# Synthesis of (Pivaloyloxy)methyl 6α-Fluoropenicillanate

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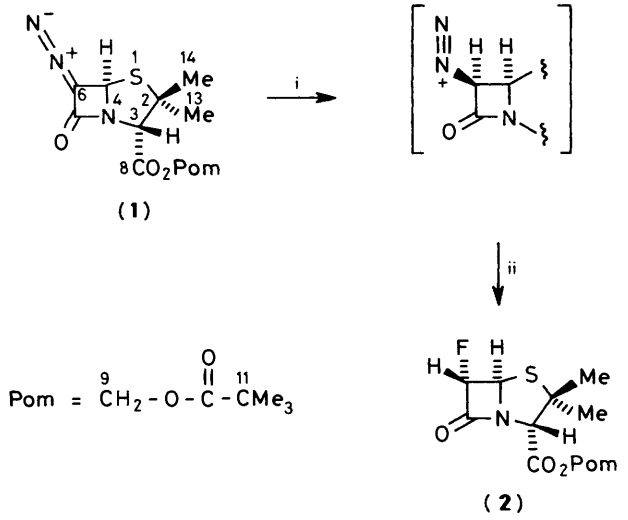
(Pivaloyloxy)methyl (Pom) 6α-fluoropenicillanate (**2**) was prepared in 15% yield from the readily available (pivaloyloxy)methyl 6-diazopenicillanate (**1**) and pyridinium poly(hydrogen fluoride). Its structure was established by $^1$H, $^{13}$C, and $^{19}$F n.m.r. spectroscopy and mass spectrometry. A new synthesis of Pom 6β-aminopenicillanate is described.

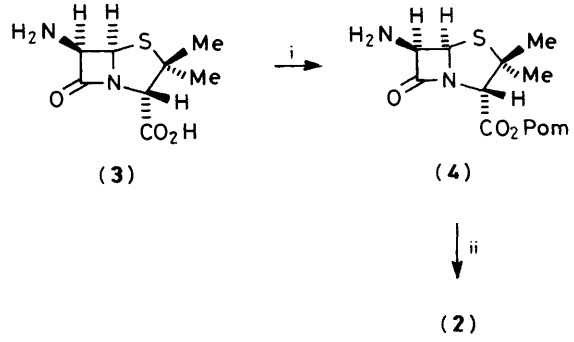
Significant attention in recent years has been focused on the chemistry of β-lactamase inhibitors.[1] Such compounds include 6β-bromopenicillanic acid,[2] 6β-iodopenicillanic acid,[3] penicillanic acid 1,1-dioxide,[4] and 6α-chloropenicillanic acid 1,1-dioxide.[5]

Our primary interest in introducing a fluorine atom at specific sites of the penicillin molecule was due to the knowledge that replacement of hydrogen atoms or functional groups in organic compounds by fluorine atoms may cause a dramatic change in biological activity[6] and that the presence of a sufficiently acidic hydrogen at C-6 is one of the structural requirements for penicillanic acid 1,1-dioxide[4b] and 6α-chloropenicillanic acid[5a] to act as suicide substrates for β-lactamases.[1,4b] We were interested therefore in preparing C-6 fluoro-substituted penicillins. Actually, fluorine is the only element which can replace hydrogen probably without causing significant steric consequences at enzyme binding sites. Furthermore, fluorine, with its very high electronegativity, when placed in the vicinity, will presumably alter the acylating reactivity of the β-lactam carbonyl group. The synthesis and structural elucidation of 6-fluoropenicillin[7] and 7-fluorocephalosporin[8] derivatives have aroused considerable interest. The first general method for the functionalization of the C-6 position of penicillins and C-7 of cephalosporins was to use the carbanion generated from the benzaldehyde Schiff base[8a] or benzylimino chloride[7a] and the electrophilic reagent perchloryl fluoride. We recently reported[9] failure in an attempt to introduce a fluorine atom in the β-orientation at C-6 of penams *via* $S_N2$ displacement on (pivaloyloxy)methyl 6α-[(fluorosulphonyl)oxy]penicillanate.




