4 mmol) was added to a solution of **60** (45 mg, 0.17 mmol) in CH_2Cl_2 (2.3 mL) at –78 °C. The solution became yellow. After 1.5 h at –78 °C, the solution was allowed to warm to 0 °C. After 1 h at 0 °C, the solution was carefully quenched with a saturated aqueous solution of potassium sodium tartrate (Rochelle's salt, 5 mL). Et_2O (5 mL) was added to the solution, and it stirred vigorously at rt for 12 h. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (7 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography afforded 31 mg (83% yield) of **61** as a sticky, colorless oil. $[\alpha]_D^{24.9}$ = +28.4 (c = 1.09). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.65 (d, J = 1.4 Hz, 1H), 4.04 (s, 1H), 3.96 (s, 2H), 3.74 (q, J = 6.3 Hz, 1H), 2.58 (br s, 3H), 1.80 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.31, 132.58, 86.51, 82.47, 81.05, 77.86, 68.59, 22.43, 16.53, 14.78, 14.28. HRMS (CI) *m/z* calc. for $C_{11}H_{21}O_4$ (M^+ + H) 217.1440, found 217.1443.

(*E*)-3-((2*R*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylaldehyde ((+)-5-*epi*-citreoviral, (+)-2). To a solution of **61** (17 mg, 0.080 mmol) in 2.7 mL of CH_2Cl_2 was added activated MnO_2 (85%, 81 mg, 0.80 mmol), and the mixture stirred vigorously. After 2 h at rt, the mixture was filtered through Celite, and the Celite was washed with CH_2Cl_2 (3 × 10 mL) and ethyl acetate (3 × 10 mL). The filtrate was evaporated to an oil, which was purified by flash chromatography (60% ethyl acetate in hexanes) to afford 8.7 mg (52% yield) of (+)-**2** as a colorless oil. $[\alpha]_D^{25.0}$ = +13.2 (c = 1.74). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.37 (s, 1H), 6.63 (d, J = 1.4 Hz, 1H), 4.11 (s, 1H), 3.74 (q, J = 6.3 Hz, 1H), 2.02 (br s, 2H), 1.89 (d, J = 1.4 Hz, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 195.82, 160.64, 138.17, 85.40, 82.69, 80.53, 78.41, 21.20, 16.78, 14.70, 9.66. HRMS (EI) *m/z* calc. for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1196.

X-ray Crystallographic Data

Complex	**26**	**55**
Empirical formula	$C_{25}H_{34}O_4Si$	$C_{16}H_{20}O_5$
Formula weight	426.61	292.32
Crystal habit	Tabular	Fragment
Crystal size	0.40 × 0.31 × 0.19 mm^3	0.42 × 0.41 × 0.30 mm^3
Crystal color	Colorless	Colorless
Diffractometer	Bruker SMART 1000	Bruker SMART 1000
Wavelength	0.71073 Å MoKα	0.71073 Å MoKα
Temperature	100(2) K	100(2) K
Unit cell dimensions	a = 34.970(2) Å	a = 8.3224(3) Å
	b = 9.6943(5) Å	b = 9.9930(4) Å
	c =14.8230(9) Å	c =17.8237(7) Å
	β = 110.1100(10)°	β = 97.0980(10)°
Volume	4718.7(5) $Å^3$	1470.96(10) $Å^3$
Z	8	4
Crystal system	Monoclinic	Monoclinic
Space group	Cc	$P2_1/c$
Density (calculated)	1.201 Mg/m^3	1.320 Mg/m^3
Theta range	2.19 to 32.74°	2.30 to 42.65°
h min, max	–49, 53	–13, 15
k min, max	–14, 14	–18, 15
l min, max	–20, 19	–33, 32
Reflections collected	37444	28796
Independent reflections	13856	9804
R_{int}	0.0595	0.0680
GOF on F^2	2.147	1.384
Final R indicies [I>2σ(I)]	0.0657	0.0507
Final weighted R [F_o^2]	0.1272	0.0892

References

[1] Seebach, D.; Weidmann, B.; Wilder, L. In *Modern Synthetic Methods 1983*; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, 1983; p 323.

[2] Shizuri, Y.; Nishiyama, S.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 4771–4774.

[3] Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231–234.

[4] Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron* **1977**, *33*, 3077–3081.

[5] (a) Boyer, P. D.; Chance, B.; Ernster, L.; Mitchell, P.; Racker, E.; Slater, E. C. *Annu. Rev. Biochem.* **1977**, *46*, 955–1026. (b) Muller, J. L. M.; Rosing, J. Slater, E. C. *Biochim.*

Biophys. Acta **1977**, *462*, 422–437. (c) Gause, E. M.; Buck, M. A.; Douglas, M. G. *J. Biol. Chem.* **1981**, *256*, 557–559.

[6] Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Osselton, M. D. *J. Chem. Soc., Chem. Commun.* **1974**, *21*, 874–876.

[7] (a) Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem Commun.* **1985**, *22*, 1531–1532. (b) de Jesus, A. E.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem Commun.* **1985**, *22*, 1633–1635.

[8] Bowden, M. C.; Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1947–1950.

[9] Lai, S.; Matsunaga, K.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5503–5506.

[10] Ebenezer, W.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4053–4056.

[11] (a) ref. 8. (b) Forbes, J. E.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1959–1966. (c) Forbes, J. E.; Bowden, M. C.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1967–1973. (d) ref. 10.

[12] Murata, Y.; Kamino, T.; Aoki, T.; Hosokawa, S.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3175–3177, and references therein.

[13] (a) Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485–6488. (b) ref. 12.

[14] (a) Whang, K.; Venkataraman, H.; Kim, Y. G.; Cha, J. K. *J. Org. Chem.* **1991**, *56*, 7174–7177. (b) Mulzer, J.; Bilow, J.; Wille, G. *J. Prakt. Chem.* **2000**, *342*, 773–778.

[15] (a) ref. 3. (b) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470–481. (c) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223–226.

[16] Trost, B. M.; Lynch, J. K.; Angle, S. R. *Tetrahedron Lett.* **1987**, *28*, 375–378.

[17] Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067–5079.

[18] Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945–2948.

[19] (a) Garner, C. M.; Prince, M. E. *Tetrahedron Lett.* **1994**, *35*, 2463–2464. (b) Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85–88.

[20] Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96–102.

[21] Yao, Q. *Org. Lett.* **2001**, *3*, 2069–2072.

[22] For acyclic stereocontrol in allylic alcohol epoxidation, see (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta*, **1979**, *12*, 63–74. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733–4736. (c) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3387–3390.

[23] Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819–3822.

[24] Formation of the 2,6-dioxabicyclo[3.2.1]octane core in nature in one step from a cascade epoxide opening sequence has been proposed. See references 11b and 11c.

[25] (a) Nishiyama, S.; Shizuri, Y.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 3243–3246. (b) Bowden, M. C.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4797–4800. (c) Nishiyama, S.; Toshima, H.; Yamamura, S. *Chem. Lett.* **1986**, 1973–1976. (d) Nishiyama, S.; Toshima, H.; Kanai, H.; Yamamura, S. *Tetrahedron* **1988**, *44*, 6315–6324.

[26] Intermolecular trapping of 2,3-epoxy alcohols: (a) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1378–1380. (b) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687–5696. (c) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta*. **1983**, *16*, 67–79.

[27] Santaniello, E.; Manzocchi, A.; Farachi, C. *Synthesis*, **1980**, 563–565.

[28] Tempo oxidation: (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452–7454. For examples of $BaMnO_4$ in the synthesis of citreoviral, see (b) ref. 12. (c) ref. 15c.