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STUDIES OF TETRASUBSTITUTED TETRAHYDROFURANS

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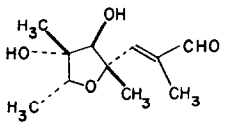
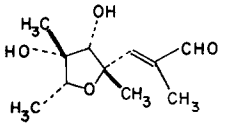
Summary: Unambiguous stereochemical assignments, detailing the course of iodine-induced cyclizations of the γ,δ-olefinic benzyl ethers 3ab, are available from X-ray studies. Pure samples of all four diastereomeric tetrahydrofuran alcohols 8, 9, 12, and 15 have been produced for direct spectroscopic comparison.

Recently Yamamura and coworkers have reported the isolation of (+)-citreoviral (1) from *Penicillium citreoviride*, and several synthetic studies of this microbial metabolite have appeared.[2,3] Our earlier report had inadvertently reversed the identity of synthetic 1 and 2.[4] In this Letter, we describe further studies of iodine-induced cyclizations of γ,δ-olefinic benzyl ethers yielding highly substituted tetrahydrofurans, and provide clarification and revision of our previous stereochemical assignments.[5]



1



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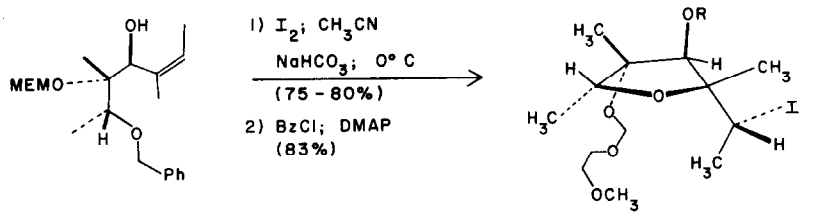
Preparation of the isomeric allylic alcohols 3ab has been previously discussed.[4] Each individual alcohol 3a and 3b was submitted to conditions of iodoetherification affording yields of 75-80% for highly selective cyclizations to the tetrahydrofurans 4 and 5, respectively.[6] Smooth conversion to benzoates 6 and 7 occurred at room temperature (BzCl, DMAP, 1 equiv., CH_2Cl_2, 8 hr), although the hindered alcohol 4 required much longer reaction times (72 hr). The stereochemical consequences of our cyclizations have been unambiguously established by X-ray diffraction studies of the crystalline tetrahydrofuran 5 (mp 54.4-55°C), and further transformations presented below confirm our remaining stereochemical assignments.[7]

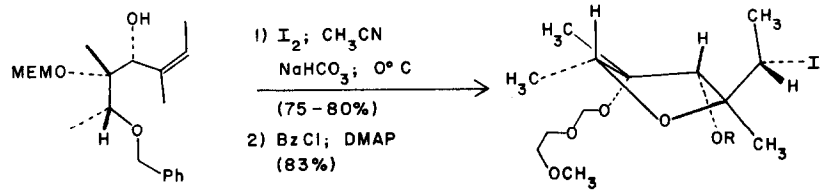
The crystallographic data establish the result of an *anti*-periplanar addition of the electrophilic iodine and the benzylic ether oxygen. However, the secondary allylic hydroxy has assumed a "directing" influence, which positions the α-iodoethyl substituent in an *anti*(*trans*) arrangement in both of the tetrahydrofurans 4 and 5. This stereochemical result is opposite that which is commonly observed in the iodolactonization of 3-hydroxy-4-alkenoic acids, and amides.[8] In fact, this methodology has been recently extended for the highly stereoselective formation of *cis*-2-halomethyl-3-hydroxypyrrolidines, as well as the analogous *cis*-2,3-disubsti-



