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Stereoselection in the Prins-Pinacol Synthesis of 2,2-Disubstituted 4-Acyltetrahydrofurans. Enantioselective Synthesis of (−)-Citreoviral

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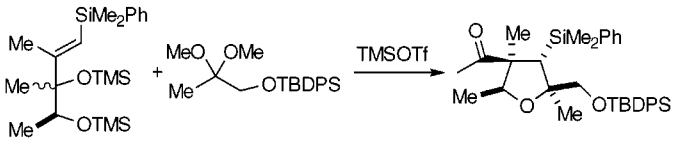
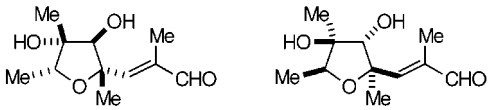
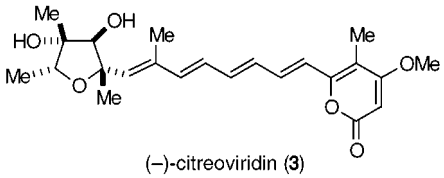
ABSTRACT



The condensation of allylic diols with unsymmetrical ketones proceeds with high stereoselection to form 2,2-disubstituted 4-acyltetrahydrofurans when the α-substituents of the ketone differ substantially in size. A Prins-pinacol condensation of this type is the central strategic step in an enantioselective synthesis of (−)-citreoviral.

(+)-Citreoviral (**1**) and the related polyene pyrone (−)-citreoviridin (**3**) co-occur in *Penicillum citreoviride*.[1] Citreoviridin is a potent neurotoxic mycotoxin because of its specific inhibition of mitochondrial F_1,F_0-ATPase.[2] These and related mycotoxins[3] have stimulated the development of imaginative methods for preparing polysubstituted tetrahydrofurans, with total syntheses of citreoviridin (**3**) and citreoviral (**1**) being achieved by several groups in both racemic[4] and optically active form.[5]





A wide variety of polysubstituted tetrahydrofurans can be prepared by condensation of allylic diols with aldehydes or ketones in a reaction sequence whose central step is a pinacol-terminated Prins cyclization (Scheme 1).[6,7] Recent publications from these laboratories have illustrated the utility of this strategy level reaction for preparing oxacyclic natural

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[⊥] Current address: Allergan, Inc., Chemical Sciences, 2525 Dupont Drive, RD3D, Irvine, CA 92623-9534.

(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.

(2) (a) Boyer, P. D.; Chance, B.; Ernster, L.; Mitchell, P.; Racker, E.; Slater, E. C. *Annu. Rev. Biochem.* **1977**, *46*, 955−1026. (b) Mitchell, P. *FEBS Lett.* **1977**, *78*, 1−20. (c) Chang, T.; Penefsky, H. S. *J. Biol. Chem.* **1974**, *249*, 1090−1098. (d) Muller, J. L. M.; Rosing, J.; Slater, E. C. *Biochim. Biophys. Acta* **1977**, *462*, 422−437. (e) Gause, E. M.; Buck, M. A.; Douglas, M. G. *J. Biol. Chem.* **1981**, *256*, 557−562.

(3) The synthesis of asteltoxin by Schreiber and Satake is an early notable example: Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186−4188.

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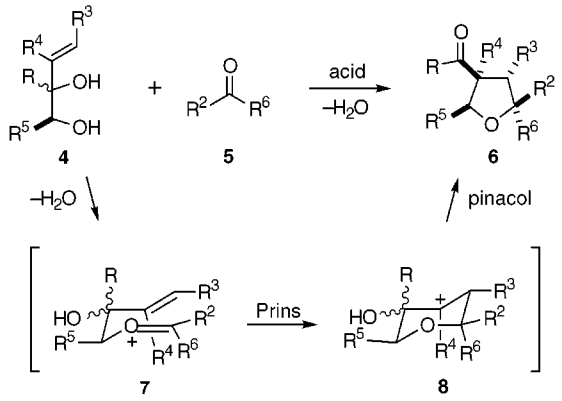
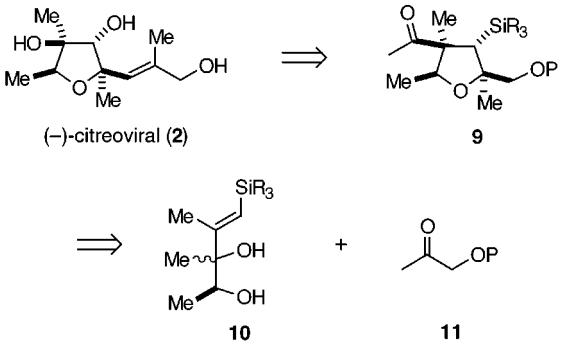
Scheme 1



