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A NOVEL SYNTHETIC METHOD FOR α-METHYLENE-γ-BUTYROLACTONES

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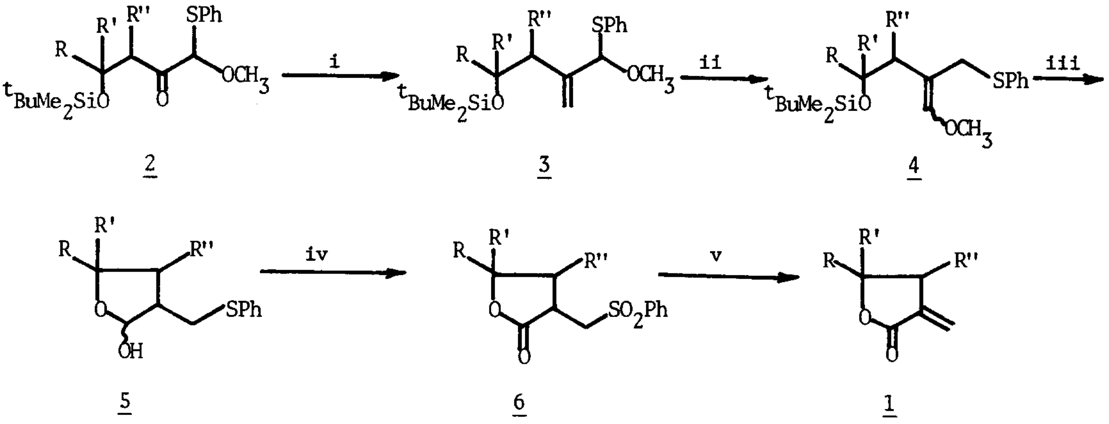
Summary: A novel synthetic method for α-methylene-γ-butyrolactones involving a thioallylic rearrangement as a key step was developed.

Various efforts have been devoted to development of effective synthetic method for α-methylene carbonyl compounds on account of their biological activities.$^{1)}$ In the course of our studies on the synthetic application of methoxy(phenylthio)methane,$^{2)}$ we have found that α-methoxyallyl sulfides can be effectively transformed to α-methylene-γ-butyrolactones through an acid-catalyzed thioallylic rearrangement.

Our strategy is depicted in Scheme 1. β-Siloxyketones 2$^{3)}$ were converted into α-methoxyallyl sulfides 3 through the Peterson olefination.$^{2)}$ Then, the hexane solution of 3 was heated at reflux in the presence of silica gel (Wako Gel C-200, 1.5 g/1 mmol) for 10 h.$^{4)}$ The reaction mixture was diluted with ethyl acetate, stirred at room temperature for 30 min, and filtered to give γ-methoxyallyl sulfides 4 in excellent yields. Treatment of 4 with 30% H_2SO_4 in acetone for 20 h at room temperature afforded hemiacetals 5. Jones type oxidation effected conversion of 5 into lactones 6. Finally, desulfonylation of 6 with DBU in Et_2O gave the desired compounds 1.

Scheme 1



i) Me_3SiCH_2MgCl, NaH-HMPA ii) SiO_2, hexane, reflux iii) 30% H_2SO_4, acetone, r.t. iv) CrO_3-H_2SO_4, acetone, 0 °C v) DBU, ether, r.t.

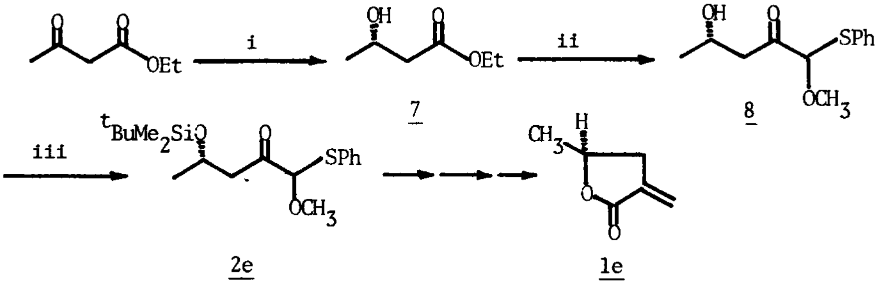
Table 1. Synthesis of α-Methylene-γ-butyrolactones 1.

				yield (%)[a] of				
entry	R	R'	R''	3	4	5	6	1
1	C_5H_{11}	H	H	72	94	65	76	1a 79
2	Ph	H	H	60	93	64	60	1b 88
3	C_6H_{13}	CH_3	H	-	60[b]	53	77	1c 85
4	C_5H_{11}	H	CH_3	82	91	61	72	1d 74

[a] Isolated yields after column chromatography (silica gel).

[b] Based on 2.

The utility of the method is further attested by the synthesis of the optically active α-methylene-γ-butyrolactone 1e. Ethyl (S)-3-hydroxybutyrate (7) ($[\alpha]_D^{23}$ = +32.7°, 86% ee) was prepared from ethyl acetoacetate through reduction with baker's yeast.[5] Then, 7 was treated with the anion of methoxy(phenylthio)methane (2.6 equiv) in THF at -78 °C for 30 min to afford β-hydroxyketone 8 (68%) which was converted into β-siloxyketone 2e. Subjection of 2e to the present procedure gave rise to optically active (S)-1e ($[\alpha]_D^{23}$ = -30.0°) in 21% overall yield based on 2e. The optical purity of (S)-1e thus obtained is believed to be 84% on the basis of reported $[\alpha]_D$ (33.8°).[6]



i) baker's yeast ii) $PhSCH(Li)OCH_3$ iii) $^tBuMe_2SiCl$, imidazole

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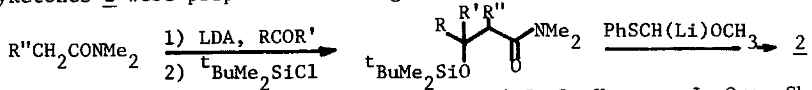
(3) β-Siloxyketones 2 were prepared according to the following procedure:



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