

## THE SYNTHESSES OF 1 $\alpha$ -FLUORO-1 $\beta$ -METHYLCARBAPENEM ESTERS

Kenneth J. Wildonger\*, William J. Leanza, Ronald W. Ratcliffe, and James P. Springer†

Departments of Medicinal Chemistry and Biophysical Chemistry†, Merck Research Laboratories,  
P. O. Box 2000, Rahway, NJ 07065, U. S. A.

**Abstract** - The synthesis of *p*-nitrobenzyl (1*S*,3*R*,5*S*,6*S*)-1-fluoro-1-methyl-2-oxo-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]carbapenam-3-carboxylate and allyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-[(allyloxycarbonyloxy)ethyl]-1-fluoro-1-methyl-2-phenylcarbapen-2-em-3-carboxylate is detailed. The difficulties encountered in further chemical elaboration of these analogs are reported.

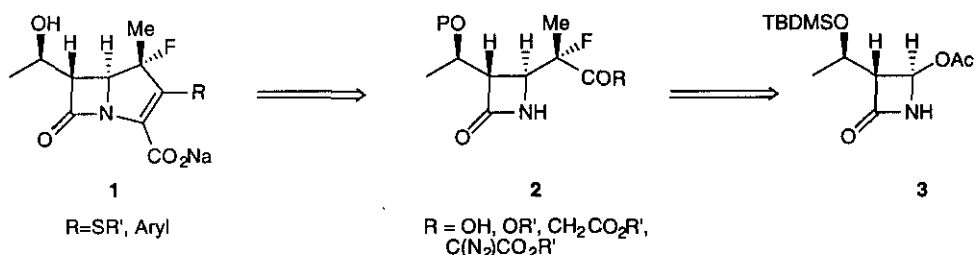
1 $\beta$ -Methylcarbapenems possess enhanced chemical stability, reduced susceptibility to renal dehydropeptidase enzyme (DHP-I), and generally undiminished antibacterial activity in comparison to parent 1-*H*-carbapenems.<sup>1</sup> These features have shifted the focus of carbapenem chemistry and elucidation of biological activity towards 1-methylcarbapenem 2-thio<sup>2</sup> and 2-aryl<sup>3</sup> derivatives. However, there are only limited reports of 1,1-dimethyl substituted carbapenems<sup>4,5</sup> and a single reference to a 1-heteroatom(OMe)-1-methyl-2-thio substituted carbapenem.<sup>5</sup> A recent disclosure<sup>6</sup> on the preparation of a monocyclic intermediate for 1-fluoro-1-methylcarbapenems has prompted us to communicate our efforts in this area.

Our interest in 1-fluoro-1-methylcarbapenems originates from questions regarding the steric and electronic effects of fluorine substitution on chemical reactivity and bioactivity. We were also interested in evaluating the effects of fluorine substitution on binding to the target PBP enzymes as well as to DHP-I. The C-F bond (1.39 Å) is the second shortest carbon bond after the C-H bond (1.09 Å) and is similar to that of a C-O bond (1.43 Å). The van der Waals radius of fluorine (1.35 Å) is only slightly larger than that of hydrogen (1.20 Å),<sup>7</sup> yet Taft E<sub>s</sub> parameters place the steric bulk of a CF<sub>3</sub> group on a level with the isopropyl group.<sup>8</sup> Fluorine is, of course, the most electronegative element (4.0 on the Pauling scale, 3.5 for oxygen). It is also recognized that fluorine substitution increases the lipophilicity of a molecule.

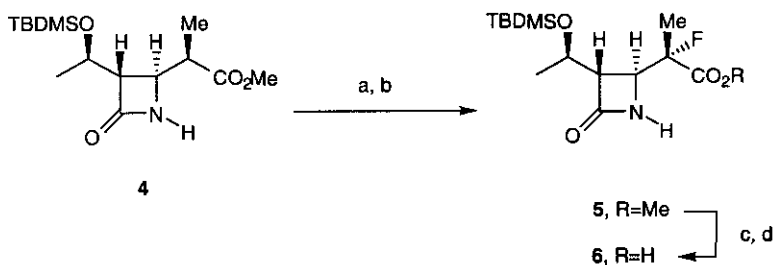
Retrosynthetically, it was envisioned (Scheme 1) that a preparation of 1-fluoro-1-methylcarbapenems (**1**) could follow from the fluoro substituted azetidinone (**2**) using established carbapenem chemistry.<sup>9</sup> The key intermediate (**2**) should be accessible from the commercially available acetoxy azetidinone (**3**), also using

established chemistry. Our interest was in the 1 $\alpha$ -fluoro-1 $\beta$ -methyl isomer series, although a route preparing both diastereomers of **2** would offer the possibility of preparing the epimeric carbapenem.

