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ASYMMETRIC SYNTHESIS OF β-LACTAMS. II. HIGHLY EFFECTIVE ASYMMETRIC INDUCTION BY MEANS OF "TITANIUM TEMPLATE"

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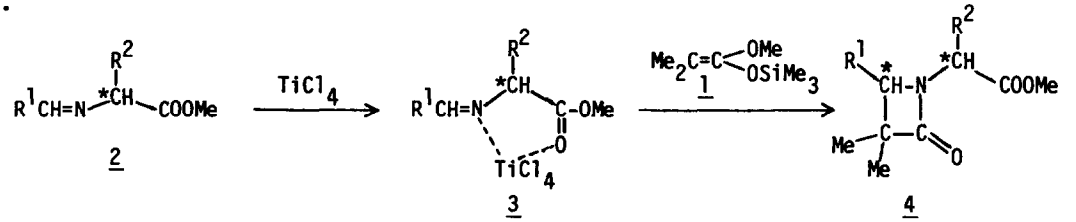
Summary: The reaction of dimethylketene methyl trimethylsilyl acetal with the Schiff bases of chiral α-amino esters in the presence of titanium tetrachloride gave the corresponding β-lactams with extremely high stereoselectivity (up to > 99% diastereomeric purity). Possible mechanism for the highly effective asymmetric induction using " titanium template" is proposed.

Of late years, considerable interest has been focused on the synthesis of mono-cyclic β-lactams with regard to the antibiotics such as nocardicin A[1] or a precursor of thienamycin.[2] It has been shown that one of the most convenient method for the synthesis of mono-cyclic β-lactams is the cycloaddition of ketenes generated in situ from acyl chlorides and base with imines,[3] which may involve an electrophilic attack of the ketene species to imine. Most recently, we found that the asymmetic synthesis of β-lactams could be easily accomplished by the combination of ketene silyl acetal, chiral imine and titanium tetrachloride, which must involve a nucleophilic addition of "ketene equivalent" to the carbon-nitrogen double bond.[4] Taking a look at the possible transition states, we anticipated that if titanium moiety could act as effective "template" which enabled polydentate rigid transition state, an extremely efficient asymmetric induction should be attained. Thus, we employed Schiff bases of chiral α-amino esters as substrate, which could form a five membered ring chelate with titanium tetrachloride and then provide a tridentate rigid transition state. Now, we describe here highly effective asymmetric synthesis of β-lactams by means of the "titanium template".



2 3 4

Table 1. Chiral β-lactams (4) obtained by the reaction of dimethylketene methyl trimethylsilyl acetal with the Schiff bases of (S)-α-amino esters in the presence of titanium tetrachloride[a]

	R^1	R^2	Yield(%)[b]	NMR(δ ppm)[c] (S,R)	NMR(δ ppm)[c] (S,S)	Asymmetric Induction(%)
a	Et	^{i}Pr	73	3.78 (97)	3.88 (3)	94
b	^{n}Pr	^{i}Pr	74	3.78 (95)	3.89 (5)	90
c	^{n}Bu	^{i}Pr	77	3.79 (95)	3.90 (5)	90
d	^{i}Bu	^{i}Pr	81	3.76(>99)	3.89 (<1)	>98
e	Et	Me	28	4.23 (73)	4.43 (27)	46
f	Et	CH_2COOMe	53	4.44 (57)	4.34 (43)	14
g	Et	^{i}Bu	49	4.12 (70)	4.34 (30)	40
h	Et	CH_2Ph	45	4.27 (79)	4.88 (21)	58

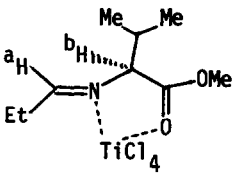
[a] All reactions were run with 10 mmol of 1, 10 mmol of 2 and 10 mmol of titanium tetrachloride in 25 ml of dichloromethane at -78°C∿room temperature for 24 hr. [b] Isolated yield based on 1. [c] Chemical shifts of the methine protons (H^b) of two diastereomers, 4 (S,R) and 4 (S,S). Values in the parentheses show the diastereomeric purities.

We carried out the reaction of dimethylketene methyl trimethylsilyl acetal (1) with a variety of Schiff bases of α-amino esters (2) in the presence of titanium tetrachloride in dichloromethane. Results are listed in Table 1. As Table 1 shows, the extent of asymmetric induction remarkably depends upon the substituent R^2, and excellent results are obtained on using (S)-valine methyl ester as chiral source.

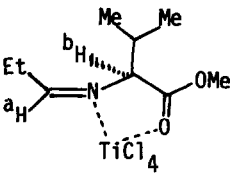
As to the structure of the titanium complexes of the Schiff bases (3), NMR and IR spectra provide a significant information. Namely, it turns out that the complex 3a(A) formed kinetically at -78°C exclusively by mixing the Schiff base and titanium tetrachloride in chloroform-d is converted to an equilibrium mixture of 3a(A) and 3a(B) above -20°C, the latter of which is thermodynamically more stable than the former (3a(A)/3a(B) = 1/4 at 30°C). The assignment of the spectra of 3a(A) and 3a(B) was unambiguously made by taking into account the pseudo-contact shift caused by titanium tetrachloride and a long range coupling observed for 3a(B) (see Table 2).

