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Highly Stereoselective and Practical Synthesis of a Key Intermediate for 1-β-Methylcarbapenems

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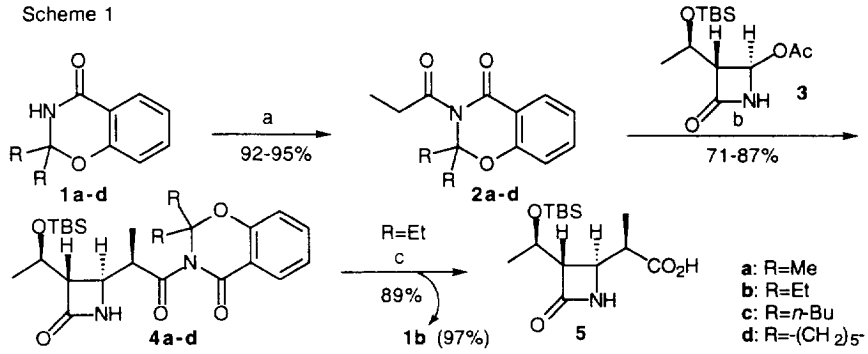
Abstract: The sodium enolate generated from *N*-propionyl-2, 2-diethyl-1, 3-benzoxazinone **2b** was allowed to react with acetoxyazetidinone **3** to give an adduct **4b** in 87% yield with virtually complete β-selectivity which was transformed by simple hydrolysis into the optically pure azetidinone-4-iso-propionic acid derivative **5**, a key intermediate of 1-β-methylcarbapenems.

The antibiotic 1-β-methylcarbapenems have been intensively studied because of their excellent chemical and metabolic stability as well as the broad and potent antimicrobial activities.[1] The pioneering researches by Merck Sharp & Dohme group have established an azetidinone-4-isopropionic acid derivative **5** as a key intermediate for the synthesis of antibiotics of this important class.[1] Since then, have been developed a number of stereoselective syntheses of **5**[2] which involve those based on aldol-type reactions of propionate enolates bearing various types of achiral or chiral auxiliaries with acetoxyazetidinone **3**.[3] Both high yields and high stereoselectivities have been attained in these syntheses, however, they have either one of the following drawbacks which are not suitable for large scale preparation: requirement of expensive and toxic reagent such as $Sn(OTf)_2$ or Et_2BOTf; a tedious preparation procedure of the auxiliary. A significant improvement was made by the use of the Reformatsky reaction of 2-bromopropionic acid derivatives bearing a 2-oxazolidone[3d] or 1, 3-benzoxazinone[3f] auxiliary with **3**. Although the high yields and the high β-selectivities were achieved in these reactions, we considered that the β-selectivity should be further improved for an industrial process. We have recently developed a highly *syn*-selective aldol reaction of a sodium enolate of a propionic acid derivative with aldehydes by the use of a novel chiral 1, 3-benzoxazinone auxiliary.[4] With this information kept in mind, we had envisioned a possibility that the reaction of the sodium enolate of *N*-propionyl-1, 3-benzoxazinones **2** with **3** at lower temperature might further improve the β-selectivity. Herein we report a successful result in which highly stereoselective and practical synthesis of **5** was worked out utilizing aldol-type reaction of **2b** with **3** mediated by the less toxic and inexpensive sodium enolate.

The *N*-propionyl derivatives **2a-d** with various C-2 substituents were readily prepared in high yields by acylation of 1, 3-benzoxazinones **1a-d**[3f] with propionyl chloride in toluene using a weak base (Et_3N) (Scheme 1). Generation of the sodium enolate of **2a-d** (2 eq.) was conducted by the use of $NaN(TMS)_2$ at -60°C for 1 h. Then, addition of **3** (1 eq.) to the solution of the enolate at the same temperature effected almost spontaneously the condensation to give the desired products **4a-d** in from 70% to 87% yields with virtually complete β-selectivities [β:α=99:1 to ≥99:1 (HPLC)] (Table 1).[5] To the best of our knowledge, the β-selectivities achieved here are the highest one so far obtained in this type of reaction.[2] Among the compounds **4a-d**, the diethyl derivative **4b** was the most preferable one as the key intermediate because of the high yield and ease in crystallization (Table 1, Entry 2). It was suggested that a soft base such as tin or borane enolate reacted successfully with the acyl imine (soft acid) genarated *in situ* from **3**.[3e] Thus, the successful condensation of the present synthesis might be due to the unprecedently soft acidity of the sodium enolate of **2**.

Scheme 1

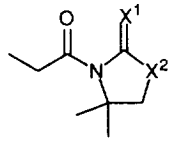


a: $EtCOCl$, Et_3N, 60°C, 3 h; b: i) $NaN(TMS)_2$, THF, -60°C, 1 h ii) **3**, -60°C,10 min.; c: H_2O_2, $LiOH{\cdot}7H_2O$, THF, H_2O, 5°C, 10 min.

Table 1

4	R	β:α[a]	Yield(%)[b]	mp(°C)	$[\alpha]_D^{25}$ (*c*, MeOH)
a	Me	99:1	70	133-134	+39.0 (1.0)
b	Et	≥99:1[c]	87	181-183	+47.7 (1.0)
c	*n*-Bu	≥99:1[c]	85	99-100	+40.5 (1.0)
d	$-(CH_2)_5-$	99:1	69	155.5-156.5	+39.2 (1.0)

[a]Determined by HPLC. [b]Isolated yields. [c]No α-isomer was detected by HPLC.



6a: X^1=X^2=O
6b: X^1=S, X^2=O
6c: X^1=X^2=S

It should be noted that propionyl derivatives of other known auxiliaries **6a-c**[3a-e] did not yield any coupling products under the same reaction conditions. This might be attributed to these sodium enolates generated from **6a-d** being too hard to react with **3**.

A facile removal of the auxiliary from **4b** was next conducted by the treatment with LiOH and H_2O_2 in aqueous THF[6] to give the carboxylic acid **5** {mp 146-147°C, $[\alpha]_D^{25}$ -33.5° (*c*, 1.1, MeOH)}in 89% yield combined with the recovered auxiliary **1b** in 97% yield. The physicochemical properties of **5** obtained by the present synthesis were in complete agreement with those reported in the literature.[3d]

As descrived above, an efficient and practical synthesis of 1-β-methylcarbapenems key intermediate **5** was worked out. The simple operation and high overall yield of the present synthesis would provide an easy access to a variety of highly potent 1-β-methylcarbapenems of ongoing pharmaceutical interests.

References and Notes

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5. A typical procedure, synthesis of **4b**: Into a solution of **2b** (5.23 g, 20 mmol) in THF (30 ml) was added $NaN(TMS)_2$ (1M in THF)(22 ml, 22 mmol) at -60°C. After being stirred at -60°C for 1 h, **3** (2.87 g, 10 mmol) in THF (15 ml) was added and the mixture was stirred for 10 min. Usual work-up and purification by silica-gel column chromatography (*n*-hexane:AcOEt=4:1) gave **4b** (4.27 g, 87%) [β:α=≥99:1 (HPLC)] in colorless crystals. Direct crystallization of the crude concentrated extracts from a mixture of MeOH and H_2O (5:1, 30 ml) gave 4.04 g (82.3%) of **4b** [β:α=≥99:1 (HPLC)].
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