CHEMISTRY LETTERS, pp. 1117-1120, 1993.

Diastereoselective Synthesis of *cis*-4,5-Substituted δ-Lactones by the Reaction of 2-Methoxy-2-(trimethylsiloxy)cyclobutanecarboxylic Esters with Carbonyl Compounds

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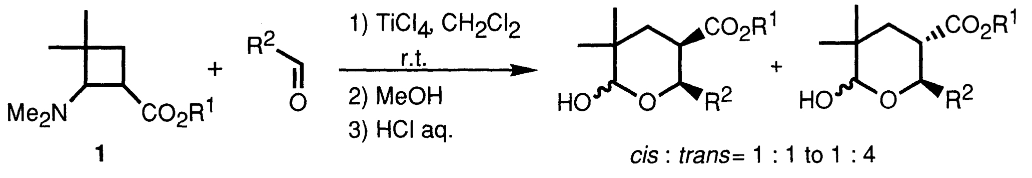
The ring-opening aldol-type reaction of 2-methoxy-2-(trimethylsiloxy)cyclobutanecarboxylic esters with aldehydes smoothly proceeded in the presence of a Lewis acid. Subsequent treatment of the crude products with a catalytic amount of *p*-TsOH gave *cis*-4,5-substituted δ-lactones in good yields with high diastereoselectivity. Similar reactions with unsymmetrical ketones also gave δ-lactones in good yields with moderate diastereoselectivity.

Vicinally donor-acceptor-substituted cyclopropanes are considered as equivalents of 1,3-zwitterions and are valuable building blocks in organic synthesis.1), 2) Since cyclobutane has almost the same magnitude of strain energy as cyclopropane,3) vicinally donor-acceptor-substituted cyclobutanes would have a potential for the heterolytic cleavage to form 1,4-zwitterionic species. As observed for the 1,3-zwitterions derived from the cyclopropanes,2) the 1,4-zwitterions are also expected to react with electrophiles or nucleophiles. To our knowledge, however, only one example has been reported concerning a ring-opening carbon-carbon bond-forming reaction using such cyclobutane derivatives.4) We have recently reported a $TiCl_4$-promoted ring-opening aldol-type reaction of 2-(dimethylamino)cyclobutanecarboxylic esters **1** with carbonyl compounds, giving δ-lactols or dihydropyran derivatives in good yields (Scheme 1).5) In order to demonstrate the usefulness of vicinally donor-acceptor-substituted cyclobutanes, a similar type of aldol reaction was investigated in the hope of developing a stereoselective reaction. Herein we report on a diastereoselective synthesis of *cis*-4,5-substituted δ-lactones by the Lewis acid-promoted reaction of 2-methoxy-2-(trimethylsiloxy)cyclobutanecarboxylic esters **2** with carbonyl compounds.

Cyclobutanes **2a** and **2b** were prepared from the corresponding ketene silyl acetals and methyl propiolate according to the procedure of Quendo and Rousseau.6)

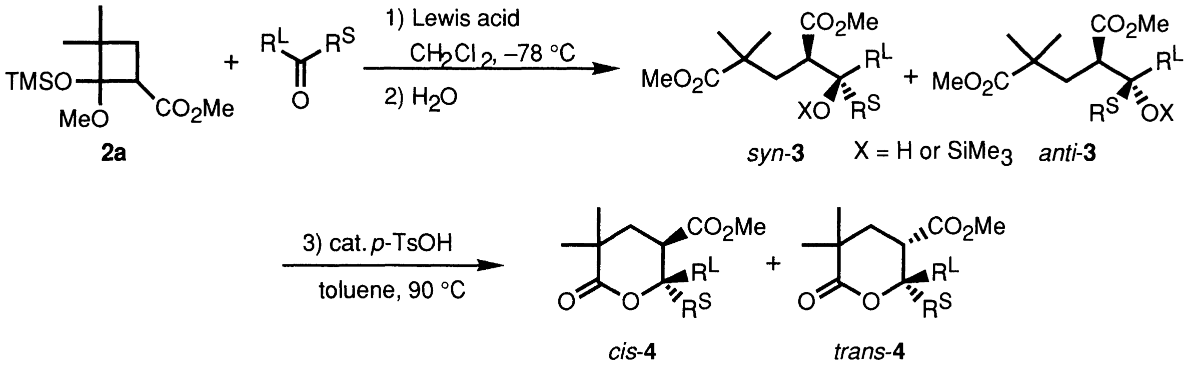
The reaction of **2a** with 3-phenylpropanal smoothly proceeded in dichloromethane at –78 °C in the presence of 1.0 equivalent of $TiCl_4$ (the reaction of **1** with aldehydes required higher temperature (≥ 0 °C)).