## Scheme 1



We initially attempted the most straightforward preparation of an ester derivative of **2**. The 1 $\beta$ -methyl-carbapenem precursor (**4**)<sup>1</sup> was converted to its enolate (LDA (2.0 eq.), HMPA (2.1 eq.) in THF, -78°C) which was allowed to react with *N*-fluoro-*N*-(*exo*-2-norbornyl)-*p*-toluenesulfonamide<sup>10</sup> (1.0 eq., -78°C to room temperature). The desired diastereomer (**5**)<sup>11</sup> was isolated by chromatography and crystallized in a 35% overall yield. The structure of **5**, Figure 1, was established by single crystal X-ray analysis.<sup>12</sup> The ester was hydrolyzed to afford the acid (**6**).<sup>13</sup>



Reagents: (a) LDA, HMPA, THF; (b) *N*-fluoro-*N*-(*exo*-2-norbornyl)-*p*-toluenesulfonamide; (c) 1N LiOH; (d) 2N HCl.

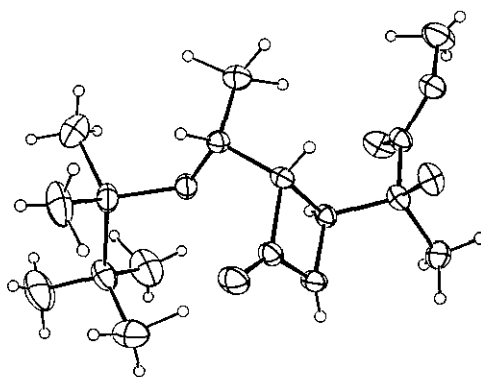
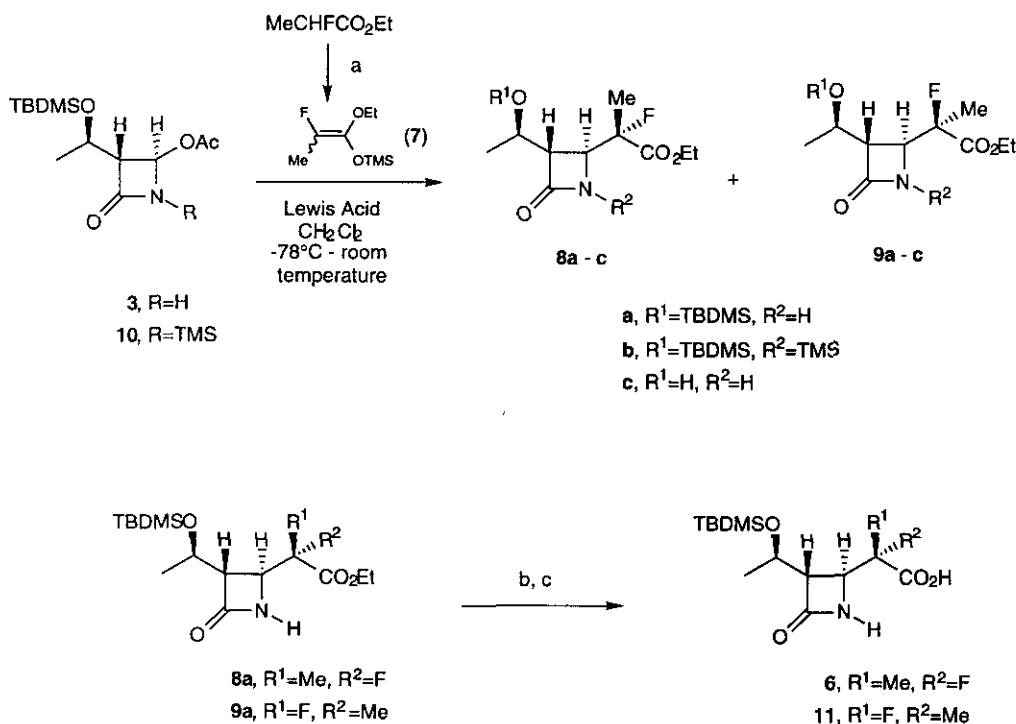


Figure 1. X-ray structure of **5**

In order to improve the yield of ester (**5**) and facilitate its preparation from a readily available intermediate, the established methodology<sup>14</sup> which utilizes a Lewis acid to mediate carbon-carbon bond formation between C-4 of an acetoxy azetidione and a ketene acetal was explored.<sup>15</sup> Treatment of ethyl 2-fluoropropionate with LDA and chlorotrimethylsilane gave the silyl ketene acetal (**7**)<sup>16</sup> which by <sup>1</sup>H nmr showed a 61:39 isomer ratio. Attempts to assign the *E* and *Z* isomers by various nmr techniques were unsuccessful. The use of freshly fused ZnI<sub>2</sub> (0.5 eq.) with acetoxyazetidione (**3**) (1.0 eq.) and **7** (2.0 eq.) in methylene chloride (0°C to room temperature) gave a mixture of two pairs (each pair a 1:1 ratio) of diastereomers in approximately a 2:1 ratio. The major pair of isomers was identified as **8a** and **9a** and the minor pair as the *N*-silylated diastereomers (**8b**) and (**9b**) (77% overall yield based on observed product distribution). The use of TMSOTf (1.0 eq.) with acetoxyazetidione (**3**) (1.0 eq.) and silylketene acetal (**7**) (2.0 eq.) in methylene chloride (-78°C to room temperature) gave an 87% yield of a 1:1 mixture of diastereomers (**8a**)<sup>17</sup> and (**9a**).<sup>18</sup> When less than 2 equivalents of ketene acetal (**7**) was used, the yield of **8a** and **9a** decreased and a concomitant increase in side products developed.

