Pergamon

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Synthesis of a Novel Fluoro-tribactam Utilising an *N*-Fluorosulfonimide in the key step

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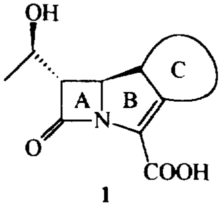
Abstract: The electrophilic reagent *N*-fluorobenzenesulfonimide (NFSI) was used in the synthesis of the α-fluoro ketone **7**, a key intermediate for the synthesis of the β-lactam **13**. This highly reactive fluorinated tribactam **13** was rapidly hydrolysed in aqueous solution.

Introduction

The introduction of fluorine into biologically active compounds has been widely investigated since it alters the physico-chemical properties of the molecule and can potentiate biological activity.[1,2] The substitution of hydrogen with fluorine does not affect the steric demand of the molecule. In fact, the Van der Waals radii of hydrogen (1.10 Å) and fluorine (1.36 Å), and therefore the C-H (1.08-1.11 Å) and C-F (1.26-1.41 Å) bond lengths, are very similar.[1] However, the electron distribution within the molecule will be affected due to the high electronegativity of fluorine. In addition the lipophilicity of the fluorinated compound is greatly enhanced.[2] Finally fluoride is also a good leaving group in E_2 elimination reactions and this can be influential when such a mechanism is involved in the *in situ* formation of an enzyme inhibitor.

In recent years the synthesis of fluorinated derivatives of non-classical β-lactam antibacterial agents, such as the carbapenems, has received particular attention. In this context, Shah and Cama prepared 1,1-difluorocarbapenem in order to accentuate the reactivity of the β-lactam ring.[3] However, due to its enhanced reactivity, this compound could not be tested as an antibacterial agent.[3] In a related study Watanabe and co-workers prepared a series of 8-fluorocarbapenem derivatives.[4] The most interesting result was the improvement of the water solubility of the fluorinated compounds compared to imipenem (ratio *ca* 30 : 1), (a major drawback of imipenem in the clinic is that its use is restricted to infusion).[5] Fukumoto *et al* published the synthesis of potentially useful intermediates for 1-fluorocarbapenems by coupling of 4-acetoxy-2-azetidinone and the lithium enolate of dimethyl fluoromalonate.[6] Furthermore 3-fluoro substituted β-lactams have been prepared by Welch *et al* using the ketene-imine condensation[7] and by Fuchigami and co-workers *via* anodic monofluorination of 2-aryl-4-thiazolidinones followed by oxidation of the fluorinated heterocycle to the corresponding sulfones followed by thermal ring contraction.[8] Glaxo S. p. A. recently discovered a new family of synthetic β-lactam antibiotics, the tribactams **1**, possessing a tricyclic skeleton.[9] 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. This methodology was used as the key step in the synthesis of the tribactam of type **2**.[10]



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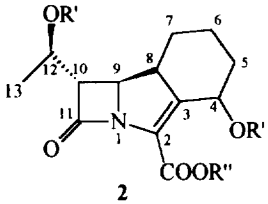

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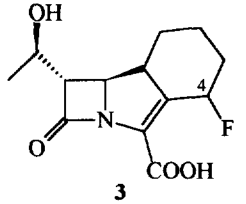


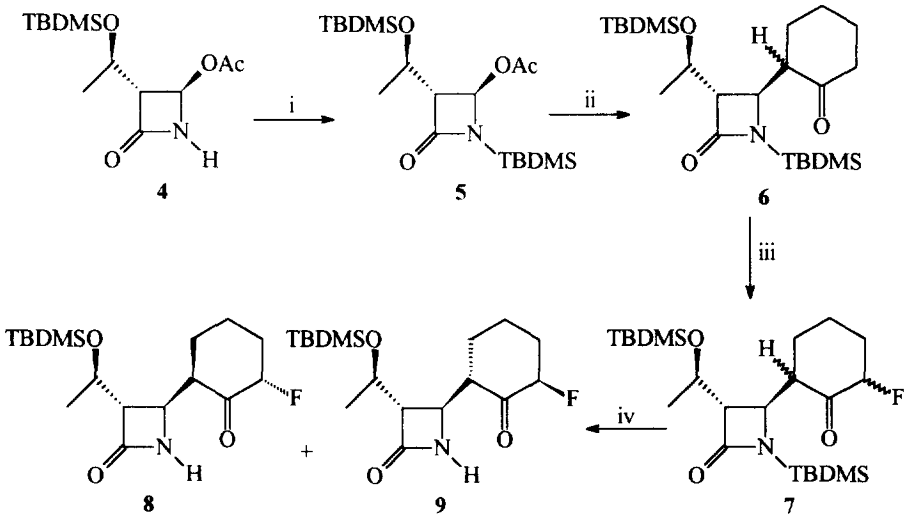
3

In order to extend the range of electron withdrawing and/or nucleofugic substituents at the C-4 position within the tricyclic molecule, we set out to prepare the 4-fluoro substituted tribactam **3**.[11]

Results and Discussion

Commercially available 4-acetoxy-azetidin-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,[12] *N*-fluorobenzene sulfonimide (NFSI). The latter compound is an easy-to-handle, stable white crystalline solid and has been used heretofore to fluorinate lithium enolates.[12] 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.



