CHEMISTRY LETTERS, pp. 213 - 216, 1984. © The Chemical Society of Japan 1984

A CONVENIENT SYNTHESIS OF γ-ACYL- AND RELATED δ-LACTONES

Michiharu KATO, Hiroaki SAITO, and Akira YOSHIKOSHI*
Chemical Research Institute of Non-Aqueous Solutions, Tohoku University,
Sendai 980

γ-Acyl- and related δ-lactones having no δ substituents were synthesized in a sequence of reactions, 1,4-conjugate additions of sulfur-stabilized acetate anions to α,β-unsaturated ketones, followed by trapping of the resultant ketone enolates with formaldehyde, mild lactonization, and desulfurization.

In the course of our study for natural product synthesis, we required a convenient synthetic method for γ-acyl-δ-lactones having no substituents at their δ positions.

In order to prepare γ-acyl-δ-hydroxypentanoic acid derivatives which are promising precursors for the synthesis of lactones of this type, we planned to employ α,β-unsaturated ketones and formaldehyde as the sources of the acyl and terminal hydroxy groups, respectively. The total approach we pursued is delineated in Fig. 1, i.e. ketone enolate resulting from conjugate addition of ester enolate to conjugate enone A is quenched with formaldehyde, and the resultant hydroxy ester B is treated with acid to form the γ-acyl-δ-lactone C. In this communication, we wish to report the result obtained by this procedure.

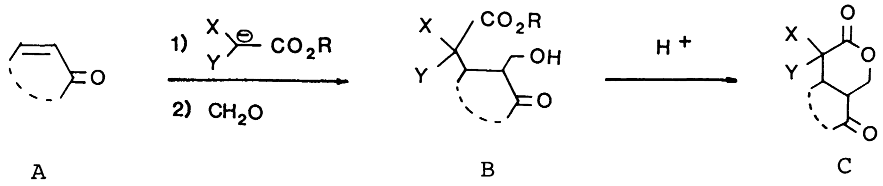
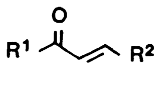
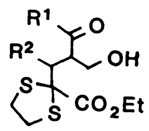
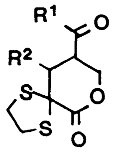
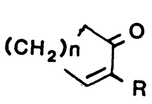
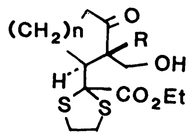
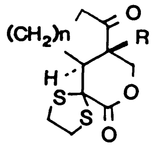


Fig. 1.

As the Michael acceptors, easily available acyclic and cyclic enones, **1a**-**d** and **1e**-**g**, shown in Table 1 were chosen. On the other hand, we started our investigation of one-pot conjugate addition-hydroxymethylation for the synthesis of B by employing the lithium enolate of ethyl (phenylthio)acetate, which was known to furnish mainly 1,4-conjugate adduct.1) The yield of the desired hydroxy ester corresponding to B, however, was quite low, probably because of facile proton transfer from the acetate moiety to the kinetically formed ketone enolate, prior to treatment with formaldehyde. After some experimentations,2) the best result was obtained by employing the lithium enolate of ethyl (ethylenedithio)acetate3) as the Michael donor. All reactions proceeded smoothly and afforded the desired hydroxy esters **2** in moderate yields. For lactonization of **2**, treatment with catalytic *p*-

Table 1. Hydroxy ester 2 and δ-lactone 3

Enone	Product and isolated yield /%	
1	2	3
		
a, R^1= Me, R^2= H	71	71
b, R^1= Et, R^2= H	79	79
c, R^1= Pr, R^2= H	54	67
d, R^1= Me, R^2= OMe	47	78
		
