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Highly Stereodivergent Approach to Both Enantiomers of 4-Substituted β-Lactams via Diastereofacially Controlled Addition of Enolates of *t*-Butyl Acetate to a Chiral Imine†

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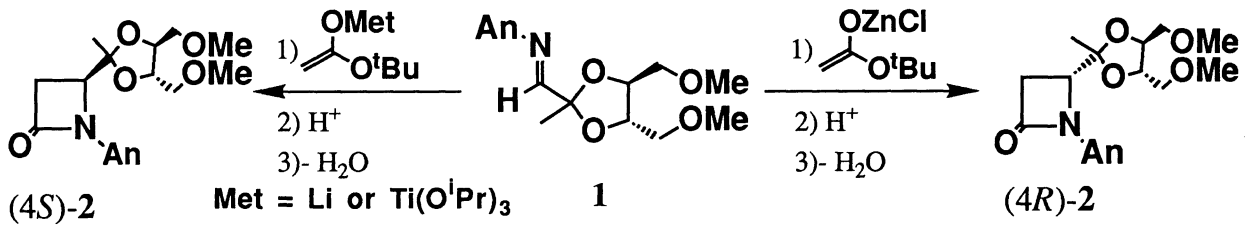
Addition of lithium or triisopropoxytitanium enolate derived from *t*-butyl acetate to a chiral imine possessing dioxolane ring as a chiral auxiliary gave (3*S*)-β-amino ester exclusively, whereas chlorozinc enolate underwent *re*-facial attack to give (3*R*)-isomer with good selectivity. The β-amino esters thus obtained were readily converted to the corresponding (4*S*)- and (4*R*)-β-lactams respectively without loss of the stereochemical integrity at C-4 of the β-lactam rings.

Among biologically important classes of antibiotics β-lactam antibiotics constitute one of the most widely utilized materials due to their highly therapeutic index in humans.[1] From the stand point of their preparation monocyclic β-lactams without substituents at 3-position have received considerable attention because of ready transformation to a variety of β-lactam antibiotics and β-lactamase inhibitors such as penicillin, thienamycin, PS-5, monobactam, calvulanic acid, and so on.[2] We have recently developed an efficient method for the construction of both enantiomers with respect to β-lactam skeletons possessing substituents at 3 and 4 positions starting from a single chiral imine **1** and ethyl esters of α,α–disubstituted acetic acid by utilizing the abilities of enolate metal species to coordinate to heteroatoms.[3] Namely, the lithium enolates prepared from ethyl α,α-disubstituted acetates underwent addition-cyclization with a chiral imine **1** having a chiral auxiliary derived from (2*S*,3*S*)-1,4-dimethoxy-2,3-butandiol to give (4*R*)-β-lactams, whereas the triisopropoxytitanium enolates effected the formation of (4*S*)-β-lactams. However, for the selective preparation of both (4*S*)- and (4*R*)-β-lactams without substituents at 3-position, this methodology met with considerable difficulty, *i. e.*, the addition of enolates of ethyl acetate gave the predominant formation of (4*S*)-isomer regardless of the metal enolates used. We have now found that the diastereo-discrimination is controlled by the steric bulk of the ester part as well as the metal species of the enolates, and wish to report herein a stereodivergent synthesis of either (4*S*)- or (4*R*)-β-lactam **2** via addition of the enolates derived from bulky *t*-butyl acetate.

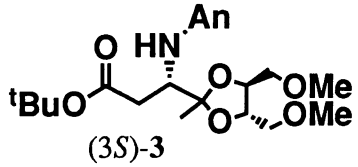


†Dedicated to Professor Emeritus Osamu Simamura on the occasion of his 80th birthday.

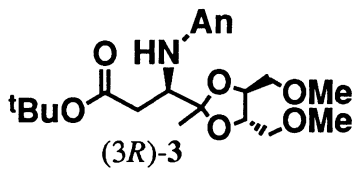
Table 1. Addition Reaction of Metal Enolates of *t*-Butyl Acetate to the Chiral Imine **1**[a)]

Entry	Met	Temp/°C	Yield of **3**/%[b)]	$3S : 3R$[c)]
1	Li	-78--40	68	>99 : <1
2	$Ti(O^iPr)_3$	-78--40	63	>99 : <1
3	$Ti(O^iPr)_3$	-78- rt	68	>99 : <1
4	ZnBr	-78- rt	68	14 : 86
5	ZnCl	-78- rt	77	8 : 92

a) All reactions were performed on 0.6 mmol scale with a reactant ratio of enolate : **1** = 3.0 : 1.0. b) Isolated yields by TLC. c) The ratio was determined by HPLC.