Scheme 1 *Reagents and Conditions* : i, Et_3N, TBDMSCl, CH_2Cl_2, 88 %; ii, $SnCl_4$, CH_3CN, 1-trimethylsilyloxycyclohexene, 75 %; iii, $LiN(SiMe_3)_2$, $FN(PhSO_2)_2$, THF, -78°C, 95 %; iv, NH_4F, MeOH, 90%.

N-Desilylation using ammonium fluoride in methanol afforded the ketones **8** and **9** (90 % yield). Relevant nOe's that allowed an allocation of structure 8 and 9 to the major and minor isomers respectively are shown in the Figure 1. Note that for both isomers, no nOe's were observed between the 2' and 6' protons, denoting an *anti*-axial-equatorial relationship between these two protons.

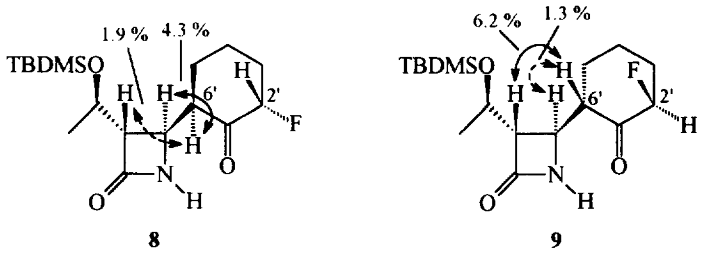
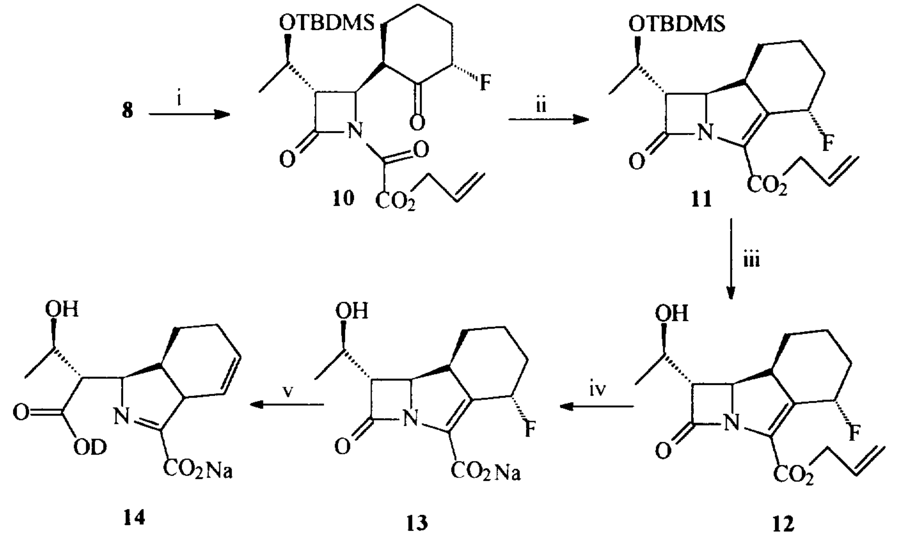


Figure 1

The 2'*S*, 6'*R* isomer **8** was *N*-acylated with allyl oxalyl chloride in the presence of triethylamine in xylene to give the oxalimide **10** (Scheme 2), which was transformed *in situ* into the tricyclic structure **11** *via* an intramolecular Wittig-type cyclization[13] (triethyl phosphite, xylene, reflux, 67 %). Compound **11** was deprotected in standard fashion to give the alcohol **12**. Palladium catalysed deallylation[14] of the ester furnished the 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**.



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

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 hours. 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. Thus the nucleofugicity of the substituent at C-4 in the tribactam must be attenuated to provide a good "sink" for negative charge after nucleophilic opening of the β-lactam ring (*cf* the parallel situation with the cephalosporin series, Figure 2). The nucleofuge should be lost readily following attack on the tribactam by the serine-based nuclephile of the target transpeptidase but should not be so highly active as to precipitate attack on the β-lactam carbonyl group by other, weaker nucleophiles, such as water.

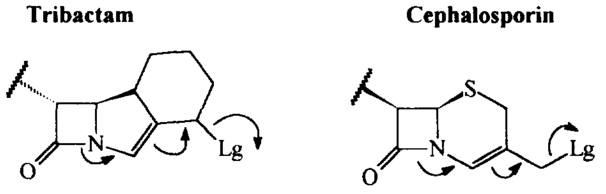


Figure 2

Acknowledgements

We wish to thank Dr. V. Šik (University of Exeter) for NMR experiments and Mr. E. Underwood (University of Exeter) for mass spectral data. We thank Glaxo S. p. A. for a research studentship to A. Padova.