**Scheme 1.** *Reagents:* i, $C_5H_5NH^+(HF)_xF^-$; ii, $F^-$

Treatment of diazo ester (**1**) with pyridinium poly(hydrogen fluoride)[10] (30% pyridine–70% hydrogen fluoride) in chloroform gave, after chromatographic separation, the fluorinated penicillin (**2**) in 15% yield (Scheme 1). Several attempts were made to improve the low yield of compound (**2**). Use of anhydrous hydrogen fluoride in ether at 0 °C gave, after 30 min, only a 10% yield of the desired fluoride (**2**). Similarly unsuccessful was the reaction of Pom 6β-aminopenicillanate with pyridinium poly(hydrogen fluoride)–tetrabutylammonium nitrite in ether at 0 °C which gave rise to only a 7% yield of compound (**2**) (Scheme 2).




**Scheme 2.** *Reagents:* i, $ClCH_2OCOCMe_3$, DBU; ii, $\overset{+}{N}Bu_4NO_2^-$, $C_5H_5NH^+(HF)_xF^-$

The assignment of structure (**2**) was based on n.m.r. spectral evidence. The three doublets of the $^{13}$C spectrum confirmed that a fluorine atom was located at C-6: δ 98.1 (d, $^1J_{C,F}$ 238 Hz, C-6), 68.6 (d, $^2J_{C,F}$ 25 Hz, C-5), 165.2 (d, $^2J_{C,F}$ 22 Hz, C-7). The stereochemistry of the fluorine substituent was determined to be α based on the *trans* coupling[11] of the protons on C-5 and C-6: δ 5.34 (dd, $J_{5,6}$ 1.6, $J_{6,F}$ 53 Hz, 6β-H), 5.46 (dd, $J_{5,6}$ 1.6, $J_{5,F}$ 4.8 Hz, 5-H), and 4.54 (s, 3-H). The $^{19}$F n.m.r. spectrum consisted of a doublet at δ −182.9 p.p.m. with $^2J_{H,F}$ 53 Hz. The chemical ionization mass spectrum was consistent with the assignment of structure (**2**): *m/z* 334 (*M* + 1), and 276 (*M* + 1 − Bu$^t$), plus those ions due to the t-butyl moiety and the known fragmentation of penicillins.[12]

We attribute the exclusive formation of compound (**2**) to the steric control approach. It is already well established that the least hindered face of the penicillin molecule is α,[13,14] and therefore a proton tends to be added from this side, affording a β-oriented diazonium group that subsequently undergoes $S_N2$ displacement for the fluoride ion.

In conclusion, in this report we have described conditions that enable fluoride ion to be introduced at the C-6 position with α-orientation in a displacement reaction. This work

represents another method for the introduction of a fluoride atom at the C-6 position of penicillins.*

## Experimental

I.r. spectra were taken on a Beckman IR-10 spectrometer. $^1H$ and $^{13}C$ n.m.r. spectra were taken on a Bruker WP 80 SY instrument. The $^{19}F$ n.m.r. spectrum was recorded at Ruhr-Universitat Bochum (Germany). The chemical ionization mass spectrum was recorded at the Ohio State University. Chromatographic purification (t.l.c.) was carried out with silica gel $GF_{254}$ (Type 60, Merck). Spots were visualized by staining with iodine, ninhydrin, or anisaldehyde–sulphuric acid.[15] Chloromethyl pivalate was prepared by the method of Rasmussen and Leonard.[16] Tetrabutylammonium nitrite and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Fluka. All reactions were carried out under an atmosphere of nitrogen.

