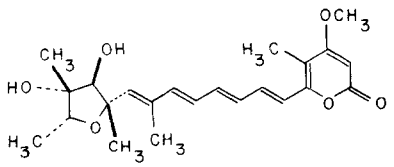
Tetrahedron Letters,Vol.26,No.21,pp 2529-2532,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

HYDROXYL-DIRECTED IODOETHERIFICATIONS OF ALLYLIC ALCOHOLS. SYNTHESIS OF (±)-CITREOVIRAL.

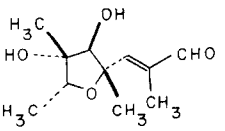
D.R. Williams*[1] and Franklin H. White
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Summary: Iodine-induced cyclizations of γ,δ-olefinic benzyl ethers have afforded highly substituted tetrahydrofurans with complete stereocontrol as directed by the configuration of an allylic alcohol. Evidence for stereochemical assignments and conversion to citreoviral, a known microbial metabolite, have been presented.

Recent literature has documented considerable interest in the formation of complex tetrahydrofurans.[2] Results from our laboratories have demonstrated a number of methodologies for the stereocontrolled preparation of highly substituted tetrahydrofurans.[3] Citreoviridin (1) is a dangerous and ubiquitous mycotoxin, which functions as a potent specific inhibitor of mitochondrial ATPase and oxidative phosphorylation.[4,5] Very recently Yamamura and coworkers have characterized related metabolites including citreoviral (2), and their synthetic studies have established the absolute configurations as shown below.[6,7] We wish to describe a stereospecific hydroxyl-directed ring closure of allylic alcohols which has led to a preparation of tetrahydrofurans bearing four contiguous chiral centers and synthesis of racemic citreoviral (2).



