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Enantioselective Synthesis of 5-*epi*-Citreoviral Using Ruthenium-Catalyzed Asymmetric Ring-Closing Metathesis

Timothy W. Funk*

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, and the Department of Chemistry, Gettysburg College, Gettysburg, Pennsylvania 17325

tfunk@gettysburg.edu

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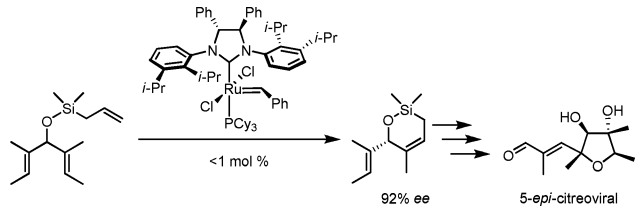
ABSTRACT



Chiral ruthenium olefin metathesis catalysts can perform asymmetric ring-closing reactions in ≥90% ee with low catalyst loadings. To illustrate the practicality of these reactions and the products they form, an enantioselective total synthesis of 5-*epi*-citreoviral was completed by using an asymmetric ring-closing olefin metathesis reaction as a key step early in the synthesis. All of the stereocenters in the final compound were set by using the chiral center generated by asymmetric olefin metathesis.

Asymmetric olefin metathesis has been extensively explored since its initial report more than a decade ago.[1] While most of the focus has been on using high oxidation-state molybdenum alkylidene complexes,[2] chiral ruthenium alkylidenes (Figure 1) have been shown to catalyze asymmetric olefin metathesis reactions efficiently and in ≥90% ee.[3] Considering the volume of work on asymmetric olefin metathesis there have been very few applications of either molybdenum- or ruthenium-catalyzed asymmetric olefin metathesis catalysts in the synthesis of complex, biologically relevant compounds.[4] The air and moisture stability of ruthenium alkylidenes makes them attractive for use in complex molecule synthesis. To illustrate the practicality of asymmetric olefin metathesis and the utility of the products formed in these

(1) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499–2500.

(2) For reviews on asymmetric olefin metathesis, see: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633. (b) Hoveyda, A. H. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 2.3. (c) Hoveyda, A. H.; Schrock, R. R. *Chem.—Eur. J.* **2001**, *7*, 945–950. For other examples, see: (d) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *465*, 933–937.

(3) (a) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228. (b) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (c) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508. (d) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290. (e) Van Veldhuizen, J. J.; Campbell, J. E.; Guidici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882. (f) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840–1846. (g) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591–7595.

(4) (a) Burke, S. D.; Muller, N.; Beudry, C. M. *Org. Lett.* **1999**, *1*, 1827–1829. (b) Weatherhead, G. S.; Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5805–5809. (c) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864. (d) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943–953.

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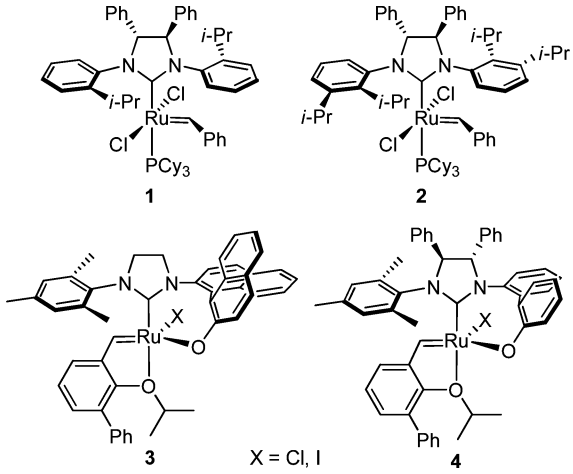


Figure 1. Chiral ruthenium olefin metathesis catalysts.

reactions, an enantioselective synthesis of 5-*epi*-citreoviral was undertaken.

