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A STEREOCONTROLLED METHOD FOR THE SYNTHESIS OF EACH OF THE FOUR DIASTEREOMERS OF 3,4-DIALKYL-SUBSTITUTED β-LACTAMS USING DIFFERENT METAL ESTER ENOLATES AND A CHIRAL IMINE

Tamotsu FUJISAWA,* Mitsuhiro ICHIKAWA, Yutaka UKAJI, and Makoto SHIMIZU
Department of Chemistry for Materials, Mie University, Tsu, Mie 514, Japan

SUMMARY: The reaction of the different metal ester enolates of *t*-butyl α-alkyl substituted acetates with a chiral imine possessing a dioxolane ring derived from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol as a chiral auxiliary followed by cyclization of the initial products of β-amino esters gave each of the diastereomers of 3,4-dialkyl-substituted β-lactams in a highly stereoselective manner, *i.e.*, the titanium enolate gave *trans*-(3*R*,4*S*)-isomer, while the lithium and zinc ones afforded *cis*-(3*S*,4*S*)- and (3*R*,4*R*)-isomers, respectively, and the *cis*-(3*R*,4*R*)-β-lactams thus obtained were readily epimerized to the corresponding *trans*-(3*S*,4*R*)-β-lactams without loss of the stereochemical integrity at C_4.

Recently considerable attention has been focused on carbapenem antibiotics such as thienamycin and PS-5, because of their high therapeutic activity in humans.[1] Accordingly the need for the synthesis of β-lactam ring with alkyl chains at C_3 and C_4 has prompted many organic chemists to develop methodology for the stereocontrolled construction of the lactam ring.[2] Although the aldol-like reactions to a chiral imine,[3] the cycloaddition of an imine and a ketene,[4] and the ring closure reaction of some amino esters or *t*-amides[5] represent the typicl methods for the preparation of the β-lactams, there are few reports describing the regulation of the two contiguous asymmetric carbons. Previously, we have reported that the ester enolate addition to a chiral imine possessing a dioxolane ring as a chiral auxiliary using titanium and lithium metals affords stereodivergent products with high diastereoselectivity.[6] Namely, the lithium enolates prepared from ethyl α,α-disubstituted acetates underwent addition-cyclization with a chiral imine to give (4*R*)-β-lactams, whereas the triisopropoxytitanium enolates effected the formation of (4*S*)-β-lactams. To extend the scope of diastereoselective carbon-carbon bond formation by the ester enolate-imine condensation reaction, the use of α-monoalkyl-substituted acetate derivatives is intriguing because of the creation of another stereogenic center at the 3-position of the corresponding β-lactams, where the enolate geometry as well as the different coordination state of the metal used should influence the stereochemical course of the ester-imine condensation.[7] We now

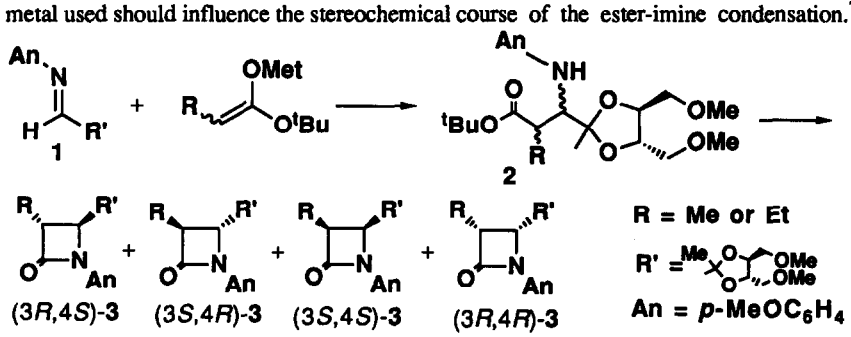


Table 1. Addition Reaction of Metal Enolate of *t*-Butyl Alkanoate to the Chiral Imine 1[a]

