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A NOVEL SYNTHESIS OF THE 1β-METHYLCARBAPENEM KEY INTERMEDIATE EMPLOYING THE [2+2]-CYCLOADDITION REACTION OF CHLOROSULFONYL ISOCYANATE WITH A 4*H*-1,3-DIOXIN DERIVATIVE

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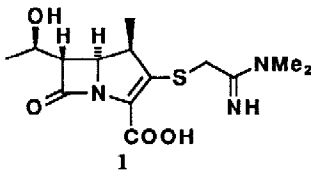
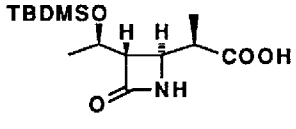
Abstract: A highly stereoselective synthetic route to the title compound was explored by featuring the [2+2]-cycloaddition reaction of chlorosulfonyl isocyanate with the 4*H*-1,3-dioxin derivative readily obtainable from methyl (*R*)-3-hydroxybutyrate, the Baeyer-Villiger reaction resulting in novel cleavage of the acetal moiety, and the Reformatsky reaction with sterically crowded 3-(2-bromopropionyl)-2-oxazolidone derivatives.

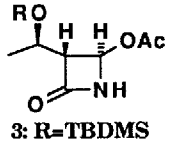
Since the 1β-methylcarbapenem (**1**) was found as a synthetic carbapenem antibiotic showing enhanced chemical and metabolic stability as well as excellent antibacterial activity and broad spectrum,[1] a number of synthetic efforts have been devoted to (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (**2**) employed as a key synthetic intermediate in the original synthesis of **1**.[2] Recently, we have succeeded in developing a highly stereoselective synthetic route to **2** by employing the Reformatsky reaction of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**3**) with sterically crowded achiral 3-(2-bromopropionyl)-2-oxazolidone derivatives.[3] This novel process is anticipated to be one of the most practical methods for preparing **2** because of its high β-selectivity, high overall yield, mild reaction conditions, and uses of inexpensive reagents such as zinc dust. Aiming to further improve efficiency of the Reformatsky route to **2**,[3] another synthetic scheme was sought which may produce **3** or its equivalents more effectively than those reported.[4]



1



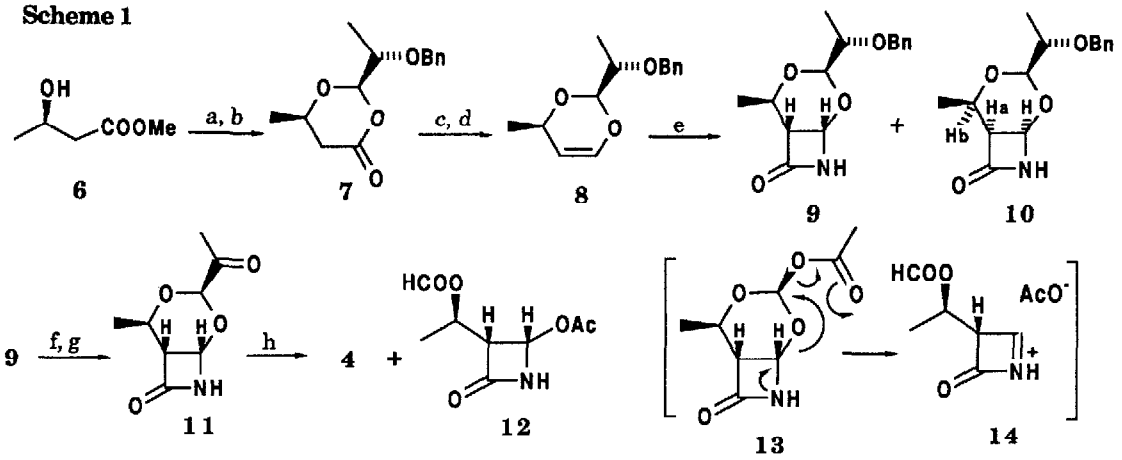
2



3: R=TBDMS
4: R=HCO
5: R=H

It has been well recognized that chlorosulfonyl isocyanate (CSI) reacts with a carbon-carbon double bond to readily afford a β-lactam having unprotected NH-group after cleavage of the initially formed sulfonamide group.[5] While the [2+2]-cycloaddition of CSI with the silyl enol ether prepared from methyl (*R*)-3-hydroxybutyrate (**6**) has been ingeniously applied to the synthesis of **3** by a Kanegafuchi research group,[4e] we have now found that the 2,4-*cis*-disubstituted 4*H*-1,3-dioxin derivative (**8**) stereoselectively obtainable from the same **6**, similarly reacts with CSI, resulting in a highly stereoselective formation of the bicyclic β-lactam (**9**), and that

