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Allylic protection of thiols and cysteine : II: The *N*-[2,3,5,6-Tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-allyloxycarbonylaminomethyl (Fnam) Group.

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Abstract: *S*-[*N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-allyloxycarbonyl]-aminomethyl (Fnam) derivatives of thiols in general and cysteine in particular are readily deprotected by palladium catalysed allylic cleavage in the presence of various nucleophilic species. They are perfectly stable in both the basic conditions (piperidine/DMF) of Fmoc group removal and the acidic conditions (TFA/CH_2Cl_2) of *t*-Bu and Boc group removal.

INTRODUCTION

As stated in the preceding paper[1], Allocam derivatives of thiols slowly decompose in the presence of trifluoroacetic acid (TFA). The firs step in this decomposition is likely to be a proton induced fragmentation reaction leading to the *N*-allyloxycarbonylmethyleniminium cationic species **1**. A possible way to circumvent this problem could be to devise new allylic protections derived from the Allocam group by attachment of an electronegative substituent either at the carbon or at the nitrogen atom in order to disfavour the formation of the acyliminium species. For instance, introduction of a trifluoromethyl group at carbon (giving the 2,2,2-trifluoro-1-allyloxycarbonylamino-ethyl group **2a**) could be envisioned; indeed, closely related protecting groups, namely the 2,2,2-trifluoro-1-benzyloxycarbonylamino-ethyl group **2b**, the 2,2,2-trifluoro-1-*tert*-butyloxycarbonylamino-ethyl group **2c**, and the 2,2,2-trifluoro-1-trifluoroacetylamino-ethyl group **2d** have been proposed in the past by Weygand and coworkers for side chain protection of serine, threonine, histidine or cysteine.[2-4] However, a drawback of such protecting groups with an asymmetric center is that they lead to diastereoisomers when applied to optically active compounds. For this reason and also because, to the best of our knowledge, there exists no precedent in the literature, we chose to

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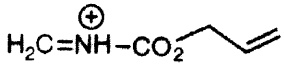
investigate the second alternative consisting in substituting the nitrogen atom with an electron withdrawing group (EWG) as schematically represented in **3**.



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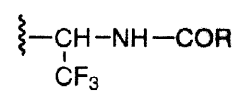
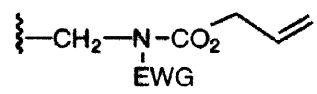


2 **a** R = O-allyl **c** R = O-*tert*-butyl
b R = O-benzyl **d** R = CO-CF_3

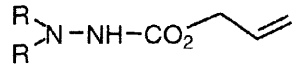


3

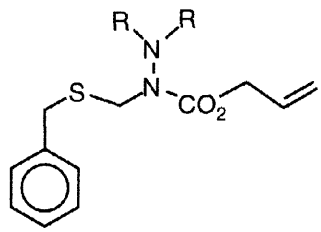
RESULTS AND DISCUSSION

The N-dimethylamino-N-allyloxycarbonyl-aminomethyl and the N-diphenylamino-N-allyloxycarbonyl-aminomethyl protecting groups .[5]

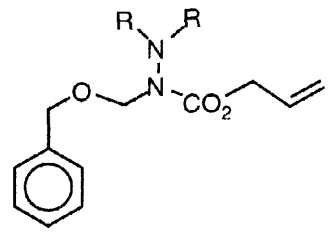
We first investigated the possible utilization of the *N*-dimethylamino-*N*-allyloxycarbonyl-aminomethyl and of the *N*-diphenylamino-*N*-allyloxycarbonyl-aminomethyl protecting groups, in the hope that the formation in acidic medium of the corresponding allyloxycarbonyliminium species would be prevented by protonation of the dimethylamino moiety or by the inductive effect of the diphenylamino moiety.
N,N-dimethyl- and *N,N*-diphenyl-*N'*-allyloxycarbonyl-hydrazine **4a** and **4b** were conveniently prepared by reacting respectively *N,N*-dimethyl and *N,N*-diphenylhydrazine hydrochlorides with allyl chloroformate in the presence of excess potassium carbonate in acetonitrile (CAUTION: *N,N*-dimethyl- and *N,N*-diphenylhydrazine are highly carcinogenic compounds). **4b** was then converted to its sodium salt by HNa in DMF and condensed with benzyl chloromethyl sulfide.[6] In this way, the model derivatives **5b**, *i. e* benzyl mercaptan



