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A Highly Stereoselective Synthesis of γ-Acyl-δ-lactones by the Trityl Perchlorate Catalyzed Tandem Michael-aldol Reaction

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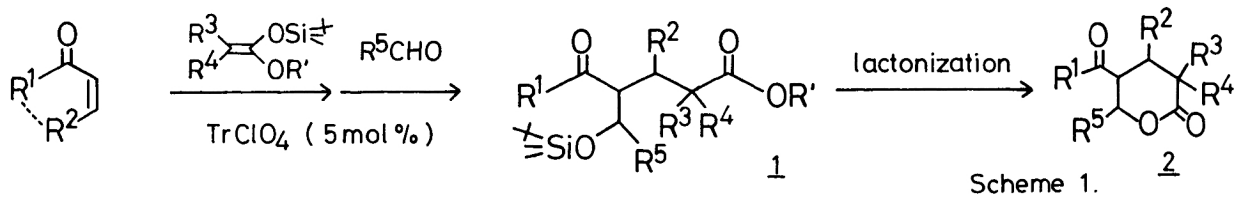
γ-Acyl-δ-lactones are prepared in high yields with high stereoselectivities by the trityl perchlorate catalyzed tandem Michael-aldol reaction between α,β-unsaturated ketones, ketene silyl acetals, and aldehydes.

Lactones are one of the most interesting compounds often found in various natural products. In addition, they are versatile building blocks in organic synthesis, particularly, acyl-substituted lactone derivatives[1] are frequently employed as useful synthetic intermediates[2] because of their functionalized skeleton, therefore several methods for the synthesis of these compounds have already been reported.[1] However, most of these methods required strongly basic conditions, tedious procedures, or starting materials which were not easy to prepare, and the yields of the lactones and the selectivity concerning the relative configuration of chiral centers on the lactone ring were not necessarily good. Further, as far as we know, no procedure has been presented for the stereoselective synthesis of acyl-substituted ring fused lactones, which are versatile intermediates of terpenes.[3]

In the previous paper,[4] we have shown that, in the presence of a catalytic amount of trityl perchlorate,[5] the tandem reaction of conjugate addition of silyl enol ethers to α,β-unsaturated ketones and the sequential aldol addition with aldehydes can be carried out to afford smoothly γ-acyl-δ-hydroxyketone derivatives stereoselectively in high yields. In this reaction, a catalytic amount of trityl perchlorate effectively catalyzes both the Michael[6] and the successive aldol reactions[7] leading to the formation of two carbon-carbon bonds at the α and the β positions of α,β-unsaturated ketones in one pot. Moreover, the relative configuration of three asymmetric carbon atoms of the products is almost completely controlled, and it was expected that valuable compounds could be prepared by this procedure. In this communication, we wish to describe the utilization of this tandem Michael-aldol reaction for a facile stereoselective synthesis of γ-acyl-δ-lactones.

The present procedure for the synthesis of the lactones is shown in Scheme 1. In the first place, 4-methyl-3-penten-2-one (mesityl oxide), the ketene silyl acetal derived from methyl isobutyrate, and benzaldehyde were chosen as model compounds, and the reaction was carried out in the presence of a catalytic amount of trityl perchlorate (5 mol%) in dichloromethane at -78 °C. The Michael reaction and the successive aldol reaction proceeded smoothly to afford the γ-acyl-δ-