Scheme 1.

After aqueous work-up, the crude product, mainly consisting of hydroxy diester **3**, was treated with a catalytic amount of *p*-TsOH in toluene at 90 °C to give δ-lactone **4** in moderate yield with good *cis*-selectivity (R^L = $PhCH_2CH_2$, R^S = H, 54%, *cis*:*trans* = 82:18).[7] Among reaction conditions examined, solvent and Lewis acid highly influenced the yield and the diastereoselectivity (Table 1). The reaction in toluene exhibited slightly better selectivity but lower yield than that in dichloromethane (entry 2), while the reaction did not proceed in acetonitrile at all (entry 3). Titanium(IV) derivatives generally showed good *cis*-selectivity, and $Ti(O^iPr)Cl_3$ was the best among them regarding not only the selectivity but also the yield. The effect of reaction temperature was also examined using $Ti(O^iPr)Cl_3$ in dichloromethane. When the reaction was performed at –23 °C, the diastereomer ratio was the same as the reaction at –78 °C, although the yield was slightly depressed. Above 0 °C, both the yield and the stereoselectivity apparently decreased.

Under the optimized reaction conditions (see the following typical procedure), the reaction of **2a** with several kinds of aldehydes or unsymmetrical methyl ketones was carried out (Table 2). The reaction of **2a** with aldehydes generally gave *cis*-**4** in good to excellent yields with good selectivity,[8] except for the case of



Scheme 2.

Table 1. Effects of Solvent and Lewis Acid for the Reaction of **2a** with 3-Phenylpropanal

Entry	Lewis acid	Solvent	Time / h	Yield / %	*Cis* : *Trans*
1	$TiCl_4$	CH_2Cl_2	5.5	54	82 : 18
2		Toluene	16	39	85 : 15
3[a)]		CH_3CN	23	0	——
4	$TiBr_4$	CH_2Cl_2	3.5	84	85 : 15
5	$Ti(O^iPr)Cl_3$		2	85	92 : 8
6	$Ti(O^iPr)Br_3$		1.5	79	90 : 10
7	$Ti(O^iPr)_2Cl_2$		4	47	83 : 17
8	$Ti(OTf)_2Cl_2$		1.5	15	78 : 22
9	$SnCl_4$		4.5	54	80 : 20
10	$AlBr_3$		4	81	69 : 31
11	$GaCl_3$		5	53	60 : 40
12	$BF_3 \cdot OEt_2$		3.5	48	31 : 69

a) The reaction was performed at –45 °C.

benzaldehyde (entry 8).[9)] The reaction of **2a** with unsymmetrical methyl ketones was also proceeded similarly, although it was less selective than the reaction of **2a** with aldehydes. $Ti(O^iPr)Cl_3$ was not effective for the reaction of **2a** with pinacolone, a bulky methyl ketone, while $TiBr_4$ gave a mixture of hydroxy and siloxy diesters **3** in good yield. In the case of isopropyl methyl ketone and pinacolone, acidic treatment of a mixture of hydroxy and siloxy diesters **3** caused partial dehydration to give olefinic compounds **5**; the dehydration of *anti*-**3** occurred more easily than did *syn*-**3**, resulting in the improvement of the selectivity of δ-lactones **4**.[10)]

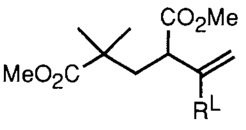


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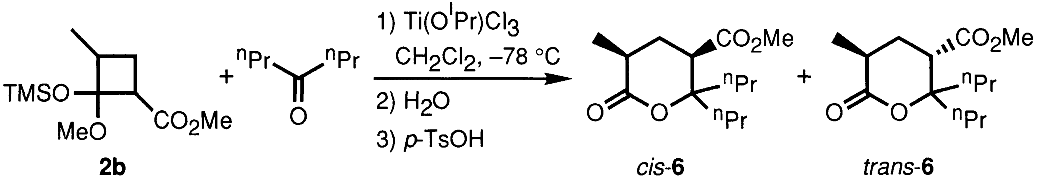
Table 2. Reaction of **2a** with Carbonyl Compounds

