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Synthesis of (±)-5-*epi*-Citreoviral and (±)-Citreoviral and the Kinetic Resolution of an Allylic Silane by a [3 + 2] Annulation

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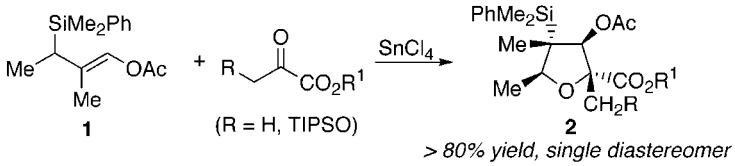
ABSTRACT



The [3 + 2] annulation reaction of allylsilane 1 with an α-keto ester provided the highly substituted tetrahydrofuran 2 as a single diastereomer in high yield. The synthesis of (±)-5-*epi*-citreoviral and (±)-citreoviral has been accomplished with this annulation reaction as the key step. Using the pantolactone-derived α-keto ester, the allylsilane 1 has been resolved with high enantiomeric purity.

(+)-Citreoviral (**1**) and the related polyene α-pyrone mycotoxins (−)-citreoviridin (**2**) and (+)-verrucosidin (**3**) were isolated from a variety of *Penicillium* fungi (Figure 1).[1] Other

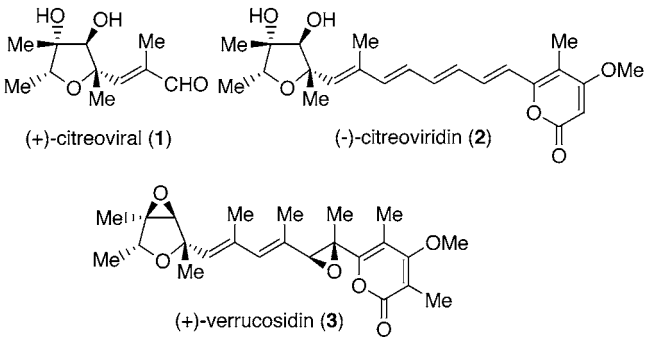


Figure 1.

structurally related natural products include citreoviridinol,[2a] isocitreoviridinol,[2a] asteltoxin,[2b] and the aurovertins.[2c] These compounds are known to be potent inhibitors of mitochondrial ATPase and oxidative phosphorylation.[3] Because of this biological activity and the complexity of the core tetrahydrofuran moiety possessing two tetrasubstituted carbon atoms, these compounds have become attractive targets for synthesis.[4,5]

The [3 + 2] annulation of allylic silanes is a highly stereoselective reaction and a powerful method to prepare functionalized five-membered carbocycles or heterocycles.[6,7] This reaction seemed to be amenable to the synthesis of the densely functionalized tetrahydrofuran ring in citreoviral and related mycotoxins. Previously reported total syntheses of (+)-citreoviral, (−)-citreoviridin, and (+)-verrucosidin utilized epoxide **4** as the common advanced intermediate

(1) (a) Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron* **1977**, *33*, 3077−3081. (b) Shizuri, Y.; Nishiyama, S.; Imai, D.; Yamamura, S.; Furukawa, H.; Kawai, K.; Okada, N. *Tetrahedron Lett.* **1984**, *25*, 4771−4774. (c) Burka, L. T.; Ganguli, M.; Wilson, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 544−545.

(2) (a) Nishiyama, S.; Shizuri, Y.; Imai, D.; Yamamura, S.; Terada, Y.; Niwa, M.; Kawai, K.; Furukawa, H. *Tetrahedron Lett.* **1985**, *26*, 3243−3246. (b) Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1979**, 441−442. (c) Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Osselton, M. D. *J. Chem. Soc., Chem. Commun.* **1974**, 874−876.

(3) (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.

