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Highly Diastereoselective Synthesis of *cis*-2,3-Disubstituted γ-Lactones by the Reaction of 2,2-Dialkoxy-3-alkylcyclopropanecarboxylic Esters with Symmetric Ketones

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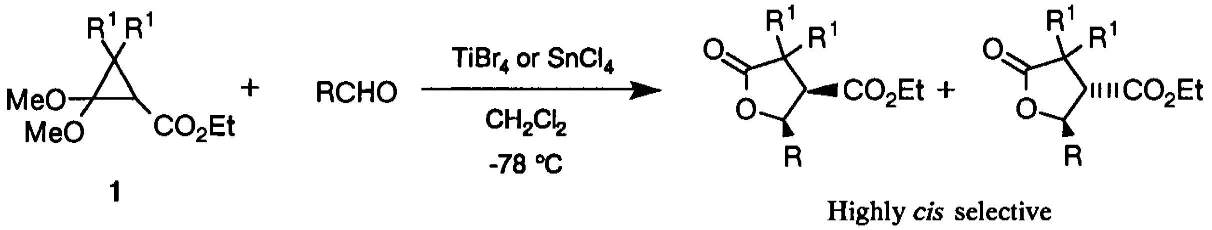
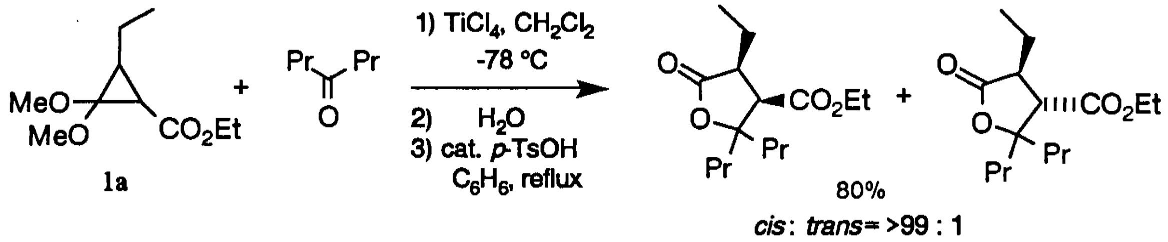
In the presence of titanium(IV) chloride, 2,2-dialkoxy-3-alkylcyclopropanecarboxylic esters reacted with symmetric ketones to give *cis*-2,3-disubstituted γ-lactones with high diastereoselectivity. The resulting *cis*-lactones were easily converted into *trans*-isomers by treatment with a catalytic amount of sodium ethoxide.

Vicinally donor-acceptor-substituted cyclopropanes have been shown to be versatile building blocks in organic synthesis.[1)] We previously reported the highly diastereoselective synthesis of *cis*-3,4-disubstituted γ-lactones by the Lewis acid-mediated reaction of donor-acceptor-substituted cyclopropane, 2,2-dialkoxycyclopropanecarboxylic esters, with aldehydes (Scheme 1).[2,3)] So far, there is no systematic study on the diastereoselective synthesis of this type of γ-lactones, 3-alkoxycarbonyl-4-butanolides (paraconic esters).[4,5)] In the previous study,[2)] we focused our attention on the diastereoselectivity between 3-C and 4-C substituents of the γ-lactones. On the basis of this result, we attempted, as the second step, to clarify the diastereoselectivity between 2-C and 3-C substituents of the γ-lactones in order to achieve simultaneous control of three stereo centers, 2-C, 3-C, and 4-C positions of the γ-lactones. Here we report the highly diastereoselective synthesis of *cis*-2,3-disubstituted γ-lactones by the Lewis acid-mediated reaction of 2,2-dialkoxy-3-alkylcyclopropanecarboxylic esters with symmetric ketones.



Scheme 1.

We first tried the reaction of ethyl 3-ethyl-2,2-dimethoxycyclopropanecarboxylate **1a**[6)] with 4-heptanone under almost the same conditions as in the reaction of 1 with aldehydes. A solution of titanium(IV) chloride in dichloromethane was added drop by drop to a mixture of cyclopropane **1a** and 4-heptanone in dichloromethane at -78 °C. After 2 h, the reaction mixture was allowed to warm to room temperature and quenched by adding water. A solution of the resulting product in benzene was heated under reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid to complete lactonization. Purification of the crude product by column chromatography gave γ-lactone, 3-ethoxycarbonyl-2-ethyl-4-propyl-4-heptanolide, in 80% yield, which almost exclusively consisted of *cis*-isomer (*cis* : *trans* = >99 : 1) (Scheme 2).[7)]



Scheme 2.

