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A Novel Synthesis of a Key Intermediate for Penems and Carbapenems Utilizing Lipase-catalyzed Kinetic Resolution

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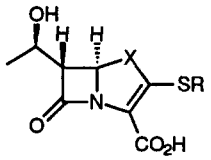
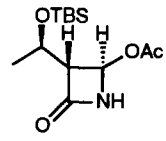
Abstract: Titanium enolate-mediated aldol reaction of *N*-phthaloyl-β–alanyl-1, 3-benzoxazinone **5** with acetaldehyde gave the (±)-*syn*-aldol (±)-**6** in a high yield with high diastereoselectivity. Lipase-catalyzed hydrolysis of the corresponding laurate (±)-**7b** furnished enantiomerically pure (2*S*, 3*R*)-*N*-(2-phthaloylaminomethyl-3-hydroxybutyryl)-1, 3-benzoxazinone **6** in 49% yield. Silylation of the hydroxy group of (2*S*, 3*R*)-**6** follwed by deprotection of the amino and carboxy groups gave the β-amino acid derivative **9** which was transformed into the acetoxyazetidinone **3**, a key intermediate of penems and carbapenems.

Penems **1** and carbapenems **2** have recently attracted keen interest as promising antibiotics due to their potent and broad antimicrobial activities as well as excellent metabolic stability.[1] Acetoxyazetidinone **3** with three contiguous stereogenic centers corresponding to the C-5, C-6 and C-8 carbons of **1** and **2** has been recognized as a key intermediate for synthesizing β-lactam antibiotics of this important class.[2] Synthesis of



1: X=S
2: X=CH_2, CH(Me)

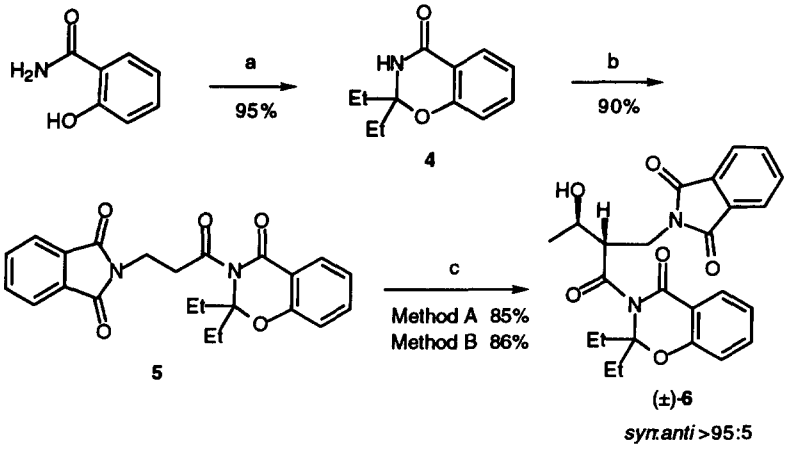


3

3 has been extensively studied and some efficient methods including industrially applicable asymmetric reactions have been developed.[3, 4] As an alternative approach, enzymatic synthesis of **3** is attractive. However, no satisfactory result has been achieved . For instance, a method based on the microbial reduction of the carbonyl group of ethyl 2-benzoylaminomethyl-3-oxobutanoate was mostly unfruitful due to the lack of selectivity and/or the need to invert the configuration of the stereogenic center bearing the hydroxy group.[5] Recent successful application of lipase to the synthesis of optically active compounds[6] has prompted us to investigate an alternative enzymatic synthesis of **3**. Our strategy is based on the elabolation of the required (2*S*, 3*R*)-2-aminomethyl-3-*tert*-butyldimethylsilyloxybutyric acid **9** by a *syn*-selective aldol reaction followed by lipase-catalyzed resolution of the resulting racemic aldol. Highly efficient *syn*-selective Reformatsky reactions have recently been achieved utilizing a novel 1, 3-benzoxazinone auxiliary.[1e] The racemic substrate (±)-**6** with the desired relative configuration might thus be prepared efficiently by the aldol reaction of *N*-phthaloyl-β-alanyl-1, 3-benzoxazinone **5** with acetaldehyde.

