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A Facile Synthesis of the Key Intermediate for Penems, Carbapenems, and Related β-Lactam Antibiotics

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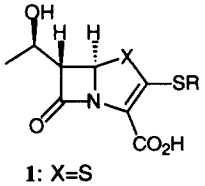
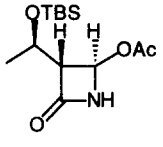
Abstract: Michael addition of the hydroxylamine **14** to the *N*-acryloyl-1, 3-benzoxazinone **13** followed by the titanium enolate-mediated aldol reaction with acetaldehyde gave *syn*-aldol **16** in a high yield with excellent diastereoselectivity. Silylation of **16** followed by treatment with BnOLi and acetylation gave benzyl ester **19** together with the recovered chiral auxiliary **12** both in high yields. Mild hydrogenolysis of **19** furnished the β-amino acid derivative **20** which was transformed into acetoxyazetidinone **3**, the key intermediate of penems **1** and carbapenems **2**.

The potent activity and broad antimicrobial spectra as well as metabolic stabilities of penems **1** and carbapenems **2** are mainly responsible for their current considerable interest.[1] Acetoxyazetidinone **3**, which is their common intermediate and is now supplied on an industrial scale,[2] dominates a considerable proportion of their cost of materials. Therefore, it is highly desirable to achieve an efficient synthesis of **3** for development of **1** and **2**.



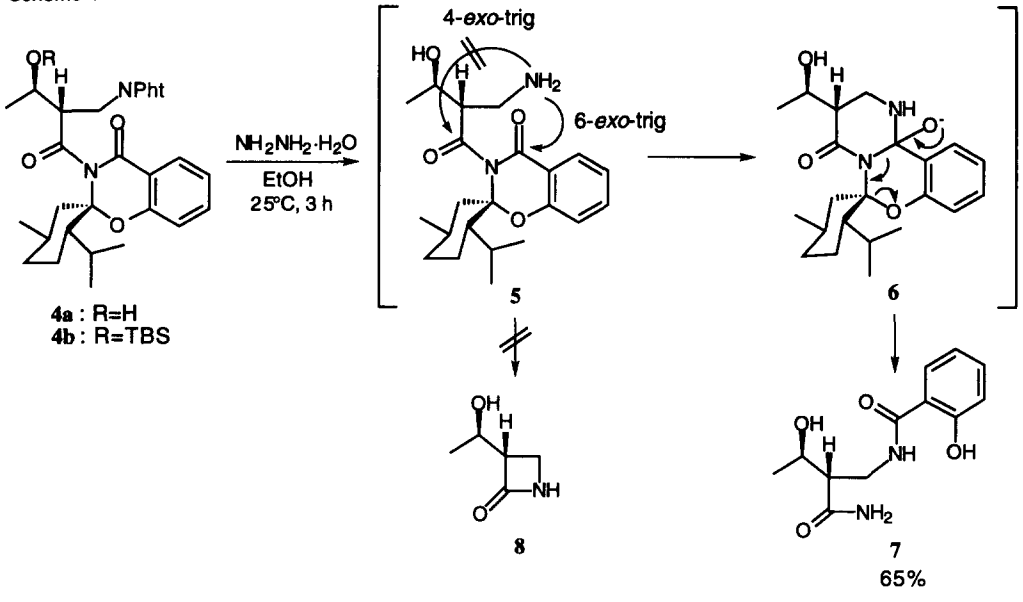
1: X=S
2: X=CH_2, $CHCH_3$



3

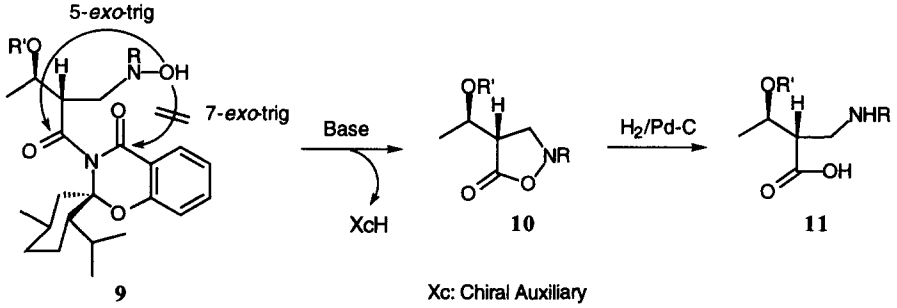
We have recently reported the highly stereocontrolled syntheses of **3** in which the key step is the diastereoselective aldol reaction of the β-alanyl-1, 3-benzoxazinone with acetaldehyde[3a] or its combination with enzymatic resolution.[3b] In these syntheses, removal of the auxiliary and the phthaloyl group (from **4b**[3a] in the former case) was conducted by sequential treatments of **4** with BnOLi and hydrazine followed by the hydrogenolysis of the resulting benzyl ester. Although the deprotected β-amino acid was obtained in a good yield by the three-step sequence, it seemed rather tedious for a large scale preparation and the recovery of the auxiliary turned out to be unsatisfactory (*ca.* 65%). In search for a more straightforward synthesis and a method to improve recovery of the auxiliary, we attempted direct formation of the β-lactam ring by sequential reaction initiated by the bond cleavage of the protected amino group (Scheme 1). However, treatment of **4a** with hydrazine exclusively gave the degradation product **7** derived from unfavorable intramolecular attack of the deprotected amino group of **5** to the carbonyl group of 1, 3-benzoxazinone auxiliary.[4] The reaction course may be accounted for by the Baldwin's rules for ring closure.[5] The ring formation *via* 6-*exo*-trigonal mode leading to **7** is preferred to that by 4-*exo*-trigonal one leading to the desired β-lactam **8**. A solution to this problem was envisaged by the use of the compound **9** as an intermediate which carrys an extra oxygen atom on the amino group. Governed by the Baldwin's rules, this may effect smooth removal of the auxiliary and formation of