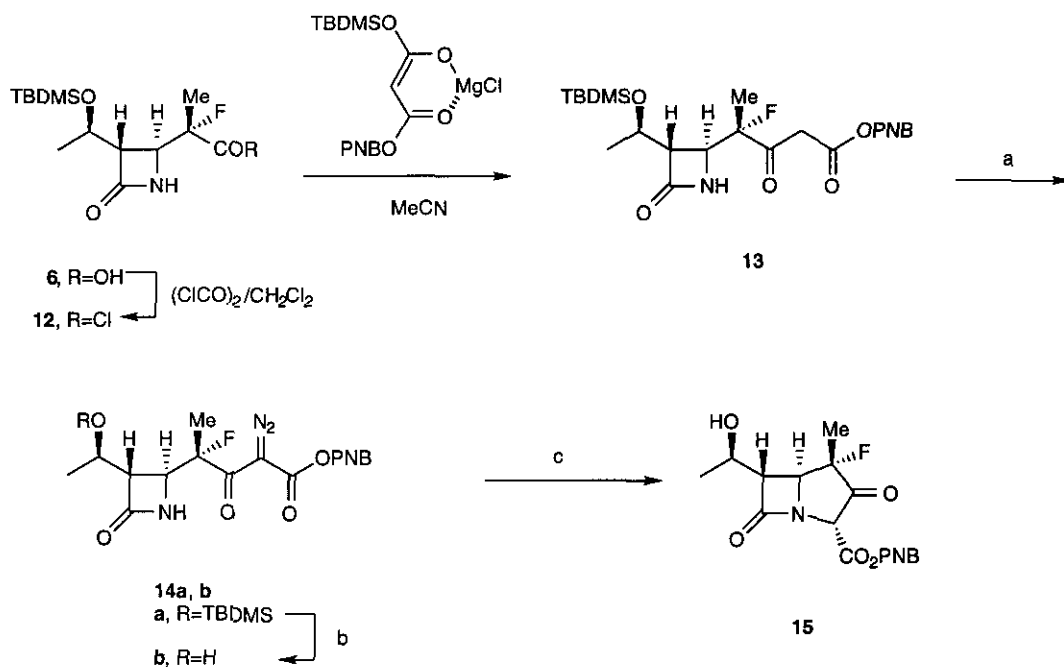


Reagents: (a) LDA, TMSCl, THF, -78°C to room temperature; (b) 1N LiOH; (c) 2N HCl.

The improved product yield of **8a** and **9a** using TMSOTf as Lewis acid led us to explore the addition reaction between ketene acetal (**7**) and acetoxyazetidione (**3**) to determine the optimum equivalents of ketene acetal required. It appeared that for the desired reaction to proceed, intermediate silylation of the lactam nitrogen was required. When the *N*-TMS derivative (**10**) was employed using a reduced quantity of ketene acetal (**7**) (1.25 eq.), two pairs of diastereomers were produced in an 87:13 ratio with both pairs in 1:1 ratios. The major pair of

diastereomers were **8a** and **9a** and the minor pair were the *O*-desilylated products (**8c**) and (**9c**) (total yield 89%). To facilitate work-up, the entire crude reaction was subjected to *O*-silylation conditions (TBDMSCl, imidazole, DMF, room temperature) and chromatographed into the individual diastereomers (**8a**) and (**9a**). The ethyl ester diastereomers were individually hydrolyzed to give acids (**6**) and (**11**),<sup>19</sup> respectively.<sup>20</sup> The absolute configurations of the individual acids isolated from this route were established by comparison to the acid derived from methyl ester (**5**).

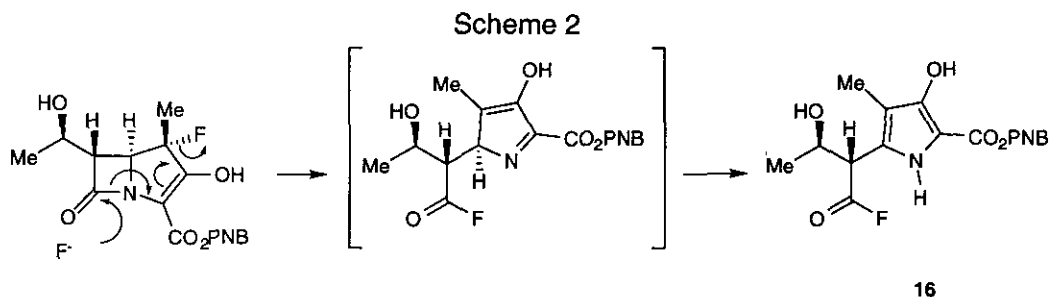
Complete elaboration of the  $\alpha$ -fluorocarboxylic acid (**6**) to a 2-thio substituted carbapenem was modeled after the chemistry developed at Merck.<sup>1</sup> The first step in the scheme, side-chain extension to a  $\beta$ -keto ester, proved unexpectedly difficult. After examining various methods of  $\beta$ -keto ester formation,<sup>21</sup> a modified method described by Rathke<sup>22</sup> was employed. The carboxylic acid (**6**) was converted to acid chloride (**12**) which was allowed to react with a magnesium malonate to give **13** (81%). The keto ester (**13**) was converted to the diazo derivative (**14a**) (98%) which was desilylated to provide **14b**.<sup>23</sup>