N-Phthaloyl-β-alanyl-1, 3-benzoxazinone **5** was readily prepared in 86% yield by condensation of salicylamide with 3-pentanone followed by acylation with *N*-phthaloyl-β-alanylchloride (Scheme 1). The aldol reaction of **5** with acetaldehyde was undertaken by transmetallation of the sodium enolate of **5** with

Scheme 1

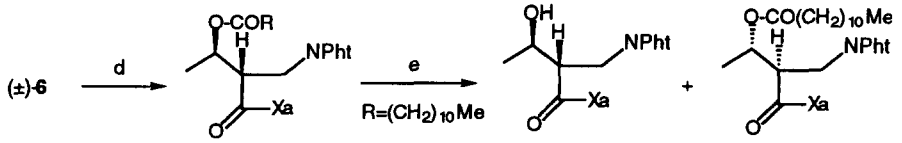


a: Et_2CO, *p*-TsOH (10 mol%), toluene, reflux, 17 h; b: $PhtN(CH_2)_2COCl$, *i*-Pr_2EtN, CuCl (cat.), toluene, 70°C, 5 h; c: i) $NaN(TMS)_2$, THF, -78°C, 1 h ii) $ClTi(O\text{-}Pr)_3$ -78°C, 1 h iii) CH_3CHO, -78°C-0°C, 2 h (Method A); i) $TiCl_4$, Et_3N, -78°C, 20 min. ii) CH_3CHO, -78°C-0°C, 2 h (Method B).

$ClTi(O\text{-}Pr)_3$ and subsequent reaction with acetaldehyde to give the desired *syn*-aldol (±)-**6** in 85% yield with high selectivity (*syn*:*anti* >95:5) (Method A).[7] The structure of (±)-**6** was unequivocally confirmed by X-ray crystallographic analysis.[8] The α-methylene proton of the carbonyl group of **5** complexed with $TiCl_4$ was acidic enough to be deprotonated by a weak base. Thus, as an alternative procedure, chlorotitanium enolate directly generated by treatment of **5** with $TiCl_4$ and Et_3N in CH_2Cl_2 at -78 °C [9] was allowed to react with acetaldehyde to afford (±)-**6** as well in 86% yield with excellent selectivity (*syn*:*anti* >95:5) (Method B).

Enzymatic resolution of the racemic aldol (±)-**6** was the next subject of our investigation (Scheme 2). Lipase QL (*Alcaligenes* sp.) was selected as the enzyme of choice because of it's outstanding stability and activity in organic media.[10] Since many lipases including Lipase QL show a preference for the *R*-configuration at the hydroxy bearing carbon,[11] lipase-catalyzed asymmetric hydrolysis of racemic esters (±)-**7a,b** derived from (±)-**6** was examined to afford the required (2*S*, 3*R*)-**6**. The racemic esters (±)-**7a,b** were synthesized from (±)-**6** by usual acylation and were subjected to react with Lipase QL in a phosphate buffer (0.1 M, pH

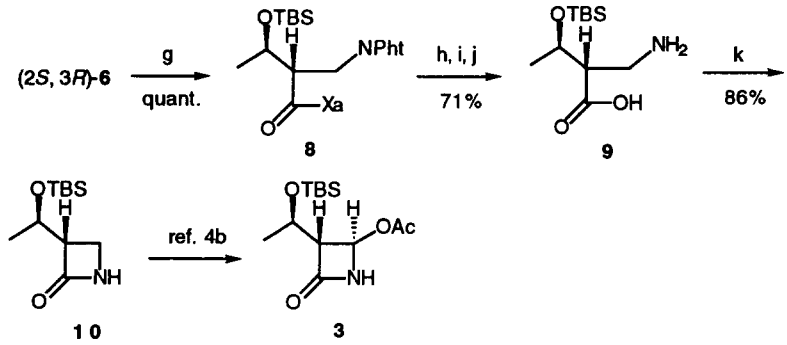
Scheme 2



d: RCOCl, Et_3N, DMAP, THF, 25°C, 3 h; e: Lipase QL, phosphate buffer (pH 7.5), DMF, 40°C, 22 h.