Scheme 1



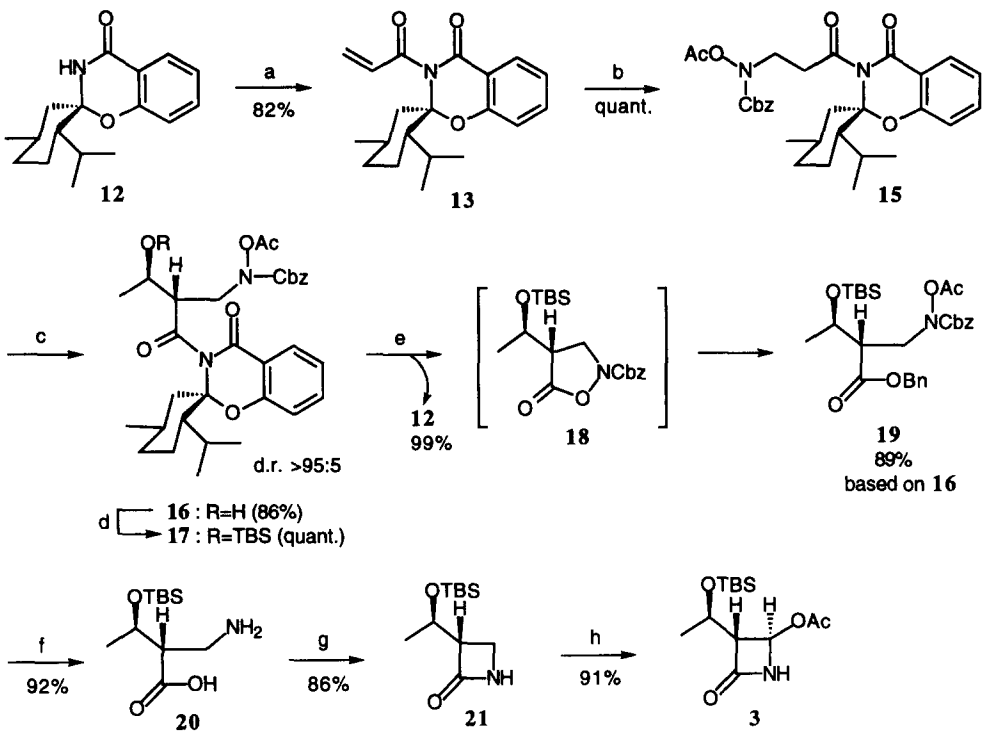
the five-membered 3-oxazolidinone derivative **10** (Scheme 2).[6] The compound **10** would be converted into the desired β-amino acid **11** by simple hydrogenolysis of the N-O bond. We report herein the successful synthesis of acetoxyazetidinone **3** based on this strategy (Scheme 3).

Scheme 2



The chiral 1, 3-benzoxazinone auxiliary **12**[7] was acylated with acryloyl chloride in the presence of *i*-Pr_2EtN and catalytic amount of CuCl to give the *N*-acryloyl-1, 3-benzoxazinone **13** in a high yield. The Michael addition of the hydroxylamine **14**[8] to **13** smoothly took place upon treatment with a catalytic amount of NaH (0.1 equiv.) in DMF to afford the fully protected 3-hydroxyaminopropionic acid derivative **15** in a quantitative yield.[9] The aldol reaction of **15** with acetaldehyde was conducted by employing a readily accessible chlorotitanium enolate. Treatment of **15** with $TiCl_4$ (1.0 equiv.) and Et_3N (1.0 equiv.) in CH_2Cl_2 at -78°C followed by addition of an excess amount of acetaldehyde (10 equiv.) at the same temperature furnished the desired *syn*-aldol **16** in 86% yield with an excellent diastereoselectivity (d.r. >95:5).[10] After silylation of

