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A HIGHLY STEREOSELECTIVE SYNTHESIS OF A KEY INTERMEDIATE OF 1β-METHYLCARBAPENEMS EMPLOYING THE REFORMATSKY REACTION OF 3-(2-BROMOPROPIONYL)-2-OXAZOLIDONE DERIVATIVES

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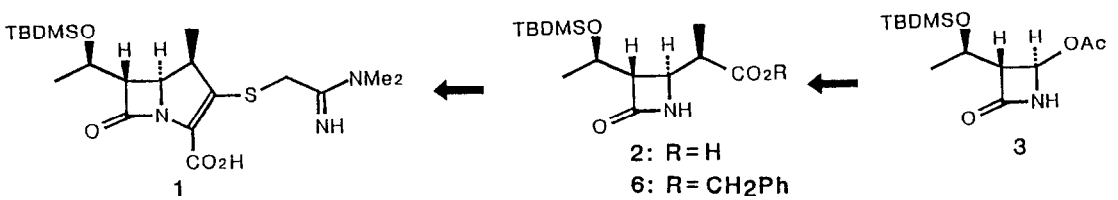
Abstract: Reaction of sterically crowded achiral 3-(2-bromopropionyl)-2-oxazolidone derivatives with (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone in the presence of zinc dust in refluxing tetrahydrofuran was found to give the 1β-methyl substituted β-lactams as major products (at most, β:α=95:5). The major products were readily converted into the key intermediate of 1β-methylcarbapenems.

Since the 1β-methylcarbapenem (**1**) was found as a synthetic carbapenem antibiotic showing an enhanced chemical and metabolic stability in addition to excellent antibacterial activity and broad spectrum,[1] numerous synthetic efforts [2-8] have been devoted to (3S,4S)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone (**2**) employed as a key synthetic intermediate in the original synthesis of **1**.[1] Among a number of the synthetic methods of **2** so far reported,[2-9] stereoselective C_4-alkylation of (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone (**3**) with various types of enolates derived from propionic acid derivatives[3,5,6,8] is currently recognized as one of the most promising methods since several efficient synthetic routes to **3** or its equivalents have recently been explored.[10]

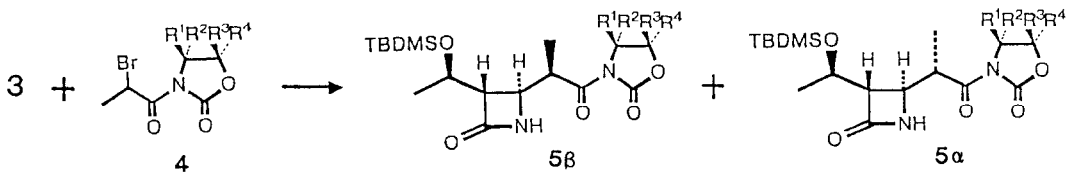
Stereoselective introduction of the 1β-methyl substituent into **3** has hitherto been achieved using tin enolate of 3-propionyl-2-thiazolidinethione[5a,b] or 3-propionyl-2-oxazolidone derivative,[5b] boron enolate of 3-propionyl-2-oxazolidone[6a] or 3-propionyl-2-benzoxazolidone derivative,[6b] zirconium enolate of the thiol ester of propionic acid,[8] and so on. However, these methods seem to accompany much difficulties in a large-scale preparation of **2** because more than stoichiometric amounts of the precious chiral sources and/or the expensive or toxic reagents are required.

With an aim to overcome these problems, we paid attention to the Reformatsky reaction of 2-bromopropionic acid derivatives with **3** in the presence of zinc dust. While all the preliminary attempts performed with 2-bromopropionic acid esters turned out to be fruitless, we found that, as shown in **Table I** run 1, the zinc enolate prepared from 3-(2-bromopropionyl)-2-oxazolidone (**4a**)[11] and zinc dust could efficiently react with **3**[10d] at 0 °C in tetrahydro-



furan (THF) to give the β-lactam (**5a**) as a mixture of the two diastereomers (**5aβ** and **5aα**, **5aβ**:**5aα**=45:55) in 75 % yield. However, this disappointingly low diastereoselectivity could not be improved by changing reaction solvent and temperature (runs, 1-3) and by employing various Lewis acids such as diethylchloroalane, tributylboron, tin(II) chloride and titanium-(IV) tetraisopropoxide. Accordingly, effects of substituents of the 2-oxazolidone ring on the diastereoselectivity were next studied.