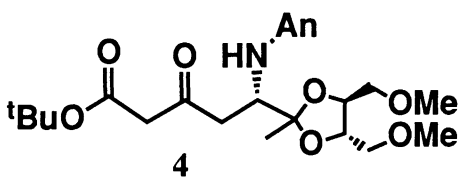
(3*S*)-**3**



(3*R*)-**3**

To a solution of LDA prepared from diisopropylamine (184 mg, 1.8 mmol) and *n*-BuLi (1.00 ml, 1.87 M in *n*-hexane) was added a solution of *t*-butyl acetate (215 mg, 1.9 mmol) in THF (3 ml) at -78 °C. Then a solution of the imine **1** (190 mg, 0.60 mmol) in THF (4 ml) was added dropwise at -78 °C, and the mixture was allowed to stand at -40 °C for 3.5 h. Then the mixture was quenched by adding a saturated aq NaCl (5 ml). Extraction of the entire mixture with ethyl acetate followed by drying (Na_2SO_4) and concentration of the combined extracts gave an oil, which was purified on TLC to give (3*S*)-β-amino ester (3*S*)-**3** (150 mg, 68 %) as a yellow oil. The ratio of (3*S*)- vs (3*R*)-isomers was determined by HPLC (*n*-C_6H_{14} : AcOEt = 2 : 1 as an eluent) to be >99 : <1. This result is in a strong contrast to the enolates of ethyl acetate which directly underwent cyclization to afford β-lactams **2**.[3)] Although switching the metal species to triisopropoxytitanium[4)] via transmetalation of the lithium enolate with chlorotitanium triisopropoxide[5)] did not meet with the reversal of the diastereofacial discrimination but resulted also in the stereoselective formation of (3*S*)-β-amino ester (3*S*)-**3** in good yield, reversal of the diastereofacial discrimination was observed with bromozinc enolate prepared via transmetalation of the corresponding potassium enolate with zinc bromide, where (3*R*)-β-amino ester (3*R*)-**3** was formed predominantly. Better diastereoselectivity was obtained using chlorozinc enolate[6)] prepared similarly from zinc chloride, with the isomeric ratio of (3*S*) : (3*R*) = 8 : 92, and these results are summarized in Table 1.

Effects of reaction temperature should be noted in the case of lithium enolate. At -78--40 °C the reaction gave β-amino ester (3*S*)-**3** as described above with excellent diastereoselectivity, whereas at room temperature the β-amino ester underwent Claisen type condensation[7)] with another enolate species to afford δ-amino-β-keto ester **4**[8)] in moderate yield, the structure of which was confirmed by comparison with an authentic sample prepared via cross-Claisen condensation reaction of the lithium enolate of *t*-butyl acetate[9)] with the β-amino ester (3*S*)-**3**. In this case diastereoselectivity at C-5 was also excellent in THF or DME as solvent, and the results are shown in Table 2. This type of Claisen condensation did not proceed by the use of titanium and zinc enolate, and



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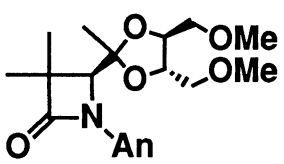
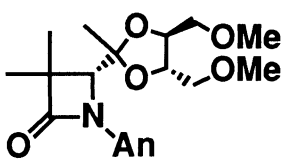


(4*S*)-**5**



(4*R*)-**5**

Table 2. Addition Reaction of Lithium Enolate of *t*-Butyl Acetate to the Chiral Imine **1**[a]

Entry	Solvent	Temp/°C	Yield of **3**/%[b] (3*S* : 3*R*)[c]	Yield of **4**/%[b] (5*S* : 5*R*)[c]
6	THF	-78--40	68 (>99 : <1)	0
7	THF	-78- rt	27 (>99 : <1)	44 (>99 : <1)
8	DME	-78--40	63 (>99 : <1)	0
9	DME	-78- rt	0	52 (>99 : <1)
10	Et_2O	-78--40	61 (59 : 41)	0
11	Et_2O	-78- rt	13 (53 : 47)	39 (53 : 47)

a) All reactions were performed on 0.6 mmol scale with a reactant ratio of enolate : **1** =3.0 : 1.0. b) Isolated yields after purification by TLC. c) The ratio was determined by HPLC.

in those cases the reaction gave β-amino ester exclusively with excellent selectivity regardledss of varying the reaction temperature.

