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A SITE-SELECTIVE SOLVOLYSIS OF A CYCLOPROPYLCARBINYL METHANESULFONATE ESTER: A ROUTE TO OXYGENATED α-METHYLENE-γ-BUTYROLACTONES

Frederick E. Ziegler,*[1] Anthony F. Marino, O.A.C. Petroff and William L. Studt

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut, 06520

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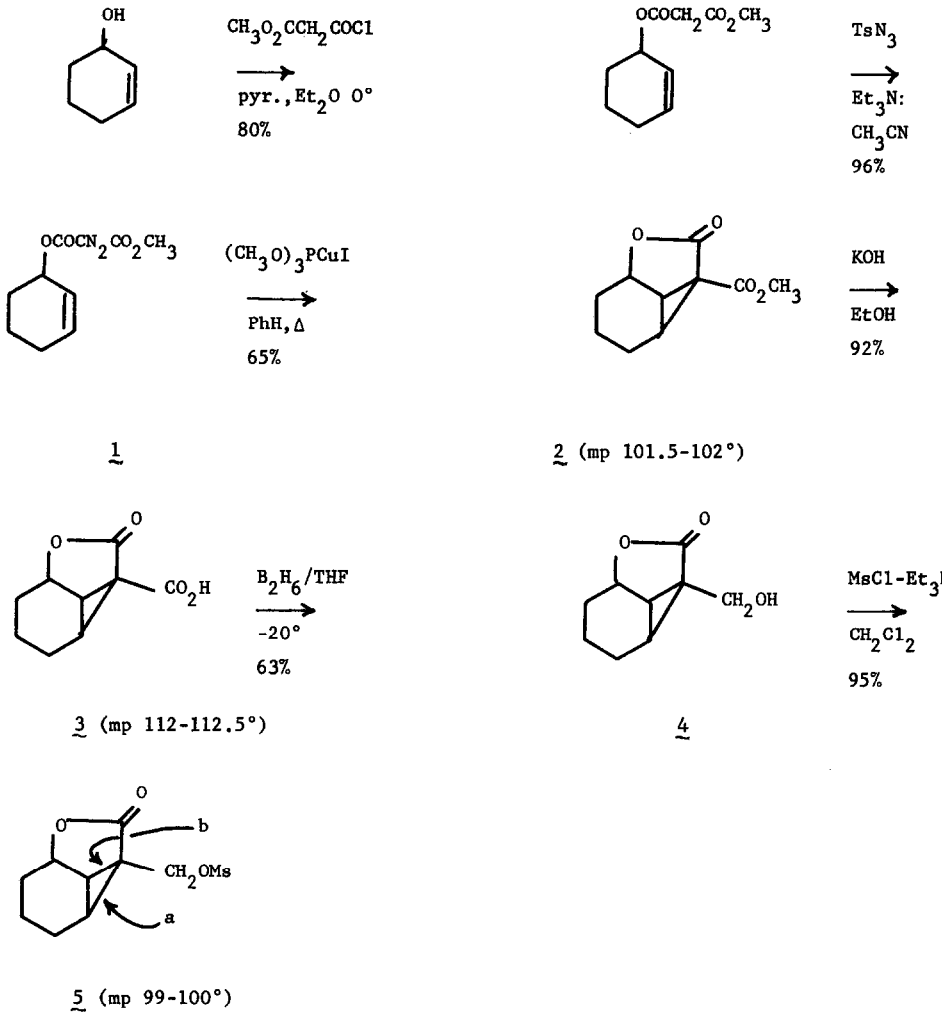
It has been concluded[2] that the presence of a lipophilic, conjugated ester or haloester situated homoallylic to the double bond of many naturally occurring α-methylene-γ-butyrolactones, enhances the cytotoxic activity of these substances. Synthetic efforts to date[3] have focused only upon the construction of the α-methylene-γ-butyrolactone to the exclusion of the homoallylic oxygenated center. We wish to detail in this Letter an initial solution to this problem.