Experimental Section

General. - IR spectra were recorded on a Perkin-Elmer 881 spectrometer. Absorption maxima were recorded in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded on a Bruker AM 250 spectrometer operating at 250 MHz and/or a Bruker AC 300 spectrometer operating at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer operating at 62.9 MHz or a Bruker AC 300 spectrometer operating at 75.4 MHz. 400 and 500 MHz ^1H NMR Spectra were recorded at Glaxo S.p.A., Verona, Italy. All chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are quoted in Hz. Mass spectra were recorded on a Kratos Profile instrument. Fast atom bombardment (FAB) spectra were recorded at Glaxo S.p.A. (Verona, Italy) using a V.G.Quattro instrument. Optical rotations were measured on a AA-1000 polarimeter. Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Reagents were used as supplied, with the exception of the following which were purified as described : -

triethylamine, distilled from and onto, potassium hydroxide pellets; 1,1,1,3,3,3-hexamethyldisilazane, distilled from and onto, potassium hydroxide pellets; *N*-fluorobenzene sulphonimide, purified by column chromatography (CH_2Cl_2).

Light petroleum refers to the fraction of b.p. 40-60°C and was distilled prior to use. Ethyl acetate was distilled prior to use. Ether and tetrahydrofuran were distilled from sodium using benzophenone ketyl radical as indicator. Dichoromethane was distilled from calcium hydride. Xylene was dried over sodium wire. TLC was performed using pre-coated glass plates (Merck silica gel 60F 254). The plates were visualised using UV light (254 nm) and/or phosphomolybdic acid in ethanol, or ninhydrin in ethanol/hydrochloric acid. Flash chromatography was performed using Merck silica 60 (40-63 μm).

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-4-acetoxy-3[(*R*)-(*tert*-butyldimethyl-silyloxy)-ethyl]-2-azetidinone (5)
(3*S*,4*R*)-4-Acetoxy-3[(*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**4**) (14.37 g, 50 mmol) and *tert*-butyldimethylsilylchloride (11.3 g, 75 mmol) were dissolved in anhydrous dichloromethane (100 cm^3) and the reaction mixture cooled down to 0°C. Triethylamine (10.4 cm^3, 75 mmol) was then added. The reaction mixture was stirred at 0°C for 2 h and then allowed to warm up to room temperature. After stirring for 30 h, the mixture was poured into water (75 cm^3) and extracted with dichloromethane (2 x 100 cm^3). The combined organic extracts were washed with brine (75 cm^3) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the residue was purified by column chromatography (CH_2Cl_2) to give the β-lactam (**5**), produced as a yellow oil (17.74 g, 88%); $[\alpha]_D^{25}$ -35 (c = 1, $CHCl_3$), ν_{max} ($CHCl_3$)/cm^{-1} 1767 (C=O, β-lactam) and 1750 (C=O); δ_H (300 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$), 0.23 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.23 (3H, d, *J* 6.2, CH_3), 2.04 (3H, s, CH_3CO), 3.10 (1H, d, $J_{3,4\ trans}$ 1.5, *J* 3.0, 3-H), 4.18 (1H, m, CH_3CH), 6.17 (1H, d, $J_{4,3\ trans}$ 1.5, 4-H); δ_C (75.5 MHz, $CDCl_3$) -6.44 ($SiCH_3$), -5.77 ($SiCH_3$), -4.80 ($SiCH_3$), -4.68 ($SiCH_3$), 17.91(SiC), 17.94 (SiC), 21.10 ($CHCH_3$), 22.10

($COCH_3$), 25.78 ($SiC(CH_3)_3$), 25.87 ($SiC(CH_3)_3$), 64.10 (3-CH), 67.58 (CH_3CH), 76.44 (4-CH), 169.52 (C=O), 171.05 (C=O). LRMS (EI) : m/z 344 $[M-C(CH_3)_3]^+$ (48%), 302 $[M+H-COCH_3-C(CH_3)_3]^+$ (80%), 242 $[M-CH_3CH(OTBDMS)]^+$ (11%), 87 $[M+H-TBDMS-CH_3CH(OTBDMS)CHC=O]^+$ (100%).

HRMS (EI) Found: $[M]^+$ 401.24000. $C_{19}H_{39}NO_4Si_2$ requires M 401.24176.

