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SYNTHESIS OF A NOVEL CARBAPENEM-POTASSIUM (5R,6R)-1,1-DIFLUORO-2-PHENYL-6-(1R-HYDROXYETHYL)-CARBAPEN-2-EM-3-CARBOXYLATE. THE USE OF A NEW N-PROTECTING GROUP IN β-LACTAM SYNTHESIS

Nalini V. Shah and Lovji D. Cama*

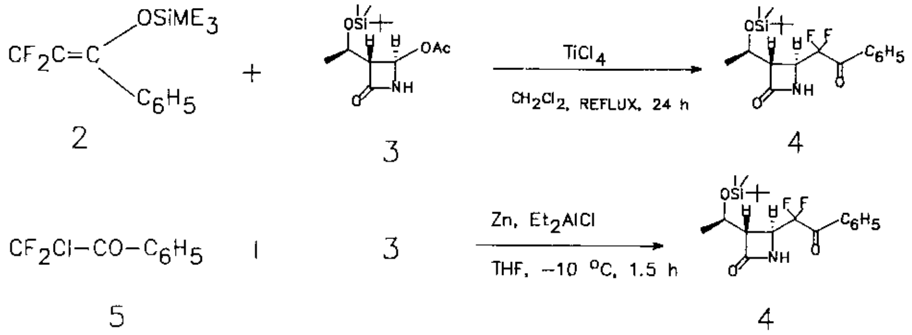
Merck Sharp and Dohme Research Laboratories, Rahway, N.J. 07065, USA

This publication is dedicated to Prof. Gilbert Stork on the occasion of his 65th birthday.

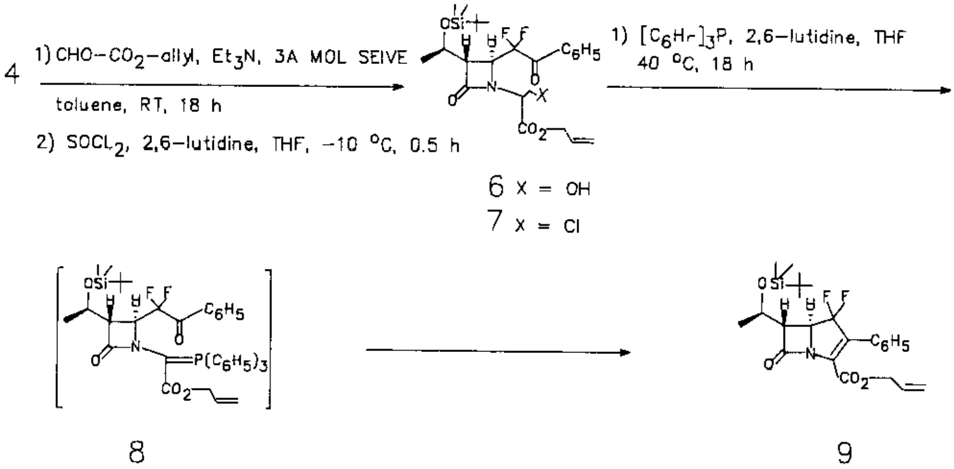
Abstract — A synthesis of a novel 1,1-difluorocarbapenem (1), utilizing a new N-protecting group for the 1-position of 2-azetidinones is described.

The discovery that substitution of a β-methyl group at the 1-position of carbapenems often results in high stability to the renal dehydropeptidase enzyme DHP-1, without loss of antibiotic activity[1] led us to investigate the effects of other groups at the 1-position. Substitution of the 1-position by hydroxy and methoxy groups has been described by us[2] and others[3]. Herein we wish to report on the synthesis of a 1,1-difluorocarbapenem and the use of a novel N-protecting group which we discovered during the course of this synthesis. We were interested in fluorine substitution because the strong electron withdrawing effect of fluorine could result in a highly reactive β-lactam, while its relatively small steric size, in between H and CH_3 could still contribute towards stability to the DHP-1 enzyme, without loss of activity.