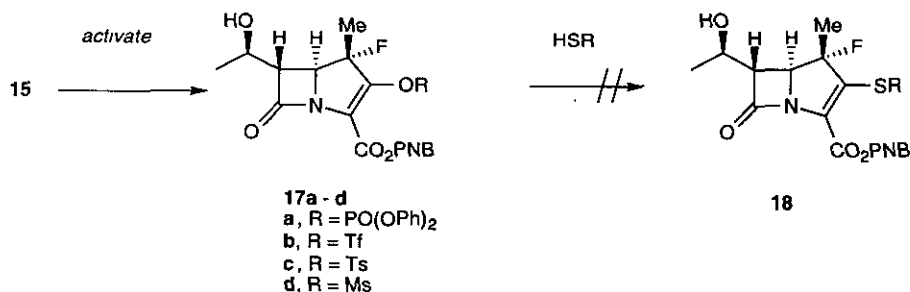
Reagents: (a) *p*-(HO<sub>2</sub>C)C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>N<sub>3</sub>, *i*-Pr<sub>2</sub>NEt, MeCN; (b) BF<sub>3</sub>Et<sub>2</sub>O, MeCN; (c) Rh<sub>2</sub>(Oct)<sub>4</sub> (0.2%), benzene.

Cyclization of **14b** was accomplished using rhodium octanoate (0.2 mol %) in toluene (80°C) to give the bicyclic keto ester (**15**)<sup>24</sup> and several decomposition products, one of which predominated. The bicyclic keto ester (**15**) was unstable towards silica gel chromatography and decomposed slowly in solution. The major decomposition product lacked large proton-fluorine couplings by <sup>1</sup>H nmr and contained two signals attributed to methyl groups at  $\delta$ (CDCl<sub>3</sub>, 400 MHz) 1.16 (d, J=6.3 Hz) and 1.94 (s). Additionally, two signals appeared at  $\delta$  3.83 (t, J~3 Hz) and 4.62 (dq, J=3.0, 6.3 Hz). An nmr COSY experiment showed cross-peaks between the downfield signal pair, and the upfield methyl doublet and the downfield doubled quartet. These resonances are

consistent with the pyrrole structure (16), shown as arising *via* Scheme 2, where  $\beta$ -lactam ring opening is initiated by fluoride attack leading to an acyl fluoride. The acyl fluoride structure (16) is supported by a small ( $\sim 3$  Hz) three bond H-F coupling to the  $\alpha$ -carbonyl proton<sup>25</sup> and by a high frequency carbonyl stretching band in the  $\text{ir}(\text{CH}_2\text{Cl}_2, 1820 \text{ cm}^{-1})$ .



