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A New Finding in the Dieckmann Type Annulation of a Chiral Half-Thiol Diester Having Latent σ-Symmetry

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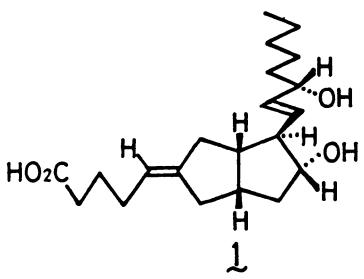
It was revealed that the Dieckmann type annulation of a half-thiol diester having latent σ-symmetry did not always proceed in the regiocontrolled fashion even though the reaction yielded the desired β-keto ester. Direction of the regioselectivity dramatically differed depending on the base employed, which was demonstrated by treating an optically pure half-thiol diester with lithium diisopropylamide, dimsylsodium, and dimsylpotassium, respectively.

Recently, we have reported chiral syntheses of (+)-carbacyclin (1)[1] and a useful intermediate (3)[2] for (+)-isocarbacyclin (2) utilizing a new chiral induction procedure into prochiral σ-symmetric dicarboxylic acid (4) and regiocontrolled Dieckmann-type annulation of optically active half-thiol diester (5) [$[\alpha]_D^{25}$ -3.8° (c 1.0, $CHCl_3$), > 98% enantiomeric excess (ee)]. Through these syntheses, we recognized an interesting new fact that the Dieckmann type annulaiton of half-thiol diester 5 does not always proceed regioselectively.



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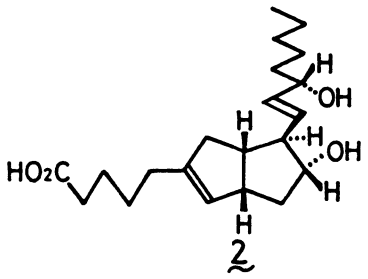

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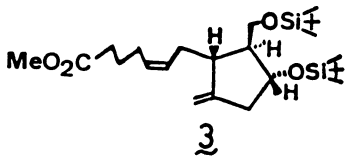

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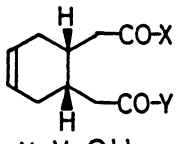
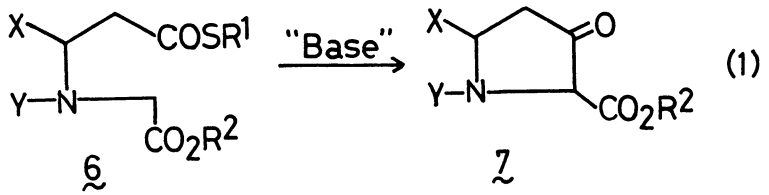


4 X=Y=OH
5 X=OMe, Y=SPh

Dieckmann type condensation reaction has been well known as a fascinating synthetic method for cyclic compounds having the β-keto ester system.[3] However, in the case of unsymmetrical diester, two kinds of annulation products due to the regioisomeric β-keto ester moiety could be formed.[3] Therefore, an improved method of the Dieckmann type annulation involving the complete regiocontrolled

reaction of half-thiol diester 6 into 7 was reported (Eq. 1).[4,5]



(1)

In due consideration of the previous excellent result,[4,5] we investigated regiocontrolled Dieckmann type annulation of a chiral key-intermediate (5) for the (+)-carbacyclin synthesis.[1]

Firstly, we attempted the annulation employing lithium diisopropylamide (LDA) as follows. To a stirred solution of half-thiol diester (5) (3.16 mmol) in THF (16 ml) and HMPA (3.16 mmol) was added at -78 °C a solution of LDA (7.9 mmol) in THF (16 ml). After being stirred at -55 °C under N_2 for 1 h, the reaction mixture was subjected to the usual work-up to give the desired bicyclic β-keto ester (-)-8 in 57% yield together with the starting material 5 in 13% recovery.[1] Enantiomeric purity of compound (-)-8 was shown to be > 98% by its ^{1}H-NMR analysis in the presence of Eu(hfc)$_3$ (Run 1 in Table 1).[1]