7.5) solution with 10% DMF at 40 °C for 22 h. Employing the laurate (±)-**7b** as the substrate, the desired enantiomerically pure aldol (2*S*, 3*R*)-**6** was obtained in 49% yield along with unreacted ester (2*R*, 3*S*)-**7b** (c.y. 50%, >99% e.e.).[12] Use of the acetate (±)-**7a** resulted in a dramatic decrease in the reaction rate and did not reach an acceptable level even after prolonged reaction periods (conversion <5% after 72 h at 40 °C). The aldol (2*S*, 3*R*)-**6** was transformed into **3** employing the reaction sequence illustrated in Scheme 3. After silylation of the hydroxy group of (2*S*, 3*R*)-**6**, removal of the 1, 3-benzoxazinone auxiliary and the amino and carboxy protective groups were sequentially conducted to yield the β-amino acid **9** in good yield (overall 71% in three steps). Cyclization of **9** to β-lactam **10** was carried out by Ohno's procedure in a high yield.[13] The physicochemical properties of **10** obtained by the present synthesis were in complete accordance with those reported in the literature.[14] Synthesis of **3** from **10** was achieved according to the reported procedure.[4b, 15]

Scheme 3



Xa: Auxiliary

g: TBS-Cl, imidazole, DMF, 25 °C, 24 h; h: BnOLi, THF, 0°C, 24 h; i: $NH_2NH_2 \cdot H_2O$, EtOH 25 °C, 17 h; j: H_2 (1 atm), Pd-C, MeOH, 25 °C, 5 h. k: $(2\text{-PyS})_2$, PPh_3, CH_3CN, 60 °C, 7 h

As described above, a new and facile synthesis of acetoxyazetidinone **3** was developed by combination of the highly diastereoselective aldol reaction and the efficient lipase-catalyzed kinetic resolution. Use of readily accessible materials under industrially applicable mild conditions allows an easy access to the acetoxy-azetidinone, a key intermediate of penems and carbapenems.

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12. (2*S*, 3*R*)-**6**: mp 94-96 °C. IR (KBr) ν_{max}: 3544, 1773, 1718, 1611 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88-1.01 (m, 6H), 1.34 (d, *J* = 6.3 Hz, 3H), 2.05-2.26 (m, 3H), 2.34-2.53 (m, 1H), 3.72-3.79 (m, 2H), 4.08-4.27 (m, 2H), 4.37-4.46 (m, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.98-7.06 (m, 1H), 7.45-7.54 (m, 1H), 7.68-7.84 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 17.2, 168.8, 163.9, 155.88 (4s), 136.1, 133.9 (2d), 132.2 (s), 128.6, 123.3, 122.0, 117.0 (4d), 116.9, 100.2 (2s), 67.1, 54.7 (2d), 35.88, 29.0, 28.4 (3t), 21.0, 8.03, 7.81 (3q). MS *m/z*: 451 (M^++1). $[\alpha]_D^{25}$ +7.22 (*c*, 1.11, MeOH). (2*R*, 3*S*)-**7**: oil. IR (KBr) ν_{max}: 1721, 1611, 1467 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (t, *J* = 6.6Hz, 3H), 0.94 (t, *J* = 7.3Hz, 3H), 0.81-0.98 (m, 3H), 1.25 (brs, 18H), 1.45 (d, *J* = 6.4Hz, 3H), 1.53-1.64 (m, 2H), 2.02-2.42 (m, 4H), 3.95-4.18 (m, 1H), 4.26-4.41 (m, 2H), 5.34-5.40 (m, 1H), 6.88 (d, *J* = 8.2Hz, 1H), 6.99 (dt, *J* = 1.0, 15.1Hz, 1H), 7.47 (dt, *J*=1.7, 7.4Hz, 1H), 7.64-7.73 (m, 2H), 7.76-7.83 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ: 178.6, 176.0, 172.8, 168.2, 163.9, 155.8 (6s), 136.0, 133.8, 133.8 (3d), 132.3 (s), 128.7, 123.2, 123.2, 122.0, 117.0 (5d), 100.2 (s), 69.9, 51.5 (2d), 36.2, 34.5, 33.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.8, 28.4, 24.9, 22.1 (13t), 18.3, 14.1, 8.0, 7.8 (4q). MS *m/z*: 633 (M^++1). $[\alpha]_D^{25}$ +3.57 (*c*, 1.23, MeOH). The enantiomeric purity of (2*S*, 3*R*)-**6** and (2*R*, 3*S*)-**7** was >99% e.e. which were confirmed by HPLC [Chiralcel OD (Daicel)].
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15. **3**: mp 106-107 °C. $[\alpha]_D^{25}$ +51.0 (*c*, 0.9, $CHCl_3$). [lit.[4b] mp 108.5 °C. $[\alpha]_D^{25}$ +51.2 (*c*, 1.0, $CHCl_3$)].

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