Although the use of 3-(2-bromopropionyl)-2-benzoxazolidone gave no improved results in light of the yield and diastereoselectivity, it was found that the reaction performed with 3-(2-bromopropionyl)-4,4-dimethyl-2-oxazolidone (**4b**) at 0 °C could produce the 1β-methyl substituted β-lactam (**5bβ**) as a major product (run 4) and that the diastereoselectivity highly depends upon the reaction temperature. Thus, contrary to our expectation, the increased β-diastereoselectivity was obtained at higher reaction temperatures (runs 4-6) and the formation ratio of **5bβ** to **5bα** reached at 79:21 in refluxing THF (run 6). While the reaction of **3** with



a: R^1=R^2=R^3=R^4=H, **b**: R^1=R^2=Me, R^3=R^4=H, **c**: R^1=Me_2CH, R^2=R^3=R^4=H,
d: R^1=$PhCH_2$, R^2=R^3=R^4=H, **e**: R^2=Ph, R^1=R^3=R^4=H, **f**: R^1=R^2=C_4H_9, R^3=R^4=-$(CH_2)_5$-

Table I. Reformatsky Reaction of Various 3-(2-Bromopropionyl)-2-oxazolidone Derivatives (**3**) with (3R,4R)-4-Acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone (**4**)[1)]

Run	**4**	Solv.	Temp. (°C)	Time (min)	Product (**5**)[2)] Yield[3)] (%)	Ratio **5β**:**5α**[4)]
1	**a**	THF	0	60	75	45:55
2	**a**	THF	25	10	97	45:55
3	**a**	THF	67[5)]	1	82	48:52
4	**b**	THF	0	30	90	63:37
5	**b**	THF	25	5	95	73:27
6	**b**	THF	67[5)]	1	94	79:21
7	**b**	DMF	25	10	81	69:31
8	**b**	DME	25	10	88	62:38
9	**b**	DME	70	1	96	81:19
10	**b**	Dioxane	25	10	99	62:38
11	**b**	Dioxane	70	1	99	78:22
12	**c**	THF	0	30	99	91: 9[6)]
13	**c**	THF	25	10	99	87:13
14	**c**	THF	67[5)]	1	99	81:19
15	**d**	THF	0	30	91	90:10[6)]
16	**e**	THF	0	30	99	35:65
17	**e**	THF	67[5)]	1	90	56:44
18	**f**	THF	25	10	99	90:10[7)]
19	**f**	THF	67[5)]	2	99	95: 5[7)]

1) The reactions were carried out by a similar procedure to that described for run 19 (see ref 12). 2) The two diastereomers (**5β** and **5α**) separated by column chromatography (SiO_2) showed satisfactory spectral (IR, ^1H NMR, and MS) and/or analytical data (for **5f**, see footnote 7). Successful preparations of the benzyl ester (**6**) from **5β** obviously supported the assigned structures (see the text). 3) Combined yields of **5β** and **5α**. 4) Determined by measuring ^1H NMR spectra of the mixtures of **5β** and **5α** except for runs 12 and 15. 5) The reaction was performed in refluxing THF. 6) Determined by the weights of **5β** and **5α** separated by column chromatography (SiO_2). 7) Separation of the minor 1α-methyl substituted β-lactam (**5fα**) in a pure state was not attempted.

4b was further examined in various solvents, more improved β-diastereoselectivity could not be realized (runs 7-11).

Since it had been uncovered that the tin enolate of chiral 2-propionyl-2-thiazolidinethione derivatives[5a] and the boron enolate of chiral 2-oxazolidone derivatives[6a] could effect highly stereoselective formation of the 1β-methyl substituent, the Reformatsky reaction of chiral 3-(2-bromopropionyl)-2-oxazolidone derivatives (**4c-e**)[11,13] with **3** was similarly examined (runs 12-17). The reaction of **4c,d**[12] having the (S)-4-isopropyl or benzyl group with **3** slightly improved the diastereomeric ratios at 0 °C and 25 °C (runs 12,13, and 15), but almost the same diastereomeric ratio as that observed for **4b** was obtained for **4c** in refluxing THF (run 14). Being different from **4c,d**, **4e** carrying the (R)-4-phenyl group gave a low α-diastereoselectivity at 0 °C and the proportion of **5eβ** increased up to 56 % in refluxing THF (runs 16 and 17).

The results accumulated using **4a-e** obviously suggest that increase of steric bulkiness at the C_4-position of **4** may improve the β-diastereoselectivity of the Reformatsky reaction in refluxing THF. Based on this assumption, sterically crowded 3-(2-bromopropionyl)-4,4-dibutyl-5,5-pentamethylene-2-oxazolidone (**4f**)[14] was allowed to react with **3** in the presence of zinc dust. As expected, the desired 1β-methyl substituted β-lactam (**5fβ**) could be produced in a highly stereoselective manner (**5fβ**:**5fα**=95:5) by the reaction performed in refluxing THF (run 19).[12] Similarly to the cases for **4b**, the diastereoselectivity lowered at 25 °C (run 18). Single recrystallization of the mixture of **5fβ** and **5fα** (95:5) from methanol gave rise to an 85 % yield of pure **5fβ**.[12]