Scheme 3



a: acryloyl chloride, *i*-Pr2EtN, CuCl (cat.), 50°C, 3 h; b: CbzNHOAc **14**, NaH (0.1 eq.), DMF, 25°C, 2.5 h; c: i) $TiCl_4$, Et_3N, -78°C, 40 min. ii) CH_3CHO, -78°C-0°C, 2 h; d: TBS-Cl, imidazole, DMF, 25°C, 17 h; e: i) BnOLi (1 eq.), BnOH, THF, 0°C, 10 min. ii) Ac_2O, Et_3N, DMAP (cat.), THF, 25°C, 30 min. f: H_2 (1 atm), Pd-C, MeOH, 25°C, 3 h; g: $(2\text{-PyS})_2$, PPh_3, CH_3CN, 60°C, 7 h; h: $RuCl_3 \cdot H_2O$, O_2, CH_3CHO, AcONa, AcOH, AcOEt, 40°C, 3 h.

the hydroxy group of **16**, removal of the chiral auxiliary and the amino protective groups from **17** were cleanly achieved by the following simple procedure in good accordance of our expectation. Thus, addition of BnOLi (1.0 equiv.) to **17** in THF in the presence of excess BnOH at 0°C almost instantaneously effected the removal of the chiral auxiliary and esterification. Then, the crude mixture was treated with Ac_2O and Et_3N in the presence of DMAP (cat.) to give acetoxy benzyl ester **19**[11] together with the recovered chiral auxiliary **12** in 89% and 99% yield, respectively. Although the 3-oxazolidinone intermediate **18** was not isolated, intervention of **18** is unambiguous because of the extremely fast reaction rate of this procedure compared with that of alcoholysis of the β-alanine derivative **4b**.[12] Hydrogenolysis of **19** furnished β-amino acid **20** in a high yield. Cyclization of **20** to β-lactam **21** was conducted by the use of Mukaiyama's reagent in a high yield.[13] Synthesis of **3** from **21** was accomplished according to Murahashi's procedure.[2c] The physicochemical properties of **3** obtained by the present synthesis were in complete agreement with those reported in the literature.[14]

As described above, a facile and economical synthesis of **3** was worked out, in which almost complete stereocontrol in the construction of three contiguous stereogenic centers was attained by the use of the chiral 1, 3-benzoxazinone auxiliary **12** readily accessible from *l*-menthone. The *in situ* formation of the 3-oxazolidinone

derivative **18** governed by the Baldwin's rules for ring closure, permitted instantaneous and almost quantitative recovery of the chiral auxiliary **12**. The high overall yield and use of readily accessible materials under mild conditions allows an easy access to acetoxyazetidinone **3**, the key intermediate of penems, carbapenems, and related β-lactam antibiotics.

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10. **16**: ^{1}H-NMR ($CDCl_3$) δ: 7.86-7.90 (m, 1H), 7.48-7.57 (m, 1H), 7.30-7.43 (m, 5H), 7.09-7.13 (m, 1H), 6.91-6.93 (m, 1H), 5.14-5.27 (m, 2H), 4.30-4.40 (m, 1H), 4.21-4.27 (m, 1H), 3.98-4.09 (m, 1H), 3.81-3.88 (m, 1H), 2.88 (d, *J*=2.4 Hz, 1H), 2.70-2.77 (m, 1H), 1.50-2.50 (m, 7H), 2.16 (s, 3H), 1.29 (d, *J*=6.5 Hz, 3H), 0.74-1.20 (m, 7H). $[\alpha]_D^{25}$ -21.7 ° (*c*, 0.94, MeOH).
11. **19**: ^{1}H-NMR ($CDCl_3$) δ: 7.20-7.50 (m, 10H), 5.14 (s, 2H), 5.09 (d, *J*=1.7 Hz, 2H), 4.17-5.86 (m, 3H), 2.72-2,82 (m, 1H), 2.01 (s, 3H), 1.14 (d, *J*=6.2 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 6H). $[\alpha]_D^{25}$ -20.1 ° (*c*, 0.67, MeOH).
12. Removal of the auxiliary from **4b** by alcoholysis required 24 h under the same reaction conditions.[3]
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14. **3**: mp 107-108 °C. $[\alpha]_D^{25}$ +51.1 ° (*c*, 1.1, $CHCl_3$). [lit.[3c] mp 108.5 °C. $[\alpha]_D^{25}$ +51.2 ° (*c*, 1.0, $CHCl_3$)].

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