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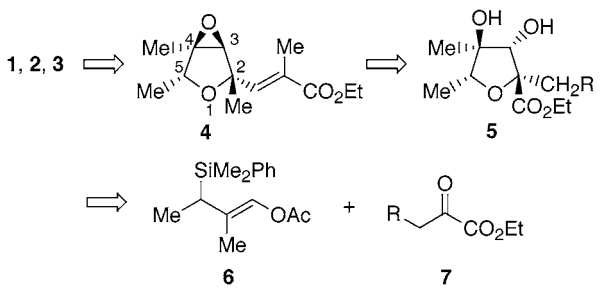
(Scheme 1).[4b,5] We envisioned that tetrahydrofuran **5**, a precursor to epoxide **4**, could be accessed by the [3 + 2]

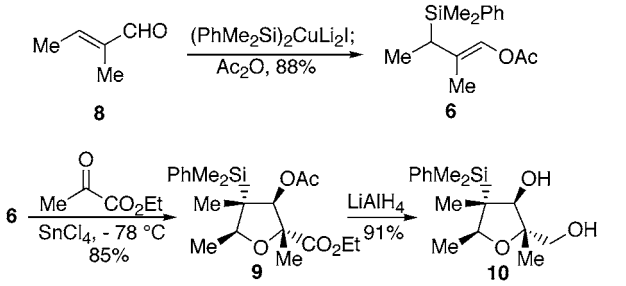
Scheme 1



annulation of the substituted allylic silane **6** with α-keto ester **7**.[8] This communication reports the synthesis of (±)-citreoviral and its C-5 epimer by this strategy and a highly selective kinetic resolution to obtain the allylic silane **6** in enantiomerically pure form. This compound could be applied to the asymmetric synthesis of (+)-citreoviral, (−)-citreoviridin, (+)-verrucosidin, and their unnatural enantiomers.

The annulation reaction of allylic silane **6** with α-keto ester **7** indeed provided rapid access to the core ring structure of the targets. The allylic silane **6** was synthesized in one step by the conjugate addition of dimethylphenylsilyl cuprate to α,β-unsaturated aldehyde **8** followed by the in situ acetylation of the enolate with acetic anhydride (Scheme 2).[9] Treatment of the allylic silane **6** with ethyl pyruvate in the presence of $SnCl_4$ at −78 °C gave the [3 + 2] annulation product **9** as a single diastereomer in 85% yield.[10] This process involves a silyl migration from a tertiary β-silyl carbocation to a

Scheme 2

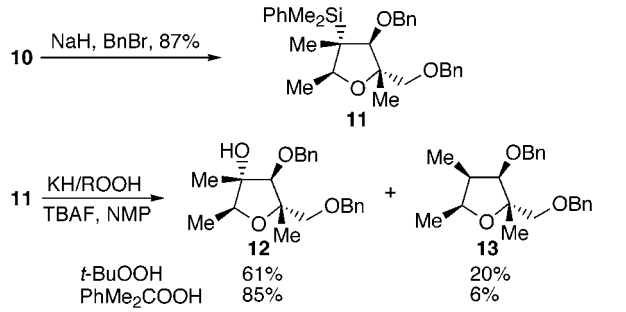


secondary β-silyl carbocation, a process that is likely to be energetically unfavorable but not unprecedented.[11,12] The configuration of tetrahydrofuran **9**, which is consistent with the proposed mechanism for the [3 + 2] annulation,[6a] was proven by X-ray crystallographic analysis of the reduction product, diol **10**.

Because a dimethylphenylsilyl group can be oxidized to a hydroxyl group by the Tamao−Fleming protocol,[13] the tetrahydrofuran **9** has all the required functionality and stereochemistry of citreoviral with the exception of an incorrect configuration at C-5. Before solving this problem, we decided to synthesize (±)-5-*epi*-citreoviral to optimize the remaining steps of the synthesis.