Scheme 1



a) aq NaOH, then HCl, 87% b) (*S*)-MeCH(OBn)CHO-PPTS in CH_2Cl_2, 69% (cis:trans=>49:1). c) DIBAL in Et_2O, -78°C, 96%. d) $SOCl_2$-Et_3N in CH_2Cl_2, 82%. e) CSI in C_6H_5Me, -50°C, then vitride, 56% for **9** (2 steps), **9**:**10**=>98:2. f) H_2-$Pd(OH)_2/C$, 100%. g) $RuCl_3$-HIO_4·$2H_2O$, 94%. h) MCPBA (1.2 equiv.) in AcOH, 86% (**4**:**12**=10:1) or AcOOH (2.0 equiv.)-AcONa (4.0 equiv.) in AcOH, 83% (**4**:**12**=11:1).

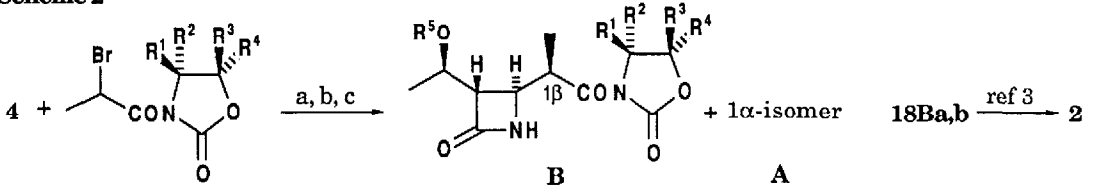
produced **9** can be readily elaborated to (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-formyloxyethyl]-2-azetidinone (**4**). The Reformatsky reaction of this novel 4-acetoxy-β-lactam (**4**) is found to proceed in completely the same manner as that for **3**, yielding **2** after sequential chemical manipulations including exchange of protective group.

As shown in **Scheme 1**, the explored synthetic route to **4** commences with hydrolysis of the methyl ester of commercially available **6**. Condensation of the formed β-hydroxy acid with (*S*)-2-benzyloxypropanal[4f,6] according to the reported methods[7] underwent highly stereoselectively, giving a diastereomeric mixture of the 1,3-dioxan-4-one derivatives. The ratio of these isomers could be calculated as >49:1 by the ^{1}H-NMR spectrum. The major product (**7**) was rigorously assigned to have the 2,6-*cis* configuration, based on the reported results.[7] Single recrystallization of the diastereomeric mixture from diisopropyl ether gave rise to a pure sample of **7**, mp 74.5~75.0°C and $[\alpha]_D^{20}$ -51.4° ($CHCl_3$). Reduction of **7** with diisobutylaluminium hydride (DIBAL) afforded a diastereomeric mixture of the hemiacetals, which without separation was dehydrated with thionyl chloride in the presence of triethylamine to yield **8**,[8] $[\alpha]_D^{20}$ -51.9° ($CHCl_3$). The [2+2]-cycloaddition of CSI which constitutes one of the key stereoselective reactions of the explored scheme, was effectively achieved by adding CSI to a solution of **8** in toluene at -50°C. Subsequent reductive work-up with sodium bis(methoxyethoxy)aluminium hydride (vitride®) furnished desired **9** highly stereoselectively in 56% yield based on **8**. The yield of the undesired isomer (**10**) isolated with column chromatography was found to be less than 1%.[9] Thus, the ratio of **9** to **10** could be calculated as more than 98:2. Single recrystallization of **9** readily afforded a pure sample of **9**, mp 103.0~103.5°C and $[\alpha]_D^{20}$ -30.9° ($CHCl_3$).

With **9** in hand, it was first envisioned that **9** can produce (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone (**5**) directly by successive cleavage of the acetal moiety and addition of an acetate anion to the formed C=N bond when treated with acetic acid in the presence of an acidic catalyst. Additionally, the bicyclic β-lactam (**9**) was also expected to be utilized as a substrate for the Reformatsky reaction similarly to **3**.[3] However, all the attempts to realize these synthetic steps turned out to be fruitless. After numerous experimentations, it was finally found that **9** could be converted to **4** by the following sequential reactions. Thus, hydrogenolysis of **9** gave rise to the corresponding alcohol which was immediately oxidized to yield the methyl ketone (**11**). Surprisingly, when **11** was treated under the standard conditions for the Baeyer-Villiger reaction using *m*-chloroperbenzoic acid (MCPBA) in acetic acid, a mixture of **4** and its C4-epimer (**12**) could be directly produced in a ratio of 10:1 in 84% yield. Single recrystallization of the mixture from diisopropyl ether gave **4** in a pure state, mp 48.0~48.5°C and $[\alpha]_D^{20}$ +123° ($CHCl_3$). In place of MCPBA, a combination of peracetic acid and sodium acetate could also effect the rearrangement, giving a mixture of **4** and **12** (11:1) in a little lower yield.[10] This unprecedented Baeyer-Villiger reaction could be accounted for by the mechanism depicted in the parenthesis (**Scheme 1**). Thus, after the usual Baeyer-Villiger reaction of **11** has produced the corresponding acetate (**13**), subsequent cleavage of the acetal moiety of **13** with concomitant loss of an acetate anion gives rise to the *N*-acyl immonium cation (**14**) which can be trapped with acetic acid present in the reaction medium.[11]