(+)-Citreoviral (**5**) was isolated from *Penicillium citreoviride* in 1984 (Figure 2).[5] Other structurally similar

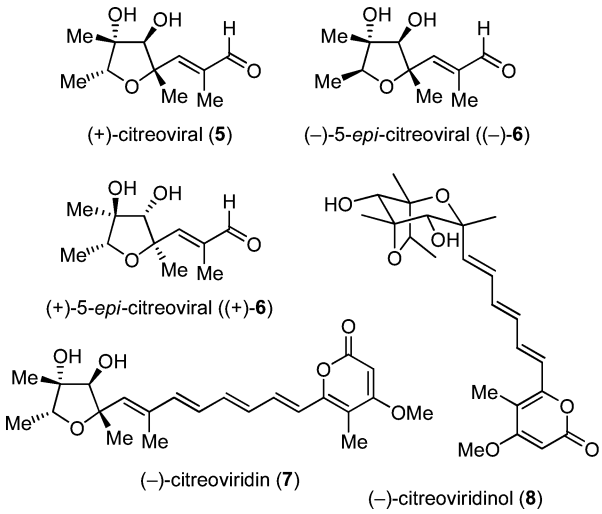
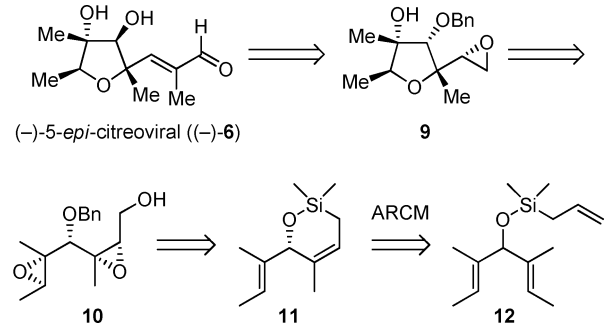


Figure 2. Citreoviral and related compounds.

metabolites were isolated from the same fungus (**7** and **8**),[6] and most have been found to be potent inhibitors of mitochondrial ATPase and oxidative phosphorylation.[7] Additionally, a number of naturally occurring stereoisomers of (−)-citreoviridinol (**8**) have been isolated.[8] The complexity of the tetrahydrofuran and 2,6-dioxabicyclo[3.2.1]octane rings have made these families of compounds attractive synthetic targets, and citreoviral, which has been used as an intermediate in syntheses of the more complex metabolites, has been generated in racemic and enantioenriched forms.[9] Unnatural (±)-3-*epi*-citreoviral[10] and (±)-5-*epi*-citreoviral[11] have also been made and could be used as synthetic intermediates to access unnatural diastereomers of citreoviridin and citreoviridinol. Of all of the syntheses of citreoviral and its unnatural isomers, there has been only one report that used asymmetric catalysis.[12]

It was suspected that (−)-5-*epi*-citreoviral ((−)-**6**) could be generated from intermediate **11**, which is easily accessible by using ruthenium-catalyzed asymmetric ring-closing metathesis (ARCM) (Scheme 1).[3f] The highly substituted

Scheme 1. Retrosynthesis of (−)-5-*epi*-Citreoviral ((−)-**6**)



tetrahydrofuran **9** was to be made from a Payne rearrangement/epoxide opening sequence of bis-epoxide **10**. Ideally **10** could be formed by using a substrate-directed bis-epoxidation that would use the stereocenter generated by ARCM.

The synthesis commenced as shown in Scheme 2. As previously reported, gram quantities of **11** in 92% ee were available from silyl ether **12** by using 0.75−0.8 mol % of catalyst **2**.[3f] Tamao−Fleming oxidation of **11** afforded **13** in 64% over two steps.[13] It has been reported that a one-pot olefin metathesis/Tamao−Fleming oxidation process is possible,[14] but attempts to oxidize **11** to **13** without removing the ruthenium byproduct by flash chromatography resulted in an exothermic decomposition of hydrogen peroxide and

(5) (a) Shizuri, Y.; Nishiyama, S.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 4771–4774. (b) Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231–234.

