AN EFFICIENT AND CONVENIENT ROUTE TO SPIRO-FUSED γ-BUTYRO- AND δ-VALEROLACTONES

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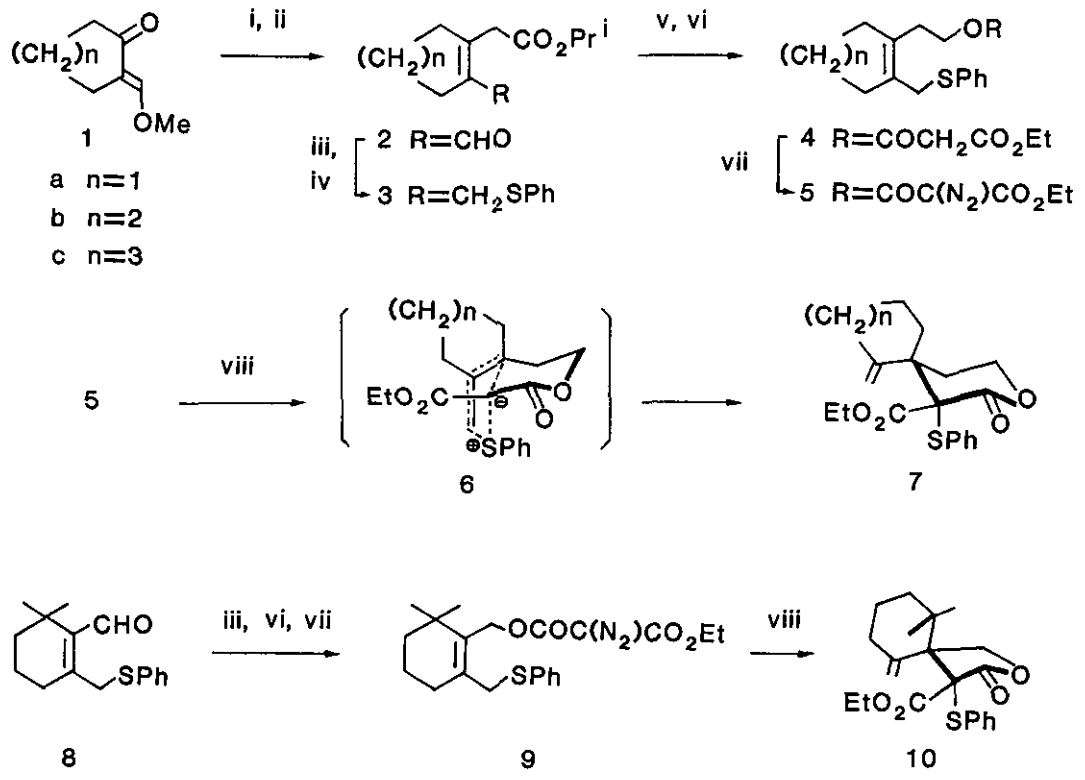
Abstract — Treatment of the α-diazomalonates (**5a-c**) of 2-[(2-phenylthiomethyl)-1-cycloalkenyl]ethanols with rhodium acetate led to the [2,3] sigmatropic rearrangement of the cyclic allylsulfonium ylides (**6a-c**) to give the spiro-fused δ-valerolactones (**7a-c**) in excellent yields. Similarly, the spiro-fused γ-butyrolactone (**10**) was prepared starting with the α-diazomalonate (**9**) of [(2-phenylthiomethyl)-1-cyclohexenyl]methanol analog.

We have recently reported a highly efficient and stereoselective synthesis of contiguously substituted γ-butyro- and δ-valerolactones from a variety of acyclic α-diazomalonates by use of the [2,3] sigmatropic rearrangement via the eight- and nine-membered cyclic allylsulfonium ylides.[1a,b] In connection with utilization of this novel methodology toward the synthesis of spirocyclic compounds, the above findings prompted us to examine the rearrangement of the cyclic allylsulfonium ylides derived from 1,2-disubstituted cycloalkenes possessing diazomalonyl and phenylthiomethyl functions vicinally, giving spiro-fused lactones having the spirocyclic center at the β-position. We wish to describe herein that the [2,3] sigmatropic rearrangement generated from the α-diazomalonates (**5a-c**) of 2-[(2-phenylthiomethyl)-1-cycloalkenyl]ethanol and the analog (**9**) afforded excellent



i) $LiCH_2CO_2Pr^i$, THF, -78 °C; ii) pyridinium p-toluenesulfonate, MeOH, room temperature; iii) $NaBH_4$, MeOH, -20 °C; iv) $(PhS)_2$, Bu_3P, Py, room temperature; v) $LiAlH_4$, Et_2O, 0 °C; vi) $HO_2CCH_2CO_2Et$, dicyclohexylcarbodiimide, 4-N,N-dimethylaminopyridine, CH_2Cl_2, room temperature; vii) TsN_3, Et_3N, MeCN; viii) $Rh_2(OAc)_4$ (0.01 mole equiv.), PhH, reflux.

Scheme 1

yields of the spiro-fused δ- and γ-lactones, (**7a-c**) and (**10**), possessing an exocyclic methylene group adjacent to the spirocyclic center, respectively. Starting with the known 2-methoxymethylenecycloalkanones (**1a-c**),[2] preparation of the diazomalonates (**5a-c**) was performed by a sequence of conventional reactions as shown in Scheme 1: a) condensation of **1a-c** with the lithium enolate of isopropyl acetate followed by hydrolysis with formation

of the aldehydes (**2a-c**, 67-76%);[3] b) sodium borohydride reduction of **2a-c** and subsequent displacement[4] of the resulting hydroxy group with thiophenyl group, giving the sulfides (**3a-c**, 50-58%); c) lithium aluminum hydride reduction of **3a-c**, followed by esterification[5] with malonic acid monoethyl ester, and d) diazotization[6] of the resulting malonates (**4a-c**), providing the required diazomalonates (**5a-c**, 73-85%).

Construction of the spirocyclic center was readily performed by use of our standard reaction conditions; treatment of **5a-c** with catalytic amount of rhodium acetate in refluxing benzene resulted in the [2,3] sigmatropic rearrangement of the nine-membered cyclic sulfonium ylide intermediates (**6**) to produce the spiro-fused δ-valerolactones (**7a-c**)[7] in excellent yields (92-93%). The stereochemistry of two substituents, the ethoxycarbonyl and phenylthio groups, in the lactone rings was surmised, as depicted, on the basis of the favorable conformation (**6**) of the transition state on the rearrangement.

This approach was then extended to the synthesis of a spiro-fused γ-lactone. The α-diazomalonate (**9**) prepared from the known aldehyde (**8**)[8] in three steps was submitted to our rearrangement reaction conditions, providing the expected γ-butyrolactone (**10**) in 82% yield.[7]

This synthetic methodology would provide not only a convenient synthetic route to spiro-fused lactones, but also a promising access toward construction of the spiro-fused carbocyclic system. A further study toward natural product synthesis is now ongoing.

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Received, 20th June, 1991