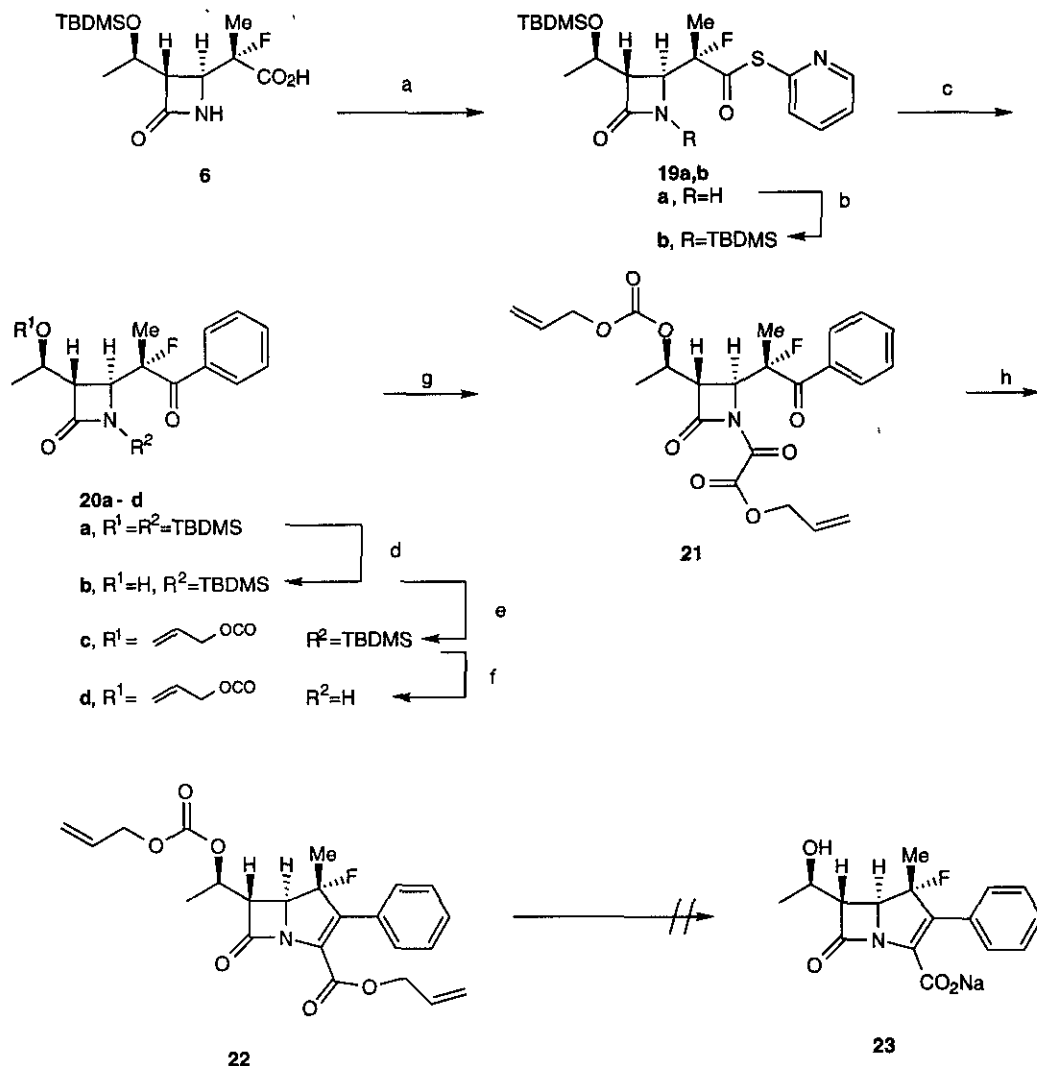
Activation of the 2-position of the bicyclic keto ester for addition of an appropriate thiol to give a penultimate 2-thio derivative was next explored. Attempts to prepare the (diphenylphosphono)oxy derivative (17a) cleanly and in good yields from the bicyclic keto ester ( $\text{ClPO}(\text{OPh})_2$ ,  $i\text{-Pr}_2\text{NEt}$ , MeCN,  $-35$  to  $-16^\circ\text{C}$ ) proved elusive. Generally, decomposition occurred during reaction and a very low yield of presumed 17a formed. Attempts to isolate 17a were unsuccessful. The enol phosphate which was produced was allowed to react *in situ* with *N*-*p*-nitrobenzyloxycarbonylcysteamine without any indication (followed by uv) of addition. Attempts were made to prepare the enol triflate (17b), enol tosylate (17c), and enol mesylate (17d), without any indication of their formation. The *in situ* addition of thiol to reactions directed at preparing 17b-d failed to give any indication of their addition to yield 18. Extensive decomposition occurred in all cases.



Frustrated in these attempts to prepare a 2-thio derivative, we turned our attention towards preparing a 2-aryl derivative *via* the established oxalimide route.<sup>26</sup> The 2-phenyl derivative was selected as a target for preparation, being the simplest 2-aryl derivative, with known  $1\beta$ -methyl- and 1-*H*-carbapenem counterparts. Allyl protection of both the ester and alcohol functionality was chosen for facility of deblocking.

The  $\alpha$ -fluorocarboxylic acid (6) was converted to the pyridylthiol ester (19a) using 2-pyridyl disulfide in the presence of triphenylphosphine. The lactam nitrogen of the thiol ester was silylated to provide 19b which was allowed to react with phenylmagnesium bromide to give the phenyl ketone (20a). To interconvert the hydroxyl

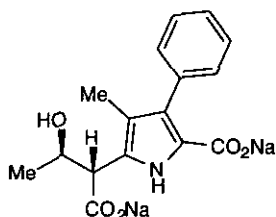
protection, the TBDMS ether was deblocked to give alcohol (**20b**) and the alcohol was protected as its allyloxycarbonyl derivative (**20c**). Desilylation of the lactam nitrogen provided **20d**. Condensation of allyl chlorooxalate with lactam (**20d**) gave the oxalimide (**21**). Cyclization of **21** was best achieved in a single step by heating with triethyl phosphite (10 eq.) in refluxing *p*-xylene (2.5 h) to afford the carbapenem (**22**).<sup>27</sup> The crude product was found to be unstable on preparative thin layer chromatography; however, the desired product could be purified by silica gel flash chromatography (53% isolated yield).