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*R*)-1′-oxocyclohex-2′-yl]-2-azetidinone and (3*S*,4*R*)-1-(*tert*-butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*S*)-1′-oxocyclohex-2′-yl]-2-azetidinone (6). Tin tetrachloride (8 cm^3, 68 mmol) was added dropwise to a solution of acetonitrile at -35°C. The reaction mixture was allowed to warm up to 5°C and then a mixture of β-lactam (**5**) (20 g, 50 mmol) and 1-cyclohexenyloxytrimethylsilane (15.2 cm^3, 100 mmol) in acetonitrile (60 cm^3) was added to the mixture at 10°C. After 1 h, the reaction mixture was poured into a mixture of 0.4M sodium hydroxide (800 cm^3) and diethyl ether (300 cm^3). After stirring for 15 min, the organic phase was washed with water (2 x 100 cm^3) until neutral by pH indicator paper, then brine (100 cm^3) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the crude product (23.5 g) was dissolved in isopropyl alcohol (75 cm^3) at 40°C. Water (75 cm^3) was added until a solid crystallised out of solution. After stirring for 15 min, the solid was filtered off and washed with a ice-cold mixture of isopropyl alcohol and water (1 : 2) (20 cm^3). The product was dissolved in diethyl ether (150 cm^3), washed with brine (50 cm^3), dried ($MgSO_4$) and the solvent was evaporated under vacuum to give the mixture of azetidinones (**6**), obtained as a white solid (14.2 g, 63%) (mixture of two diastereoisomers in the ratio 7 : 3). δ_H (300 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.24 (3H, s, $SiCH_3$), 0.84 (9H, s, $SiC(CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.94 (18H, s, 2 x $SiC(CH_3)_3$), 1.22 (3H, d, *J* 6.2, CH_3), 1.24 (3H, d, *J* 6.2, CH_3), 1.40-1.74 (5H, m), 1.90-2.14 (5H, m), 2.16-2.44 (5H, m), 2.52-2.64 (2H, m), 2.90 (1H, dd, *J* 3.0, $J_{3,4\ trans}$ 4.5, 3-H), 3.24 (1H, dd, $J_{3,4\ trans}$ 3.0, *J* 7.5, 3-H), 3.97 (1H, t, $J_{4,3\ trans}$ 2.5, $J_{4,2'\ cis}$ 2.5, 4-H), 4.05 (1H, m, CH_3CH), 4.13 (1H, dd, $J_{4,3\ trans}$ 2.5, $J_{4,2'\ trans}$ 4.5, 4-H), 4.20 (1H, m, CH_3CH); δ_C (75.5 MHz, $CDCl_3$) -5.45 ($SiCH_3$), -5.13 ($SiCH_3$), -5.04 ($SiCH_3$), -4.73 ($SiCH_3$), -4.67 ($SiCH_3$), -4.51 ($SiCH_3$), -4.43 ($SiCH_3$), -4.34 ($SiCH_3$), 17.90 (SiC), 18.04 (SiC), 18.39 (SiC), 18.87 (SiC), 21.94 (CH_3), 22.86 (CH_3), 24.96 (CH_2), 25.03 (CH_2), 25.80 ($SiC((CH_3)_3$, 25.94 ($SiC(CH_3)_3$), 26.24 ($SiC(CH_3)_3$), 26.36 ($SiC(CH_3)_3$), 26.89 (CH_2), 27.61 (CH_2), 28.54 (CH_2), 28.91 (CH_2), 42.30 (CH_2), 42.35 (CH_2), 50.67 (2′-CH), 52.16 (2′-CH), 52.67 (3-CH), 53.65(3-CH), 60.58 (4-CH), 62.07 (CH_3CH), 66.01 (4-CH), 67.64 (CH_3CH), 173.54 (N-C=O), 173.82 (N-C=O), 209.58 (1′-C=O), 210.46 (1′-C=O). LRMS (EI) : m/z 382 $[M-C(CH_3)_3]^+$ (76%), 182 $[M-CH_3CH(OTBDMS)CHC=O-C(CH_3)_3]^+$ (11%), 75 $[(CH_3)_2SiOH]$ (100%). HRMS (EI) Found: $[M]^+$ 439.29501. $C_{23}H_{45}NO_3Si_2$ requires M 439.29380.

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*R*,6′*S*)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone and *S*,4*R*)-1-(*tert*-butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*S*,6′*R*)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone (7). *n*-BuLi (2.5 M in hexane) (0.56 cm^3, 1.4 mmol) was added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.295 cm^3, 1.4 mmol) in THF (5 cm^3) at -78°C. After 30 min at -78°C, a mixture of β-lactams (**6**) (7 : 3) (0.439, 1 mmol) in THF (5 cm^3) was cannulated in the reaction vessel. The mixture was allowed to warm up to -50°C. After 30 min, the mixture was cooled down to -78°C. *N*-Fluorobenzene sulphonimide (0.441, 1.4 mmol) in THF (2 cm^3) was then added and the mixture was allowed to warm up to -30°C. After stirring for 30 min at -30°C, saturated ammonium chloride solution (10 cm^3) was carefully added to the reaction mixture which was then extracted with ethyl acetate (2 x 75 cm^3). The organic phase was stirred with 10% aqueous sodium thiosulphate (50 cm^3) for 30 min, washed with 10% aqueous sodium hydrogen carbonate solution (2 x 50 cm^3), brine (50 cm^3) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the residue purified by column chromatography [ethyl acetate / light petroleum (b.p. 40-60°C) (1 : 4)] to yield the fluorinated ketone (7) as a mixture of two inseparable isomers in the ratio 7 : 3. The ketone (7) was obtained as a white residue (0.435 g, 95%). A sample of pure (2′α,6′β) diastereoisomer was obtained by repeated column chromatography purification. ν_{max} neat/cm^{-1} 1745 (C=O); δ_H (250 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.80 (9H, s, $SiC(CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.25 (3H, d, *J* 6.2, CH_3), 1.45-2.00 (6H, m), 2.92 (1H, dd, $J_{3,4\ trans}$ 2.5, *J* 5.5, 3-H), 3.18 (1H, m, $J_{6',4}$ 5.5, 6′-H), 4.08 (1H, dd, $J_{4,3\ trans}$ 2.5, $J_{4,6'\ cis}$ 5.5, 4-H), 4.18 (1H, m, CH_3CH), 4.75 (1H, ddd, *J* 2.0, *J* 4.5, $J_{H,F}$ 51.5, 2′-H); δ_C (75.5 MHz, $CDCl_3$) -5.35 ($SiCH_3$), -4.93 ($SiCH_3$), -4.64 ($SiCH_3$), -4.31 ($SiCH_3$), 18.01 (SiC), 18.41 (SiC), 19.48 (4′-CH_2, d, *J* 2.5), 22.30 ($CHCH_3$), 25.92 (SiC(CH$_3$)$_3$), 26.25 (SiC(CH$_3$)$_3$), 30.76 (5′-CH$_2$), 34.21 (3′-CH$_2$, d, *J* 22), 50.44 (3-CH), 50.88 (6′-CH, d, *J* 2), 61.00 (4-CH), 66.29 (CH$_3$*CH*), 93.37 (2′-CH, d, *J* 180), 173.55 (N-C=O), 207.54 (C=O, d, *J* 21.8).