3a

4 R=H

6 R=Bz



3b

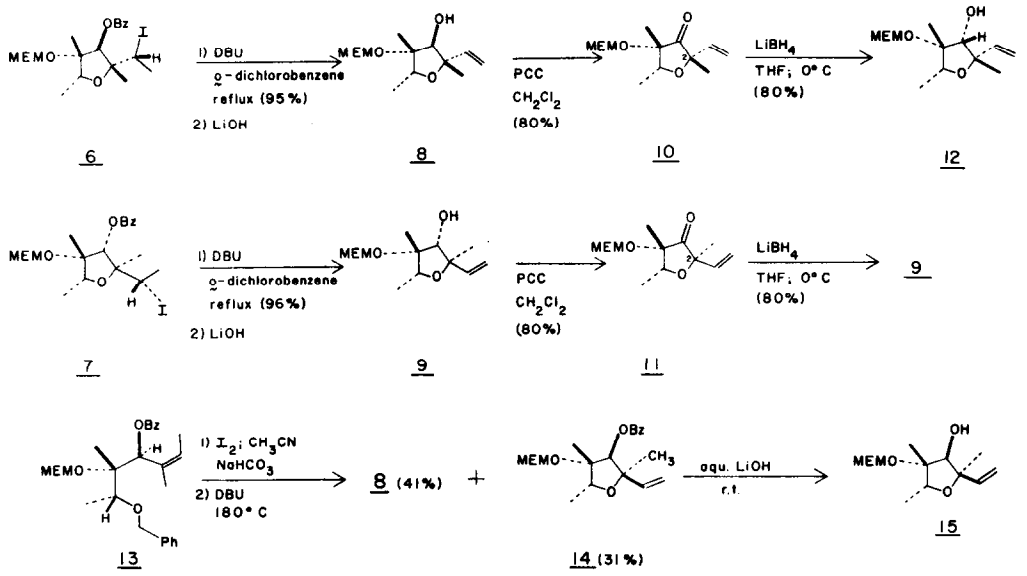
5 R=H

7 R=Bz

tuted tetrahydrofurans.[9] Chamberlin and Hehre have undertaken calculations based on conformational analysis of the starting allylic alcohols with kinetically controlled iodocyclizations which support formation of *syn*(*cis*) orientations in the ring closure.[10] Reasons for the complete reversal of stereoselectivity as observed in the *anti*(*trans*) arrangements of our tetrahydrofurans 4 and 5 remain unclear. The premature quenching of experiments or resubmission of either 4 or 5 to the buffered iodoetherification conditions failed to provide evidence of a reversible reaction process. However, rapid addition of iodine and/or exclusion of sodium bicarbonate may allow *in situ* formation of hydrogen iodide. The stereoselectivity of these reactions remained unchanged with isolation of the corresponding diols of 4 and 5 resulting from cleavage of the acid-sensitive MEM-ethers. These observations may suggest thermodynamic product development.[11]

Although the stereochemical assignments of these tetrahydrofurans were only unambiguous following the crystallographic studies, our further chemical transformations led to important characterizations. Elimination of hydrogen iodide (DBU in *ortho*-dichlorobenzene at reflux) cleanly yielded the terminal alkenes, and oxidations (PCC, CH_2Cl_2, 22°C) of the alcohols 8 and 9 gave two distinct ketones 10 and 11, demonstrating different stereochemistry at C-2. Subsequent reduction of 10 with lithium borohydride (THF at 22°C) afforded exclusively a new tetrahydrofuran 12 (85% yield), whereas 11 gave back its starting alcohol. In addition, the iodoetherification-elimination sequence using benzoate 13 afforded a separable mixture of 8 (41%) and the new isomer 14 (31%), which was converted to its corresponding alcohol 15 via standard saponification conditions (LiOH, aqu. MeOH).[12] Therefore, we had available pure

samples of all four diastereoisomeric tetrahydrofurans (alcohols 8, 9, 12 and 15), which might have been reasonably produced in the cyclization process.[13] Formation of tetrahydropyranyl products were not detected in these ring closure reactions.[14]



Finally, the total synthesis of (+)-citreoviral (1) was completed by the reaction sequence as previously described.[4] Our synthetic citreoviral was obtained as colorless, highly crystalline plates (mp 144.5-145°C from $CHCl_3$:Hex), and provided ^{1}H-NMR (360 MHz) spectra which were superimposable with data obtained from a sample of the natural product, as kindly supplied by Professor Yamamura.[15,16] Fortunately we can now report decoupled ^{13}C-NMR results which have provided for the convenient distinction of citreoviral (1).[17]

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References:

1. Alfred P. Sloan Foundation Fellow (1983-1987).

2. S. Nishiyama, Y. Shizuri and S. Yamamura, *Tetrahedron Letters*, *26*, 231 (1985), and Y. Shizuri, S. Nishiyama, H. Shigemori and S. Yamamura, *Chem. Comm.*, 292 (1985).