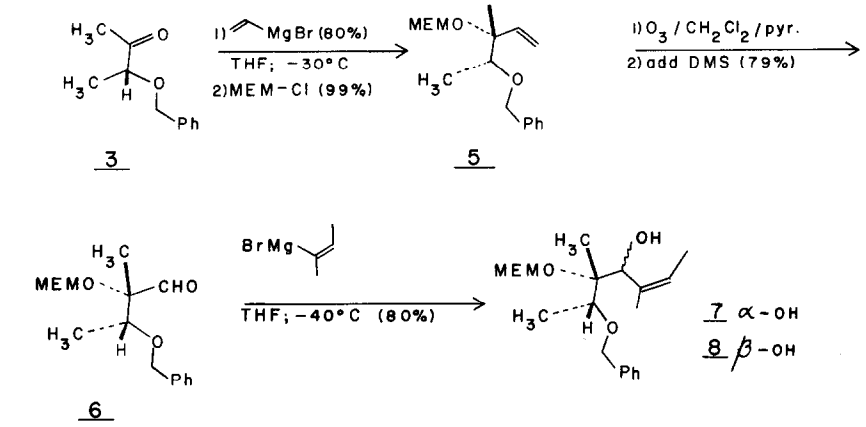
1



2

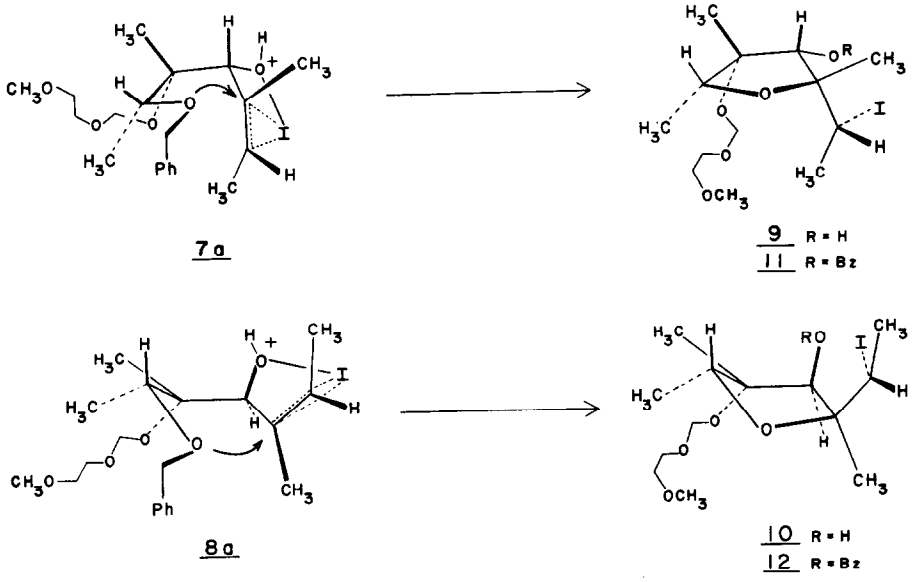
As illustrated in Scheme I,[8] the known methyl ketone 3 reacted with vinylmagnesium bromide (-30°C, THF) affording only alkene 4 by chelation-controlled addition (80% yield). Protection of the tertiary alcohol as its β-methoxyethoxymethyl ether 5 (MEMCl, i-Pr_2NEt, CH_2Cl_2), and subsequent ozonolysis at -78°C (CH_2Cl_2, pyridine, then Me_2S) gave aldehyde 6 in 79% yield. A Grignard reaction, utilizing *trans*-2-bromo-2-butene,[9] gave a 3:2 ratio of the allylic alcohols 7 and 8 (THF at -40°C) in 82% yield. Iodoetherification under conditions as described by Bartlett and coworkers[10] led to a highly selective cyclization. Each individual alcohol 7 and 8 afforded a single tetrahydrofuran 9 and 10 (75% yields), respectively. Thus, the configuration of the allylic alcohol has conferred facial selectivity for electrophilic attack at the neighboring olefin, providing a hydroxy-directed iodoetherification as displayed below. It may be most significant that transition states for ring formation in each case should feature developing *cis*-fused [3.3.0] bicyclic systems.[11] Benzyl iodide was produced as a by-product by dealkylation of the intermediate oxonium ion.

SCHEME I



3 5 6 13 14

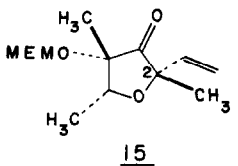
Smooth conversion to benzoates 11 and 12 occurred at room temperature (BzCl, DMAP, 1 equiv., CH_2Cl_2), although alcohol 9 required longer reaction times. Elimination of hydrogen iodide (DBU in *ortho*-dichlorobenzene at reflux) cleanly yielded the terminal alkenes 13 and 14.



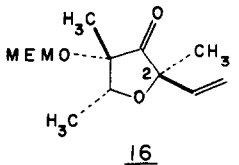
7a 9 R = H 11 R = Bz

8a 10 R = H 12 R = Bz

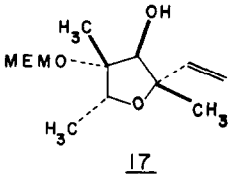
Unfortunately, stereochemical assignments of these tetrahydrofurans were not unambiguously feasible. However, further chemical transformations and conversion to racemic citreoviral confirmed all configurations. Thus oxidations (PCC, CH_2Cl_2, 22°C) of the corresponding alcohols of 13 and 14 gave two distinct ketones 15 and 16 differing in stereochemistry at C-2, and subsequent reduction of 15 with lithium borohydride (THF at 22°C) afforded exclusively a new tetrahydrofuran 17 (85% yield), whereas 16 gave back its starting β-alcohol.[12]