LRMS (EI) : m/z 400 [M-C(CH$_3$)$_3$]$^+$ (67%), 285 [M-TBDMS-C(CH$_3$)$_3$]$^+$ (3%), 242 [M-CH$_3$-CH(OTBDMS)-C(CH$_3$)$_3$]$^+$ (14%), 159 [CH$_3$CH(OTBDMS]$^+$ (100%). HRMS (EI) Found: [M]$^+$ 457.28380. $C_{23}H_{44}FNO_3Si_2$ requires M 457.28436.

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(2′*R*,6′*S*)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone (9) and (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(2′S,6′R)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone (8). The ketone (7) (0.1 g, 0.218 mmol) was dissolved in anhydrous methanol (2.5 cm^3). Ammonium fluoride (0.009 g, 0.261 mmol) was added and the mixture was stirred for 30 min. The solvent was then evaporated under vacuum and the residue was purified by column chromatography [ethyl acetate / light petroleum (2 : 1)] to give the ketone as a mixture of two diastereoisomers. The less polar compound, the ketone (**9**) was obtained as a clear viscous oil (0.023 g, 31%) (R$_f$ 0.61); $[\alpha]_D^{25}$ -9.7 (c = 1, CHCl$_3$); ν_{max} (CHCl$_3$)/cm^{-1} 1783 (C=O, β-lactam), 1721 (C=O, ketone) and 1644; δ_H (300 MHz, CDCl$_3$) 0.05 (3H, s, SiCH$_3$), 0.06 (3H, s, SiCH$_3$), 0.86 (9H, s, SiC(CH$_3$)$_3$), 1.20 (3H, d, *J* 6.2, CH$_3$), 1.35 (1H, m, 5′-H), 1.64-1.80 (2H, m, 4′-H and 3′-H), 1.97 (1H, m, 4′-H), 2.15 (1H, m, 5′-H), 2.40 (1H, m, 3′-H), 2.75 (1H, ddd, $J_{3,NH}$ 0.8, $J_{3,4\,trans}$ 2.0, *J* 5.5, 3-H), 2.93 (1H, m, 6′-H), 3.65 (1H, dd, $J_{4,3\,trans}$ 2.0, $J_{4,6'trans}$ 10.0, 4-H), 4.15 (1H, m, CH$_3$C*H*), 4.70 (1H, ddd, *J* 2.0, *J* 4.5, $J_{H,F}$ 51.0, 2′-H), 6.08 (1H, br s, NH); δ_C (69.9 MHz, CDCl$_3$) -4.70 (Si*CH$_3$*), -4.38 (Si*CH$_3$*), 17.91 (Si*C*), 18.66 (4-CH$_2$, d, *J* 3), 22.89 (CH$_3$), 25.78 (SiC(*C*H$_3$)$_3$), 31.40 (5-CH$_2$), 33.76 (3-CH$_2$, *J* 25), 50.10 (3-CH), 52.40 (6′-CH), 63.68 (4-CH), 65.60 (CH$_3$*CH*), 92.68 (2′-CH, d, *J* 197), 167.60 (N-C=O), 207.89 (1′-C=O, d, *J* 24); δ_F (235.5 MHz, CDCl$_3$) -(26.96)-(-26.40) (CF, m).

LRMS (EI) : m/z 286 [M-C(CH$_3$)$_3$]$^+$ (100%), 268 [M+H-C(CH$_3$)$_3$-F]$^+$ (3%), 143 [M-CH$_3$CH(OTBDMS)CHC=O]$^+$ (11%), 75 [(CH$_3$)$_2$SiOH]$^+$ (100%). HRMS Found: [M]$^+$ 343.19866. $C_{16}H_{30}FNO_3Si$ requires M 343.19788.