Entry	R^L	R^S	Lewis acid	Yield / %[a)]	*Cis* : *Trans*[b)]
1	$Ph(CH_2)_2$	H	$Ti(O^iPr)Cl_3$	85	92 : 8
2			$TiBr_4$	84	85 : 15
3	$CH_3(CH_2)_8$	H	$Ti(O^iPr)Cl_3$	93	88 : 12
4	$(CH_3)_2CHCH_2$	H		89	92 : 8
5	$(CH_3)_2CH$	H		83	91 : 9
6	C_6H_{11}	H		70	89 : 11
7	$(CH_3)_3C$	H		69	96 : 4
8	Ph	H		77	65 : 35
9	$CH_3(CH_2)_7$	CH_3		85	59 : 41[c)]
10	$(CH_3)_2CH$	CH_3		57 (75)[d)]	85:15 (67:33)[d)]
11	$(CH_3)_3C$	CH_3	$TiBr_4$	41 (67)[d)]	93: 7 (57:43)[d)]

a) Isolated yield. b) Determined by GC. c) The relative stereochemistry was not determined. d) The values in parentheses represent the yields and diastereomer ratios of **3**.

A typical procedure is as follows: To a stirred solution of **2a** (158 mg, 0.61 mmol) and 3-phenylpropanal (68 mg, 0.51 mmol) in dichloromethane (3 ml) was added drop by drop a solution of $Ti(O^iPr)Cl_3$ in dichloromethane (1.03 mol•dm^{-3}, 0.60 ml, 0.62 mmol) at –78 °C. The reaction mixture was stirred for 2 h, and quenched at the same temperature by adding water (1 ml). After being stirred vigorously for 15 min, the mixture was allowed to warm to room temperature. The mixture was extracted with dichloromethane (3 × 5 ml), and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation, the crude product, which mainly comprised hydroxy diester **3**, was treated with a catalytic amount of *p*-TsOH in toluene at 90 °C for 2 h. The mixture was concentrated to afford the crude product, which was purified by preparative TLC (hexane/CH_2Cl_2/EtOAc = 5/1/1) to give δ-lactone **4** (85%, *cis*:*trans* = 92:8).

The reaction of 3-methylcyclobutane **2b** with 4-heptanone was also examined. δ-Lactone **6** was obtained in excellent yield, while the diastereoselectivity was not so high (93%, diastereomer ratio=65:35, Scheme 3), in spite of high diastereoselectivity for the reaction of a 2,2-dialkoxy-3-alkylcyclopropanecarboxylic ester with symmetrical ketones.[2d)] The observed low selectivity for the reaction of **2b** would be explained as follows: The chiral center in the 1,4-zwitterionic intermediate generated from **2b** is located at β-position from the reacting point.[8)] This means that 1,3-induction works much less effectively than 1,2-induction occurring in the reaction of the cyclopropane derivative.



Scheme 3.

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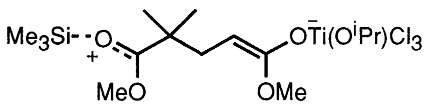
7) The relative stereochemistry of δ-lactones **4**, derived from aldehydes, was determined on the basis of ^{1}H NMR coupling constants; $^3J_{4\text{-}5}$s for the *cis*-isomers were 2.1–6.4 Hz, while those of the *trans*-isomers were 10.4–10.7 Hz. For δ-lactones **4** derived from isopropyl methyl ketone and pinacolone, the relative stereochemistry was determined by NOE experiments.

8) Although the mechanism of the present reaction is not clear at present, following explanation is considered to be possible similarly to the reaction of 2,2-dialkoxycyclopropanecarboxylic esters with aldehydes.[2c] Cyclobutane **2a** reacts with $Ti(O^iPr)Cl_3$ to form an *E*-enolate intermediate like **7**, and the reaction with carbonyl compounds proceeds via a six-membered ring transition state like **8** to give *syn*-**3**, which cyclizes to afford *cis*-**4**.



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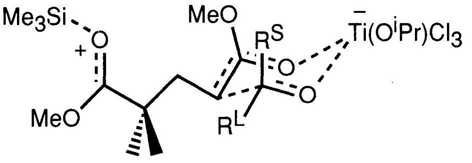

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9) In the case of benzaldehyde, diastereomer ratio of **3** was not determined. However, the TLC analysis of **3** indicated that the reaction was not so selective (about 2:1). Consequently, the relatively low diastereoselectivity observed was not due to epimerization during the lactonization reaction.

10) Such a dehydration could not be observed at all in the cyclization of **3** derived from **2a** and aldehydes. Kinetic differentiation of two diastereomers during lactonization would not be so important in this case, since the complete consumption of **3** was confirmed by TLC. Therefore, the change in diastereomer ratio between **3** and **4** is considered to be mainly caused by preferential dehydration of *anti*-**3**.

(Received March 26, 1993)