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STEREOSPECIFIC ACETOXYLATION OF 4-METHYL-4-DICHLOROMETHYL-5-(METHOXYCARBONYL)METHYL-2-CYCLOHEXEN-1-ONE WITH LEAD(IV) ACETATE

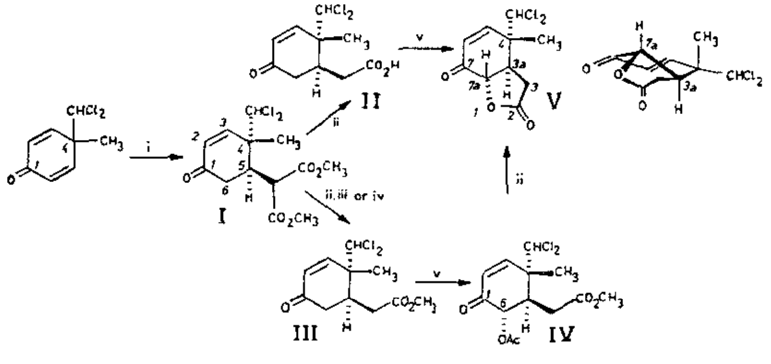
Slavica Solujić*, Slobodan Sukdolak and Zoran Ratković

Chemical Department, Faculty of Science, University of Kragujevac,
34000 Kragujevac, po box 60, YUGOSLAVIA

SUMMARY: Acetoxylation of 4-methyl-4-dichloromethyl-5-(methoxycarbonyl)methyl-2--cyclohexen-1-one[1] with lead(IV) acetate in the presence of Lewis acids gives the corresponding 6-<u>trans</u>-α-acetoxylated derivative which, in an excess of boron trifluoride etherate (or in acidic media), undergoes cyclization to a <u>trans</u>-γ-lactone.

Lactones of various structures are often constituents of natural products. They exhibit different biological activities and hence are the subject of interest for chemists and biochemists.

In this work we have attempted to carry out a stereospecific oxidation of 4-methyl-4-dichloromethyl-5-(methoxycarbonyl)methyl-2-cyclohexen-1-one, **III**, with lead(IV) acetate (LTA) aimed at obtaining a γ-lactone of <u>trans</u> stereochemistry. The LTA oxidation of **III** was carried out in absolute benzene with catalytic $BF_3.Et_2O$ at 20°C, for 1 h. The sole reaction product was identified as 4-methyl-4-dichloromethyl-5-(methoxycarbonyl)methyl-6-<u>trans</u>-acetoxy-2-cyclohexen-1-one, **IV**[7]; the later product is a very suitable intermediate for the preparation of the <u>trans</u>-γ-lactone, **V**[8], in a high yield (Scheme).



Reagents: *i NaOMe, $CH_2(CO_2Me)_2$, MeOH, ii HCl, iii CH_2N_2, Et_2O, MeOH iv DMSO, NaCl, v LTA, BF_3 Et_2O*

High stereospecifity of aforementioned reaction is governed by the stereochemical orientation of substituents of compound **III** as confirmed by ^{1}H NMR study of compounds **IV** and **V**$^{2-5}$. The stereochemistry of substituents at C-4 and C-5 was established as being <u>trans-</u>equatorial, whereas the orientation of the substituents at C-6 was determined relative to that of the substituent at C-5.

In LTA oxidation of compound **III** (or **II**) the acetoxy radical approaches the C-6 position (for 1,5-hydrogen abstraction) from the equatorial (less hindered) side, on account of the axially oriented methyl group at C-4. Molecular models and ^{1}H NMR spectra of products obtained suggest a <u>trans</u> equatorial orientation of acetoxy group at C-6 relative to the substituent at C-5.

In acidic media the acetoxy derivative undergoes lactonization into <u>trans</u> -3H,3aH,7aH-4-methyl-4-dichloromethyl-2,7-benzofuran-2,7-dione, **V**. The same product is obtained in a high yield (85%) by LTA oxidation of the acid **II**, 4-methyl-4-dichloromethyl-5-(methoxycarbonyl)methyl-2-cyclohexen-1-one in boron trifluoride etherate as solvent.

Due to a high regio and stereospecifity at C-1, C-2, C-3 and C-9, the products **IV** and **V** are useful precursors in chemical syntheses of lactones of eudesman and eleman groups.

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6. Compound **I**, $C_{13}H_{16}O_5Cl_2$, ^{1}H NMR: 1.5 (s,3H,$C\underline{H}_3$-C), 2.9 (d,2H,CH-$C\underline{H}_2$-C=O, ^3J=8 Hz) 3.9 (s,6H,$C\underline{H}_3$-O-C=O), 6.05 (s,H,$C\underline{H}Cl_2$), 6.15-6.98(AB_q,2H,$C_2\underline{H}$=$C_3\underline{H}$, $^3J_{AB}$=10 Hz),
7. Compound **IV**, $C_{13}H_{16}O_5Cl_2$, ^{1}H NMR: 1.35 (s,3H,C-$C\underline{H}_3$), 2.15 (s,3H, $OOCC\underline{H}_3$), 2.40 (m,2H, $C\underline{H}_2$-$COOCH_3$), 3.40 (m,H, C_5-$\underline{H}$), 3.70 (s,3H, $COOC\underline{H}_3$), 5.4 (d,H,$C_6\underline{H}$ J=16Hz) 5.75 (s,H, $C\underline{H}Cl_2$), 6.15-7.05 (AB_q,2H, -C$\underline{H}$=C$\underline{H}$-, $^3J_{AB}$=12 Hz)
8. Compound **V**, $C_{10}H_{10}O_3Cl_2$, ^{1}H NMR: 1.40 (s,3H, $C\underline{H}_3$), 2.40-2.60 (qd.2H, C-$C\underline{H}_2$-COO (^3J=5 Hz), (^3J=10 Hz), (^2J=30 Hz), 3.50 (m,H,C$\underline{H}$), 5.15 (d,H, $C_7\underline{H}$, ^3J=10 Hz), 5.8 (s,1H, $C\underline{H}Cl_2$), 6.25-6.75 (AB_q,2H, $C_5\underline{H}$=$C_6\underline{H}$, J=12 Hz)
9. All new compounds are characterized by spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, Mass). They have correct elementar analysis.

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