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AN APPROACH TO THE STEREOCONTROLLED SYNTHESIS OF POLYSUBSTITUTED CHIRAL BUTENOLIDES AND γ-LACTONES

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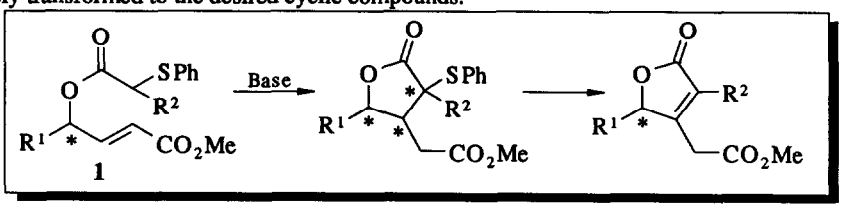
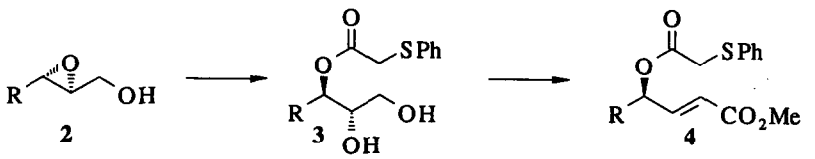
Summary: The enantioselective synthesis of polysubstituted butenolides and γ–lactones by an intramolecular Michael addition of chiral thiophenylacetates of γ-hydroxy-α,β–unsaturated esters is described.

Butenolides and saturated γ-lactones are encountered frequently in a large number of natural products.[1] The synthesis of such units as optically active fragments is currently receiving considerable attention considering their utility as useful synthons for the syntheses of biologically active natural products.[1] A challenging aspect of the synthetic effort is the stereocontrolled functionalization of acyclic olefinic systems which in a further step are stereoselectively transformed to the desired cyclic compounds.



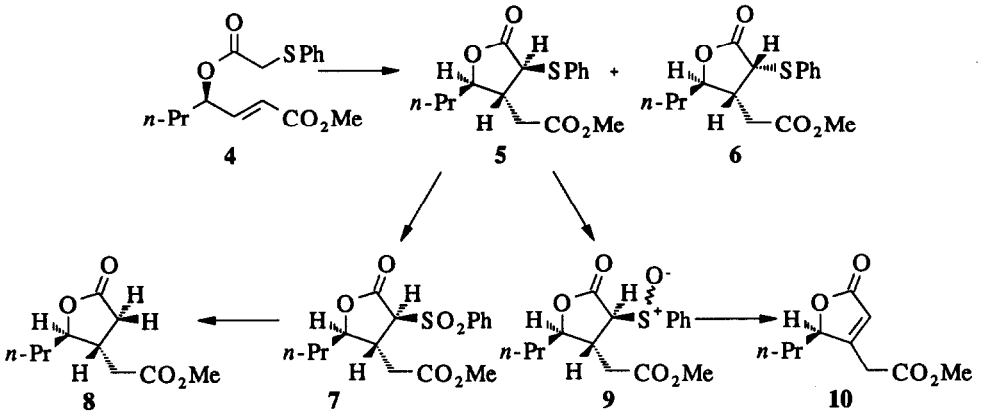
We disclose here a new aspect of the diastereoselective introduction of a nucleophilic carbon directly into the β-position of chiral thiophenylacetates of γ-hydroxy-α,β–unsaturated esters by an intramolecular Michael addition which permits the stereocontrolled synthesis of the lactone unities.



The enantiomeric synthesis of the precursor (R)-**1** (R^1=Pr-*n*, R^2=H) was performed taking advantage of the procedure recently developed in our group for the synthesis of benzoates of γ-hydroxy-α,β–unsaturated esters using chiral 2,3-epoxy alcohols.[2] Thus **2** (R= Pr-*n*) $[\alpha]_D^{25}$ -40.2 (c 2.93, $CHCl_3$)[3c] was opened regioselectively (>100:1) with thiophenyl acetic acid assisted by titanium tetraisopropoxide[4] leading to the diol ester **3** $[\alpha]_D^{25}$ +11.1 (c 1.3,

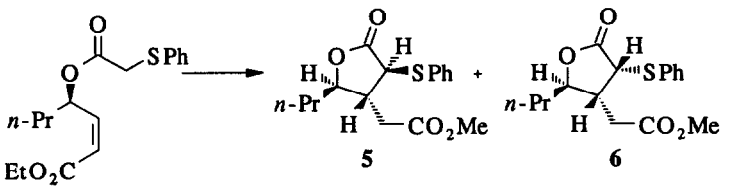
$CHCl_3$), which was oxidized with $NaIO_4$/MeOH and the resulting aldehyde was treated, without purification, with (MeO)P(O)CH^-CO_2Me, in benzene at 0°C, yielding the *E*-ester **4** $[\alpha]_D^{25}$ +19.9 (c 1.24, $CHCl_3$) (*E*:*Z* > 20:1).

The cyclization of **4** was performed in different solvents and at different temperatures and it was found that the optimal conditions make use of DMF at -78°C [5] to afford the saturated lactone **5** in 88% yield (>90% de).[6] Oxidation of **5** with ruthenium tetroxide led to the crystalline sulfone **7** m.p. 81°C, $[\alpha]_D^{25}$ +8.2(c 1.75, $CHCl_3$) in 91% yield.[7] Reduction of **7** with Al/Hg then led to the γ-lactone **8** $[\alpha]_D^{25}$ +21.5(c 0.9, $CHCl_3$) in 78% yield.