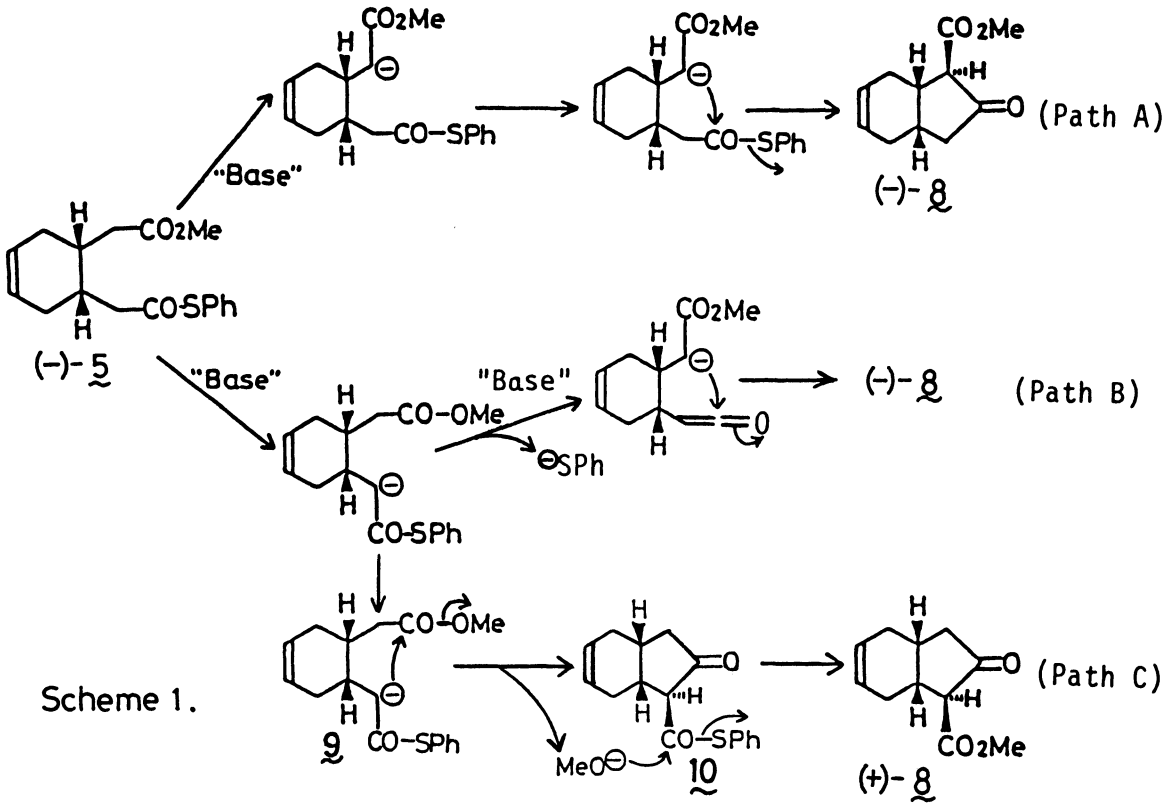
Table 1. Dieckmann type annulation of (-)-5

Run	Base (mol equiv.)	Reaction conditions: Solvent	Temp/°C	Time	Yield/% of 8	$[\alpha]_D^t$/°[a] (c, t/°C) of 8	Enantiomer ratio[b] (-)-8 : (+)-8
1	LDA (2.5)	THF-HMPA[c]	-55	1 h	57	-160.9 (0.21,23)	>99 : <1
2	NaH (3.0)	DMSO	15	5 s	42	+35.7 (2.40,21)	38 : 62
3	NaH (3.0)	DMSO-DME (1 : 3)	0	5 min	25	+36.0 (0.20,23)	40 : 60
4	NaH (3.0)	DMSO-DME (1 : 3)	-35	4 min	23	0.0 (0.37,23)	49 : 51
5	KH (2.7)	DMSO	18	2 h	42	+16.1 (0.36,23)	45 : 55

a) Determined in $CHCl_3$. b) Determined by 100 MHz ^{1}H-NMR analysis in the presence of Eu(hfc)$_3$. c) One mol equiv. of HMPA was employed to (-)-5.