15

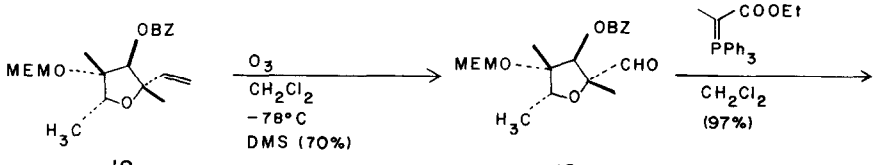


16

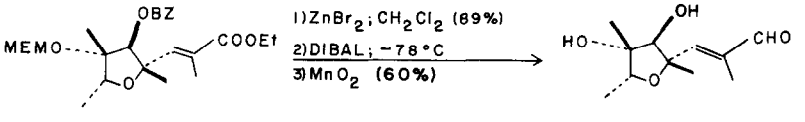


17

Finally the total synthesis of (+)-citreoviral (2) was completed as shown below. Oxidation of iodoalcohol 9 (PCC, CH_2Cl_2, 80% yield) followed by elimination of HI (DBU, *ortho*-dichlorobenzene, 180°C, 30 mins, 90%) gave ketoalkene 15, and lithium borohydride reduction with subsequent benzoylation provided 18 (70% yield). Ozonolysis of benzoate 18 gave a non-enolizable aldehyde 19, and treatment with (carbethoxyethylidene)triphenylphosphorane afforded solely the *E*-α,β-unsaturated ester 20. Facile removal of MEM ether protection ($ZnBr_2$ in CH_2Cl_2 at 0°C, 40 min), DIBAL reduction at -78°C (5.2 equivs in CH_2Cl_2), and subsequent manganese dioxide oxidation of the resulting primary allylic alcohol (CH_2Cl_2 at 22°C, 60% yield) provided formation of citreoviral (2).[13]



18 19



20 2

Further studies toward an efficient preparation of (-)-citreoviridin are underway.

Acknowledgement: We thank the Alfred P. Sloan Foundation and the National Institutes of Health (AI 17674) for generous support of our research and acknowledge assistance of the National Science Foundation for purchase of high field NMR (CHE81-05004) and high resolution mass spec instrumentation (CHE81-11957).

References:

1. Alfred P. Sloan Foundation Fellow (1983-1986).

2. P.C. Ting and P.A. Bartlett, *J. Am. Chem. Soc., 106,* 2668 (1984), and references therein. See also citations published within the reports of reference 3.

3. For leading references; D.R. Williams, J. Grote, and Y. Harigaya, *Tetrahedron Letters, 25,* 5231 (1984); and D.R. Williams, Y. Harigaya, J.L. Moore, and A. D'Sa, *J. Am. Chem. Soc., 106,* 2641 (1984).

4. N. Sakabe, T. Goto, and Y. Hirata, *Tetrahedron, 33,* 3077 (1977).

5. Related metabolites include: citreoviridins B-F, B. Franck and H.-P. Gehrken, *Angew. Chem. Int. Ed. Engl., 19,* 461 (1980); verrucosidin, L.T. Burka, M. Ganguli, and B.J. Wilson, *Chem. Commun., 544* (1983); aurovertins, L.J. Mulheirn, R.B. Beechey, D.P. Leworthy, and M.D. Osselton, *Chem.Commun., 874* (1974); Asteltoxin, G.J. Kruger, P.S. Steyn, R. Vleggaar, and C.J. Rabie, *Chem. Commun., 441* (1979), and see reference 6a. For recent synthetic studies: S.L. Schreiber and K. Satake, *J. Am. Chem. Soc., 105,* 6723 (1983), and C.S. Wilcox, G.W. Long, and H. Suh, *Tetrahedron Letters, 25,* 395 (1984).

6. Y. Shizuri, S. Nishiyama, D. Imai, S. Yamamura, H. Furukawa, K. Kawai, and N. Okada, *Tetrahedron Letters, 25,* 4771 (1984); and S. Nishiyama, Y. Shizuri, and S. Yamamura, *ibid., 26,* 231 (1985).

7. Although details have remained unpublished, the absolute configuration of (-)-citreoviridin was apparently established several years ago. See,P.E. Linnett, A.D. Mitchell, M.D. Osselton, L.T. Mulheirn, and R.B. Beechey, *Biochem. J., 170,* 503 (1978).