The more polar isomer (R$_f$ 0.44) was the ketone (**8**), isolated as a white solid (0.046 g, 62%), m.p. 110°C; $[\alpha]_D^{25}$ +1.2 (c = 1, CHCl$_3$); ν_{max} (CHCl$_3$)/cm^{-1} 3419 (NH), 1760 (β-lactam, C=O), 1730 (ketone, C=O); δ_H (300 MHz, CDCl$_3$) 0.04 (3H, s, SiCH$_3$), 0.05 (3H, s, SiCH$_3$), 0.90 (9H, s, SiC(CH$_3$)$_3$), 1.20 (3H, d, *J* 6.2, CH$_3$), 1.55-1.65 (1H, m, 5′-H), 1.60 (3H, m, 4′-H$_a$ 4′-H$_e$ and 3′-H), 2.10 (1H, m, 5′-H), 2.34 (1H, m, 3′-H), 2.87 (1H, dd, $J_{3,4\,trans}$ 2.5, *J* 4.5, 3-H), 3.07 (1H, m, 6′-H), 3.95 (1H, d, $J_{4,3\,trans}$ 2.5, $J_{4,6'\,cis}$ 4.5, 4-H), 4.18 (1H, m, CH$_3$C*H*), 4.72 (1H, ddd, $J_{2',5'}$ 2.0, $J_{2',5'}$ 4.5, $J_{H,F}$ 51.0, 2′-H), 6.20 (1H, br s, NH); δ_C (75.5 MHz, CDCl$_3$) -5.01 (Si*CH$_3$*), -4.28 (Si*CH$_3$*), 17.92 (Si*C*), 18.68 (4′-CH$_2$, d, *J* 3), 22.49 (CH*CH$_3$*), 25.72 (SiC(*C*H$_3$)$_3$), 28.31 (5′-CH$_2$), 34.01 (3′-CH$_2$, d, *J* 22), 48.77 (3-CH), 49.59 (6′-CH, d, *J* 5.4), 61.17 (4-CH), 65.55 (CH$_3$*CH*), 93.10 (2′-CH, d, *J* 179), 168.55 (N-C=O), 207.86 (1′-C=O, d, *J* 22); δ_F (235.5 MHz, CDCl$_3$) (-27.16)-(-26.50) (CF, m). LRMS : m/z 286 [M-C(CH$_3$)$_3$]$^+$ (96%), 143 [M-CH$_3$CH(OTBDMS) CHC=O]$^+$ (14%).

HRMS Found: [M]$^+$ 343.19866. $C_{16}H_{30}FNO_3Si$ requires M 343.19788.

Allyl (4*S*, 8*S*, 9*R*, 10*S*, 12*R*)-4-fluoro-10-[(*S*)-1-(*tert*-butyldimethylsilyl-oxy)ethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (11). A solution of triethylamine (1.23 cm^3, 9.2 mmol) in xylene (20 cm^3) was cooled to 0°C. Allyl oxalyl chloride (0.655 cm^3, 6.9 mmol) was added to the solution. After 15 min the β-lactam (**9**) (0.792 g, 2.3 mmol) in xylene (7 cm^3) was added and the mixture was stirred at 0°C for 30 min. The mixture was washed with 1% aqueous sodium hydrogen carbonate (2 x 5 cm^3), water (5 cm^3), brine (5 cm^3) and dried (MgSO$_4$). The volume of the organic phase, containing the oxalimide (**10**), was then reduced under high vacuum to *ca* 10 cm^3 and triethyl phosphite (1.17 cm^3, 6.9 mmol) was added. The reaction mixture was heated to 140°C for 6 h. The reaction can be conveniently monitored by IR spectroscopy (disappearance of oxalimide C=O band at ~ 1810 cm^{-1}). The solvent was then evaporated under high vacuum and the oily residue purified by column chromatography [light petroleum (b.p. 40-60°C) / ethyl acetate (2 : 1)] to give the fluoro tribactam (**11**), obtained as a colourless oil (0.65 g, 67%) ν_{max} (CHCl$_3$)/cm^{-1} 1783 (β-lactam, C=O), 1721 (ketone, C=O) and 1664; δ_H (250 MHz, CDCl$_3$) 0.10 (6H, s, Si(CH$_3$)$_2$), 0.90 (9H, s, SiC(CH$_3$)$_3$), 1.20 (3H, d, *J* 6.20, CH$_3$), 1.25-2.00 (6H, m), 2.20 (1H, m), 3.20 (1H, dd, *J* 3.5, *J* 6.5, 10-H), 3.30 (1H, m, 8-H), 4.12-4.25 (2H, m, 9-H, 12-H), 4.73 (2H, 2 x dddd, ^4J 1.2, ^4J 1.5, $^3J_{vic}$ 5.5, $^2J_{gem}$ 11.0, -C*H$_2$*CHCH$_2$), 5.24 (1H, dddd, ^4J 1.2, ^4J 1.2, $^2J_{gem}$ 1.5, $^3J_{vic,cis}$ 10.5, -CH=C*H$_2$*), 5.40 (1H, dddd, $^2J_{gem}$ 1.5, ^4J 1.5, ^4J 1.5, $^3J_{vic,trans}$ 17.0, CH=C*H$_2$*), 5.93 (1H, dddd, $^3J_{vic}$ 5.5, $^3J_{vic}$ 5.5, $^3J_{vic,cis}$ 10.5, $^3J_{vic,trans}$ 17.0, CH$_2$C*H*=CH$_2$), 6.12 (1H, ddd, *J* 2.5, *J* 2.5, J_{HF} 51.0, 4-H); δ_C (75.5 MHz, CDCH$_3$) -5.00 (Si*CH$_3$*), -4.27 (Si*CH$_3$*), 17.88 (Si*C*), 20.08 (7-CH$_2$), 22.27 (CH_3), 25.69 ($SiC(CH_3)_3$), 30.25 (6-CH_2), 32.52 (5-CH_2, d, J 24), 44.32 (10-CH), 55.12 (8-CH), 61.34 (9-CH), 65.73 (CO_2CH_2), 66.15 (12-CH), 87.13 (4-CH, d, J 163), 118.44 ($CH=CH_2$), 126.17 (2-C, d, J 8), 131.28 ($CH=CH_2$), 144.23 (3-C, d, J 20), 160.26 (C=O, d, J 3), 175.57 (C=O, d, J 2).