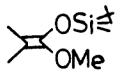
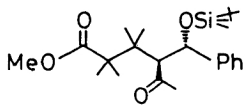
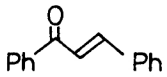
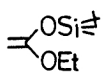
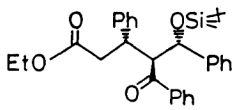
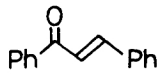
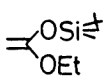
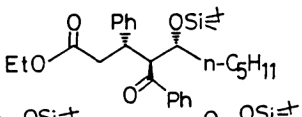
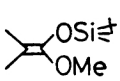
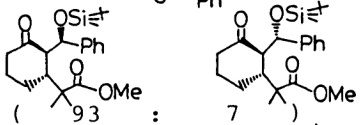
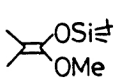
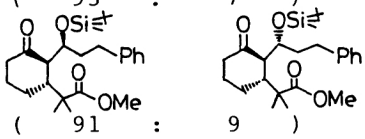
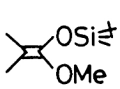
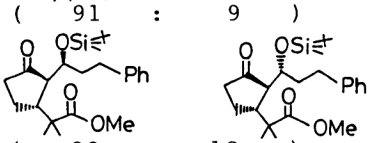
1 2

Scheme 1.

hydroxyester derivative (1) in 74% yield. This product was confirmed to be a single stereoisomer by ^{1}H NMR spectrum[8] and HPLC. The ester thus obtained was easily lactonized under acidic conditions (CH_3CO_2H : THF : H_2O : CF_3CO_2H = 5 : 1 : 1 : 1) to produce the desired γ-acyl-δ-lactone (2) in 62% yield. The configuration of this lactone was assigned as trans by ^{1}H NMR spectrum,[9] and no epimerization was observed during the lactonization.

Several examples for the synthesis of 1 by the tandem Michael-aldol reaction and the further lactonization of 1 are shown in Table 1 and 2, respectively. In each case, the ester (1) and the corresponding lactone (2) was obtained in good to excellent yields. In those cases using a mono β-substituted acyclic α,β-unsaturated ketone, only one of four diastereomers was obtained, and consequently the

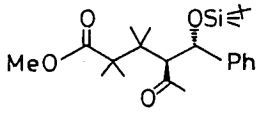
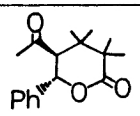
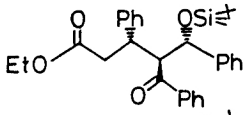
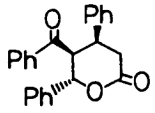
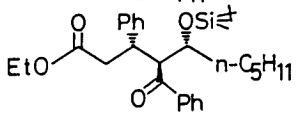
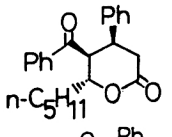
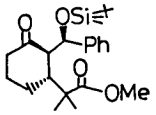
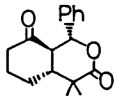
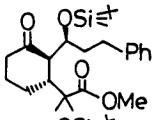
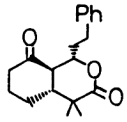
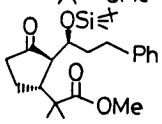
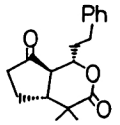
Table 1. A synthesis of γ-acyl-δ-hydroxyester derivatives[a]

α,β-Unsaturated ketone	Ketene silyl acetal	Aldehyde	Product (Diastereomer ratio)	Yield/%
		PhCHO	 b)	74
		PhCHO	 b)	quant.
		n-C_5H_{11}CHO	 b)	83
		PhCHO	 (93 : 7)	92
		$Ph(CH_2)_2CHO$	 (91 : 9)	63
		$Ph(CH_2)_2CHO$	 (88 : 12)	77

a) All the products gave satisfactory spectral data.

b) The single stereoisomer was obtained (^{1}H NMR, ^{13}C NMR, and/or HPLC).

Table 2. A synthesis of γ-acyl-δ-lactone derivatives[a)]

Starting Material	Product	Yield/%
		62
		98
		70
		81
		quant.
		73

a) All the products gave satisfactory spectral data.

corresponding δ-lactone was obtained in perfectly controlled manner with respect to the relative configuration of three contiguous chiral carbons.