Reagents: (a) PPh<sub>3</sub>, 2-pyridyl disulfide, CH<sub>2</sub>Cl<sub>2</sub>; (b) TBDMSCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (c) PhMgBr, THF; (d) BF<sub>3</sub>·Et<sub>2</sub>O, MeCN; (e) allyl chlorooxalate, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; (f) TBAF, HOAc, THF; (g) allylchloro oxalate, pyridine, CH<sub>2</sub>Cl<sub>2</sub>; (h) P(OEt)<sub>3</sub>, xylene, 110°C - reflux.

Attempts to deblock the allyl ester and carbonate protecting groups of penultimate intermediate (**22**) to give carbapenem (**23**) using catalytic tetrakis(triphenylphosphine)palladium(0) in the presence of triphenylphosphine, sodium hexanoate, and hexanoic acid in ethyl acetate provided a fully deblocked product

lacking fluorine and a  $\beta$ -lactam ring. On the basis of  $^1\text{H}$  nmr<sup>28</sup> this compound has been identified as the pyrrole derivative (24).



24

Deblocking attempts using tributyltin hydride (2.1 eq.) in the presence of triphenylphosphine (0.33 eq.) and palladium(0) bis(dibenzylideneacetone) (0.04 eq.) in tetrahydrofuran followed by glacial acetic acid quench similarly failed to give any indication of desired product. Extensive decomposition was observed. The failure of these deblock attempts caused us to reassess our efforts at producing a fully deblocked  $1\alpha$ -fluoro- $1\beta$ -methyl-carbapenem.

The instability of a our  $1\alpha$ -fluoro- $1\beta$ -methylcarbapenem target carbapenems is surprising in view of the successful synthesis of a 1,1-difluorocarbapenem.<sup>29</sup> It is clear from the results described herein that the  $1\alpha$ -fluoro substituent imparts considerable chemical instability to the carbapenem amide bond, presumably by an inductive effect.<sup>30</sup> This is evidenced by the isolation of the  $\beta$ -lactam ring opened product (24). The electronic effect of the fluorine substituent overwhelms any gains realized by addition of steric bulk at 1-position and ultimately, prevents isolation of desired deblocked final product. The failure to activate and add a thiol to the bicyclic keto ester (15) may also be influenced by the increased steric bulk introduced at the 1-position. For example, the 1,1-dimethyl keto ester analogous to 15 cannot be converted to a 2-thio derivative because of the steric hindrance of the 1,1-dimethyl group.<sup>5</sup>