When the lactonic cyclopropylcarbinyl mesylate 5[4,5] prepared as outlined in Scheme I[6], was exposed to refluxing glacial acetic acid containing 1.2 equivalents of sodium acetate for 90 minutes, four substances were isolated upon silica gel chromatography. The least polar of these compounds was identified as olefin 6 (42% yield; ir ($CHCl_3$) 1770 cm^{-1}; nmr ($CDCl_3$)δ 3.62 (1H,m, =CHCRH-CH=), 4.81 (1H,m,-CH-O_2C), 5.60 (1H,m), 5.65 (1H,d, J=2Hz), 5.90 (1H,m), and 6.21 (1H,d, J=2Hz)) resulting from ring opening followed by elimination. The trans-acetate 7 (35% yield; mp 87-88°; ir ($CHCl_3$) 1770 and 1740 cm^{-1}; nmr ($CDCl_3$)δ 2.02 (3H,s,AcO), 3.07 (1H,m, allylic CH), 4.68 (1H,m, w = 23Hz, -CHO_2C), 4.92 (1H,m, w = 18Hz,-AcOCH-),5.61 (1H,d, J=2Hz), and 6.21 (1H,d, J=2Hz))[7] was the second product resulting from ring cleavage. A later fraction contained an additional 10% of acetate 7 (45% total yield), cyclopropylcarbinyl acetate 8 (7%)[8] and 3% of an unidentified product containing exo-methylene protons (nmr ($CDCl_3$) δ 5.55 (1H,d, J=2Hz) and 6.13 (1H,d, J=2Hz)).[9]

When excess sodium acetate was employed in the solvolysis, the direct substitution product 8 was produced at the expense of the ring cleavage products. Omission of sodium acetate did not alter the product ratios, but caused a decrease in the yield.

Site selectivity can be attributed to the fact that cyclopropane bond a of mesylate 5 receives stabilization in the solvolysis transition state from overlap with the π-electrons of the lactone carbonyl. Because of its geometry, cyclopropane bond b is necessarily orthogonal

Scheme I



1

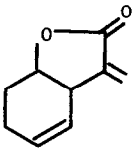
2 (mp 101.5-102°)

3 (mp 112-112.5°)

4

5 (mp 99-100°)

to the π-framework, thereby receiving no stabilization. This argument can be applied to the observed opening of ester 2 with dialkyl cuprates to produce the trans-adduct 9.[10,11]



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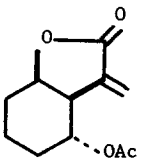
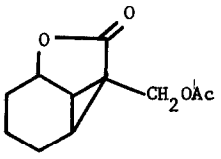
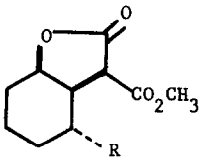


7



8



9 R=CH_3
R=-CH=CH_2

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4. Satisfactory spectroscopic (ir and nmr) data were obtained for all compounds. All compounds provided correct combustion analyses. Diazomalonate 1 was identified only spectroscopically.
5. α-Hydroxymethyl cyclopropylcarboxylates have been rearranged to α-methylene γ-butyrolactones under acid conditions. See ref. 3b.
6. The ester 2 (lit. mp 93-94°) has been prepared[10] under conditions analogous to those outlined here.

7. The width of the proton multiplets adjacent to the oxygenated centers in 7 is best accommodated by the trans isomer. In addition, the solvolysis of bicyclo[4.1.0]heptane-7-methyl tosylate gives predominately trans products. F.T. Bond and L. Scerbo, Tetrahedron Lett., 4255 (1965); K.B. Wiberg and J.G. Pfeiffer, J. Amer. Chem. Soc., 92, 553 (1970).

8. An authentic sample of 8 was prepared by Ac_2O-pyridine acylation of alcohol 4: ir ($CHCl_3$) 1765 and 1745 (sh)cm^{-1}; nmr ($CDCl_3$) δ 2.02 (3H,s), 2.40 (1H,t, J=7Hz), 3.98 (1H,d, J=12Hz), 4.58 (1H,d, J=12Hz) and 4.88 (1H,m).

9. This substance was presumed to be the acetoxy epimer of 7 or the α-methylene-δ-valerolactone from "wrong bond" cleavage. The product ratios of the mixture were obtained by nmr integration.

10. E.J. Corey and P.L. Fuchs, J. Amer. Chem. Soc., 94, 4014 (1972).

11. We are grateful to the donors of the Petroleum Research Fund administered by the American Chemical Society (5854-AC1), the National Science Foundation (GP-30960X), the National Cancer Institute, National Institutes of Health (CA-08869), and Hoffmann-LaRoche for generous support of this work.