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CATIONIC ENOL ETHER-IRON COMPLEXES AS VINYL CATION EQUIVALENTS. SYNTHESIS OF PROTOLICHESTERINIC ESTER

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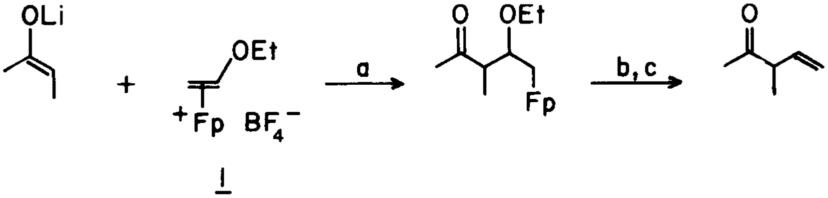
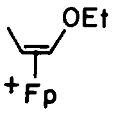
Summary: The reaction of lithium enolates derived from β-keto esters with complex cation 4 provides a facile route to 3,4-disubstituted α-methylene-γ-lactones.

We have recently shown[1] that the readily accessible, storable organoiron salt 1[2] [Fp = $C_5H_5Fe(CO)_2$] functions effectively as a vinyl cation equivalent in the α-vinylation of ketones (eq. 1).[3]



a. THF, -78°   b. HBF_4, THF, -78°   c. NaI, acetone, 25°

The salt 1 may be regarded as the parent of a potentially large family of complexes derived by skeletal elaboration of the cation, either by further substitution of groups on the olefin or by the introduction of additional functionality. Thus, cation 2, carried through the sequence shown in equation 1, introduces a trans-propenyl group α to a ketone,[1] while 3 serves as an effective isopropenylating reagent.[4] Finally, cation 4 has been shown to function as an α-acrylic ester and has been put to use in the stereocontrolled synthesis of the cis- or trans-α-methylene-γ-lactones 5 from cyclohexanone.[5]



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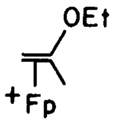

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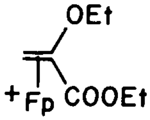

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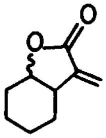

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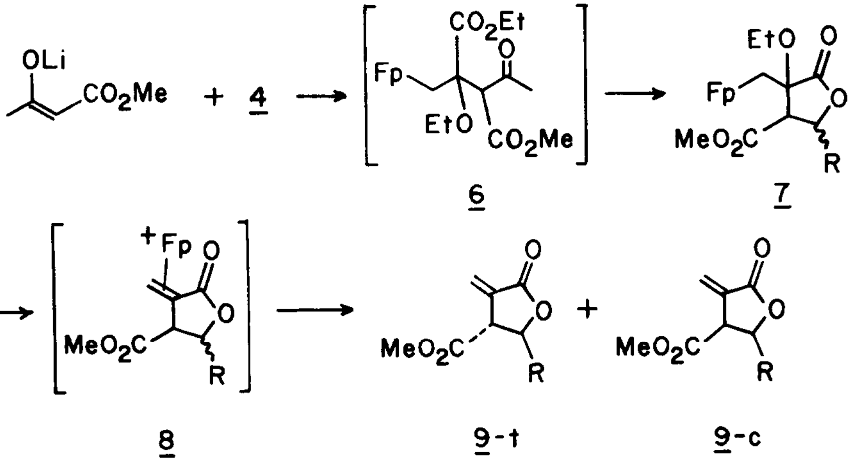
We now report that the use of β-ketoester enolates as reaction partners with 4 provides a novel and efficient stereoselective route to protolichesterinic ester[6] and members of this class of disubstituted α-methylene-γ-lactone.

The synthesis of 9 (R=Me) illustrates the general methodology. A suspension of complex 4 (BF_4 salt) in THF solution at -78° is treated with an equivalent of the lithium enolate of methyl acetoacetate. After 0.5 h, two molar equivalents of L-selectride were added and the reaction was allowed to continue for an additional two hours. Quenching with alcohol, workup and chromatography on silica gel gave 7 (R=Me) as the only product in 85% yield: IR (CH_2Cl_2) 2010, 1950 (M-C≡O), 1770 (lactone C=O), 1735 (ester C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.90, 4.86, 4.80 (3s, 5H, 3Cp), 4.8-4.5 (m, 1H, OCHO), 3.76, 3.74, 3.72 (3s, 3H, OCH_3) 3.7-3.0 (m, 3H, CH, OCH_2), 2.1-1.0 (m, 8H, $FpCH_2$, CH_3). Treatment of this material in methylene chloride solution at -78° with an equivalent of $HBF_4 \cdot Et_2O$ for 0.5 h converts it smoothly to the olefin complex 8, which is readily decomposed by treatment with aqueous acetone at room temperature for 0.5 h, liberating the organic ligand as the sole product in 77% yield, as a 9:1 mixture of the trans- and cis-isomers respectively: IR (CH_2Cl_2) 1765 (lactone C=O), 1740 1H (ester C=O) cm^{-1}; NMR ($CDCl_3$) of trans-isomer 9-t (R=Me) δ 6.42 (d, 1H, J = 3 Hz, CH_2=), 5.95 (d, 1H, J = 3 Hz, CH_2=), 4.90 (m, 1H, J = 6 Hz, OCH), 3.80 (s, 3H, OCH_3), 3.55 (m, 1H, J = 3 Hz, CH), 1.50 (d, 3H, J = 6 Hz, CH_3); NMR ($CDCl_3$) of cis-isomer 9-c (R=Me) δ 6.42 (d, 1H, J = 3 Hz, CH_2=), 5.88 (d, 1H, J = 3 Hz, CH_2=),4.90 (s, 1H, OCH), 3.90 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 1.37 (d, 3H, J = 6 Hz, CH_3). Predominant formation of trans-9 is in accord with Cram's rule[7] for hydride addition to the chiral ketone 6, followed by lactonization. Subsequent exposure of the protected exo-methylene group leaves the stereochemistry at C-3,4 in the lactone unchanged.



Reaction of the more hindered enolate derived from methyl 3-oxohexadecanoate[8] with 4 is complicated by the predominant formation of O-alkylated product In THF solution this is virtually the sole course of reaction, but a mixture of donor and acceptor salts as a suspension in toluene at -78° gave the adduct 6 ($R=C_{13}H_{27}$) in 33% yield. The adduct resists reduction with L-selectride, but lithium aluminum hydride in ether at -78° followed by chromatography on silica gel, afforded 7 ($R=C_{13}H_{27}$, 47%) as a 2:1 mixture of diastereomers (R and COOMe *trans*), and in addition, 50% of 6 was recovered unchanged. Finally, treatment of 6 in methylene chloride solution at -78° with 1.3 equivalents of tetrafluoroboric acid etherate, followed, without isolation, by exposure of the resulting cationic complex 8 to acetone and then water, gave d,ℓ-protolichesterinic acid methyl ester 9-t ($R=C_{13}H_{27}$) as the sole product in 95% isolated yield.[9] This substance was identified by comparison of its IR and ^1H NMR spectral data with that reported by Gelbard et al.[6b]

Further elaborations and synthetic applications of the chemistry of iron-stabilized vinyl cation equivalents are being examined.

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