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11. **5**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.07 (2 s,  $\text{Si}(\text{CH}_3)_2$ ), 0.87 (s,  $\text{C}(\text{CH}_3)_3$ ), 1.13 (d,  $J=6.2$  Hz,  $\text{CH}_3\text{CHOSi}$ ), 1.62 (d,  $J=21.3$  Hz,  $\text{CH}_3\text{CF}$ ), 3.27 (t,  $J=2.3$  Hz,  $\text{SiOCHCH}$ ), 3.82 (s,  $\text{OCH}_3$ ), 4.01 (dd,  $J=2.3$ , 15.9 Hz,  $\text{CHC}(\text{CH}_3)\text{F}$ ), 4.23 (m,  $\text{CH}_3\text{CHOSi}$ ), 6.04 (s, NH); mp. 181-182°C; Anal. Calcd for  $\text{C}_{15}\text{H}_{28}\text{NO}_4\text{FSi}$ : C, 54.03; H, 8.46. Found: C, 53.85; H, 8.45.
12. Compound  $\text{C}_{15}\text{H}_{28}\text{NO}_4\text{FSi}$  (**5**),  $M_r = 333.479$ , monoclinic,  $P2_1$ ,  $a = 9.818(2)$ ,  $b = 7.667(9)$ ,  $c = 13.518(6)$  Å,  $\beta = 109.97(3)^\circ$ ,  $V = 956(2)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_x = 1.158$  g cm<sup>-3</sup>, monochromatized radiation  $\lambda(\text{Cu } K\alpha) = 1.541838$  Å,  $\mu = 1.29$  mm<sup>-1</sup>,  $F(000) = 360$ ,  $T = 294$  K. Data were collected on a Enraf-Nonius CAD4 diffractometer to a  $\theta$  limit of  $57^\circ$  which yielded 1399 measured (1394 unique) reflections. There are 1336 unique, observed reflections (with  $I \geq 3\sigma(I)$  as the criterion for being observed) out of the total measured. The structure was solved by direct methods (SHELXS-86; G. M. Sheldrick, *Acta Crystallogr.*, 1990, A46, 467) and refined using full-matrix least-squares on  $F$  (SDP-PLUS; Structure Determination Package Version 3, Enraf-Nonius, Delft, 1985). The final model was refined using 185 parameters and the observed data. All non-hydrogen atoms were refined with anisotropic thermal displacements. The hydrogen atoms were located by difference Fourier and calculation and included in the calculations with fixed isotropic thermal parameters of approximately the same size as those of the attached atom. The hydrogen positional parameters, except for those on C13, were allowed to refine in the final cycles. The final agreement statistics are:  $R = 0.047$ ,  $wR = 0.064$ ,  $S = 2.82$  with  $(\Delta/\sigma)_{\text{max}} = 1.41$ . The least-squares weights were defined using  $1/\sigma^2(F)$ . The maximum peak height in a final difference Fourier map is  $0.19(5)$  eÅ<sup>-3</sup> and this peak is without chemical significance. The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
13. **6**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.07 and 0.09 (2 s,  $\text{Si}(\text{CH}_3)_2$ ), 0.88 (s,  $\text{C}(\text{CH}_3)_3$ ), 1.22 (d,  $J=6.3$  Hz,  $\text{CH}_3\text{CHOSi}$ ), 1.64 (d,  $J=21.2$  Hz,  $\text{CH}_3\text{CF}$ ), 3.39 (m,  $\text{SiOCHCH}$ ), 4.05 (dd,  $J=2.1$ , 14.1 Hz,  $\text{CHC}(\text{CH}_3)\text{F}$ ), 4.23 (m,  $\text{CH}_3\text{CHOSi}$ ), 6.94 (s, NH); mp. 149.5-150.0°C. Anal. Calcd for  $\text{C}_{14}\text{H}_{26}\text{NO}_4\text{FSi}$ : C, 52.64; H, 8.20; N, 4.39. Found: C, 52.49; H, 8.18; N, 4.18.
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16. J.T. Welsh, J.S. Plummer, and T-S. Chou, *J. Org. Chem.*, 1991, **56**, 353. **7**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.22 (s,  $\text{Si}(\text{CH}_3)_3$ ), 1.22 and 1.24\* (t,  $J=7.1$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.89\* and 1.93 (d,  $J=17.0$  Hz,  $\text{CH}_3$ ), 3.80 and 3.89\* (q,  $J=7.1$  Hz,  $\text{CH}_2\text{CH}_3$ ), \* denotes major isomer; bp 95-98°C (128 torr); Anal. Calcd for  $\text{C}_8\text{H}_{17}\text{O}_2\text{FSi}$ : C, 49.97; H, 8.91. Found: C, 50.16; H, 8.65.
17. **8a**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.08 (2 s,  $\text{Si}(\text{CH}_3)_2$ ), 0.88 (s,  $\text{C}(\text{CH}_3)_3$ ), 1.16(d,  $J=6.4$  Hz,  $\text{CH}_3\text{CHOSi}$ ), 1.33 (t,  $\text{CH}_2\text{CH}_3$ ,  $J=7.2$  Hz), 1.62 (d,  $J=21.2$  Hz,  $\text{CH}_3\text{CF}$ ), 3.29 (t,  $J=2.5$  Hz,  $\text{SiOCHCH}$ ), 4.03 (dd,  $J=2.5$ , 15.2 Hz,  $\text{CHC}(\text{CH}_3)\text{F}$ ), 4.24 (m,  $\text{CH}_3\text{CHOSi}$ ), 4.28 (q,  $J=7.2$  Hz,  $\text{CH}_2\text{CH}_3$ ), 5.90(s, NH); mp 142-143°C; Anal. Calcd for  $\text{C}_{16}\text{H}_{30}\text{NO}_4\text{FSi}$ : C, 55.30; H, 8.70. Found: C, 55.38; H, 8.70.
