Communications

2-Substituted 2,3-Dihydro-4*H*-1,3-benzoxazin-4-ones: A Novel Auxiliary for Stereoselective Synthesis of 1-β-Methylcarbapenems

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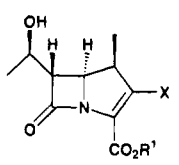
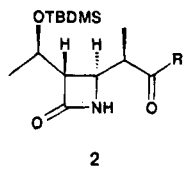
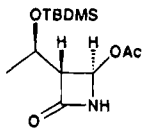
The antibiotic 1-β-methylcarbapenems **1a** have been the subject of much investigation[1] because of their broad spectrum antibacterial activity and enhanced chemical and metabolic stability.[2] A highly efficient synthesis has been needed to produce **1a** in large quantities for clinical trials. One of the most successful constructions of 1-β-methylcarbapenem key intermediates **2** employs the stereoselective aldol-type reactions of acetoxyazetidinone **3** with enolates derived from carboximide auxiliaries. Since the structure of the auxiliary determines the stereochemistry of the C-1 methyl group, various auxiliaries have been devised for these aldol reactions, such as 1, 3-thiazolidine-2-thione (**4a**),[3] 2-oxazolidone (**4b**),[4] and 1,3-oxazolidine-2-thione (**4c**)[5] . The stereoselective synthesis of **2** via the Reformatsky reaction using 2-oxazolidone has recently been reported.[6] These auxiliaries each possess at least one of the following drawbacks: difficult accessibility, necessity of refunctionalization before the subsequent ring construction, and requirement of expensive reagents, such as $Sn(OTf)_2$. Therefore, a more efficient auxiliary is still in demand.



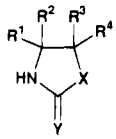


2

1a: X= SR^2, R^1=H
1b: X= OP(O)$(OPh)_2$, R^1= $CH_2CH=CH_2$



3



4a: X, Y=S
4b: X, Y=O
4c: X=O; Y=S

In connection with our studies of a salicylic acid-derived synthetic auxiliary,[7] we became interested in the use of 2-substituted 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones **6**, available in a single step from salicylamide, as an auxiliary for the synthesis of 1-β-methylcarbapenems. The route envisioned for the construction of the 1-β-methylcarbapenem skeleton is based on the auxiliary-controlled Reformatsky reaction of the acetoxyazetidinone **3**, followed by Dieckmann-type cyclization[5b,8] (Scheme 1). The benzamide group and the substituents at C-2 of the dihydrobenzoxazone **6** were expected to lead to a rigid transition state which might result in the stereoselective Reformatsky reaction. In addition, the auxiliary dihydrobenzoxazone **6** was expected to function as a leaving group in the Dieckmann-type cyclization. In the present paper, we describe the use of auxiliary dihydrobenzoxazone **6a** in an efficient synthesis of 1-β-methylcarbapenem **1b**, a key precursor of **1a**.[2]

Table 1. Reformatsky Reaction of 3 with 7

8	R^1	yield[a] (%)	β:α[c]	mp (°C)
a	$-(CH_2)_5-$	95(75[b])	92:8	149–151[d]
b	$-(CH_2)_4-$	77(60[b])	85:15	oil
c	Me	94	85:15	133–134[d]
d	Bu	87	98:2	oil
e	Bzl	76	99.6:0.4	oil

[a] Isolated yield. [b] Yield of the pure β-isomer. [c] Determined by HPLC. [d] Melting point of the pure β-isomer.

The auxiliary, dihydrobenzoxazone **6a,** was prepared by the acid catalyzed condensation of salicylamide **5** with cyclohexanone in toluene in 92% yield.[9] Acylation of **6a** with 2-bromopropionyl bromide in the presence of pyridine in toluene gave the carboximide **7a** in 87% yield. The Reformatsky reaction of the acetoxyazetidinone **3** with 1.5 equiv of **7a** and 3 equiv of zinc dust was conducted in refluxing tetrahydrofuran. After silica gel column chromatography of the crude product, the pure diastereomeric mixture of the azetidinone **8a** was obtained in 96% yield (β:α = 92:8, HPLC). When the crude product was directly recrystallized from aqueous ethanol, the essentially pure β-isomer **8a**β was obtained in 75% yield, based on **3.** The structure of **8a**β was confirmed by means of X-ray crystallography.[10]

In order to improve the selectivity obtained with **7a**, the carboximides **7** bearing various substituents at C-2 were prepared and subjected to the Reformatsky reaction in a similar manner (Table 1). Although higher diastereoselectivities were observed for some of the azetidinones (**8d,e**), we preferred the cyclohexyl derivative **8a**β as the key intermediate because of its higher yield and easy crystallization.

The cyclohexyl derivative **8a**β was converted into the allyl ester **9** in 95% yield by treatment with allyl

(1) For example, see: (a) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519. (b) Ubukata, K.; Hikita, M.; Yoshida, M.; Nishiki, K.; Furukawa, Y.; Tashiro, K.; Konno, M.; Mitsubashi, S. *Antimicrob. Agents Chemother.* **1990**, *34*, 994.

(2) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

(3) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673.

(4) Fuentes, L. M.; Shinkai, I.; Saltzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675.

(5) (a) Deziel, R.; Favreau, D. *Tetrahedron Lett.* **1986**, *27*, 5687. (b) **1989**, *30*, 1345.

