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-phenylselenoazetidin-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-acetoxyazetidin-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 $LiN(SiMe_3)_2$ 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 cyclization[5] (triethyl phosphite, xylene, reflux) afforded the tricyclic structure **11** (67% yield) which was deprotected in standard fashion to give the alcohol **12**. Palladium-catalysed deallylation[6] of the ester revealed the

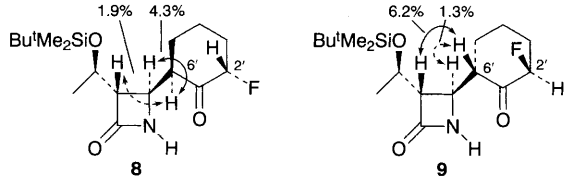

Fig. 1

Scheme 1 *Reagents and conditions*: i, Et_3N, Bu^tMe_2SiCl, CH_2Cl_2, 88%; ii, $SnCl_4$, MeCN, 1-trimethylsilyloxycyclohexene, 75%; iii, $LiN(SiMe_3)_2$, $FN(PhSO_2)_2$, THF, −78 °C, 95%; iv, NH_4F, MeOH, 90%

Scheme 2 *Reagents and conditions*: i, Et_3N, $ClCOCO_2CH_2CHCH_2$, xylene, 0 °C; ii, $P(OEt)_3$, xylene, 140 °C, 3 h, 67%; iii, AcOH, Bu^tNF, THF, 65%; iv, $Pd(PPh_3)_4$, PPh_3, sodium 2-ethylhexanoate, THF, 90%; v, D_2O, 30 min.

carboxylate **13** as the sodium salt in 90% yield. The tribactam **13** was rapidly hydrolysed in D_2O (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.

We wish to thank Dr V. Sik (University of Exeter) for NMR experiments and Mr E. Underwood (University of Exeter) for MS data. We thank Glaxo S.p.A. for a research studentship (A. P.).

Received, 19th December 1994; Com. 4/07731H

Footnotes

† *NMR data* for **8**: δ_H (300 MHz, $CDCl_3$) 0.04 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.90 (9H, s, $SiCMe_3$), 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, $CDCl_3$) −5.01 (Me), −4.28 (Me), 17.92 (C), 18.68 (CH_2, d, *J* 3 Hz), 22.49 (Me), 25.72 (CMe_3), 28.31 (CH_2), 34.01 (CH_2, 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, $CDCl_3$) −26.83 (m, CF).

For **9**: δ_H (300 MHz, $CDCl_3$) 0.05 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.86 (9H, s, $SiCMe_3$), 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, $CDCl_3$) −4.70 (Me), −4.38 (Me), 17.91 (C), 18.66 (CH_2, d, *J* 2.9 Hz), 22.89 (Me), 25.78 (3 × Me), 31.40 (CH_2), 33.76 (CH_2, *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, $CDCl_3$) −26.68 (m, CF).

‡ *NMR data* for **14**: δ_H (500 MHz, D_2O) 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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