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Synthesis of 3-Fluoro Azetidinone By Electrophilic Fluorination.

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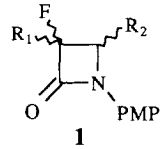
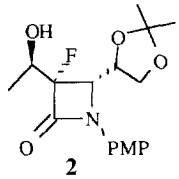
Abstract : An easy access to the 3-fluoroazetidinone **4a** based on electrophilic fluorination, is reported. The fluorination of the β-lactam **7** with Differding's N-fluorosulfonimide proceeds stereoselectively, under mild conditions and in good yield. Copyright © 1996 Published by Elsevier Science Ltd

Fluorination of organic compounds has been shown to be particularly important in fields such as material science, agro-chemistry, medicinal chemistry[1]. In the course of our work on carbapenem antibiotics[2], we were interested in 3-fluoroazetidinones[3] as potential intermediates to new antibiotics and β-lactamases inhibitors. Only a few methods, following two main strategies, are known to give these highly functionalized molecules.



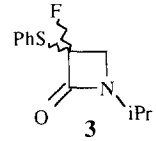
1

R_1: H, Me, Et, Ph
R_2: Ph, CO_2Et

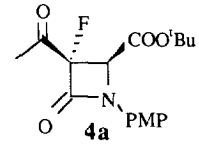


2

PMP : paramethoxyphenyl



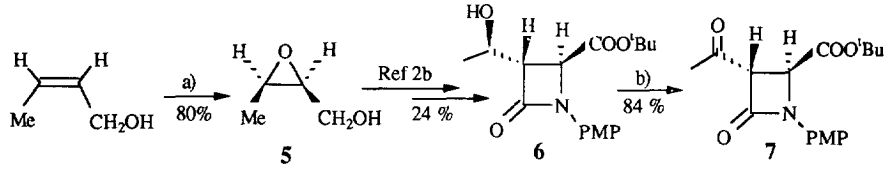
3



4a

The first approach, leading to β-lactams of type **1**, elaborates the β-lactam ring usually in a non-selective manner from fluorinated building blocks[4]. This strategy involves the Reformatsky reaction of halogenofluoroacetates with imines[4cd], the addition of fluoroenolates to imines[4b], the intramolecular cyclisation of α-fluoro-β-bromopropionamides[4eh], the cycloaddition of a nitrone to hexafluoropropene[4g], the 2+2 cycloaddition of fluoroketenes to imines[4ab]. Only one example of a 3-fluoroazetidinone **2**, in an enantiomeric pure form, and containing the functionalities required in the penems and carbapenems series, has been obtained with this last method[4f]. The second strategy involves the direct fluorination of a preexisting β-lactamic compound[5]. Nucleophilic or electrophilic fluorinations have been performed on penicillin[5a-c] and cephalosporin[5de] derivatives; fluorinated azetidinones of type **3** have been obtained by anodic electrochemical fluorination[5fg]. To our knowledge, this procedure has not been used for the fluorination of penem and carbapenem monocyclic precursors. The methods described so far in the literature are non-general, tedious procedures, requiring sometimes toxic or dangerous reagents (α-fluoroesters[4f], $FClO_3$[5bd]). In this paper, we wish to describe an easy access to compound **4a**, a key intermediate for the elaboration of fluorinated antibiotics.

In our approach, We have investigated the electrophilic fluorination of a functionalized azetidinone, a strategy which has so far never been applied to a monocyclic β-lactam ring. Considerable progress has been made recently in the field of electrophilic fluorination by the introduction of new reagents possessing an N-F bond[6]. These compounds are easy to handle, they are stable and crystalline, and their reactivity can be modulated by the substituents on the nitrogen atom. The enantiomerically enriched substrate **7** of our study was obtained on a preparative scale, using the methodology previously developed for the preparation of penem and carbapenem key intermediates[2b], and summarized in the following scheme :



a) $Ti(OiPr)_4$, L- (+)-DET tBuOOH, CH_2Cl_2, -20°C b) Jones' reagent, Acetone 0°C.

The Sharpless epoxidation on (Z) but-2-en-1-ol afforded the chiral epoxide **5** in 80% yield and in 90% ee, which was converted into the β-lactam **6** in 3 steps[2b] in a highly stereoselective manner. Oxidation of the hydroxyethyl side chain using Jones reagent afforded the crystalline compound **7**[9] which contains functionalities of the penem and the carbapenem antibiotics and a β-dicarbonyl system suitable for electrophilic fluorination. With this material in hand, we first verified that the enolate **8** is easily generated with NaH. We found that **8** reacts readily with a classical electrophile such as MeI, to give **9** in 80% yield. The enolate **8** was then reacted with various commercially available electrophilic fluorinating reagents, table 1.