The oxidation of the dimethylphenylsilyl group was problematic because of the steric hindrance and the sensitivity of the reactant. After considerable experimentation, we found that the oxidation could be achieved with the conditions reported from our laboratory.[14] Thus, treatment of the ether **11** with KH/*t*-BuOOH/TBAF in NMP gave the desired alcohol **12** in 61% yield as well as 20% of the protodesilylation product **13** (Scheme 3). Substitution of cumene

Scheme 3



hydroperoxide for *tert*-butyl hydroperoxide increased the yield of the oxidation product to 85%.

(4) For the synthesis of citreoviral and citreoviridin in both racemic and optically active form, see: (a) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223−226. (b) Whang, K.; Venkataraman, H.; Kim, Y. G.; Cha, J. K. *J. Org. Chem.* **1991**, *56*, 7174−7177. (c) Begley, M. J.; Bowden, M. C.; Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1951−1958. (d) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470−481. (e) Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067−5079. (f) Bowden, M. C.; Patel, P.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4793−4796. (g) Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231−234. (h) Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485−6488. (i) Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1985**, *26*, 2529−2532.

(5) For the synthesis of (+)-verrucosidin, see: (a) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201−5203. (b) Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985−8987.

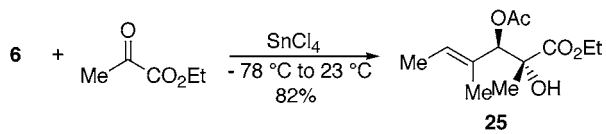
(6) (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. (b) Knölker, H.-J. *J. Prakt. Chem.* **1997**, *339*, 304−314.

(7) For the applications of [3 + 2] annulation of allylic silanes in natural product synthesis, see, for example: (a) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675−678. (b) Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621−623. (c) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949−1952.

(8) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627−630.

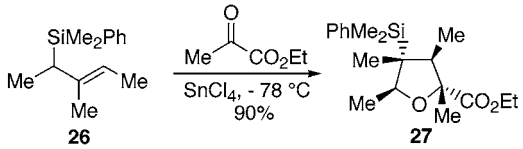
(9) Isaka, M.; Williard, P. G.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2115−2116.

(10) Raising the reaction temperature from −78 °C to room temperature led to the Sakurai product **25** completely:



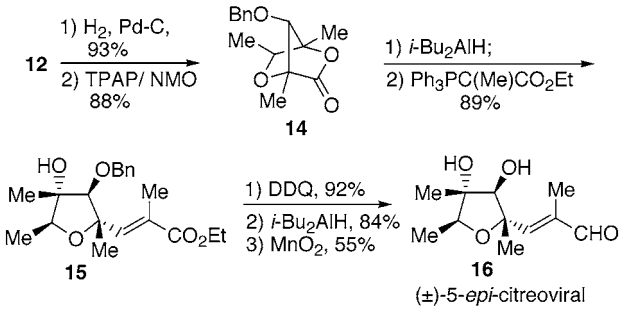
(11) (a) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1993**, *58*, 2345−2348. (b) Radeitch, B.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 2430−2431.

(12) The reaction of allylic silane **26**, the methyl analogue of **6**, with ethyl pyruvate gave tetrahydrofuran **27** in 90% yield as a single diastereomer:



Further elaboration of the oxidation product **12** to (±)-5-*epi*-citreoviral is shown in Scheme 4. Because of the

Scheme 4

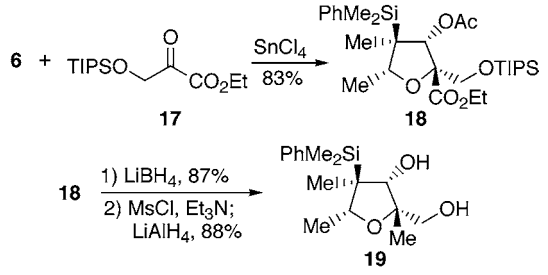


difference in accessibility of the two benzyl ether groups of **12**, the primary benzyl group could be removed selectively. The resulting diol was treated with TPAP/NMO to afford the bicyclic lactone **14**.[4a] Reduction of the lactone with *i*-Bu_2AlH afforded the lactol, which was submitted without purification to the Wittig reaction to provide the α,*β*-unsaturated ester **15** as exclusively the (*E*)-isomer. Deprotection of the secondary benzyl group with DDQ, reduction of the ester with *i*-Bu_2AlH, and oxidation of the resultant allylic alcohol with MnO_2 furnished (±)-5-*epi*-citreoviral **16**.