LRMS (EI) : m/z 382 [$M-CH_2=CH=CH_2$] (10%), 366 $[M-C(CH_3)_3]^+$ (41%), 159 $[M-CH_3CH(OTBDMS]^+$ (68%), 115 $[TBDMS]^+$ (59%), 73 $[SiC(CH_3)_3]^+$ (100%). HRMS (EI) Found: $[M]^+$ 423.22433. $C_{22}H_{34}FNO_4Si$ requires M 423.22411.

Allyl (4*S*,8*S*,9*R*,10*S*,12*R*)-4-fluoro-10-[(*S*)-1-hydroxyethyl]-11-oxo-1-aza tricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (12). Tribactam (**11**) (0.553 g, 1.3 mmol) was dissolved in THF (4 cm^3). Glacial acetic acid (1.07 cm^3, 13.7 mmol) and tetrabutylammonium fluoride (1M in THF) (15.4 cm^3, 15.4 mmol) were added and the mixture was heated to 30°C. After 2 h at 30°C, the mixture was diluted with ethyl acetate (50 cm^3), washed with ice-cold saturated ammonium chloride solution, 5% aqueous sodium hydrogen carbonate (15 cm^3), water (15 cm^3), brine (15 cm^3) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the residue was purified by column chromatography [ethyl acetate / light petroleum (b.p. 40-60°C) (2 : 1)] to yield the alcohol (**12**) as a colourless oil (0.260 g, 65%) ν_{max} ($CHCl_3$)/cm^{-1} 3613 (OH), 1776 (β-lactam, C=O), 1726 (ester, C=O) and 1647 (C=C); δ_H (250 MHz, $CDCl_3$) 1.25 (3H, d, J 6.2, CH_3), 1.30-2.00 (6H, m), 2.25 (1H, m), 3.25 (1H, dd, J 3.5, J 6.5, 10-H), 3.40 (1H, m, 8-H), 4.20 (2H, m, 9-H, 12-H), 4.65-4.80 (2H, m, ^4J 1.2, ^4J 1.5, $^3J_{vic}$ 5.5), 5.28 (1H, dddd, ^4J 1.2, ^4J 1.2, $^2J_{gem}$ 1.5, $^3J_{vic,cis}$ 10.5, $-CH_2CHCH_2$), 5.44 (1H, dddd, J_{gem} 1.5, ^4J 1.5, ^4J 1.5, $J_{vic,trans}$ 17.0, $-CH_2CHCH_2$), 5.96 (1H, dddd, $^3J_{vic}$ 5.5, $^3J_{vic}$ 5.5, $^3J_{vic,cis}$ 10.5, $^3J_{vic,trans}$ 17.0, $-CH_2CHCH_2$), 6.15 (1H, ddd, J 2.0, J 3.5, $J_{H,F}$ 51.0, 4-H); δ_C (69.9 MHz, C_6D_6) 14.07 (CH_3), 20.32 (CH_2), 20.77, 21.65 (CH_3), 30.19 (CH_2), 32.57 (5-CH_2, d, J 28), 44.58 (8-CH), 55.39 (8-CH), 61.34 (9-CH), 63.62 (12-CH), 65.24 (CO_2CH_2), 84.45 (4-CH, d, J 181), 118.20 ($CH=CH_2$), 126.61 (2-C, d, J 8), 131.98 ($CH_2=CH$), 144.00 (3-C, d, J 19), 160.65 (O-C=O), 175.57 (N-C=O). LRMS (EI) : m/z 265 $[M+H-CH_3CH(OH)]^+$ (6%), 224 $[M+H-CH_3CH(OH)CHC=O]^+$ (10%), 204 $[M-CH_3CH(OH)CHC=O-F]^+$ (19%), 84 $[CO_2CH_2CH=CH_2+H]^+$ (100%). HRMS (EI) Found: $[M]^+$ 309.13793. $C_{16}H_{20}FNO_4$ requires M 309.13763.