We next tried the reaction of ethyl 2,2-dimethoxy-3-methylcyclopropanecarboxylate **1b**, having a smaller substituent at 3-C position, with 4-heptanone under the same conditions. In this case, however, the diastereoselectivity was depressed (*cis*: *trans*= 77 : 23).[7)]

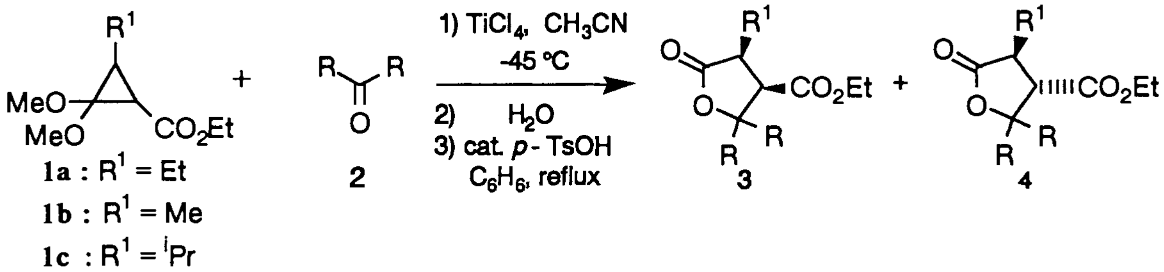
In order to improve the diastereoselectivity for the reaction of cyclopropane **1b** with 4-heptanone, we examined the reaction conditions such as order of addition of the substrates, reaction temperature, Lewis acid, and solvent. Among these conditions, order of addition of the substrates and especially solvent influenced the diastereoselectivity. Namely, the highest diastereoselectivity (*cis*: *trans*= 83 : 17) was achieved when **1b** was added to a mixture of titanium(IV) chloride and the ketone. Moreover, as shown in Table 1, the use of the solvent less polar than dichloromethane resulted in extremely low diastereoselectivity, but in the case of acetonitrile, which is more polar than dichloromethane, quite high selectivity was observed.

Table 1. The Solvent Effect to the Diastereoselectivity

Entry	Solvent	Yield / %	*cis* : *trans*
1	CH_2Cl_2	76	83 : 17
2	pentane / CH_2Cl_2 (1 : 1)	74	56 : 44
3	CH_3CN	68	94 : 6

The optimized reaction conditions are shown in typical procedure (vide infra). Under these conditions, the reactions were carried out for several ethyl 3-alkyl-2,2-dimethoxycyclopropanecarboxylates and symmetric ketones. The results are listed in Table 2. In all cases, γ-lactones were obtained in moderate to high yields with good to quite high *cis*-selectivity.

A typical procedure is as follows: Under an argon atmosphere, 1 ml of acetonitrile was added to a solution of titanium(IV) chloride (0.36 mmol) in dichloromethane (0.33 ml) at room temperature. Then, the solution was cooled to -45 °C. To this solution was added drop by drop a solution of 4-heptanone (0.29 mmol) in acetonitrile (2 ml), and the mixture was stirred at that temperature for 10 min. A solution of cyclopropane **1b** (0.36 mmol) in acetonitrile (1 ml) was added drop by drop over a period of 5 min. After being stirred for 2 h, the reaction mixture was quenched by adding water (2 ml) with vigorous stirring at -45 °C. Then, the mixture was allowed to warm to room temperature and extracted with dichloromethane (3 × 30 ml). The combined organic layers



Scheme 3.

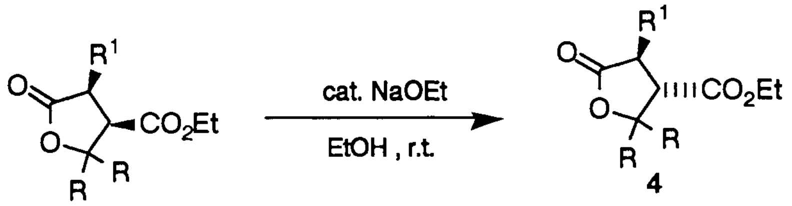
Table 2. The Reaction of Cyclopropanes 1 with Symmetric Ketones

Entry	R^1	Ketone	Yield / % [a)]	*cis*: *trans*[7)]
1	Me	4-heptanone	68 (90)[b)]	94 : 6 (77 : 23)[b)]
2		cyclohexanone	70 (92)[b)]	94 : 6 (92 : 8)[b)]
3		cyclopentanone	51	93 : 7
4		acetone	64	89 : 11
5	Et	4-heptanone	81	98 : 2
6		cyclohexanone	91	99 : 1
7	ⁱPr	4-heptanone	50	96 : 4

a) Isolated yield. b) The values in parentheses represent the yields and diastereomer ratios of γ-lactones when titanium(IV) chloride was added to a mixture of 1 and ketone in CH_2Cl_2.