With a viable synthetic route in hand, we targeted epoxide **4** for the formal synthesis of (±)-citreoviral (Scheme 1). A comparison of the stereochemistry presented in epoxide **4** and the [3 + 2] annulation product **9** revealed the necessity to invert the C-2 stereocenter of **9**. This inversion could be achieved by employing a *β*-functionalized α-keto ester as electrophile in the annulation. The ester group in the resulting tetrahydrofuran product **5** could then be reduced to the C-2 methyl group.

β-Triisopropylsilyloxy α-keto ester **17**, prepared in three steps from ethyl acrylate,[15] was found to be the appropriate electrophile (Scheme 5). The reaction of allylic silane **6** with

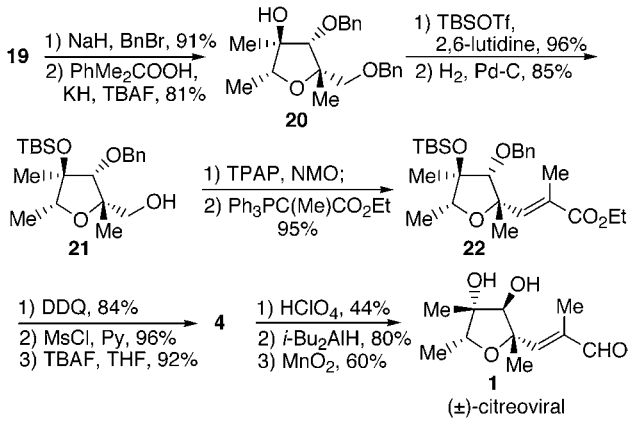
Scheme 5



α-keto ester **17** afforded the [3 + 2] annulation product **18** in 83% yield as a single diastereomer. The Sakurai product (not shown) was isolated as the only byproduct (in 14% yield). Reduction of the ester groups with $LiBH_4$ gave the corresponding diol in 87% yield. Selective formation of the primary mesylate followed by $LiAlH_4$ reduction revealed the C-2 methyl group with concomitant removal of the TIPS group to afford diol **19**.

With **19** in hand, we completed the synthesis of (±)-citreoviral by following a similar sequence as above (Scheme 6). Protection of diol **19** followed by oxidation of the C−Si

Scheme 6



bond provided alcohol **20**. The tertiary hydroxyl group was then protected, and selective debenzylation gave the primary alcohol **21**. Oxidation of the alcohol followed by the Wittig reaction afforded the α,*β*-unsaturated ester **22** as the (*E*)-isomer only. Completion of the formal synthesis target, epoxide **4**, was achieved by the deprotection of the benzyl ether, formation of the mesylate, and deprotection of the silyl ether. Following literature procedures,[4b] we were able to transform epoxide **4** to (±)-citreoviral **1** in three steps.

For the enantioselective syntheses of citreoviral, citreoviridin, and verrucosidin using the [3 + 2] annulation strategy, we utilized the reaction of an allylic silane with a chiral α-keto ester. Akiyama reported a highly stereoselective [3 + 2] annulation of an allylic silane with the chiral α-keto ester derived from L-quebrachitol. The tetrahydrofuran annulation products were obtained with up to >98% ee after removal of the chiral auxiliary.[16] The chiral auxiliary they used, however, was too expensive for our purpose. In addition, three steps were needed to prepare the chiral α-keto ester from the chiral auxiliary.