The report of a synthesis of the enol-silyl ether 2[4] attracted us to the possibility of alkylating (3R,4R)-3-(1R-t-butyldimethylsilyloxyethyl)-4-acetoxyazetidin-2-one (3)[5] with 2 to give (3R,4R)-3-(1R-t-butyldimethylsilyloxyethyl)-4-(2-phenyl-2-oxo-1,1-difluoro)-azetidin-2-one (4), which in turn could then be converted in a number of well established steps to the 1,1-difluoro-2-phenylcarbapenem 1. Since the antibiotic activity of the corresponding 1-unsubstituted 2-phenylcarbapenem is well known[6], a comparision with it would enable us to learn about the effects of 1,1-difluoro substitution.

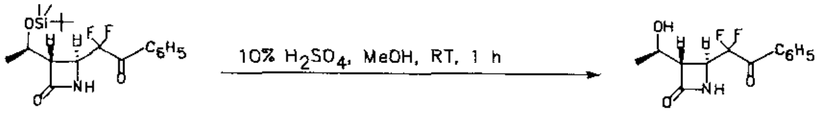


Chlorodifluoroacetic acid 1 was treated with excess phenylmagnesium bromide to yield chlorodifluoroacetophenone in 68% yield. Conversion to its enolsilyl ether 2 (Zn, TMSCl, CH_3CN, 60°C) followed by alkylation of **3** with 2 in the presence of $TiCl_4$ (CH_2Cl_2, reflux, 24 h) gave 4[7] in 20% yield. The same transformation could also be carried out by alkylation of **3** with the aluminum enolate from chlorodifluoroacetophenone (5) (Zn, Et_2AlCl, THF) giving **4** in 27% yield The difluoroketone **4** now became a key intermediate in the synthesis of the title compound.



The difluoroketone **4** was converted to the carbapenem **9** using a modification of the well established glyoxalate route[8], demonstrating the overall feasibility of constructing a 1,1-difluorocarbapenem. Thus treatment of 4 with allyl glyoxalate (Et_3N, 3A^0 Mol. Sieve, toluene, RT, 18 h, 62%) gave the carbinols 6 (mixture of isomers at the hydroxy bearing carbon) which were converted to the chloro compounds 7 ($SOCl_2$, 2,6-lutidine, THF, -10°C, 0.5 h, 63%). On treatment of the chloro derivatives with triphenylphosphine (2,6-lutidine, THF, 40°C, 18 h) one obtained the bicyclic carbapenem 9[9](42%) with only transient formation of the ylide intermediate **8**. The difluoro substitution in ketone **8** leads to its high reactivity, resulting in cyclization of the ylide under the conditions of its formation.

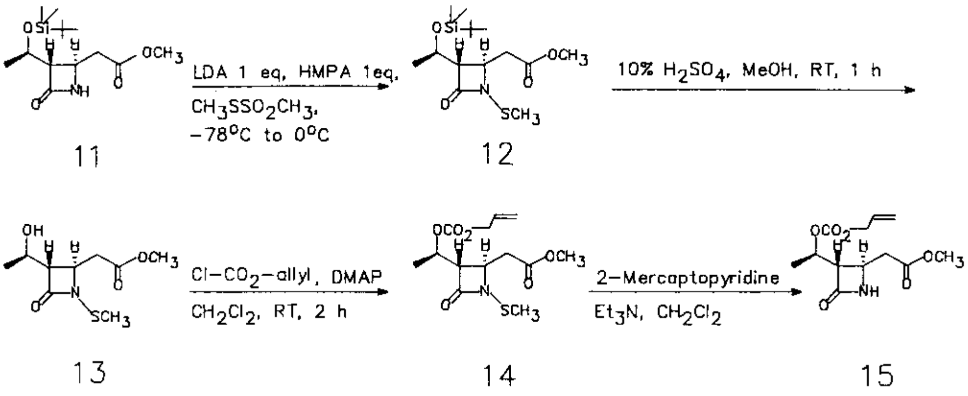
Because it was expected that the bicyclic compound **9** would not survive the conditions required for deblocking of the *t*-butyldimethylsilyl (*t*-BDMS) group, it became necessary to exchange it for an allyloxycarbonyl group, which could be removed simultaneously with the allyl ester under mild conditions[10]. Attempts at selective allyloxycarbonylation of the unprotected alcohol **10** obtained from 4 (CH_3OH, 1% H_2SO_4, RT, 1hr) failed, reaction occurring at both the OH and NH functions. Selective *t*-butyldimethylsilylation (*t*-BDMSCl, ET_3N, DMF) of **10** also failed, again reaction occurring at both OH and NH. At this point it became necessary to protect the NH function of **4** by a group stable to the acid conditions required to remove the O-*t*-butyldimethylsilyl function and yet easily removable after allyloxycarbonylation of the alcohol.