The β-amino esters thus obtained were readily converted into the correponding β-lactams possessing a substituent at their 4-positions by the established procedures: The β-amino esters (3*S*)-**3** and (3*R*)-**3** were hydrolyzed with an excess of trifluoroacetic acid in dichloromethane at room temperature to give the corresponding carboxylic acids in 89 and 88 % yields, respectively, which in turn cyclized with triphenylphosphine-dipyridyl disulfide in acetonitrile at 55 °C according to the procedure by Ohno et al.,[10] to afford the corresponding β-lactams (4*S*)-**2** and (4*R*)-**2** in yields of 75 and 65 %, respectively. Under those reaction conditions no racemization was observed at C-4 in the β-lactams.

Absolute stereochemistry was readily established by transforming the β-lactams into the known derivatives (4*S*)-**5** or (4*R*)-**5** via the standard procedures.[11] The β-lactam (4*S*)-**2** was deprotonated with LDA in THF followed by methylation with methyl iodide at -78 °C - room temperature to give 3-methylated derivative in 85 % yield, which was further methylated under the same conditions to afford the product dimethylated at 3-position (4*S*)-**5** in 54 % yield. Under similar conditions the β-lactam (4*R*)-**2** was transformed into (4*R*)-**5** in 44 % overall 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.[3]

Although the rationale of the changeover of the selectivity appears to need more work, the diastereo-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. Our previous studies concerning the diastereo-differentiating reactions on the addition to the imino groups suggest that the factors which control the diastereofacial discrimination mainly involve the characteristic coordination states of the metals such as tetra- and hexa-coordinated species, resulting in the creation of the dual environment for the induction of the either chirality.[12] In any event, the lithium and triisoporpoxytianium enolates effected the *si*-facial attack to the chiral imine **1** exclusively, whereas in the chlorozinc enolate case the preferential *re*-facial attack to the imine **1** was achieved. These may be caused by the characteristic coordination states involving different bond lengths and in part a subtle balance of the oligomerization states among the triisopropoxytitanium, lithium, and chlorozinc enolates. We are currently studying in more detail the intermediary states for the changeover of the diastereoselectivity.

In summary the high degree of the reversal of the diastereo-discrimination attained in the present study realizes a ready access to both (4*S*)- and (4*R*)-stereoisomers with respect to the β-lactam skeleton with no substituent at 3-position simply by selecting an appropriate metal enolate of *t*-butyl acetate via ready

transmetalation of the lithium or potassium ester enolate with chlorotitanium triisopropoxide or zinc chloride. Since the chiral auxiliary used in the present system is readily available[13] and functionalization at C-3 of the β-lactam ring is well precedented,[14] the present methodology offers a versatile intermediate for the synthesis of a variety of both enantiomers of β-lactam antibiotics and/or β-lactamase inhibitors.

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8) NMR ($CDCl_3$) δ = 1.40 (s, 3H), 1.43 (s, 9H), 2.64 (dd, 1H, J = 6.6 and 16.2 Hz), 2.85 (dd, 1H, J = 6.3 and 16.2 Hz), 3.36 (s, 3H), 3.38-3.56 (m, 8H), 3.42 (s, 3H), 3.72 (s, 3H), 3.97-4.13 (m, 3H), 6.62 (d, 2H, J = 8.9 Hz), 6.74 (d, 2H, J = 8.9 Hz); MS *m/z* (rel %) 467 (M^+, 7), 449 (2), 288 (2), 273 (3), 262 (4), 244 (10), 236 (10), 218 (10), 202 (4), 175 (77), 134 (56), 115 (93), 85 (98), 59 (100).

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