			Yield/%[b]			Ratio[c]				
Entry	R	Met	Addition	Hydrolysis	Cyclization	3*R*,4*S*	:	3*S*,4*R*	:	3*S*,4*S* : 3*R*,4*R*
1	Me	$Ti(O^iPr)_3$	74[d]	60	79	100	:	0	:	0 : 0
2	Me	Li	74[d]	95	81	0	:	1	:	84 : 15
3	Me	ZnCl	82[e]	90	80	2	:	1	:	4 : 93
4	Et	$Ti(O^iPr)_3$	87[d]	47	98	100	:	0	:	0 : 0
5	Et	Li	78[d]	94	85	4	:	0	:	83 : 13
6	Et	ZnCl	72[e]	96	86	5	:	1	:	8 : 86

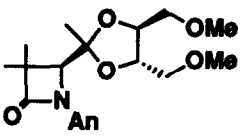
[a] All reactions were performed on 0.1-0.6 mmol scale with a reactant ratio of enolate : 1 = 6.0 : 1.0. [b] Isolated yields after purification by TLC. [c] The ratios of β-lactams were determined by GLC (SE-30, 50m). [d] The addition was conducted at -78 ~ -60 °C in the presence of HMPA (12eq). [e] The addition reaction was conducted at -78 °C ~ room temperature without HMPA.

describe here that starting from a single chiral imine having a chiral auxiliary derived from (2*R*,3*R*)-tartaric acid, an efficient method has been developed for the stereoselective construction of each of the four diastereomers with respect to β-lactam skeletons possessing substituents at C_3 and C_4 by the use of the different metal ester enolates of propionate and butyrate. The initial examination into the ester-imine condensation of methyl propionate with (4*S*,5*S*)-4,5-dimethoxymethyl-2-(*N*-*p*-methoxyphenyl)iminomethyl-2-methyl-1,3-dioxolane **1**, prepared from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol in 3 steps,[6b] gave no selectivity when the chlorozinc and lithium enolates were used, whereas the triisopropoxytitanium enolate gave a mixture of (3*R*,4*S*), (3*S*,4*R*), (3*S*,4*S*), and (3*R*,4*R*)-β-lactams **3** in a 91 : 1 : 0 : 8 ratio.

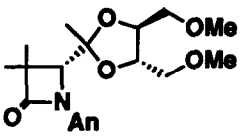
The high stereoselection was observed by controlling the steric bulk of the ester part as well as the metal species of the enolates, where β-amino esters **2** were initially obtained from the *t*-butyl ester. To a solution of LDA containing HMPA[7] was added a solution of *t*-butyl propionate in THF at -78°C, then a solution of the chiral imine **1** in THF was added dropwise at the same temperature, and the mixture was allowed to stand at room temperature. Standard work-up followed by TLC purification gave the corresponding β-amino ester. β-Lactam **3** was prepared from the corresponding β-amino ester by the following procedures. Amino ester **2**, obtained by the reaction of the imine **1** with the enolate of *t*-butyl propionate, was hydrolyzed with an excess of trifluoroacetic acid in dichloromethane at room temperature to give the corresponding carboxylic acid, which in turn was cyclized with 1-methyl-2-chloropyridinium iodide in dichloromethane at 0 °C according to the procedure by Mukaiyama et al,[8] to afford the corresponding β-lactam **3**. In contrast to the result using unsubstituted acetate,[6c] further Claisen type condensation of the β-amino ester initially formed with an excess enolate was not observed in the present cases. As shown in Table 1, the titanium enolate prepared via transmetalation[9] of the lithium enolate with chlorotitanium triisopropoxide[10] afforded *trans*-(3*R*,4*S*)-lactam **3** exclusively (Entry 1), whereas the lithium enolate yielded stereoselectively *cis*-(3*S*,4*S*)-**3** (Entry 2). A reversal of the diastereofacial discrimination in the addition step was attained by the use of chlorozinc enolate prepared via transmetalation of the corresponding potassium enolate with zinc chloride,[11] where *cis*-(3*R*,4*R*)-β-lactam **3** was formed as a major product (Entry 3).