With completion of the synthetic route to **4** from **6**, application of the reported Reformatsky reaction[3] was next examined by expecting that **4** can be utilized as a substrate in completely the same manner as that for **3** (**Scheme 2**). Thus, treatments of **4** with the sterically crowded 3-(2-bromopropionyl)-2-oxazolidone derivatives (**15a,b**) in the presence of zinc dust in refluxing THF afforded the C4-alkylated products as mixtures of the two diastereomers (**16Ba,b** and **16Aa,b**) in a similar highly stereoselective manner to that reported with **3**.[3] Without separation, sequential hydrolyses of the mixtures of **16Ba,b** and **16Aa,b** under acidic or basic conditions depending upon the structures of 2-oxazolidone moieties and protections of the formed al-

Scheme 2



15 a: R^1=R^2=Me, R^3=R^4=H
b: R^1=R^2=*n*-Bu, R^3=R^4=-$(CH_2)_5$-

16:R^5=HCO
17:R^5=H
18:R^5=TBDMS

a) Zn in refluxing THF, 94% (**16a**: **16Ba**:**16Aa**=5.6:1) or 97% (**16b**: **16Bb**:**16Ab**=20:1). b) AG 50W-X2 (ion exchange resin, acidic form), 89% (**17a**: **17Ba**:**17Aa**=5~6:1) or aq $NaHCO_3$, 97% (**17b**: **17Bb**:**17Ab**=19:1). c) TBDMSCl-imidazole, 92% (**18a**: **18Ba**:**18Aa**=5.6:1) or 92 % (**18b**: **18Bb**:**18Ab**=23:1).

cohols (**17Ba,b** and **17Aa,b**) with a TBDMS group gave rise to mixtures of the silyl ethers (**18Aa,b** and **18Ba,b**). These compounds (**18Aa,b** and **18Ba,b**) were definitely identified with authentic samples by comparisons of their ^{1}H-NMR spectra.[3] The major silyl ethers (**18Ba,b**) could be derived to **2** according to the established conditions.[3]

As mentioned above, we have succeeded in exploring a highly efficient synthetic route to **2** from **6** by way of **4** by employing the [2+2]-cycloaddition of CSI, the Baeyer-Villiger reaction, and the Reformatsky reaction. The developed scheme may be characterized by the following merits: 1) use of the commercially available inexpensive starting material (**6**), 2) introduction of a fairly expensive TBDMS group at the later synthetic stage, and 3) high stereoselectivities observed for formation of the 1,3-dioxan-4-one derivative (**6**→**7**), β-lactam formation (**8**→**9**), introduction of an acetoxy group to the C$_4$-position of β-lactam (**11**→**4**), and the Reformatsky reaction (**4**→**16**). Taking into account these novel aspects, the overall process may have potential as one of the most practical methods for preparing **2**.

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5) W. A. Szabo, *Aldrichimica Acta*, **10**, 23 (1977) and references therein.
6) The 2,6-*cis*-disubstituted 1,3-dioxan-4-one derivatives prepared from other aliphatic aldehydes such as benzyloxyacetaldehyde, 3-phenylpropanal, and phenylacetaldehyde were similarly elaborated to the [2+2]-cycloaddition products corresponding to **9**. However, being different from **9**, these compounds could not be effectively transformed to **4**. Y. Kobayashi, Y. Ito, and S. Terashima, unpublished results.
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8) The same dehydration reaction could be effected with mesyl chloride in pyridine.
9) The stereochemistry of **10** could be rigorously determined by measuring nuclear overhauser effects (NOE) in the ^{1}H-NMR spectrum. Thus, 4.8% of NOE was observed between H$_a$ and H$_b$ of **10**.
10) The combined yield of **4** and **12** increased from 51% to 83% by adding 4.0 equivalents of sodium acetate to the reaction medium.
11) Exchange of the solvent from acetic acid to propionic acid gave a 75% yield of the 4-propionyloxy-β-lactams instead of the mixture of **4** and **12**.

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