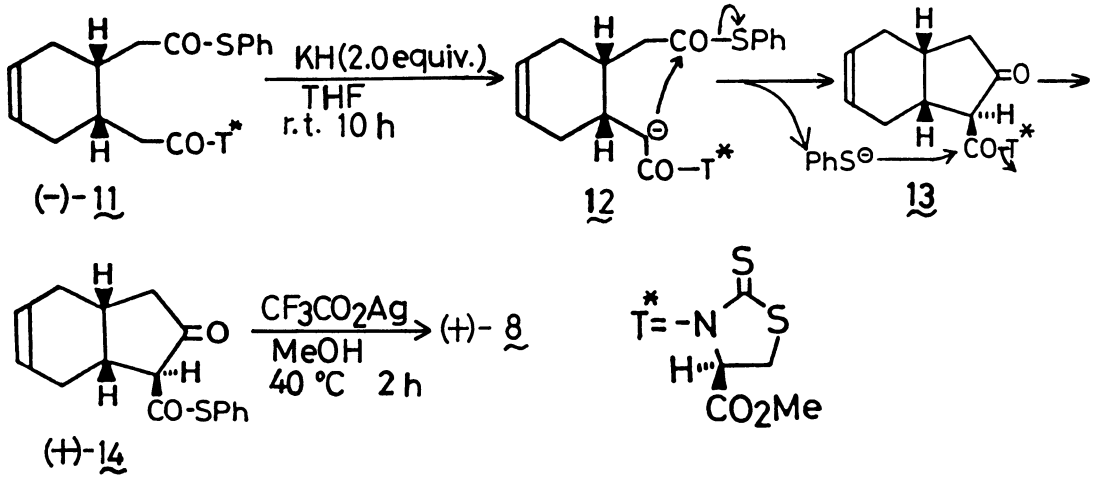
On treatment with 2 M dimsylsodium[6,7] (3 mol equiv.) solution in DMSO or 1 M dimsylpototassium[8] (3 mol equiv.) solution in DMSO at the required temperature for the required time, compound 5 was surprisingly converted to the (+)-8 excess product, respectively (Runs 2 and 5). The (+)-8 excess product was also obtained even when compound 5 was allowed to react with the same dimsylsodium solution in DMSO-DME (1:3) at 0 °C (Run 3). However, the similar annulation at -35 °C furnished racemic β-keto ester (8) in very low yield (Run 4).

Based on the experimental results mentioned above, we postulate three kinds of plausible pathways (A - C in Scheme 1) for the formation of cyclic (+)- or (-)-β-keto ester (8). Path C, in which we cannot rationalize the formation of (+)-8 without passing through transient states 9 and 10, should be particularly noteworthy. Thus, the reaction of the chiral compound 5 with LDA would adopt Path A and/or Path B to give (-)-8 exclusively while the annulation with dimsylsodium or dimsylpotassium should preferentially take Path C than Path A and B to yield the (+)-8 excess product.



Scheme 1.

Path C-like annulation was also observed when 4(R)-methoxycarbonyl-1,3-thiazolidine-2-thione monoamide (11) [$[\alpha]_D^{20}$ -120.0° (c 0.23, $CHCl_3$), > 98% diastereomer excess (de)] was allowed to react with KH in THF. Potassium hydride (24.8 wt. % dispersion in mineral oil, 0.93 mmol) was washed with anhydrous hexane under N_2 and then dried in vacuo to give an amorphous powder. To a suspension of the KH powder in anhydrous THF (2 ml) was added a solution of compound (-)-11 (0.46 mmol) in THF (4 ml) under ice-cooling with stirring. After being stirred at room temperature for 10 h, the reaction mixture was subjected to the usual work-up to give the (+)-14 excess β-keto thioester [54% yield, mp 56.5 - 57 °C (Et_2O-hexane), $[\alpha]_D^{20}$ + 35.1° (c 0.28, $CHCl_3$)]. This could be confirmed by the chemical conversion (78% yield) of the (+)-14 excess compound to the (+)-8 excess β-keto methyl ester [$[\alpha]_D^{20}$ + 73.0 ° (c 0.33, $CHCl_3$)] on treatment with CF_3CO_2Ag in MeOH at 40 °C for 2 h. Thus, participation of 11 and 12 was also strongly suggested in this annulation (Scheme 2).



Scheme 2.

Generally, one cannot realize the possibility of Path C (Scheme 1) and the course shown in Scheme 2 in the Dieckmann type annulation of racemic 5 and 11 because of their latent σ-symmetry. Nevertheless, we could clarify their significant participation by utilizing optically pure compounds 5 and 11, respectively. Detailed mechanistic studies on the differential annulation depending on the bases are currently in progress.

References

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