were dried over sodium sulfate. After filtration and evaporation, the crude product, a mixture of γ-lactones and hydroxy diesters, was dissolved in dry benzene (3 ml) and heated under reflux for 30 min in the presence of a catalytic amount of *p*-toluenesulfonic acid in order to lactonize the hydroxy diesters. The solvent was removed in vacuo, and the crude product was purified by column chromatography (eluent: petroleum ether/CH_2Cl_2/EtOAc = 15/2/1) to give the corresponding γ-lactones (50 mg, 68% yield based on 4-heptanone, *cis*: *trans* = 94 : 6).[7)]

The present reaction gave *cis*-isomers 3 with high diastereoselectivity.[8)] Moreover, *cis*-isomers could be converted into *trans*-isomers 4 in high yields by treatment with a catalytic amount of sodium ethoxide (Scheme 4). Subsequently, this new synthetic reaction is considered to be useful not only for the synthesis of *cis*-2,3-disubstituted γ-lactones but also for the synthesis of *trans*-ones.



Yield : R = Pr, R¹ = Me ; 76%
R = Pr, R¹ = Et ; 88%

Scheme 4.

The control of three stereo centers at 2-C, 3-C, and 4-C positions of lactones is now under investigation in this laboratory.

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References

1) H.-U. Reißig, *Top. Curr. Chem.*, **144**, 73 (1988).

2) K. Saigo, S. Shimada, Y. Hashimoto, and M. Hasegawa, *Chem. Lett.*, **1989**, 1293.

3) Other Lewis acid-mediated reactions of **1**, see: K. Saigo, S. Shimada, and M. Hasegawa, *Chem. Lett.*, **1990**, 905; K. Saigo, S. Shimada, T. Shibasaki, and M. Hasegawa, *Chem. Lett.*, **1990**, 1093.

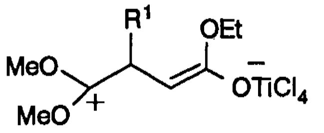
4) The synthesis of *cis,cis*-2,3,4-trisubstituted paraconic esters, see: J. Mulzer, P. deLasalle, A. Chucholowski, U. Blaschek, G. Brüntrup, I. Jibril, and G. Huttner, *Tetrahedron*, **40**, 2211 (1984).

5) Other examples for the synthesis of paraconic esters, see: N. Minami and I. Kuwajima, *Tetrahedron Lett.*, **1977**, 1423; T. Shono, H. Hamaguchi, I. Nishiguchi, M. Sasaki, T. Miyamoto, M. Miyamoto, and S. Fujita, *Chem. Lett.*, **1981**, 1217; C. Brückner and H.-U. Reißig, *J. Org. Chem.*, **53**, 2440 (1988).

6) M. L. Graziano and R. Scarpati, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 289; M. L. Graziano and M. R. Iesce, *Synthesis*, **1985**, 762.

7) The stereochemistry of γ-lactones was determined by an isomerization experiment, ^{1}H-NMR spectroscopy, and GLC analysis. As described, two isomerization experiments were performed. The results indicated that the major isomers were thermodynamically less stable *cis*-isomers and isomerized into more stable *trans*-isomers. The coupling constants between 2-H and 3-H were 7.3-8.2 Hz for all the major isomers and 11.3-11.9 Hz for all the minor isomers. Moreover, on GLC analysis, the retention time of the major isomers was longer than that of the corresponding minor isomers. A reasonable interpretation for these results is that the major and minor isomers have *cis* and *trans* configurations, respectively.

8) The mechanism of this reaction is not clear. But, the high diastereoselectivity may be explained as follows. Cyclopropane **1** reacts with titanium(IV) chloride to form an *E*-type titanated ketene acetal intermediate like **5**. Then, it reacts with ketone through a transition state like **6**.[9] In this model, the cationic substituent is aligned antiperiplaner to the forming C-C bond.



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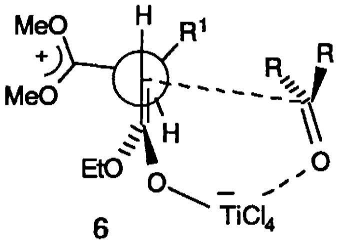

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9) M. N. Paddon-Row, N. G. Rondan, and K. N. Houk, *J. Am. Chem. Soc.*, **104**, 7162 (1982).

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