Sodium (4*S*, 8*S*, 9*R*, 10*S*, 12*R*)-4-fluoro-10-[(*S*)-1-hydroxyethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (13). A mixture of $Pd(PPh_3)_4$ (14 mg, 0.04 eq) and triphenylphosphine (2.4 mg, 0.03 eq) in THF (0.5 cm^3) was added to a solution of the alcohol (**12**) (100 mg, 0.323 mmol) in THF (1.5 cm^3). After 5 min sodium-2-ethylhexanoate (45 mg, 1 eq.) in THF (0.5 cm^3) was added. A white solid precipitated out of solution. After 1 h the volume of the reaction mixture was reduced under vacuum to *ca* 1 cm^3 and diethyl ether (~ 2 cm^3) was added. The solution was centrifuged and the supernatant decanted. The solid was washed with diethyl ether / THF mixture (9 : 1) (3 x 3 cm^3) and dried under high vacuum. The sodium salt (**13**) was obtained as a white powder (84 mg, 90%) ν_{max} (KBr)/cm^{-1} 3400 (OH), 1771 (C=O), 1730, 1617 and 1587; δ_H (300 MHz, d^{6}DMSO) 1.12 (3H, d, $J_{13,12}$ 6.2, CH_3), 1.24 (1H, m, 7-H), 1.45 (1H, m, 5-H), 1.61-1.78 (3H, m, 6-H_a, 6-H_e and 7-H), 1.90-2.08 (1H, m, 5-H), 2.95-3.04 (1H, m, 8-H), 3.07 (1H, dd, $J_{10,9\ trans}$ 3, $J_{10,12\ trans}$ 6.5, 10-H), 3.91 (1H, m, $J_{12,OH}$ 4.5, $J_{12,13}$ 6.2, $J_{12,10\ trans}$ 6.5, 12-H), 3.96 (1H, dd, $J_{9,10\ trans}$ 3.0, $J_{9,8\ cis}$ 10.0, 9-H), 4.93 (1H, d, $J_{OH,12}$ 4.5, OH) 6.34 (1H, dt, J 2.5, $J_{H,F}$ 51.0, 4-H). LRMS (EI) : m/z 205 $[M-CH_3CH(OH)CHC=O]^+$ (1%), 187 $[M+H-CH_3CH(OH)CHC=O-F]^+$ (10%). HRMS (EI) Found: $[M]^+$ 291.09323. $C_{13}H_{15}FNNaO_4$ requires M 291.08831.

Imino-Acid (14). NMR spectra were recorded over a period of time on a solution of the tribactam (**13**) in D_2O and showed complete conversion to compound (**14**) after 18 hours. δ_H (500 MHz, D_2O) 1.06 (3H, d, J 6.5), 1.42 (1H, m), 1.58 (1H, m), 1.87 (2H, m), 2.19 (1H, m), 2.27 (1H, dd, J 1.9, 6.5), 2.28 (1H, m), 3.10 (1H, m), 3.80 (1H, m), 4.71 (1H, dd, J 1.9, 9.7), 7.02 (1H, m).

References

1. J. Mann, *Chem. Soc. Rev.*, 1987, **16**, 381.
2. J. A. Wilkinson, *Chem. Rev.*, 1992, **82**, 505.
3. N. V. Shah and L. D. Cama, *Heterocycles*, 1987, **25**, 221.
4. A. Watanabe, M. Sakamoto, Y. Fukagawa and T. Yoshioka, *Chem. Pharm. Bull.*, 1991, **39** (2), 335.
5. R. Wise, *J. Antimicrob. Chemother.*, 1986, **30**, 343.
6. M. Ihara, K. Satoh, N. Taniguchi, K. Fukumoto, Y. Ishida and M. Takemura, *Heterocycles*, 1993, **35** (1), 139.

7. K. Araki, J. A. Wichtowski and J. A. Welch, *Tetrahedron Lett.*, 1991, **32**, 5461.
8. T. Fuchigami, S. Narizuka and A. Konno, *J. Org. Chem.*, 1992, **57**, 3755.
9. B. Tamburini, A. Perboni, T. Rossi, D. Donati, D. Andreotti, G.Gaviraghi, R.Carlesso and C. Bismara (Glaxo S. p. A.), Eur. Pat. Appl. 0 416 953 A2, 1991, Bulletin 91/11; B. Tamburini, A. Perboni, T. Rossi, D. Donati, G. Gaviraghi and G. Tarzia, *"Recent Advances in the Chemistry of Anti-Infective Agents"*, ed. P. H. Bentley and R. Ponsford, RSC, Cambridge, 1992, pp.21-35.
10. A. Padova, S. M. Roberts, D. Donati, A. Perboni and T. Rossi, *J. Chem. Soc., Chem. Commun.*, 1994, 441.
11. A. Padova, S. M. Roberts, D. Donati, C. Marchioro and A. Perboni, *J. Chem. Soc.,Chem. Commun.*, 1995, 661.
12. E. Differding and H. Ofner, *Synlett*, 1991, 187.
13. A. Afonso, F. Hon, J. Weinstein and A. K. Ganguly, *J. Am. Chem. Soc.*, 1982, **104**, 6139.
14. P. D. Jeffrey and S. W. McCombie, *J. Org. Chem.*, 1982, **47**, 587.

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