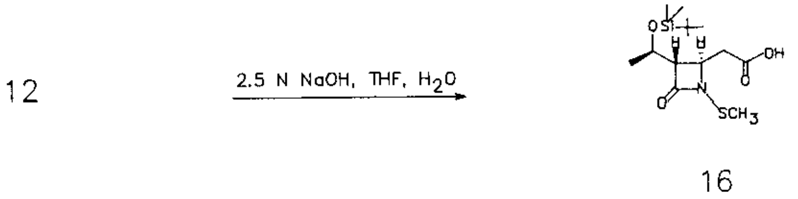
4

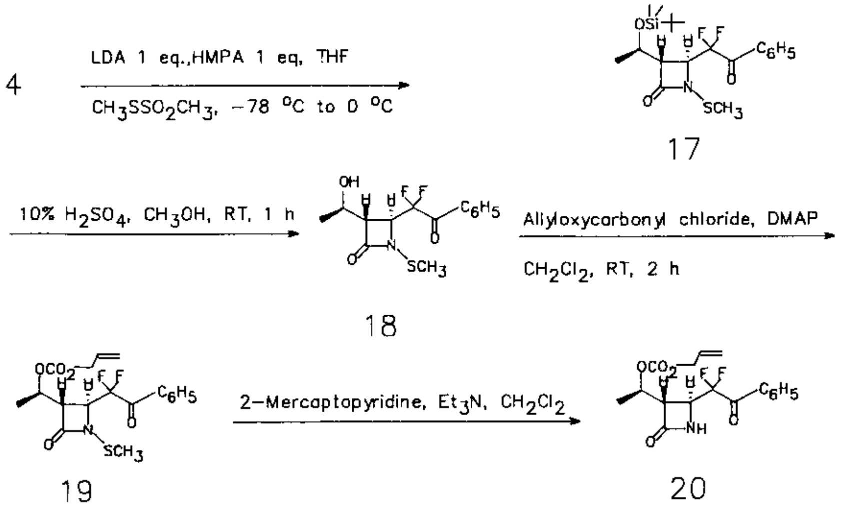
10

Sulfenamide derivatives have been used to protect amines[11], however, to our knowledge this functionality has not been used for the protection of the azetidinone NH[12]. A model study on the readily available azetidinone **11**[1] showed the usefulness of the $NSCH_3$ group. Treatment of **11** with LDA, HMPA(1 eq, each) in THF at -78^0 followed by excess methyl methanethiolsulfonate gave the sulfenamide derivative **12**[13] (94%). The t-BDMS group was then removed as described for **10** to give the alcohol **13**[14] (91%). The $N\text{-}SCH_3$ group survived the strongly acidic conditions. Allyloxycarbonylation of the free OH function (ClCOO-allyl, DMAP, CH_2Cl_2, RT, 2 h) gave the carbonate **14**[15] in 83% yield. At this stage the sulfenimide protecting group was removed by nucleophyllic displacement[16]. Among several conditions tried were $C_3H_7S^-$ Li^+/HMPA, $C_6H_5SH/Et_3N/CH_2Cl_2$ and 2-mercaptopyridine /Et_3N/CH_2Cl_2, the last being favoured because of the ease of purification of the product **15**[17] which was obtained in 95% yield. The N-sulfenated compound **12** was hydrolysed with 2.5N NaOH in THF/water to give the N-sulfenated acid **16**[18], demonstrating that the $N\text{-}SCH_3$ group is stable to aqueous basic conditions.