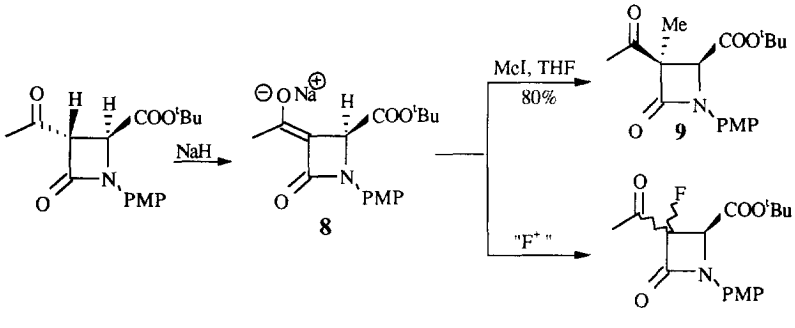
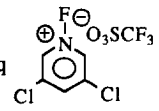
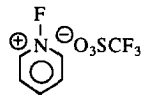
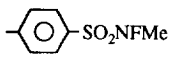
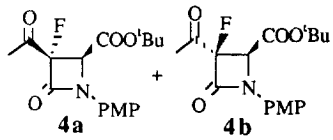
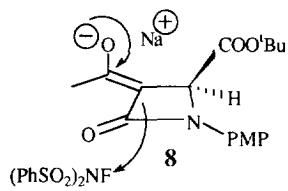


Table 1 : Electrophilic fluorination of β-lactam **8**

Entry	Fluorinating agent	Conditions*	Results	Yield
1	1 eq 	12h, -20°C 3 days, RT 12h, reflux	Starting material	/
2	1.8 eq 	3 days, RT	Starting material and degradation	/
3	2 eq 	12 h, RT Toluene, 5h, RT	Complex mixture	/
4	1.2 eq $(PhSO_2)_2NF$		 **4a** + **4b**	70%
		1h, 20°C	85 : 15	
		1h, -15°C	95 : 5	

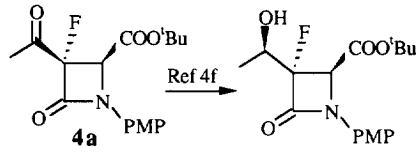
* All reactions were conducted in THF unless otherwise mentioned.

In our hands, fluoropyridinium triflates[6a-c] (entries 1 and 2) were inefficient for the fluorination of **8**. These reagents do not seem to work for the fluorination of enolates[6c]. Barnette's N-fluorosulfonamide[6d] (entry 3) gave a complex mixture of products, probably because of HF elimination[7]. The Differding's N-fluorosulfonimide[6e] (entry 4) proved to be the reagent of choice. We were pleased to observe that the fluorination proceeded diastereoselectively in good yield, and at room temperature. The structure of the major trans azetidinone[10] obtained, **4a**, was determined by ^1H and ^{19}F NMR. The vicinal fluorine hydrogen coupling constant in the trans substituted product **4a** (12 Hz) is, as expected, much larger than the same coupling constant in the cis isomer **4b** (4.7 Hz). The diastereomeric excess of the reaction could been increased by working at lower temperature. The electrophilic fluorination has been shown to proceed by an SN_2 mechanism[8]. This high selectivity can therefore been explained by an attack of the electrophile by the less hindered face of the stabilized enolate **8**.



8

In summary, we have developed a facile and selective synthesis of a 3-fluoroazetidinone in 6 steps from (Z)-but-2-en-1-ol, carrying essential functionalities of penems and carbapenems, and possessing the correct absolute configuration at the asymmetric carbon of the side chain after selective reduction of **4a**[4f].



4a

Work is in progress to generalize this methodology and to exploit the synthetic possibilities offered by **4a**.

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9. Data for **7**: mp = 112°C; [α] $_D^{25}$ = 18 (c = 0,73 $CHCl_3$). ^{1}H NMR 200 MHz ; ($CDCl_3$) δ (ppm) : 7.35 (d, ^{3}J = 6.9 Hz, 2H); 6.9 (d, ^{3}J=6.9 Hz, 2H); 4.95 (d,^{3}J = 2.5Hz, 1H); 4.8 (d,1H); 4 (s, 3H); 2.41 (s, 3H); 1.45 (s,9H).^{13}C NMR 50 MHz ; ($CDCl_3$) δ (ppm) : 195; 165.2; 156; 153.8; 127.8; 115.4; 111.5; 80.7; 63.4; 52.7; 50.2; 26.9; 25. IR (cm^{-1}): 2980; 2854; 1750; 1740; 1710; 1514; 1460; 1370; 1248; 1145; 1119; 830.

10. Data for **4a** : [α] $_D^{25}$ = -31, (c = 0,65 $CHCl_3$).^{1}H NMR 200 MHz ; ($CDCl_3$) δ (ppm): 7.35 (d, ^{3}J = 6.9 Hz, 2H); 6.9 (d, ^{3}J = 6.9 Hz, 2H); 4.72 (d,$^3J_{H\text{-}F}$ = 12 Hz, 1Hc); 3.8 (s, 3H); 2.45 (d, $^4J_{H\text{-}F}$ = 4.9 Hz, 3H); 1.43 (s, 9H). ^{13}C NMR 50 MHz ; ($CDCl_3$) δ (ppm) : 199.9; 163.9; 157.2; 135.8; 119.5; 114.4; 103.3 : (d, $^1J_{C\text{-}F}$ =237.5 Hz); 84.3; 63.45 (d, $^2J_{C\text{-}F}$ =24.7 Hz); 55.4; 27.7 ; 27,2. ^{19}F NMR 235.5 MHz ; ($CDCl_3$). δ (ppm) : -102.7 (qd, ^{4}J = 5.1 Hz, ^{3}J=11.6 Hz, 1F). IR (cm^{-1}) : 2955; 2854; 1778; 1750; 1705; 1514; 1460; 1371; 1248; 1149; 1117; 1061; 831. MH^+ : 337.1325; Found 337.13246.

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