On the other hand, **5** was oxidized with MCPBA and the corresponding diastereomeric mixture of sulfoxides **9** was submitted to thermal elimination (toluene, reflux) to obtain the substituted butenolide **10** $[\alpha]_D^{25}$ +2.39(c 0.92, $CHCl_3$) in 60% yield.

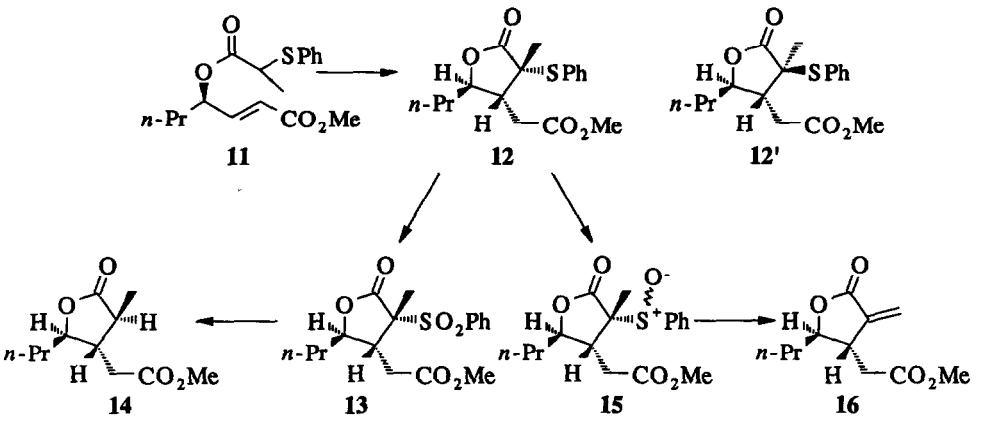
The stereoselectivity of the reaction products (**5** and **6**) in conjunction with the fact that the reaction over *Z*-unsaturated esters gave the same ratio of the cyclic products (**Scheme I**) is consistent with a thermodinamically controlled process. Considering this fact we thought that a possible way to obtain more functionalized γ-lactones in the α-carbonyl position in a stereoselective manner could be the cyclization of the suitable α-alkyl thiophenyl acetate.



Scheme I

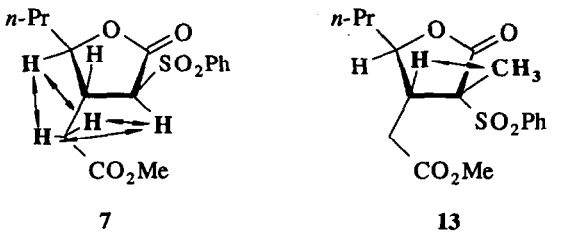
Fortunately, we found that the cyclization of **11** (**Scheme II**) in the above-mentioned conditions (NaH, DMF, -78°C) led to the lactone **12** as the sole isolated product. As can be observed, the stereochemistry of the α-carbonyl center is reversed with that corresponding to **5**. This result is, however, consonant with the idea of a thermodinamically controlled process considering the results obtained by MMX force field calculations[8] over the structures **5,6** and **12, 12'** in which the isolated materials are the less energetic compounds.

12 was submitted to the series of reactions shown in **Scheme II**, the expected results being obtained in all the cases. In this case, however, the sulfoxide elimination yielded the *exo*-cyclic methylene instead of the *endo* α,β-unsaturated lactone.



Scheme II

The absolute configuration was determined by n.O.e. experiments over the lactones **7** and **13**, assuming the oxygenated carbon as **R** according with the stereochemistry of the epoxyalcohol **2**.[3]



The cyclization reaction was also tested with different R^1 groups [R^1 = TBDPSO$(CH_2)_2$- , (*E*)-THPO-CH_2-CH=CH-CH_2- and (*E*)-AcO-CH_2-CH=CH-CH_2-], the stereochemical results being found to be identical with those obtained with R^1 = Pr-*n*.

In summary, we feel that the described procedure may be a useful and efficient way to obtain chiral polysubstituted γ-lactones and butenolides, which in conjunction with the well described chemistry of butenolides could provide even more substituted γ-lactones as very useful sunthons in the enantiomeric syntheses of a large amount of natural products.

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References and notes:

1.- Nagao, Y.; Dai, W; Ochiai, M.; Shiro, M. *J. Org. Chem.*, **1989**, *54*, 5211, and references cited therein.

2.- Martín, V.S.; Núñez, M.T.; Ramírez, M.A.; Soler, M.A. *Tetrahedron Letters*, **1990**, *31*, 763.

3.- a) Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1980**, *102*, 5976.
b) Martín, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1981**,*103*, 6237.
c) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1987**, *109*, 5765.

4.- a) Caron, M.; Sharpless, K.B. *J. Org. Chem.*, **1985**, *50*, 1560.
b) Palazón, J.M.; Añorbe, B.; Martín ,V.S. *Tetrahedron Letters*, **1986**, *27*, 4987.

5.- Non-polar solvents such benzene or toluene did not give the desired cyclic products. CH_2Cl_2 and THF induced the reaction in sluggish conditions and by-products were observed.

6.- The amount of **6** increases when the reaction is performed at higher temperatures. In order to avoid hydrolysis of the esters the reaction should be quenched by adding acetic acid.

7.- a) Rodríguez, C.M.; Ode, J.M.; Palazón, J.M.; Martín, V.S., unpublished results.
b) Núñez, M.T.; Martín, V.S. *J. Org. Chem.*, **1990**, *54*, 1928.

8.- PCModel-PI Version 3.3 released by Serena Software, P.O. Box 3076, Bloomington 47402-3076, U.S.A.. The same type of calculations performed over **5** and **6** showed the all-*trans* lactone **5** to be the more stable compound.

9.- Satisfactory spectroscopic data and low and high resolution mass data for the new products were obtained.

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