e, n = 2, R = H	51	64
f, n = 2, R = Me	-	49
g, n = 1, R = H	62	-

toluenesulfonic acid (p-TsOH) in dichloromethane at room temperature led nicely to the desired δ-lactones 3 in good yields, whereas the hydroxy groups in 2 were easily dehydrated under enforced conditions such as reflux in benzene or ether to give α-methylene ketone as the major product. The hydroxy esters 2a-g and δ-lactones 3a-f obtained are summarized in Table 1,4) and the typical procedure for the synthesis of 4-acetyl-2-(ethylenedithio)-5-pentanolide 3a is as follows. A solution of ethyl (ethylenedithio)acetate (2 mmol) in THF (4 ml)-HMPA (1 ml) was added dropwise to a stirred solution of LDA [prepared from diisopropylamine (2.2 mmol) in THF (4 ml) and n-BuLi (2.2 mmol), 1.5 M hexane solution] at -78 °C under argon. After stirring for 30 min, a solution of freshly distilled methyl vinyl ketone (2.2 mmol) in THF (6 ml) was added dropwise, and the reaction temperature was gradually raised to -50 °C over 1 h and then recooled to -78 °C. Gaseous formaldehyde, generated by pyrolysis of paraformaldehyde (ca. 2 g) at 150-160 °C, was added by means of a stream of dry nitrogen and then the reaction mixture was stirred at -40 °C for an additional hour. The usual workup and purification by silica gel TLC ($CHCl_3$:Et_2O = 1:1) gave 2a in 71% yield. A solution of an oily 2a obtained and catalytic p-TsOH in CH_2Cl_2 (40 ml) was stirred at room temperature for 3 h, and the usual workup, followed by purification with silica gel TLC ($CHCl_3$:Et_2O = 3:1) gave the δ-lactone 3a in 71% yield.

When 2-methylcyclohexenone 1f was used as the substrate, bicyclic lactone 3f was obtained directly in place of the anticipated hydroxy ester, while hydroxy ester 2g was recovered unchanged under the afore-mentioned mild lactonization conditions probably due to a trans-relationship between the acetate moiety and hydroxymethyl group.5)

The above methodology has been extended to a simple, one-pot synthesis of γ-acyl-α-alkyl-δ-lactones with methyl (phenylthio)acetate as the common Michael donor. The (phenylthio)acetate was treated with LDA (1.1 equiv. in THF, -78 °C for 1 h) and alkylated with alkyl halide (RX, 1.0 equiv. in THF-HMPA (1:2), -78 °C to -50 °C for 1 h). The reaction mixture was then submitted to the conjugate addition-hydroxymethylation in the same flask, followed by lactonization in the manner described above. The result is given in Table 2.[4]

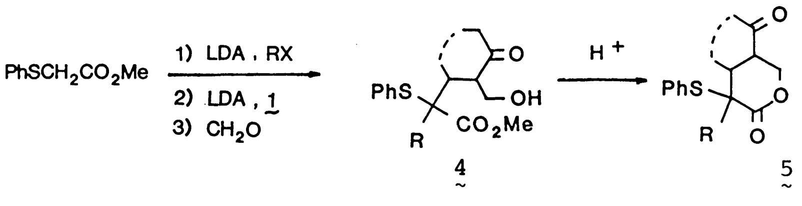
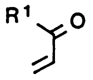
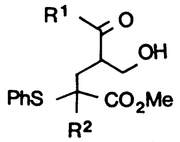
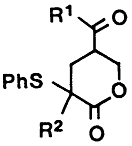
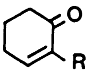
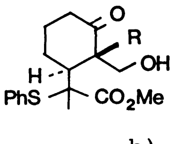
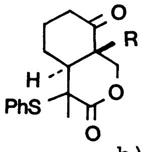


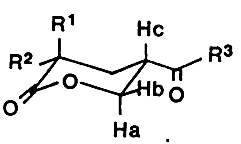
Fig. 2.

Table 2. Hydroxy ester 4 and δ-lactone 5

Enone 1	R^2X	Product and isolated yield /%	4	5
				
R^1= Me	MeI	a, R^2= Me	64[a]	89[a]
	CH_2=$CHCH_2Br$	b, R^2= CH_2CH=CH_2	56[a]	91[a]
R^1= Et	MeI	c, R^2= Me	59[a]	70[a]
	$PhCH_2Br$	d, R^2= CH_2Ph	51[a]	91[a]
				
R = H	MeI	e	42[b]	65[b]
R = Me	MeI	f	-	47[b]

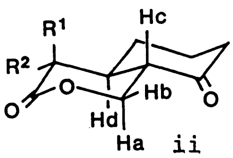
a) A mixture of diastereomeric isomers. b) Homogeneous product.