18. **9a**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.08 and 0.09 (2 s,  $\text{Si}(\text{CH}_3)_2$ ), 0.88(s,  $\text{C}(\text{CH}_3)_3$ ), 1.23 (d,  $J=6.3$  Hz,  $\text{CH}_3\text{CHOSi}$ ), 1.34 (t,  $\text{CH}_2\text{CH}_3$ ,  $J=7.1$  Hz), 1.59 (d,  $J=21.4$  Hz,  $\text{CH}_3\text{CF}$ ), 3.14 (m,  $\text{CHC}(\text{CH}_3)\text{F}$ ), 4.00 (dd,  $J=2.2$ , 20.9 Hz,  $\text{SiOCHCH}$ ), 4.23 (m,  $\text{CH}_3\text{CHOSi}$ ), 4.28 (q,  $J=7.1$  Hz,  $\text{CH}_2\text{CH}_3$ ), 5.76 (s, NH); mp 135-135°C; Anal. Calcd for  $\text{C}_{16}\text{H}_{30}\text{NO}_4\text{FSi}$ : C, 55.30; H, 8.70. Found: C, 55.22; H, 8.70.
19. **11**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.07 and 0.09 (2 s,  $\text{Si}(\text{CH}_3)_2$ ), 0.87 (s,  $\text{C}(\text{CH}_3)_3$ ), 1.25 (d,  $J=6.2$  Hz,  $\text{CH}_3\text{CHOSi}$ ), 1.62 (d,  $J=22$  Hz,  $\text{CH}_3\text{CF}$ ), 3.22 (d,  $J=6$  Hz,  $\text{SiOCHCH}$ ), 4.04 (d,  $J=21$  Hz,  $\text{CHC}(\text{CH}_3)\text{F}$ ), 4.25 (quintet,  $J=6$  Hz,  $\text{CH}_3\text{CHOSi}$ ), 6.71 (s, NH); mp 174.8-175.0°C; Anal. Calcd for  $\text{C}_{14}\text{H}_{26}\text{NO}_4\text{FSi}$ : C, 52.64; H, 8.20; N, 4.39. Found: C, 52.70; H, 8.27; N, 4.10.
20. Attempts to improve the diastereoselectivity of the "aldol" condensation by replacing ketene acetal (**7**) with the tin enolate derived from 3-(2-fluoropropionyl)-4,4-dimethyloxazolidine-2-thione were unsuccessful. No addition products were observed.
21. Attempts to utilize the Masamune procedure (D. W. Brooks, L. D.-L. Lu, and S. Masamune, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 72) or to acylate Meldrum's acid as a route towards  $\beta$ -keto ester were unsuccessful. However, the Eschenmoser reaction (M. Roth, P. Dubs, E. Götschi and E. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710) using the allyloxycarbonylmethylthio ester of **6** did successfully give the corresponding allyl  $\beta$ -keto ester (32% yield).
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23. **14b**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.29 (d,  $J=6.3$  Hz,  $\text{CH}_3\text{CHOH}$ ), 1.66 (d,  $J=22.4$  Hz,  $\text{CH}_3\text{CF}$ ), 2.00 (d,  $J=4.3$  Hz, OH), 3.25 (dd,  $J=2.5$ , 5.7 Hz,  $\text{HOCHCH}$ ), 4.11 (dd,  $J=2.5$ , 13.9 Hz,  $\text{CHC}(\text{CH}_3)\text{F}$ ), 4.21 (m,  $\text{CH}_3\text{CHOH}$ ), 5.39 (s,  $\text{CH}_2$ ), 6.11 (s, NH), 7.57 (d,  $J=8.7$  Hz,  $\text{ArH}_2$ ), 8.26 (d,  $J=8.7$  Hz,  $\text{ArH}_2$ ); mp 131-132°C.
24. **15**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.41 (d,  $J=6.3$  Hz,  $\text{CH}_3\text{CHOH}$ ), 1.54 (d,  $J=22.5$  Hz,  $\text{CFCH}_3$ ), 3.35 (dd,  $J=2.0$ , 6.4 Hz, H-6), 4.15 (dd,  $J=2.0$ , 15.7 Hz, H-5), 4.38 (m,  $\text{CH}_3\text{CHOH}$ ), 4.78 (d,  $J=1.4$  Hz, H-3), 5.29 and 5.38 (ABq,  $J=13.3$  Hz,  $\text{CH}_2\text{Ar}$ ), 7.55 (d,  $J=8.6$  Hz,  $\text{ArH}_2$ ), 8.25 (d,  $J=8.6$  Hz,  $\text{ArH}_2$ ); ir ( $\text{CH}_2\text{Cl}_2$ ) 3050, 2980, 1781, 1760, 1522, 1420, 1345  $\text{cm}^{-1}$ .
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27. **22**:  $^1\text{H}$  Nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.48 (d,  $J=21.0$  Hz,  $\text{CFCH}_3$ ), 1.51 (d,  $J=6.4$  Hz,  $\text{CH}_3\text{CHO}$ ), 3.41 (dd,  $J=4.0, 7.3$  Hz, H-6), 4.40 (dd,  $J=4.0, 31.7$  Hz, H-5), 4.57 and 4.66 (dd,  $J=5.6, 13.4$  Hz,  $\text{OCH}_2$ ), 4.64 and 4.68 (ABq,  $J=13$  Hz,  $\text{OCH}_2$ ), 5.1-5.4 (m,  $\text{CH}_2$ ), 5.23 (quintet,  $J=6$  Hz,  $\text{CH}_3\text{CHO}$ ), 5.65-5.8 (m, ester  $\text{CH}_2\text{CHCH}_2$ ), 5.85-6.00 (m, carbonate  $\text{CH}_2\text{CHCH}_2$ ), 7.34-7.40 (m,  $\text{ArH}_5$ ); ir ( $\text{CH}_2\text{Cl}_2$ ) 3060, 2980, 2960, 1795, 1745, 1730, 1450  $\text{cm}^{-1}$ ; uv (MeCN)  $\lambda_{\text{max}}$  282 nm; ms (EI)  $m/z$  429 ( $\text{P}^+$ ).
28. **24**:  $^1\text{H}$  Nmr ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  1.28 (d,  $J=6.2$  Hz,  $\text{CH}_3\text{CHO}$ ), 1.91 (s,  $\text{CH}_3$ ), 3.57 (d,  $J=8.1$  Hz,  $\text{CHCO}_2$ ), 4.35 (dq,  $J=6.2, 8.1$  Hz,  $\text{CH}_3\text{CHOH}$ ), 7.3-7.5 (m,  $\text{ArH}_5$ ).
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30. In addition, the potential for concomitant expulsion of fluoride during collapse of a lactam tetrahedral intermediate may further destabilize the bicyclic ring system.

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