The inexpensive alcohol (*R*)-(−)-pantolactone served as an efficient chiral auxiliary for the kinetic resolution of a racemic allylic silane (Scheme 7). Reaction of the racemic silane **6** (2.0 equiv) with the chiral pyruvate **23**, prepared in one step from pantolactone, provided the [3 + 2] annulation product **24** in 90% yield (based on **23**) as a single diastereomer by ^{1}H NMR spectroscopic analysis.[17] Reduction of

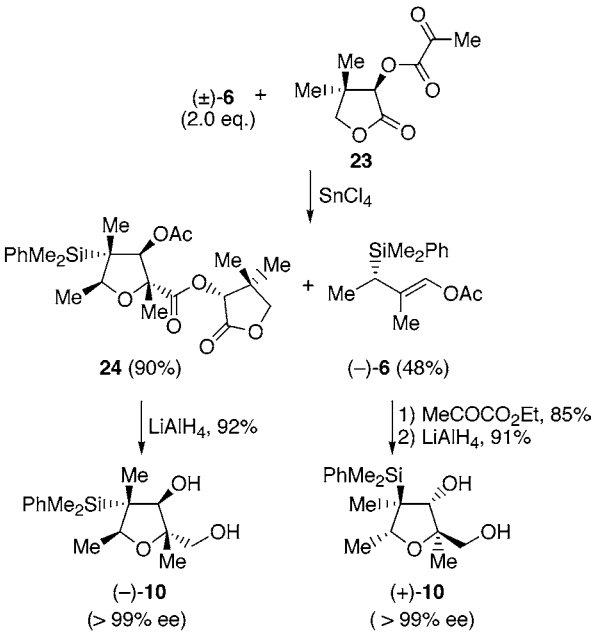
(13) (a) Tamao, K. *Advances in Silicon Chemistry*; JAI: Greenwich, CT, 1996; Vol. 3, pp 1−62. (b) Fleming, I. *Chemtracts-Org. Chem.* **1996**, *9*, 1−64.

(14) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044−6046.

(15) See Supporting Information.

(16) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 8401−8404.

Scheme 7



24 with $LiAlH_4$ afforded diol (−)-**10** with an ee greater than 99%.[18] We were also able to recover the unreacted allylic silane **6** in 48% yield and with high enantiomeric purity. Treatment of the recovered silane (−)-**6** with ethyl pyruvate followed by reduction afforded (+)-**10** in >99% ee.[18] Since both enantiomers of pantolactone are commercially available and inexpensive, we could obtain both enantiomers of the allylic silane **6** using this kinetic resolution. Thus, the asymmetric syntheses of both enantiomers of citreoviral, citreoviridin, and verrucosidin are possible using the synthetic route reported above.

In summary, we have achieved the synthesis of (±)-5-*epi*-citreoviral and (±)-citreoviral using [3 + 2] annulation reactions of allylic silanes, which also represented a formal synthesis of citreoviridin and verrucosidin. The key annulation process assembled the highly functionalized tetrahydrofuran core of these natural products in one step with high diastereoselectivity. We also demonstrated that a highly stereo- and enantioselective asymmetric annulation was possible by the kinetic resolution of the racemic allylic silane using an easily accessible chiral α-keto ester.

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Supporting Information Available: Full experimental and analytical data for all new compounds, X-ray data for (±)-**10** and the enantiomer of the 5-ethyl analogue of **24**, and the chiral HPLC traces of (±)-**10**, (−)-**10**, and (+)-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) An X-ray crystal structure of the enantiomer of the 5-ethyl analogue of **24**, which was derived from (*S*)-pantolactone, was obtained (see Supporting Information). The relative and absolute stereochemistry of **24** was determined by comparison. Consequently, the stereochemistry of (−)-**10** and (+)-**10** can be assigned, demonstrating the absolute configuration of (−)-**6** as well.

(18) The enantiomeric excess of (−)-**10** and (+)-**10** was determined by HPLC analysis using a Chiracel OJ column, and the enantiomerically enriched material was compared with racemic material.