The relative stereochemistry at C_3 and C_4 of the β-lactams **3** obtained was determined by the comparison of the coupling constants between C_3 and C_4 protons in ^1H NMR with those reported, which showed J = 2.31 Hz for the *trans*, and J = 5.94 Hz for the *cis* form.[12] Absolute stereochemistry at C_4 was readily established by

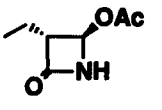
transforming the β-lactam **3** into the known dimethylated β-lactams **4** *via* the standard procedures,[13] *i.e.*, β-lactams **3** (R = Me) were deprotonated with LDA in THF followed by methylation with methyl iodide at -78 °C ~ room temperature to give 3-dimethylated lactams **4** in 85 % yield. Analyses with spectroscopic methods as well as HPLC indicated the absolute stereochemistry at C_4 of the β-lactams to be *S* and *R*, respectively.[6b]



(4*S*)-**4**

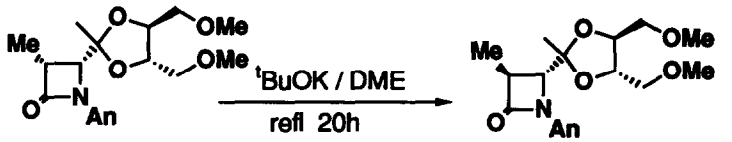


(4*R*)-**4**



(3*R*, 4*R*)-**5**

Furthermore, upon treatment with potassium *t*-butoxide *cis*-(3*R*,4*R*)-**3** readily underwent epimerization to give *trans*-(3*S*,4*R*)-**3** in 98 % epimerization yield without loss of the stereochemical integrity at C_4.[14] Thus, all four stereoisomers of β-lactams **3** could be obtained with high selectivity.



δ 4.3 (d, $J_{3,4}$= 5.94)
(3*R*,4*R*)-**3**

δ 3.8 (d, $J_{3,4}$= 2.31)
(3*S*,4*R*)-**3**

As to the preparation of another 3-alkylated β-lactam, the reaction of *t*-butyl butyrate was investigated in conjunction with the access to carbapenem PS-5.[1] As shown in Table 1 (Entries 4-6), the titanium enolate gave (3*R*,4*S*)-**3** (R = Et) exclusively in good overall yield, whereas the reversal of the diastereofacial discrimination of the addition process was also observed for the zinc enolate. The β-lactam (3*R*,4*S*)-**3** (R = Et) thus obtained exclusively from the titanium enolate was readily converted to an intermediate (3*R*,4*R*)-**5** for the PS-5 synthesis by the established procedures.[6b] The spectroscopic data and the sign of the optical rotation obtained for **5** ($[\alpha]_D^{23}$ +94 ° (c 0.18, $CHCl_3$)) were in good accordance with those reported.[15]

Although the rationale for the changeover of the selectivity appears to need more work, the diastereofacial discrimination reported above is most probably understood by considering the different coordination ability of the enolate metals as well as the steric bulk of the ester parts, *e.g.*, the characteristic coordination states of the metals such as tetra- and hexa-coordinated species involving different bond lengths and the enolate geometries reflecting highly ordered transition states such as the chair- or boat-like six-membered metalocycles.[16] We are currently studying in more detail the transition states for the changeover of the diastereoselectivity.

The high degree of the diastereofacial discrimination attained in the present study provides a ready access to each of the four diastereomers with respect to the β-lactam skeleton with alkyl substituents at C_3 and C_4 simply by selecting an appropriate metal enolate of *t*-butyl alkanoate via ready transmetalation of the lithium or potassium ester enolate with chlorotitanium triisopropoxide or zinc chloride. The characteristics of the chiral imine **1** appear especially in the reaction with the titanium enolate in which (3*R*,4*S*)-β-lactam was formed exclusively, making a contrast to the results obtained by the reaction of the trichlorotitanium enolate of 2-pyridyl thiobutyrate with a chiral imine reported recently,[2f] where the complete diastereofacial discrimination was not attained. Since the chiral auxiliary used in the present system is readily available, the present methodology

offers a versatile intermediate for the synthesis of a variety of β-lactam antibiotics and/or β-lactamase inhibitors possessing substituents at C_3 and C_4 in high optical purity.

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