3. Recently, M.C. Bowden, P. Patel and G. Pattenden, *Tetrahedron Letters*, *26*, 4793 (1985).

4. D.R. Williams and F.H. White, *Tetrahedron Letters*, *26*, 2529 (1985).

5. These results were presented at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Ontario, Canada (August, 1985), Abst. S1-4.

6. The ring closure of 3a afforded a 9.5:1 ratio of tetrahydrofuran 4 to its corresponding C-2 isomer (as measured by ^{1}H-NMR integration) prior to chromatography. Cyclization of 3b gave only 5.

7. Structure 5 was determined by single crystal analysis (-154°C). All atoms were located, including hydrogens, and refined by full-matrix techniques to final residuals of R(F)=.0369 and $R_w(F)$=.0386. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 85091.

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9. Y. Tamura, S. Kawamura, K. Tanaka and Z. Yoshida, *Tetrahedron Letters, 25,* 1063 (1984), and Y. Tamura, S. Kawamura and Z. Yoshida, *Ibid., 26,* 2885 (1985).

10. A.R. Chamberlin, R.L. Mulholland, S.D. Kahn and W.J. Hehre, *J. Am. Chem. Soc.*, in press (1986). **This paper also considers a rationale for *trans*-product orientations.**

11. We have previously reported preparation of *trans*-2,3-disubstituted tetrahydrofurans by iodo- or seleno-etherification. Starting alkenes, having *Z* geometries, afforded the highest stereoselectivity. Products were rationalized based upon a minimization of alkyl/aryl and alkyl/alkyl steric repulsions of the allylic substituent in the cyclization process. D.R. Williams, J. Grote and Y. Harigaya, *Tetrahedron Letters, 25,* 5231 (1984).

12. Iodocyclization of the corresponding benzoate of 3b gave only tetrahydrofuran 7.

13. Partial characterization by ^{1}H-NMR (360 MHz, $CDCl_3$) data: alcohol 8: δ 6.06 (m, 1H), 5.15 (AB of ABX, J_{AB}=1.3 Hx, J_{AX}=17.4 Hz, J_{BX}=10.8 Hz, $\Delta\nu$=85.7 Hz, 2H), 4.81 (AB, $\Delta\nu$= 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 9: 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, $\Delta\nu$=89.2 Hz, 2H), 4.90 (AB, $\Delta\nu$=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); alcohol 12: 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, $\Delta\nu$=44.8 Hz, 2H), 4.85 (AB, $\Delta\nu$=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); and alcohol 15: δ 6.00 (m, 1H), 5.26 (AB of ABX, J_{AB}=1.9 Hz, J_{AX}=17.6 Hz, J_{BX}=10.9 Hz, $\Delta\nu$= 65.5 Hz, 2H), 4.82 (AB, $\Delta\nu$=50.5 Hz, J_{AB}=7.4 Hz, 2H), 3.96 (d, J=4.7 Hz, 1H), 3.90 (q, J= 6.5 Hz, 1H), 3.84 (m, 1H), 3.60 (m, 3H), 3.41 (s, 3H), 3.18 (d, J=4.7 Hz, 1H), 1.41 (s, 3H), 1.22 (s, 3H), 1.21 (d, J=6.5 Hz, 3H).

14. Chamberlin and coworkers have reported a case of high *trans*-selectivity (9:1 ratio of *trans/cis*) for iodolactonization of 3-hydroxy-5-methyl-4-hexenoic acid to its butyrolactone. However, the major course of the reaction produces δ-lactone (90% yield), whereas the *trans*-butryolactone was obtained in only 8% yield (see reference 8).

15. We thank Professor S. Yamamura (Keio University) for providing an authentic sample of (+)-citreoviral for our comparison studies.

16. Our studies have also led to the characterization of several diastereoisomers of citreoviral, wherein key spectral data (including ^{1}H-NMR, IR and MS) were very similar to data as reported for (+)-citreoviral itself. A direct comparison of synthetic and natural material was essential. Complete details will be provided in a full account.

17. Citreoviral ^{13}C-NMR (75.4 MHz, 5% d_6-DMSO in d_6-acetone) δ 195.93, 163.81, 135.90, 85.42, 85.23, 80.24, 79.35, 21.01, 19.63, 13.15, 10.08.

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