products.[8] Although the condensation of allylic diols **4** and aldehydes (**5**, $R^6 = H$) has been employed to stereoselectively assemble chiral tetrahydrofurans having substituents at each ring carbon, we had not previously investigated stereoselection in the condensation of allylic diols with unsymmetrical ketones. The opportunity to rectify this deficiency in our understanding of the Prins-pinacol synthesis of tetrahydrofurans and to examine the viability of introducing a hydroxyl group at C3 of a 4-acyltetrahydrofuran by way of a silyl surrogate[9] led us to pursue the total synthesis of (−)-citreoviral (**2**) by the strategy outlined in Scheme 2. The

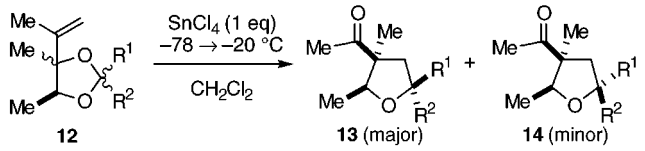
Scheme 2



unnatural enantiomer **2** was targeted since this congener had not been prepared previously and enantioenriched allylic diols **10** were anticipated to be readily available from (*S*)−(−)-ethyl lactate.[10]

For the approach adumbrated in Scheme 2 to be successful, Prins-pinacol condensation of **10** and **11** must take place with stereoselective incorporation of the ketone fragment. To gain insight into stereochemical control elements in Prins-pinacol reactions of unsymmetrical ketones, rearrangements of acetals **12** derived from 3,4-dimethyl-4-penten-2,3-diol[11] and a series of unsymmetrical ketones were investigated. Results are summarized in Scheme 3.[12] Stereoselection in the reaction

Scheme 3



	Yield (%)	stereoselectivity
a R^1 = Et, R^2 = Me	89	81:19
b R^1 = CH_2Br, R^2 = Me	67	68:32
c R^1 = cyclohexyl, R^2 = Me	94	94:6
d R^1 = Ph, R^2 = Me	98	98:2
e R^1 = CH_2OMe R^2 = Et	72	62:38

of the series of methyl ketones increased approximately with the size of the R^1 substituent. Steric effects obviously play the dominant role, with electronic effects being less important. The preference for forming tetrahydrofuran **13** having the larger C2 substituent on the β face is consistent with this group preferentially occupying a pseudoequatorial position in the Prins cyclization step (**7** → **8**, Scheme 1). We concluded from this brief study that for **9** to be highly favored in the pivotal Prins-pinacol conversion, the protecting group of the 1-hydroxy-2-propanone component **11** would need to be a large group. A *tert*-butyldiphenylsilyl (TBDPS) group was chosen both for its steric size and its stability to Lewis acids.

Our synthesis of (−)-citreoviral begins with construction of enantioenriched allylic diols **18** from (*S*)-3-(*tert*-butyldiphenylsiloxy)-2-butanone (**16**)[10] and 1-(dimethylphenylsilyl)propyne (**15**).[13] Using tantalum chemistry developed by Takai and Utimoto,[14] the tantalum alkyne complex derived

(4) (±)-Citreoviridin: (a) Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067−5079. (±)-Citreoviral: (b) Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1985**, *26*, 2529−2532. (c) Bowden, M. C.; Patel, P.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4793−4796. (d) Bowden, M. C.; Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1947−1950. (e) Begley, M. J.; Bowden, M. C.; Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1951−1958. (f) Ebenezer, W.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4053−4056.