(6) (a) Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1987**, *28*, 6625. (b) Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, *47*, 2801.

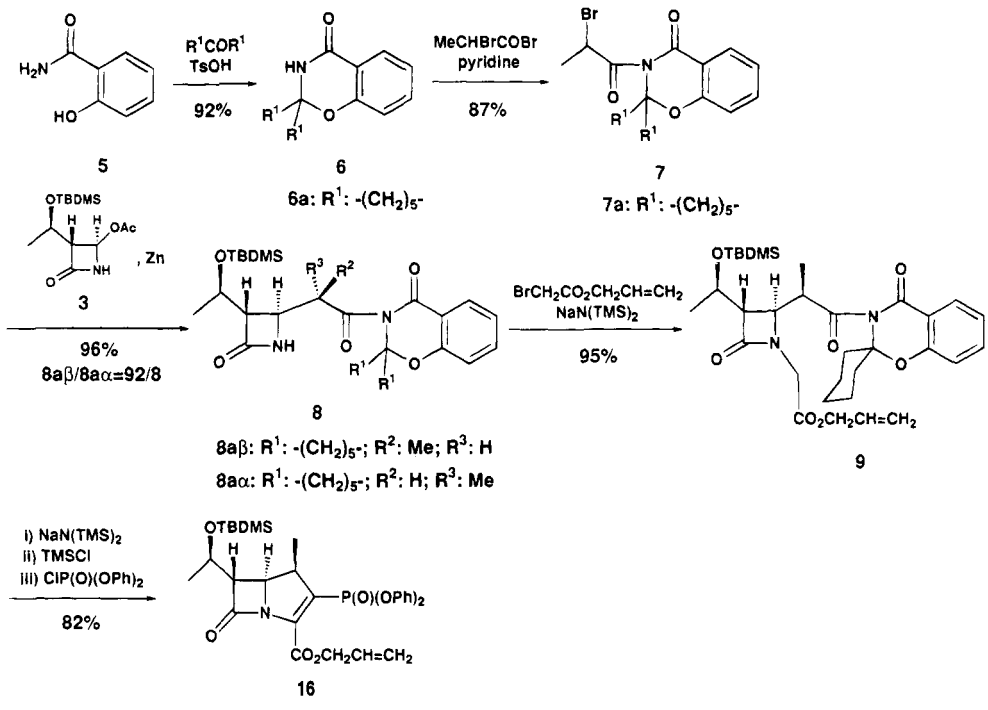
(7) Takahashi, M.; Ogiku, T.; Okamura, K.; Da-te, T.; Ohmizu, H.; Kondo, K. ; Iwasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1473 and references cited therein.

(8) (a) Shibuya, M.; Kuretani, M.; Kubota, S. *Tetrahedron* **1982**, *38*, 2659. (b) Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883. (c) Sowin, T. J.; Meyers, A. I. *J. Org. Chem.* **1988**, *53*, 4156. (d) Sunagawa, M.; Sasaki, A.; Matsumura, H.; Goda, K.; Tamoto, K. *Chem. Pharm. Bull.* **1994**, *42*, 1381.

(9) See, for example: Horrom, B. W.; Zaugg, H. E. *J. Am. Chem. Soc.* **1950**, *72*, 721.

0022-3263/95/1960-1096$09.00/0

Scheme 1



bromoacetate and sodium bis(trimethylsilylamide) in tetrahydrofuran at −50 to −45 °C. The Dieckmann-type cyclization of **9** was effected by treatment with 2.5 equiv of sodium bis(trimethylsilylamide) in tetrahydrofuran at −35 to −25 °C. After addition of 1.3 equiv of trimethylsilyl chloride,[11] the reaction mixture was treated with diphenyl phosphorochloridate at 0°C to afford the desired vinyl phosphate **1b**[12] in 82% yield. The auxiliary **6a** was recovered from the reaction mixture by direct crystallization, in 85% yield. The vinyl phosphate **1b** thus obtained can be converted into the various thiovinyl derivatives **1a** by standard procedures.[13]

Thus, the dihydrobenzoxazone serves as an effective auxiliary for the stereoselective Reformatsky reaction of the acetoxyazetidinone. We have also found that the dihydrobenzoxazone serves as a good leaving group in the Dieckmann-type cyclization, to afford the 1-β-methylcarbapenem skeleton. The application of the present novel auxiliary to other auxiliary-induced asymmetric syntheses of biologically active compounds is currently under investigation.

Acknowledgment. We express our thanks to Drs. T. Tosa and K. Matsumoto of this company for their encouragement and interest. The authors are indebted to Mr. M. Hiramatsu of this company for the X-ray analysis.

Supplementary Material Available: General experimental procedures, characterization data and copies of ^{1}H-NMR spectra of new compounds (29 pages).

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(10) The author has deposited atomic coordinates for **8aβ** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(11) When the reaction was conducted without added trimethylsilyl chloride, the yield of **1b** markedly decreased. This is probably due to side reactions associated with phosphorylation of the dihydrobenzoxazone anion formed. Trimethylsilylation of the anion prevents this phosphorylation. For a Dieckmann-type cyclization with alkyl halide used as a scavenger, see ref 8d.

(12) This and all other new compounds have been fully characterized by analytical and spectral data.

(13) See, for example: (a) reference 2 (b) Hanessian, S.; Desilets, D.; Bennani, Y. L. *J. Org. Chem.* **1990**, *55*, 3098 (c) Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371.