Stereochemistry of the lactones obtained was deduced from their ^{1}H-NMR spectra. Equatorial configurations of the acyl groups in the δ-lactones, 3a-d and 5a-d, were substantiated by coupling constants, Ja-c = 9.0-11.4 Hz (see stereoformula i). The coupling constant between Hc and Hd, J = 10.6 Hz, in the bicyclic lactones, 3e and 5e, indicated that the stereochemistry of the ring junctures was trans, as shown in ii.[6] On the other hand, the resonance of the proton on the carbon flanking methoxy group in 3d was a doublet (J = 2 Hz) with fine splittings, which showed cis relationship between the acyl and methoxy groups.



i

Jab = 10.6-11.4 Hz
Jac = 9.0-11.4
Jbc = 4.6- 5.9

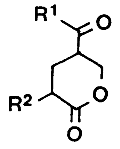
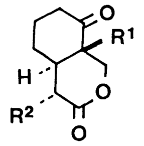


ii

Jab = 12.2 Hz
Jac = 10.5-10.6
Jbc = 4.6- 5.9
Jcd = 10.6

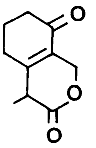
Finally, reductive desulfurization of δ-lactones, 3b, 3e-f, 5a, 5c-d, and 5f, was examined with W-4 Raney nickel deactivated with acetone (room temperature, 1 to 2 h), and desired δ-lactones 6a-g were isolated as the sole product in good to excellent yields, as listed in Table 3.[4)]

Table 3. δ-Lactone 6 obtained by reductive desulfurization

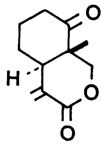
Substrate	Product 6 and isolated yield /%		
			
3b	a, R^1= Et, R^2= H		56
3e	b,	R^1= R^2= H	67
3f	c,	R^1= Me, R^2= H	70
5a	d, R^1= R^2= Me		75[a)]
5c	e, R^1= Et, R^2= Me		82[a)]
5d	f, R^1= Et, R^2= CH_2Ph		91[a)]
5f	g,	R^1= R^2= Me	83[a)]

a) Homogeneous product. Equatorial configurations are surmized for R^2.

Attempted thermal treatment (CCl_4-pyridine, reflux) of sulfoxides derived from 5 by mCPBA oxidation (1.0 equiv.) generally yielded mixtures of double bond isomers, from which, for example, enone 7 was isolable from 5e in 34% yield. In the case of 5f, however, α-methylene lactone 8 was isolated in high yield (86%).



7



8

Application of this method to natural product synthesis is in progress.

This work was supported by a Grant-in-Aid for Scientific Research (56470024).

References

1) S. Yamagiwa, N. Hoshi, H. Sato, H. Kosugi, and H. Uda, J. Chem. Soc., Perkin Trans. 1, 1978, 214.
2) Although both methyl bis(phenylthio)- and bis(ethylthio)acetates produced corresponding hydroxy esters to B (see Fig. 1), their yields were low.
3) J. L. Herrman, J. E. Richman, and R. H. Schlessinger, Tetrahedron Lett., 1973, 2599.
4) All compounds exhibited satisfactory physical properties (IR, NMR, and MS).
5) Trans-α,β-disubstituted butyrolactones were produced by conjugate addition-hydroxymethylation or -iodination reactions of butenolides. J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, J. Am. Chem. Soc., 95, 7923 (1973); R. E. Damon and R. H. Schlessinger, Tetrahedron Lett., 1976, 1561).
6) Ring junctures in 3f and 5f also seem trans by analogy with the trans stereochemistry of 3e and 5e, although no evidence was obtained from their ^1H-NMR data.

(Received November 7, 1983)