(6) Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron* **1977**, *33*, 3077–3081.

(7) (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.

(8) (a) Nishiyama, S.; Shizuri, Y.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 3243–3246. (b) Nishiyama, S.; Toshima, H.; Yamamura, S. *Chem. Lett.* **1986**, 1973–1976. (c) Nishiyama, S.; Shizuri, Y.; Toshima, H.; Ozaki, M.; Yamamura, S.; Kawai, K.; Kawai, N.; Furukawa, K. *Chem. Lett.* **1987**, 515–518. (d) Lai, S.; Matsunaga, K.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5503–5506.

(9) Murata, Y.; Kamino, T.; Aoki, T.; Hosokawa, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3175–3177, and references cited therein.

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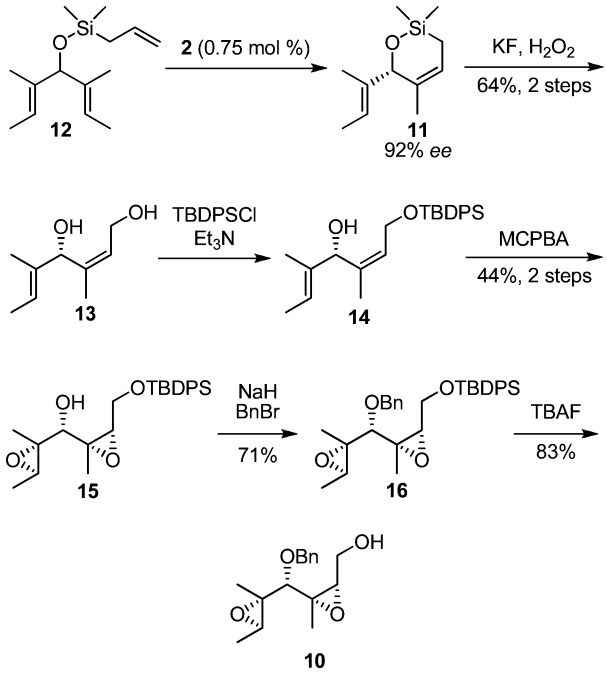
(11) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945–2948.

(12) Trost, B. M.; Lynch, J. K.; Angle, S. R. *Tetrahedron Lett.* **1987**, *28*, 375–378.

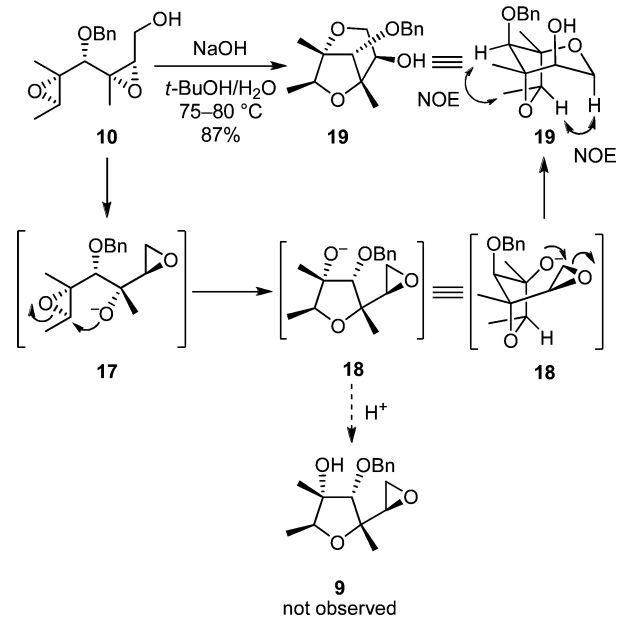
(13) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96–102.

(14) Yao, Q. *Org. Lett.* **2001**, *3*, 2069–2072.

