

Synthesis of a Novel Fluoro-tribactam utilising *N*-Fluorosulfonimide in the Key Step

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The electrophilic reagent *N*-fluorobenzenesulfonimide (NFSI) is used in the synthesis of the α -fluoro ketone **7**, a key intermediate for the synthesis of the tribactam **13**.

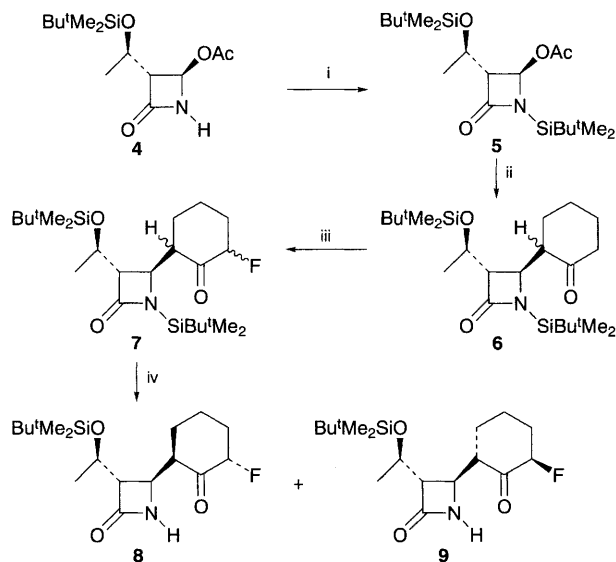
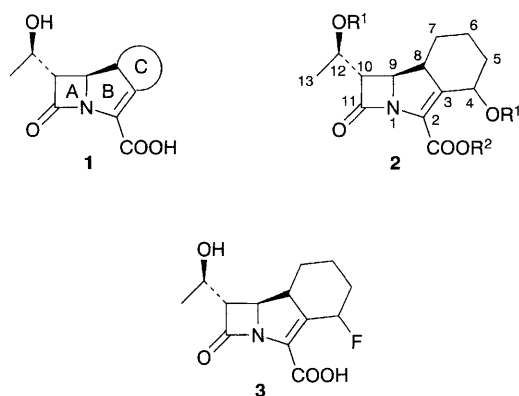
Glaxo S.p.A. has recently discovered a new family of synthetic β -lactam antibiotics, the tribactams **1**, possessing a tricyclic skeleton.¹ In connection with the preparation of compounds in this series we have shown that radical coupling of 4-phenyl-selenoazetidin-2-one with some 2-substituted cyclohexenones yields 2,6-*cis*-substituted cyclohexanones, after rearrangement of the initially formed species.² This methodology was used as the key step in the synthesis of the tribactam of type **2**. In order to extend the range of electron withdrawing substituents at the C-4 position within the tricyclic molecule, we decided to prepare the 4-fluoro substituted tribactam **3**.

The commercially available 4-acetoxiazetidin-2-one **4** was *N*-protected using standard conditions (Scheme 1). Coupling of the 4-acetoxy β -lactam **5** with 1-trimethylsilyloxycyclohexene mediated by tin(IV) chloride afforded the α -substituted ketone **6** as a mixture of two diastereoisomers in the ratio 7:3. The key

step in this synthesis involved the use of an electrophilic fluorinating reagent,³ namely *N*-fluorobenzenesulfonimide (NFSI). NFSI is an easy-to-handle, stable white crystalline solid and has been used to fluorinate other lithium enolates.⁴ We were very pleased to find that treatment of the ketone **6** with LiN(SiMe₃)₂ followed by addition of NFSI at low temperature afforded the α -fluorinated ketone **7** as a mixture of two diastereoisomers (ratio 7:3) in excellent yield. In both isomers the substituents at C-2 and C-6 in the cyclohexanone ring were *trans* oriented. *N*-Desilylation using ammonium fluoride in methanol afforded the ketones **8** and **9** (90% yield).[†]

Relevant NOEs that allowed an allocation of structures **8** and **9** to the major and minor isomers, respectively, are shown in Fig. 1. Note that for both isomers, no NOEs were observed between the 2'- and 6'-protons, denoting an *anti*-axial-equatorial relationship between these two protons.

The β -lactam **8** was *N*-alkylated with allyl oxalyl chloride in xylene to give the oxalimide **10** (Scheme 2). Intramolecular Wittig-type cyclization⁵ (triethyl phosphite, xylene, reflux) afforded the tricyclic structure **11** (67% yield) which was deprotected in standard fashion to give the alcohol **12**. Palladium-catalysed deallylation⁶ of the ester revealed the



Scheme 1 Reagents and conditions: i, Et₃N, Bu^tMe₂SiCl, CH₂Cl₂, 88%; ii, SnCl₄, MeCN, 1-trimethylsilyloxycyclohexene, 75%; iii, LiN(SiMe₃)₂, FN(PhSO₂)₂, THF, -78 °C, 95%; iv, NH₄F, MeOH, 90%