(5) (−)-Citreoviridin and (+)-citreoviral: (a) Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231−234. (b) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470−481. (c) Whang, K.; Venkataraman, H.; Kim, Y. G.; Cha, J. K. *J. Org. Chem.* **1991**, *56*, 7174−7177. (+)-Citreoviral: (d) Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485−6488.

(6) For brief reviews, see: (a) Overman, L. E. *Aldrichimica Acta* **1995**, *28*, 107−120. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (c) Overman, L. E.; Rishton, G. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. 9, pp 4−9.

(7) For the original discovery of this route to tetrahydrofurans, see: Martinet, P.; Mousset, G. *Bull. Soc. Chim. Fr.* **1970**, 1071−1076.

(8) See, inter alia: (a) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468−2477. (b) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392.

(9) Colvin, E. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon: Oxford, 1992; Vol. 7, pp 641−651.

(10) Overman, L. E.; Rishton, G. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. 9, pp 139−142.

(11) This diol was a 7:1 mixture of *anti* and *syn* isomers.[6c]

(12) Stereochemical assignments for tetrahydrofuran products **13** and **14** were secured by nOe experiments. Details are provided in Supporting Information.

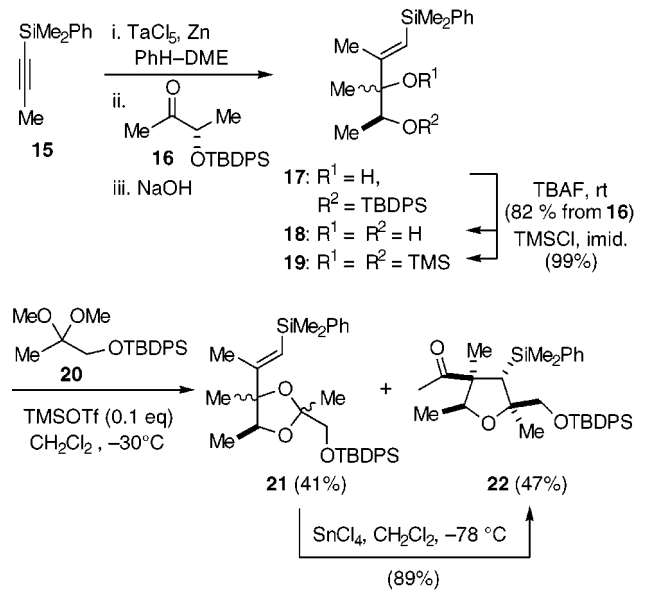
(13) Available in 89% yield from silylation of 1-lithiopropyne: Meinke, P. T.; Krafft, G. A.; Guram, A. *J. Org. Chem.* **1988**, *53*, 3632−3634.

(14) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973−1981.

from **15** was added to **16** and the vinyltantalum intermediate was cleaved with aqueous NaOH to generate (*E*)-allylic diol derivative **17** stereoselectively. Without purification, this crude product was exposed to tetra-*n*-butylammonium fluoride (TBAF) to provide allylic diol **18**, a 6:1 mixture of allylic alcohol epimers, in 82% overall yield from **16**. Standard silylation of **18** delivered bis(trimethylsilyl) derivative **19** in essentially quantitative yield.

Disiloxy alkene **19** was condensed with dimethyl ketal **20**[15] in the presence of 0.1 equiv of trimethylsilyl triflate at −30 °C in CH_2Cl_2 in the expectation that ketal **21** would be formed.[16] To our surprise, these conditions generated nearly equal amounts of **21** and the ultimately desired polysubstituted tetrahydrofuran **22**. Separation of these products on silica gel provided **22** in 47% yield and **21** in 41% yield. Since acetal **21** was unchanged when exposed to 0.1 equiv of trimethylsilyl triflate at −30 °C in CH_2Cl_2, **21** was not an intermediate on the pathway to **22** under these conditions.[17] However, **21** could be efficiently converted to **22** by exposure to 1.2 equiv of $SnCl_4$ at −78 °C in CH_2Cl_2.[18,19] The sequence summarized in Scheme 4 delivers polysubstituted tetrahydrofuran **22** in 67% overall yield and >95% ee from (*S*)-siloxybutanone **16**.[20]