This procedure was also successfully applied to the preparation of fused ring lactones, which are potential precursors for the synthesis of various sesquiterpenes.[3,10)] The reaction proceeded with highly stereocontrolled fashion and it is noteworthy that the produced lactones possessed only trans ring fusions as expected.

A typical procedure for the preparation of 2 is as follows; the mixture of an α,β-unsaturated ketone (0.53 mmol), a ketene silyl acetal (0.50 mmol), and trityl perchlorate (0.03 mmol, 5 mol%) in dichloromethane (3 ml) was stirred at -78 °C for an appropriate time (15-60 min). Then an aldehyde (0.47 mmol) in dichloromethane (1 ml) was added and the reaction mixture was further stirred at -78 °C overnight. After the reaction was completed, aqueous sodium hydrogencarbonate was added. The aqueous layer was extracted with dichloromethane and the organic layer was dried. After the solvent was removed under reduced pressure, the residue was separated by silica gel column chromatography to afford 1. This ester was treated with acetic acid, THF, water, and trifluoroacetic acid (5 : 1 : 1 :1) at 30 °C. The solvent was removed and the residue was chromatographed on silica gel to produce 2.

It should be noted that, the present method for the synthesis of acyl-

substituted lactones has the advantages over conventional procedures in chemical yields, stereoselectivities, and mild reaction conditions. Thus γ-acyl-δ-lactones, valuable synthetic intermediates, are prepared in almost perfectly controlled manner concerning the relative configuration of two or three contiguous chiral centers.

References

1) For example, a) J. Rothe and J. Zimmer, J. Org. Chem., 24, 586 (1959); b) T. Mukaiyama, J. Hanna, T. Inoue, and T. Sato, Chem. Lett., 1974, 381; c) T. Mukaiyama, M. Wada, and J. Hanna, ibid., 1974, 1181; d) T. Sato, J. Hanna, H. Nakamura, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 49, 1055 (1976); e) R. D. Miller and G. N. Fickes, J. Org. Chem. 50, 2375 (1985).

2) The antibiotic botryodiplodin was synthesized from cis-α-methyl-β-acetyl-γ-butyrolactone in our laboratory. See Ref. 1c.

3) For example, Y. Ohfune, P. A. Grieco, C.-L. J. Wang, and G. Majetich, J. Am. Chem. Soc., 100, 5946 (1978).

4) S. Kobayashi and T. Mukaiyama, Chem. Lett., 1986, 221.

5) For our recent reports on the new synthetic reactions by using trityl salts, see Y. Hashimoto and T. Mukaiyama, Chem. Lett., 1986, 755, and references cited therein.

6) S. Kobayashi, M. Murakami, and T. Mukaiyama, Chem. Lett., 1985, 953; T. Mukaiyama, M. Tamura, and S. Kobayashi, ibid., 1986, 1017.

7) T. Mukaiyama, S. Kobayashi, and M. Murakami, Chem. Lett., 1984, 1759; 1985, 447; S. Kobayashi, M. Murakami, and T. Mukaiyama, ibid., 1985, 1535.

8) 1: ^{1}H NMR ($CDCl_3$): -0.40 (s, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 1.15 (s, 3H), 1.20 (s, 3H), 1.35 (s, 6H), 1.65 (s, 3H), 3.55 (d, 1H, J=8.7 Hz), 3.60 (s, 3H), 4.90 (d, 1H, J=8.7 Hz), 7.15-7.30 (m, 5H).

9) 2: ^{1}H NMR ($CDCl_3$): 1.00 (s, 3H), 1.25 (s, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 1.85 (s, 3H), 3.45 (d, 1H, J=12.0 Hz), 5.45 (d, 1H, J=12.0 Hz), 7.00-7.50 (m, 5H); IR (KBr): 1720 cm^{-1}, mp 107-108 °C; Found: C, 74.45; H, 8.18%. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%.

10) Stereoselective syntheses of some terpenes by using this procedure are now in progress.

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