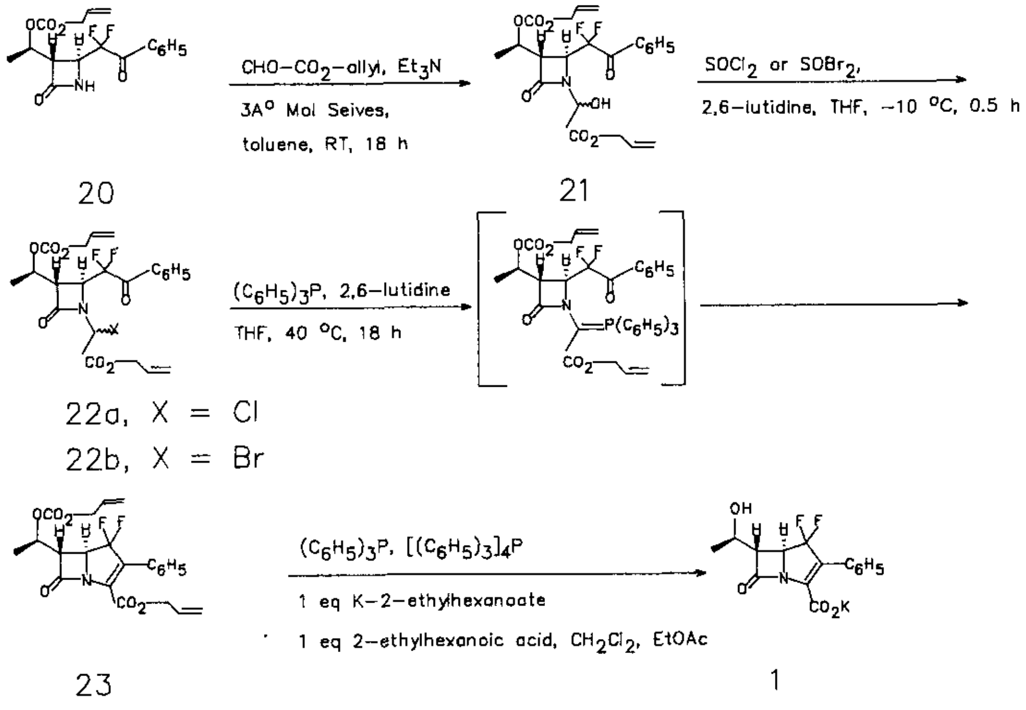


Having demonstrated the usefulness of the sulfenamide group, we turned our attention to completion of the synthesis of the title compound. The NH function of the azetidinone **4** was protected as a sulfenamide, the *O-t*-BDMS group was hydrolysed to free the OH which was then protected as the allyloxycarbonate and the SCH_3 group was removed as described in the model series to give compounds **17**[19], **18**[20], **19**[21] and **20**[22] in 68%, 73%, 83% and 97% yields, respectively.





The allyloxycarbonate-azetidinone **20** was condensed with allyl glyoxalate as described for **4** to **6**, and the carbinol isomer mixture **21**[23] (66%) was converted to the chloro-compounds **22a**[24] (62%) as described for **6** to **7**. Reaction of **22a** with triphenylphosphine and 2,6-lutidine in THF at 40°C was slow, resulting in a mixture of the desired cyclized carbapenem **23** and unreacted **22a** which were difficult to separate. However, when **21** was converted to the bromo-compounds **22b** using $SOBr_2$ in place of $SOCl_2$ the reaction with triphenylphosphine proceeded smoothly (18 hrs, THF, 2,6-lutidine) to give the cyclized carbapenem **23**[25] (41%, purified by reverse-phase HPLC, unstable on silica gel). The final deblocking of the allyl ester and carbonate groups was accomplished by treatment with catalytic amounts of ϕ_3P and $[\phi_3P]_4Pd$ in the presence of 1 eq. each of potassium hexanoate and hexanoic acid in CH_2Cl_2/EtOAc[10] to give the desired compound **1**[26] which because of its instability could only be characterized by its UV spectrum as it did not survive lyophylization. Because of its instability a meaningful assay of its in-vitro activity could not be performed, however **1** did show inhibition zones against a number of organisms (Staphylococcus aureus, Streptococcus sp. and Enterobacter sp.) at an estimated concentration of 7 mcg/disk.



The substitution at the 1-position of a carbapenem with 2-fluorine atoms appears to give a highly reactive carbapenem as indicated by the IR absorption of the β-lactam at 1795 cm^{-1} of compounds 9 and 23[27]. The result is a chemically unstable compound rather than an antibiotic with high activity. During the course of this work a new protecting group for the azetidinone NH has been discovered which is stable to acids and aqueous base and can be put on and removed in high yields. We believe this will become a useful procedure in β-lactam synthesis.