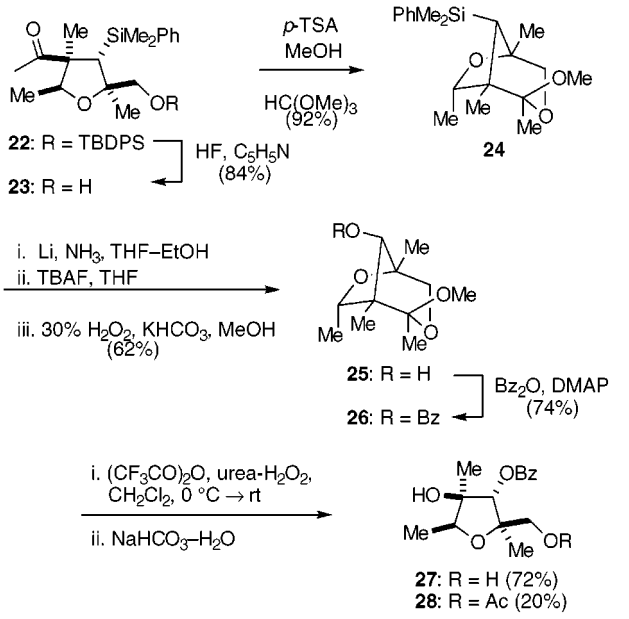
Scheme 4



Our plan for preparing (−)-citreoviral from tetrahydrofuran **22** required introducing the C3 and C4 hydroxyl groups by oxidation of the C−$SiMe_2Ph$[9,21] and C−COMe[22] bonds, processes that are well-established to proceed with retention of configuration. After exhaustive attempts to activate the C3 silyl functionality of **22** for oxidative cleavage by conversion of the phenyl substituent to an electronegative group failed,[9,21] we turned to a procedure introduced by Taber for activating dimethylphenylsilyl substituents for oxidation.[23]

The *tert*-butyldiphenylsilyl group of **22** was first discharged with 48% aqueous HF in acetonitrile to give **23** (Scheme 5).[24] To protect the ketone and simplify isolation of subsequent intermediates, **23** was converted to bicyclic acetal **24** by exposure to acidic methanol and trimethyl orthoformate. Reduction of **24** with Li in ammonia, followed by sequential reaction of the Birch reduction product with TBAF and basic hydrogen peroxide generated alcohol **25** (mp 96−98 °C) in 62% yield.[23] Protection of the secondary alcohol of **25** as a benzoate, Baeyer−Villiger oxidation of **26** with trifluoroperacetic acid in CH_2Cl_2[25] and final basification to pH 8.5 delivered diol **27** in 72% yield. Primary acetate **28** was isolated also in 20% yield.

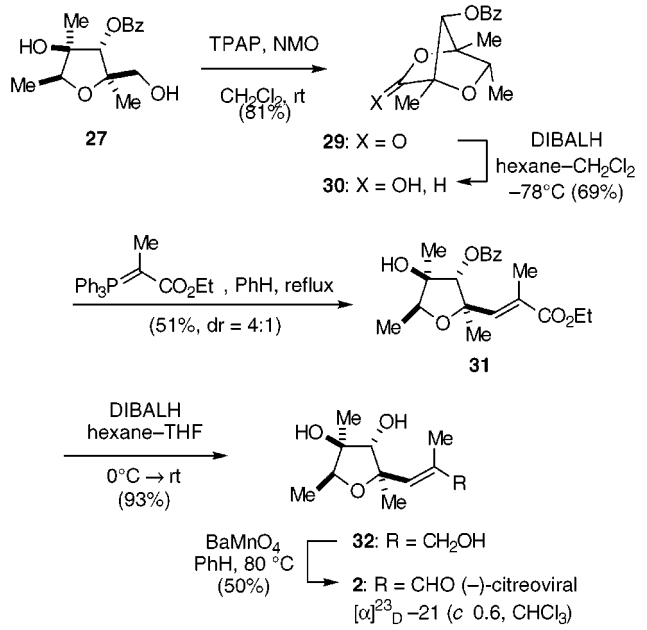
Scheme 5



The synthesis of (−)-citreoviral (**2**) was completed as summarized in Scheme 6. Tetrapropylammonium perruthenate (TPAP)-catalyzed oxidation[26] of **27** gave rise to lactone