8. All yields are reported for purified samples, characterized by infrared, nuclear magnetic resonance (360 MHz) and mass spectral data. Complete details will be provided in a full account of this work.

9. P.S. Landis and F.G. Bordwell, *J. Am. Chem. Soc., 79,* 1593 (1957).

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

11. The directive influence of hydroxyl configuration in electrophilic reactions of allylic alcohols may be quite general as seen in peracid oxidations, Simmons-Smith reactions and recently osmylations (Y. Kishi, *et. al., Tet. Lett.* (1983) *24,* 3943 and 3947).

12. Coordination with the MEM ether substituent appears to be responsible for this highly selective hydride delivery. Selected ^{1}H-NMR (360 MHz, $CDCl_3$) data: ketone 15: δ 5.89 (m,1H), 5.29 (AB of ABX, J_{AB}=1.1 Hz, J_{AX}=17.7 Hz, J_{BX}=11.0 Hz, Δν=94.3 Hz, 2H), 4.71 (AB, Δν=70.2 Hz, J_{AB}=7.2 Hz, 2H), 3.90 (q, J=6.3 Hz, 1H), 3.74 (m, 1H), 3.59 (m, 1H), 3.52 (m, 2H), 3.37 (s, 3H), 1.40 (d, J=6.3 Hz, 3H), 1.31 (s, 3H), 1.27 (s,3H);ketone 16: δ 5.72 (m, 1H), 5.25 (AB of ABX, J_{AB}=1.1 Hz, J_{AX}=17.4 Hz, J_{BX}=10.6 Hz, Δν=55.7 Hz, 2H), 4.84 (AB, Δν=87.2 Hz, J_{AB}=7.3 Hz, 2H), 3.84 (q, J=6.4 Hz, 1H), 3.75 (m, 1H), 3.64 (m, 1H), 3.53 (m,2H), 3.38 (s,3H), 1.43 (s, 3H), 1.39 (d, J=6.4 Hz, 3H), 1.24 (s, 3H); alcohol 13a: δ 6.06 (m, 1H), 5.15 (AB of ABX, J_{AB}= 1.3 Hz, J_{AX}=17.4 Hz, J_{BX}=10.8 Hz, Δν=85.7 Hz, 2H), 4.81 (AB, Δν=67.5 Hz, J_{AB}=7.5 Hz, 2H), 4.10 (s, 1H), 3.92 (q, J=6.5 Hz, 1H), 3.86 (m, 1H), 3.67 (m, 4H), 3.39 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 1.20 (d, J=6.5 Hz, 3H); alcohol 14a: δ 5.96 (m, 1H), 5.12 (AB of ABX, J_{AB}=1.5 Hz, J_{AX}=17.3 Hz, J_{BX}=10.7 Hz, Δν=89.2 Hz, 2H), 4.90 (AB, Δν=27.4 Hz, J_{AB}=7.4 Hz, 2H), 3.86 (m, 1H), 3.68 (m, 4H), 3.55 (m, 2H), 3.40 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.21 (d, J=6.3 Hz, 3H); and alcohol 17: δ 5.99 (m, 1H), 5.20 (AB of ABX, J_{AB}=1.7 Hz, J_{AX}=17.7 Hz, J_{BX}=10.9 Hz, Δν= 44.8 Hz, 2H), 4.85 (AB, Δν=31.4 Hz, J_{AB}=7.6 Hz, 2H), 3.85 (m, 2H), 3.71 (m, 1H), 3.63 (d, J= 11.4 Hz, 1H), 3.53 (m, 2H), 3.38 (s, 3H), 3.31 (d, J=11.4 Hz, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.21 (d, J=6.5 Hz, 3H).

13. Our synthetic citreoviral was identical with published data for (+)-citreoviral (ref. 6), and tetrahydrofuran 17 was related to a known degradation product of citreoviridin (ref. 4).

(Received in USA 19 February 1985)