As it is reasonable to assume a titanium enolate as a key intermediate of the reaction with a ketene silyl acetal,[4,5] the reaction should involve the expected tridentate intermediate and a rigid bicyclic transition state in which titanium(IV) species acts as effective "titanium template" to give (S,R)-4 from 3(A) or (S,S)-4 from 3(B) as shown in Scheme 1. As Table 1 shows, 3a(A) gives (S,R)-4a in excellent stereoselectivity [(S,R)/(S,S) = 97/3]. Thus, if 3(B)

Table 2. NMR data for the complexes, 3a(A) and 3a(B)

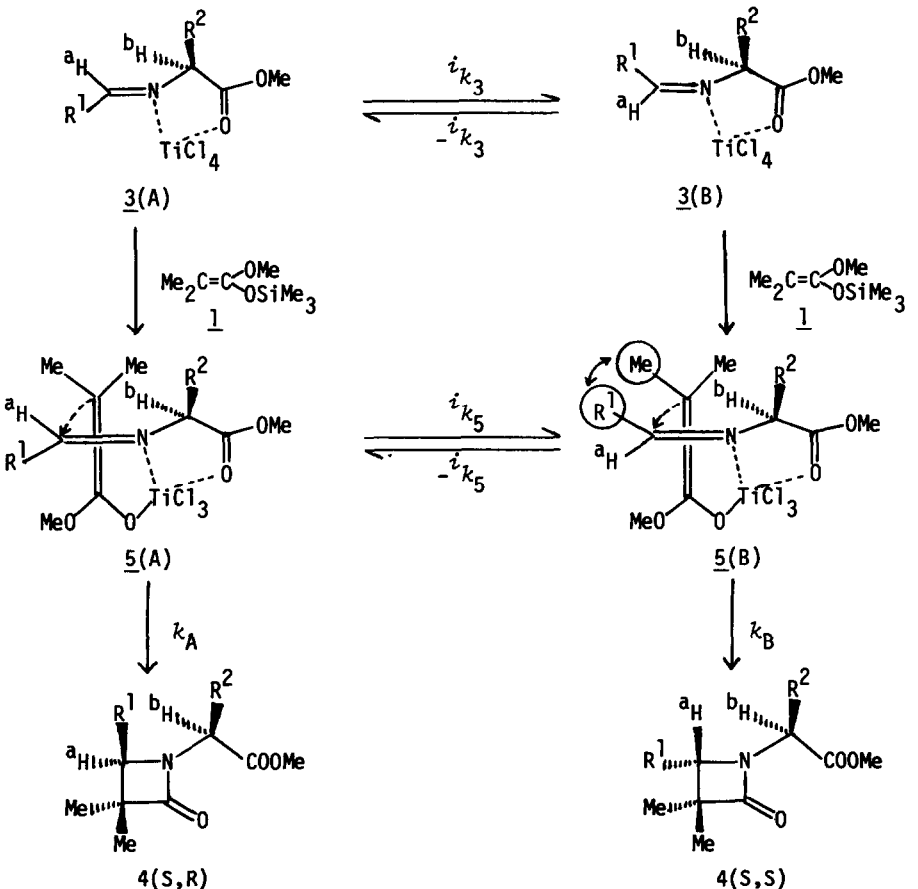


3a(A)



3a(B)

Complex	Chemical Shift (δ ppm) ($CDCl_3$)	
	a_H	b_H
3a(A)	8.12(t, Jab = 0)	4.46(d, Jab = 0)
3a(B)	8.60(d of t, Jab = 2 Hz)	4.70(d of d, Jab = 2 Hz)



Scheme 1.

is predominantly formed, the reaction must afford (S,S)-4 preferentially.[6]

Accordingly, we examined the reaction of the equilibrium mixture of 3a [3a(A)/3a(B) = 1/4] with dimethylketene methyl trimethylsilyl acetal in the presence of titanium tetrachloride at -78°C ∿ 25°C, and obtained (S,S)-4a preferentially as expected although the stereoselectivity was relatively low [(S,S)/(S,R) = 58/42]. When the reaction was carried out at room temperature, no asymmetric induction was observed, i.e., (S,S)-3a/(S,R)-3a = 50/50. The result strongly suggests the existence of rapid equilibrium between 3(A) and 3(B), and 5(A) and 5(B) at room temperature. The result may also imply that the rate of the reaction of 3a(A) is about four times faster than that of 3a(B) since the ratio 3a(A)/3a(B) is turned to be 1/4 at room temperature. This may be due to the unfavorable steric repulsion between the substituent of the Schiff base, R^1, and that of the ketene silyl acetal, Methyl, as shown in Scheme 1.

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6. In order to confirm the stereochemistry at ^{4}C position in these systems, we performed the reaction of (R)-^{i}BuCH=N-$\overset{*}{C}$H(Ph)COOMe with 1 in the presence of titanium tetrachloride, which gave the corresponding β-amino ester in 80% yield. Although the desired β-lactam was not formed directly, the stereochemistry at ^{4}C position in the β-amino ester should be the same as that of the cyclized product, β-lactam. Thus, the β-amino ester was converted to the known compound, 2,2,5-trimethyl-3-aminohexanoic acid {$[\alpha]_D^{20}$ -4.29° (1N HCl. c 2.00)} by hydrolysis and hydrogenolysis, and it turned out that the preferred configuration was S. Consequently, R configuration should be preferred on using (S)-α-amino esters as chiral source.

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