(15) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707−1712.
(16) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357−1358.
(17) This result suggests that the α-alkoxycarbenium ion initially generated[16] from condensation of **19** with the more accessible secondary trimethylsilyl ether group of **20** undergoes Prins cyclization faster than it is trapped by the proximal tertiary trimethylsilyl ether.
(18) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354−5365.
(19) A tetrahydrofuran product epimeric to **22** at C5 was not detected in this reaction or in the initial condensation of **19** and **20**.
(20) The enantiopurity of **22** was confirmed by HPLC analysis using a Chiralcel OD column.
(21) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29−31.
(22) Krow, G. R. *Org. React.* **1993**, *43*, 251−798.
(23) Taber, D. F.; Yet, L.; Bhamidipati, R. S. *Tetrahedron Lett.* **1995**, *36*, 351−354.
(24) At this point, the constitution of the tetrahydrofuran produced upon Prins-pinacol rearrangement was rigorously established by single-crystal X-ray analysis of the phenylcarbamate derivative.
(25) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533−535.
(26) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13−19.

Scheme 6



29. Reduction of this intermediate with diisobutylaluminum hydride (DIBALH) at −78 °C selectively generated lactol **30**,[5b] without cleavage of the benzoate protecting group. Wittig reaction of **30** with (carboethoxyethylidene)triphenylphosphorane in refluxing benzene yielded a 4:1 mixture of *E* and *Z* α,β-unsaturated esters; separation of this mixture on silica gel provided *E* isomer **31** in 51% yield. Reduction of **31** with DIBALH at 0 °C → room temperature gave allylic alcohol **32**, which was identical in all respects except optical rotation with an authentic sample.[4b,5c] Finally, oxidation of **32** with barium manganate in refluxing benzene furnished (−)-citreoviral (**2**), $[\alpha]^{23}_{D}$ −21 (*c* 0.6, $CHCl_3$), in 46% overall yield from **31**.[27]

The total synthesis of (−)-citreoviral (**2**) recorded herein is the first of the unnatural enantiomer of this natural product. A notable feature of the synthesis is use of a Prins-pinacol reaction to assemble highly functionalized tetrahydrofuran intermediate **22** in 65% overall yield from (*S*)−(−)-ethyl lactate. These studies extend the scope of the Prins-pinacol synthesis of tetrahydrofurans by demonstrating that (a) 2,2-disubstituted 4-acyltetrahydrofurans containing different C2 substituents can be formed with high stereoselection if the α-carbons of the unsymmetrical ketone component differ substantially in steric size and (b) 4-acyl-3-(dimethylphenylsilyl)-tetrahydrofurans, which serve as precursors of 4-acyl-3-hydroxytetrahydrofurans, can be accessed by Prins-pinacol rearrangements of allylic diols containing an (*E*)-dimethylphenylsilyl substituent on the distal vinylic carbon.[28,29]

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Supporting Information Available: Experimental procedures and characterization data for new compounds reported in Schemes 3−6. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Specific rotations at the sodium D line of +21.1 (*c* 2.5, $CHCl_3$),[5a] +18.7 (*c* 0.65, $CHCl_3$)[5b], and +23.3 (*c* 0.12, $CHCl_3$),[5c] have been reported for **1**.

(28) This successful preparation of 4-acyl-3-(dimethylphenylsilyl)tetrahydrofurans demonstrates that pinacol rearrangements of 4-hydropyranyl cations containing an equatorial dimethylphenylsilyl substituent at C3 (e.g., **8**, R^3 = $SiPhMe_2$, Scheme 1) occur faster than β-silyl elimination to form an alkene.[29]

(29) For other reports documenting the high rate of the pinacol rearrangement step in Prins-pinacol rearrangements, see: (a) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927−8940. (b) Pennington, L. D.; Overman, L. E. *Can. J. Chem.* **2000**, *78*, in press.