*(Pivaloyloxy)methyl 6α-Fluoropenicillanate* (**2**).—*Method A.* To a solution of pyridinium poly(hydrogen fluoride) (5 ml) at −10 °C in a polyethylene flask was added during 10 min a solution of Pom 6-diazopenicillanate (**1**)[13] (100 mg, 0.29 mmol) in dry ether (5 ml) and the reaction mixture was stirred and kept at −5 °C for 1 h. The reaction mixture was poured into ice–water (20 ml) and extracted with chloroform (2 × 20 ml). The organic layer was separated in a polyethylene separating funnel, washed successively with brine (2 × 10 ml) and water, dried ($Na_2SO_4$), and evaporated. Purification of the residue by preparative t.l.c. on silica gel with chloroform yielded compound (**2**) (14.7 mg, 15%) as an oil that slowly crystallized, m.p. 62—64 °C; $\nu_{max.}$(KBr) 1 800 (β-lactam), 1 750, and 1 760 $cm^{-1}$ (ester); $\delta_H$(80 MHz; $CDCl_3$; standard $Me_4Si$) 1.22 (9 H, s, $Me_3C$), 1.49 (3 H, s, 13-$H_3$), 1.56 (3 H, s, 14-$H_3$), 4.54 (1 H, s, 3-H), 5.34 (1 H, dd, $J_{6.F}$ 53, $J_{5.6}$ 1.6 Hz, 6-H), 5.46 (1 H, dd, $J_{5.F}$ 4.8, $J_{5.6}$ 1.6 Hz, 5-H), 5.80 (1 H, d, AB system, $J$ 5.6 Hz, 9-H), and 5.88 (1 H, d, AB system, $J$ 5.6 Hz, 9-H); $\delta_C$(20.15 MHz; $CDCl_3$; standard $CDCl_3$) 176.5 (C-10), 165.5 (C-8), 165.2 (d, $^2J_{C.F}$ 22 Hz, C-7), 98.1 (d, $^1J_{C.F}$ 238 Hz, C-6), 79.6 (C-9), 68.6 (d, $^2J_{C.F}$ 25 Hz, C-5), 68.6 (C-3), 64.0 (C-2), 38.5 (C-11), 33.4 (C-14), 26.6 (C-12), and 25.2 (C-13); $\delta_F$($CDCl_3$; standard $CFCl_3$) −182.9 p.p.m. (d, $^2J_{H.F}$ 53 Hz); $m/z$ (c.i./isobutane) 334 ($M^+ + 1$, 7.3%), 276 ($M^+ + 1 - Bu^t$, 40.6), 274 (2.5), 220 (17), and 85 (100).

*Method B.* To a solution of Pom 6β-aminopenicillanate (**4**) (see below) (140 mg, 0.4 mmol) and tetrabutylammonium nitrite (290 mg, 1 mmol) in anhydrous ether (3 ml) in a polyethylene flask at −10 °C was added dropwise pyridinium poly(hydrogen fluoride) (5 ml). The mixture was stirred at −10 °C for 90 min and then diluted with chloroform (15 ml) and washed with brine (2 × 10 ml). After drying and concentration of the organic layer, the residue was chromatographed similarly to method A to give compound (**2**) (10 mg, 7%) as a crystalline solid.

*(Pivaloyloxy)methyl 6β-Aminopenicillanate* (**4**).—The method of Rao[17] was followed. This method is more convenient than the conversion of potassium benzylpenicillanate.[18] In a dried 50 ml round-bottom flask, fitted with a magnetic stirring bar and a septum inlet tube and connected to a mercury bubbler, was placed 6β-aminopenicillanic acid (**3**) (0.25 g, 1.15 mmol) and a mixture of dichloromethane (3 ml) and acetonitrile (1.0 ml). To the well stirred suspension at 20 °C was added, by syringe, DBU (0.18 ml, 1.22 mmol) followed by chloromethyl pivalate (0.17 ml, 1.22 mmol). After 1 h at 20 °C the reaction was complete. The mixture was diluted with water (10 ml) and extracted with chloroform (2 × 10 ml). The organic layer was washed with water (10 ml), dried ($Na_2SO_4$), and evaporated to give the ester (**4**) (0.360 g, 95%) as an oil.† This material was identical with that previously reported.[18]

* Recently we synthesized 6,6-dibromo-3α-fluoromethyl-2,2-dimethylpenam: E. G. Mata, E. L. Setti, O. A. Mascaretti, S. B. Boggio, and O. A. Roveri, *J. Chem. Soc., Perkin Trans 1*, 1988, 1551.

† This oil must be either used immediately or transformed into a stable salt (hydrochloride, toluene-*p*-sulphonate, *etc.*).

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