SYNTHESIS OF POTENTIALLY USEFUL INTERMEDIATES FOR 1-FLUOROCARBAPENEMS#

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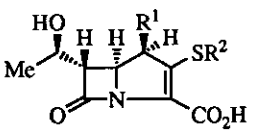
Abstract--The displacement reaction of the 4-acetoxyazetidin-2-one (**6**) with dimethyl fluoromalonate was readily performed in the presence of lithium hexamethyldisilazide. The product (**7**), quantitatively obtained, was converted into two potential synthetic intermediates (**4**) and (**5**) of 1-fluorocarbapenem derivatives.

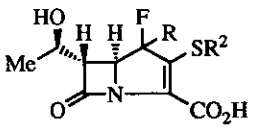
Thienamycin (**1**) possesses potent and broad-spectrum antibacterial properties,[1,2] but it suffers serious disadvantages in that it is chemically unstable and readily metabolized by renal dehydropeptidase-I. Therefore, the synthetic development of new artificial 1β-methylcarbapenem (**2**)[3] is of current interest in the study of β-lactam antibiotics.[4] Recent reports[5] concerning synthetic efforts of carbapenems having a substituent(s), other than methyl group at the C(1) position prompted us to

Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

publish our approach to the synthesis of 1-fluorocarbapenems (**3**). We wish to report a facile preparation of potentially useful intermediates (**4**) and (**5**) for **3**.



1 : R^1=H, R^2=$CH_2CH_2NH_2$
2 : R^1=Me, R^2=$CH_2\overset{\overset{NH}{\|}}{C}NMe_2$



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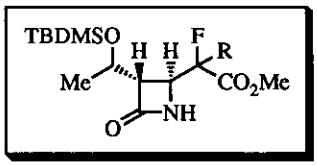
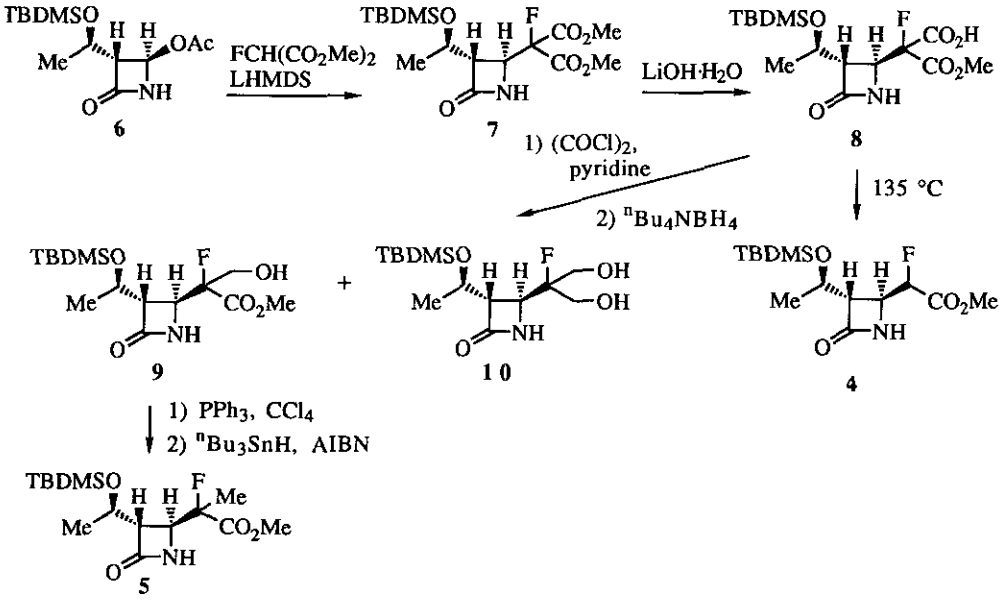


4 : R=H
5 : R=Me

In relation to our work[6] of producing chiral precursors having fluorine atom from malonic acid, substitution reaction of 4-acetoxyazetidin-2-one with fluoromalonate was examined. The displacement reaction of 4-acetoxyazetidin-2-one by the enolate anion derived from malonic esters had been reported by two groups, Kametani[7] and Greengrass.[8] Although a poor result (35% yield) was recorded for the condensation with bromomalonate in the presence of sodium hydride,[7a] the substitution reaction with fluoromalonate was effectively carried out when lithium hexamethyldisilazide was used as a base.[6] Namely, after treatment of dimethyl fluoromalonate with an equimolar of lithium hexamethyldisilazide in dry tetrahydrofuran, the resulting enolate reacted with an equimolar of **6** at -78 °C to ambient temperature to give the single *trans*-isomer (**7**), mp 158-160 °C $[\alpha]_D^{29}$-47.7°($CHCl_3$), in 97% yield. The product (**7**) was then converted into the desired compounds (**4**) and (**5**), respectively. Hydrolysis of **7** with an equimolar of lithium hydroxide in aqueous methanol produced a 1:1 diastereoisomeric mixture of mono-acid (**8**) in 98% yield. Heating **8** in xylene at 135 °C for 3 h provided a 2:1 diasteroisomeric mixture of the ester (**4**) in 77% yield.

On the other hand, after transformation of the diasteroisomeric mixture (**8**) into acid chlorides with oxalyl chloride in the presence of pyridine, the resulting product was reduced with tetrabutylammonium borohydride[9] in dichloromethane at -78 °C. It is interesting that the primary alcohol (**9**), whose stereochemistry was uncertain, was

obtained in 36% yield as a single stereoisomer together with the diol (**10**) in 41% yield. The hydroxyl compound (**9**) was converted into the methyl compound (**5**) in two steps; chlorination using triphenylphosphine and carbon tetrachloride (83%), and dechlorination employing tributyltin hydride in the presence of azoisobutyronitrile (81%).



Transformation of the above fluorides (**4**) and (**5**) into carbapenem derivatives (**3**) will be reported in due course.

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