Scheme 2. Synthesis of Intermediate **10**



Scheme 3. Proposed Mechanism of Formation of **19**



no oxidation of silane **11**. The primary alcohol of **13** was selectively protected, and **14** was treated with MCPBA at 5 °C. Gratifyingly, the desired bis-epoxide (**15**) was isolated as the major product in 44% yield over two steps.[15] In this single step, all of the remaining stereocenters needed to form 5-*epi*-citreoviral were installed. None of the starting alcohol **14** remained, and the only other compounds formed were diastereomers of **15**. When catalytic $VO(acac)_2$ with *t*-BuOOH as the stoichiometric oxidant was used, bis-epoxide **15** was isolated as a minor diastereomer in only 13% yield over two steps. Finally, protection of the secondary alcohol as a benzyl ether and removal of the silyl protecting group afforded **10**.

With compound **10** in hand, the crucial Payne rearrangement/epoxide opening reaction was explored. Treatment of **10** with sodium hydroxide in aqueous *tert*-butyl alcohol at 75−80 °C led to complete consumption of the starting material after 6 h. Instead of the expected substituted tetrahydrofuran **9**, 2,6-dioxabicyclo[3.2.1]octane **19** was isolated as the only product in 87% yield. The structure of **19** is supported by two crosspeaks in the NOESY spectrum: there is a through-space interaction between an axial hydrogen on the tetrahydropyran methylene with a methine hydrogen on the tetrahydrofuran ring and between the tetrahydrofuran methyl doublet with the methine hydrogen on the carbon bearing the benzyloxy group (Scheme 3).[16] The formation of **19** can be rationalized as shown in Scheme 3. Payne rearrangement followed by a 5-*endo-tet* epoxide opening generated intermediate **18**, which, if protonated, would have led to the expected **9**. Instead intermediate **18** preferentially underwent a second intramolecular epoxide opening, presumably through a puckered tetrahydrofuran ring and a boat-like transition state, to afford **19**. Interestingly, compound **19** is a diastereomer of the 2,6-dioxabicyclo-[3.2.1]octane core found in the citreoviridinols.[6] This result suggests that these compounds may be made efficiently by using this methodology.

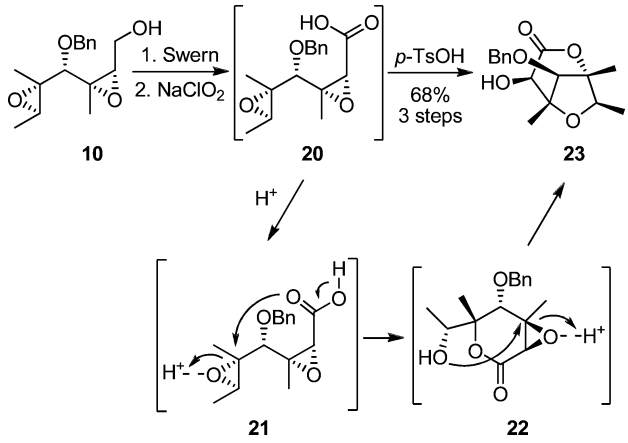
To access (−)-5-*epi*-citreoviral, the tetrahydropyran ring of **19** needed to be cleaved. No simple, direct, ring-opening process was available, so a modified approach to 5-*epi*-citreoviral was taken. It was reasoned that if the epoxides in intermediate **10** could be attacked by an internal nucleophile at the less hindered positions under basic conditions (Scheme 3), then perhaps they could be opened at the more substituted positions under acidic conditions.[17] To test this theory, the primary alcohol of **10** was oxidized in two steps to the carboxylic acid (**20**), and upon exposure to *p*-toluenesulfonic acid in benzene, compound **23** was isolated as a single diastereomer in 68% yield over three steps (Scheme 4). No purification was needed until after the cascade epoxide opening, and no erosion of the absolute stereochemistry was observed by chiral HPLC. Now instead of an ether (as in **19**), a labile lactone was present in the ring that needed to be cleaved. By using an acid-catalyzed epoxide opening in place of the base-mediated approach initially envisioned, the absolute stereochemistry of the tetrahydrofuran was the opposite of that originally intended. Therefore, by making

(15) For acyclic stereocontrol in allylic alcohol epoxidation, see: (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. 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.