Six-membered chelating transition states have previously been proposed to explain the high β-diastereoselectivity achieved using the tin enolates of chiral 3-propionyl-2-thiazolidinethione derivatives[5a] and the boron enolate of a chiral 3-propionyl-2-oxazolidone derivative.[6a] However, while a similar chelating transition state may well account for the results collected with chiral **4c-e** at low temperatures (runs 12,13,15, and 16), it will not rationalize the β-diastereoselectivity in the reaction of achiral **4b,f** which dramatically increased at high temperatures (runs 4-6, 18 and 19). The results which similarly violate simple chelating transition states have been recently reported in the reactions of **3** with the tin enolates of achiral 3-propionyl-2-thiazolidinethione and 2-oxazolidone derivatives[5b] and the boron enolate of a 2-benzoxazolidone derivative.[6b]

At the last stage of our synthetic studies, preparation of **2** from **5β** was attempted. While treatment of **5bβ** with sodium hydroxide in aq methanol accompanied hydrolysis of the 2-oxazolidone moiety to yield an amide derivative in addition to **2**, **5bβ** could be readily converted to the benzyl ester (**6**), mp 69-70 °C, $[\alpha]_D^{20}$ -13.8° (c 0.98, $CHCl_3$), in 98 % yield by treating with lithium benzylate in THF at 0 °C for 1 h. The benzyl ester (**6**) was similarly prepared from **5fβ** in 97 % yield, but fairly low yields of **6** were only obtained for **5a,c-eβ**: 54 % (from **5aβ**); 67 % (from **5cβ**); 38 % (from **5dβ**); 27 % (from **5eβ**). Catalytic hydrogenation of **6** on palladium on carbon in ethyl acetate produced **2** in 98 % yield, mp 147 °C, $[\alpha]_D^{20}$ -32.4° (c 0.17, MeOH) [lit.,[2] 143.5-144.0 °C, $[\alpha]_D^{25}$ -36.9° (c 0.469, MeOH); lit.,[9] mp 146-147 °C, $[\alpha]_D^{20}$ -34.6° (c 0.26, MeOH)]. From most sterically crowded **5fβ**, it was also possible to directly obtain **2** in 91 % yield by treating with sodium hydroxide in aq t-butanol at room temperature for 3 days.

As mentioned above, we have succeeded in exploring a highly stereoselective synthesis of

2 by employing the Reformatsky reaction of **3** with sterically crowded achiral **4b,f** in the presence of zinc dust. This process is anticipated to be one of the most practical methods because of high β-diastereoselectivity of the key step, high overall yield, mild reaction conditions, and use of inexpensive reagents.

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11) The 3-(2-bromopropionyl)-2-oxazolidone derivatives (**4**) were prepared by sequential metalation of the 2-oxazolidone derivatives with butyllithium or sodium hydride in ether or THF and acylation with 2-bromopropionyl bromide. When the chiral 2-oxazolidone derivatives were used, **4c-e** were obtained as mixtures of the two diastereomers which could be readily separated by column chromatography (SiO_2).
12) A typical procedure of the Reformatsky reaction (**Table I** run 19) is as follows. A solution of **4f** (417 mg, 1.0 mmol) in anhyd THF (1.9 ml) was added to a stirred mixture of **3** (135 mg, 0.47 mmol) and zinc dust (113 mg, 1.7 mmol) in THF (1.9 ml) under reflux. After stirring under reflux was continued for 2 min, the reaction mixture was cooled and diluted with aq phosphate buffer (2.0 ml) and ethyl acetate. The organic layer was separated, washed with satd aq NaCl, dried over anhyd $MgSO_4$, and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2: Hexane-CH_2Cl_2 1:1, then Hexane-CH_2Cl_2-EtOAc 7:1:3) to afford a mixture of **5fβ** and **5fα** (95:5 by ^1H NMR spectrum) as a solid (257 mg, 99 %). Recrystallization from methanol (1.5 ml) gave pure **5fβ** (221 mg, 85 %) as colorless crystals, mp 158-159 °C, $[\alpha]_D^{20}$ -5.0° (c 1.29, $CHCl_3$).
13) The two diastereomers of **4c-e** gave almost the same results in the Reformatsky reaction. Accordingly, they can be directly used without separation for practical synthesis of **5c-e.**
14) 4,4-Dibutyl-5,5-pentamethylene-2-oxazolidone was obtained by treating the corresponding β-aminoalcohol with carbonyl diimidazole (65 °C in THF, 4 h). Preparation of the β-aminoalcohol could be achieved from cyclohexanone according to the reported method. R. Amouroux and G. P. Axiotis, Synthesis, **1981**, 270.

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