ACKNOWLEDGEMENTS

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7. ^1H NMR ($CDCl_3$, 200 MHz) d 0.8 (s, $SiCH_3$), 0.97 (s, Si-t-C_4H_9), 1.2 (d, $C\underline{H}_3CH$-, J = 6.5 Hz), 3.8 (t, C-3 H, J = 2.5 Hz), 4.36 (ddd, C-4 H, J_{HF} = 20 and 4.5 Hz, J_{HH} = 2.5 Hz), 4.3 (m, CH_3-$C\underline{H}$-O), 6.14 (s, NH), 7.4-8.2 (m, ArH).^{19}F NMR ($CDCL_3$,300 MHz) O, 106.66 (dd, J_{FF} = 330 Hz, J_{HF} = 3.45 Hz), 114.72 (dd, J_{FF} = 330 Hz, J_{HF} = 20.5 Hz). IR ($CHCl_3$,cm^{-1}), 3420 (NH), 1770 (β-lactam), 1692 (ketone).mp. 140-141^0.
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13. ^1H NMR ($CDCl_3$, 200 MHz) d 0.01 (s, $SiCH_3$), 0.82 (s, Si-*t*-C_4H_9), 1.12 (d, $C\underline{H}_3CH$-, J = 7 Hz), 2.38 (s, SCH_3), 2.57 (dd, CH_2COO, J = 15, 7), 2.8 (dd, CH_2COO, J = 15, 6.5), 2.99 (t, C-3 H, J = 3 Hz), 3.7 (s, OCH_3), 4.16 (m, C-4 H and $CH_3C\underline{H}$).
14. ^1H NMR ($CDCl_3$, 200 MHz) d 1.28 (d, $C\underline{H}_3CH$-, J = 6.5 Hz), 2.42 (s, SCH_3), 2.54 (dd, CH_2COO, J = 16, 9), 3.0 (dd, CH_2COO, J = 16, 4.5), 2.99 (dd, C-3 H, J = 6,2.5 Hz), 3.7 (s, OCH_3),3.98 (ddd, J = 6, 4.5, 2.5), 4.14 (m, $CH_3C\underline{H}$).
15. ^1H NMR ($CDCl_3$, 200 MHz) d 1.42 (d, $C\underline{H}_3CH$-, J = 6.5 Hz), 2.42 (s, SCH_3), 2.56 (dd, CH_2COO, J = 15.5, 8), 2.87 (dd, CH_2COO, J = 15.5, 6.5), 3.2 (dd, C-3 H, J = 7, 2.5 Hz), 3.72 (s, OCH_3), 4.08 (ddd, J = 7.5, 5, 2.5, C-4 H), 4.6 (d, CH_2-O), 5.08 (m, $CH_3C\underline{H}$-), 5.3 (m, $C\underline{H}_2$=CH-), 5.9 (m, CH_2=$C\underline{H}$-).
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17. ^1H NMR ($CDCl_3$, 200 MHz) d 1.42 (d, $C\underline{H}_3CH$-, J = 6.5 Hz), 2.56 (dd, CH_2COO, J = 16.5, 9), 2.78 (dd, CH_2COO, J = 16.5, 4.5), 3.05 (dd, C-3 H, J = 6.5, 2.5 Hz), 3.7 (s, OCH_3), 3.95 (ddd, J = 8, 6.5, 2.5, C-4 H), 4.62 (d, CH_2-O), 5.08 (m, $CH_3C\underline{H}$-), 5.3 (m, $C\underline{H}_2$=CH-), 5.95 (m, CH_2=$C\underline{H}$-), 6.16 (s, NH).
18. ^1H NMR ($CDCl_3$, 200 MHz) d 0.04 and 05 (2s, $SiCH_3$), 0.85 (s, Si-*t*-C_4H_9), 1.16 (d, $C\underline{H}_3CH$-, J = 7 Hz), 2.4 (s, S-CH_3), 2.64 (dd, CH_2COO, J = 15.5, 6), 2.84 (dd, CH_2COO, J = 15.5, 6.5), 3.03 (t, C-3 H, J = 2.5 Hz), 4.16 (m, C-4 H and $CH_3C\underline{H}$). IR (film,cm^{-1}), 2340-3700 broad OH, 1738 (β-lactam), 1712 (COOH).