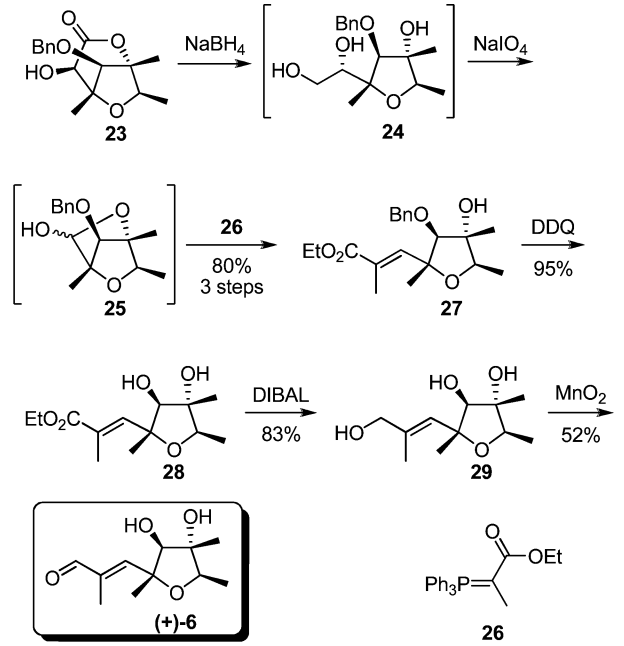
(16) For a more detailed discussion of the structure of **19** and the assignment of hydrogen atoms in the ^1H NMR spectrum, see the Supporting Information.

(17) For another example of an acid-catalyzed ring-opening of a bis-epoxide in the synthesis of citreoviral and its stereoisomers see: Ebenezer, W.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4053–4056.

Scheme 4. Acid-Catalyzed Cascade Epoxide Opening



Scheme 5. Synthesis of (+)-5-*epi*-Citreoviral



this adjustment, (+)-5-*epi*-citreoviral would be formed instead of the (−)-enantiomer. Conveniently, this modification placed the benzyl protected secondary alcohol in the correct stereochemical configuration found in 5-*epi*-citreoviral (**6**).

The final steps of the synthesis are shown in Scheme 5. Intermediate **27** was accessible in three sequential steps in an 80% yield from lactone **23** with no purification needed until after the Wittig olefination. Compound **27** is a late-stage intermediate in the synthesis of (±)-5-*epi*-citreoviral by the Woerpel group, and the final three steps used here are slight modifications of those previously described.[11,18] Compound (+)-**6** was isolated in 3.7% yield over 15 steps, and the ^{1}H and ^{13}C NMR spectral data for (+)-**6** matched those published for (±)-**6**.[11]

In conclusion, ruthenium-catalyzed ARCM has been applied to the synthesis of (+)-5-*epi*-citreoviral. The low catalyst loading (<1 mol %), good yield, and high enantiomeric excess made ARCM practical as an early step in the process. All of the stereocenters in the final product were set from the one chiral center generated in the ARCM reaction. Other key steps in the synthesis were the acyclic, substrate-directed bis-epoxidation and the acid-catalyzed cascade epoxide-opening reaction used to generate the highly substituted tetrahydrofuran ring. Additionally, a direct route to a 2,6-dioxabicyclo[3.2.1]octane ring system was discovered, which could be applied to the synthesis of more complex, biologically relevant metabolites.

(18) Attempts to improve the yield of the last step by using procedures known to selectively oxidize a primary alcohol in the presence of a secondary alcohol were unsuccessful.

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Supporting Information Available: Complete experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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