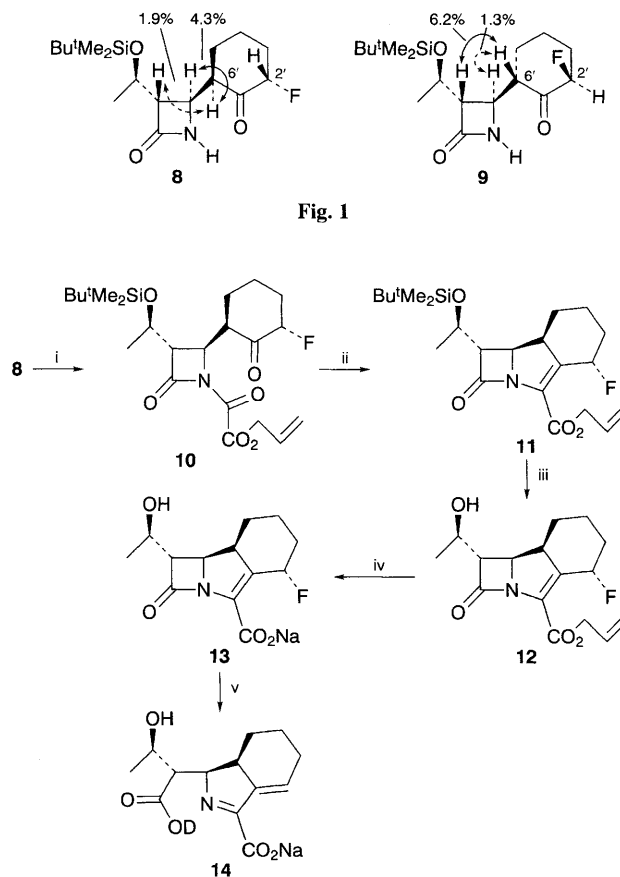


Fig. 1

Scheme 2 Reagents and conditions: i, Et₃N, ClCOCO₂CH₂CHCH₂, xylene, 0 °C; ii, P(OEt)₃, xylene, 140 °C, 3 h, 67%; iii, AcOH, Bu^tNF, THF, 65%; iv, Pd(PPh₃)₄, PPh₃, sodium 2-ethylhexanoate, THF, 90%; v, D₂O, 30 min.

carboxylate **13** as the sodium salt in 90% yield. The tribactam **13** was rapidly hydrolysed in D₂O (as shown by ¹H NMR) with consequent elimination of the fluorine atom to afford the imino acid salt **14**.[‡]

Further studies on the conversion **13** → **14** are in progress and will be reported in due course. Microbiological testing of the tribactam **13** was not possible as activity assays are run in aqueous solution over 18 h. However the mode of ring-opening of the fluoro-compound **13** may give an indication of the mechanism of action of other compounds in the tribactam series.

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Footnotes

[†] NMR data for **8**: δ_H (300 MHz, CDCl₃) 0.04 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.90 (9H, s, SiCMe₃), 1.20 (3H, d, *J* 6.5 Hz), 1.60 (1H, m), 1.65–2.05 (3H, m), 2.10 (1H, m), 2.35 (1H, m), 2.87 (1H, dd, *J* 2.5 and 4.5 Hz), 3.02–3.12 (1H, m), 3.95 (1H, d, *J* 2.5 and 4.5 Hz), 4.14–4.22 (1H, m), 4.72 (1H, ddd, *J* 2, 4.5 and 51 Hz), 6.20 (1H, br s, NH); δ_C (75.5 MHz, CDCl₃) –5.01 (Me), –4.28 (Me), 17.92 (C), 18.68 (CH₂, d, *J* 3 Hz), 22.49 (Me), 25.72 (CMe₃), 28.31 (CH₂), 34.01 (CH₂, d, *J* 22 Hz), 48.77 (CH), 49.59 (CH, d, *J* 5.4 Hz), 61.17 (CH), 65.55 (CH), 93.1 (CH, d, *J* 179 Hz), 168.55

(N–C=O), 207.86 (C=O, d, *J* 22 Hz); δ_F (235.5 MHz, CDCl₃) –26.83 (m, CF).

For **9**: δ_H (300 MHz, CDCl₃) 0.05 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.86 (9H, s, SiCMe₃), 1.20 (3H, d, *J* 6.5 Hz), 1.40 (1H, m), 1.70–2.05 (3H, m), 2.15 (1H, m), 2.40 (1H, m), 2.75 (1H, ddd, *J* 0.8, 2 and 5.5 Hz), 2.86–3.00 (1H, m), 3.65 (1H, dt, *J* 2 and 10 Hz), 4.10–4.20 (1H, m), 4.70 (1H, ddd, *J* 2, 4.5 and 51 Hz), 6.08 (1H, br s, NH); δ_C (75.5 MHz, CDCl₃) –4.70 (Me), –4.38 (Me), 17.91 (C), 18.66 (CH₂, d, *J* 2.9 Hz), 22.89 (Me), 25.78 (3 × Me), 31.40 (CH₂), 33.76 (CH₂, *J* 25 Hz), 50.10 (CH), 52.40 (CH), 63.68 (CH), 65.60 (CH), 92.68 (CH, d, *J* 197 Hz), 167.60 (N–C=O), 207.89 (C=O, d, *J* 24 Hz); δ_F (235.5 MHz, CDCl₃) –26.68 (m, CF).

[‡] NMR data for **14**: δ_H (500 MHz, D₂O) 1.06 (3H, d, *J* 6.5 Hz), 1.42 (1H, m), 1.58 (1H, m), 1.87 (2H, m), 2.19 (1H, m), 2.28 (1H, m), 2.27 (1H, dd, *J* 1.9, 6.5 Hz), 3.10 (1H, m), 3.80 (1H, m), 4.71 (1H, dd, *J* 1.9, 9.7 Hz), 7.02 (1H, m).

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