19. ^1H NMR ($CDCl_3$, 200 MHz) d 0.04 (s, $SiCH_3$), 0.84 (s, Si-*t*-C_4H_9), 1.12 (d, $C\underline{H}_3CH$-, J = 6.5 Hz), 2.38 (s, CH_3S), 3.36 (t, C-3 H, J = 2.5 Hz), 4.3 (m, CH_3-$C\underline{H}$-O), 4.6(ddd, C-4 H, J_{HF} = 14 and 9 Hz, J_{HH} = 2.5 Hz), 7.4-8.2 (m, ArH). IR (film,cm^{-1}), 1780 (β-lactam), 1700 (ketone).
20. ^1H NMR ($CDCl_3$, 200 MHz) d 1.32 (d, $C\underline{H}_3CH$-, J = 6 Hz), 2.52 (s, CH_3S) 3.4 (dd, C-3 H, J = 2.5 and 5 Hz), 4.3 (m, $CH_3C\underline{H}$-O), 4.52 (dt, J = 11, 2.5), 7.4-8.2 (m, ArH). IR (film,cm^{-1}), 1780 (β-lactam), 1695 (ketone).
21. ^1H NMR ($CDCl_3$, 200 MHz) d 1.4 (d, $C\underline{H}_3CH$-, J = 6 Hz), 2.48 (s, CH_3S) 3.52 (dd, C-3 H, J = 2.6 and 5.5 Hz), 4.58 (m, C-4 H and $C\underline{H}_2$-CH=CH_2), 5.15-5.4 (m, CH3C$\underline{H}$-O and CH_2-CH=$C\underline{H}_2$) 5.98 (m, -CH_2-$C\underline{H}$=CH_2), 7.4-8.2 (m, ArH). IR (film,cm^{-1}), 1780 (β-lactam), 1695 (ketone).
22. ^1H NMR ($CDCl_3$, 200 MHz) d 1.4 (d, $C\underline{H}_3CH$-, J = 6.5 Hz), 3.59 (dd, C-3 H, J = 2.5 and 6 Hz), 4.22(ddd, C-4 H, J_{HF} = 17 and 6.5 Hz, J_{HH} = 2.5 Hz), 4.62 (d, $C\underline{H}_2$-CH=CH_2), 5.1-5.5 (m, CH3C$\underline{H}$-O and CH_2-CH=$C\underline{H}_2$) 5.9 (m, -CH_2-$C\underline{H}$=CH_2), 6.27 (s, NH), 7.5-8.2 (m, ArH). IR (film,cm^{-1}), 3300 (NH), 1775 (β-lactam), 1695 (ketone).
23. IR (film, cm^{-1}), 3450 (OH), 1740 (ester and carbonate), 1695 (ketone).
24. IR (film,cm^{-1}), 1790 (β-lactam), 1745 (ester and carbonate), 1700 (ketone).
25. ^1H NMR ($CDCl_3$, 200 MHz) d 1.48 (d, $C\underline{H}_3CH$-, J = 6 Hz), 3.76 (dd, C-6 H, J = 3.8 and 6 Hz), 4.42(ddd, C-5 H, J_{HF} = 15 and 17 Hz, J_{HH} = 3.8 Hz), 4.52-4.86 (m, $C\underline{H}_2$-CH=CH_2), 5.1-5.5 (m, $CH_3C\underline{H}$-O and CH_2-CH=$C\underline{H}_2$) 5.6-6.1 (m, -CH_2-$C\underline{H}$=CH_2), 7.24-7.6 (m, ArH). IR (film,cm^{-1}), 1797 (β-lactam), 1730 (ester and carbonate). UV (CH_3CN) $_{max}$ 295 nm.
26. UV (H_2O) $_{max}$ 305 nm (NH_2OH extinguishable difference)
27. IR frequency of the corresponding 1-unsubstituted analog (ref. 6) is at 1780 cm^{-1}.

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