4 **a** R = Me
b R = Ph



5 **a** R = Me
b R = Ph



6 **a** R = Me
b R = Ph

protected by the *N*-diphenylamino-*N'*-allyloxycarbonyl-aminomethyl group was obtained in 76% yield. This method, however, failed to give the benzyl mercaptan derivative **5a** bearing the *N*-dimethylamino-*N'*-allyloxycarbonyl-aminomethyl protecting group. Possibly in this case, abstraction, by the anion of *N,N*-dimethyl-*N'*-allyloxycarbonyl-hydrazine, of a relatively acidic benzylic proton from the benzyl chloromethyl sulfide is preferred over the S_N2 pathway. Therefore, we decided to synthesize the model protected derivatives **6a** (as well as **6b**) derived from benzyl alcohol. These compounds were obtained in 77% and 82% yield respectively by condensation of the sodium salt of **4a** and **4b** with benzyl chloromethyl ether in DMF.

Compounds **5b**, **6a** and **6b** were totally deprotected within a few minutes by the hydrostannolytic procedure ($PdCl_2(PPh_3)_2/Bu_3SnH/AcOH$).[1] Aside from benzyl alcohol or

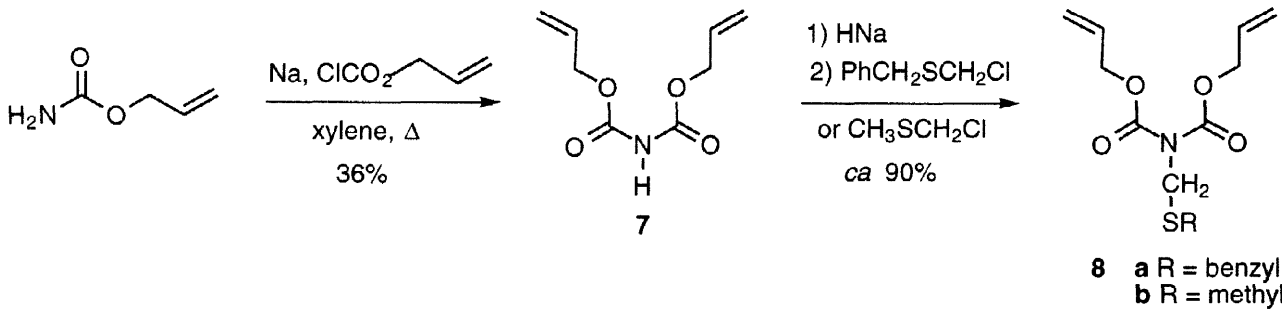
benzyl mercaptan, *N,N*-diphenylhydrazine or *N,N*-dimethylhydrazine and the corresponding methylene imines were observed as by-products of these reactions (^{1}H NMR and GC/MS).

The protected derivatives **5b**, **6a** and **6b** were completely stable in DMF/piperidine but they rapidly decomposed in the presence of trifluoroacetic acid. Our study of the hydrazine derived allylic protecting entities was therefore not pursued.

The N,N-bis(allyloxycarbonyl)aminomethyl (bis(Alloc)am) group.

Protection of primary amino groups as their *N*, *N*-bis(allyloxycarbonyl) derivatives has already been described in the literature.[7] The deprotection reaction was achieved by use of dimedone, a *C*-nucleophilic allyl group scavenger[8], in the presence of palladium catalyst. We therefore focussed on the use of the *N,N*-bis(allyloxycarbonyl)-aminomethyl group for protection of thiols.

Diallyl imidodicarbonate **7** was prepared by condensing the sodium salt of allyl carbamate with allyl chloroformate in xylene. The sodium salt of **7** was then reacted with benzyl chloromethyl sulfide, leading to the model bis(Alloc)am derivative of benzyl mercaptan



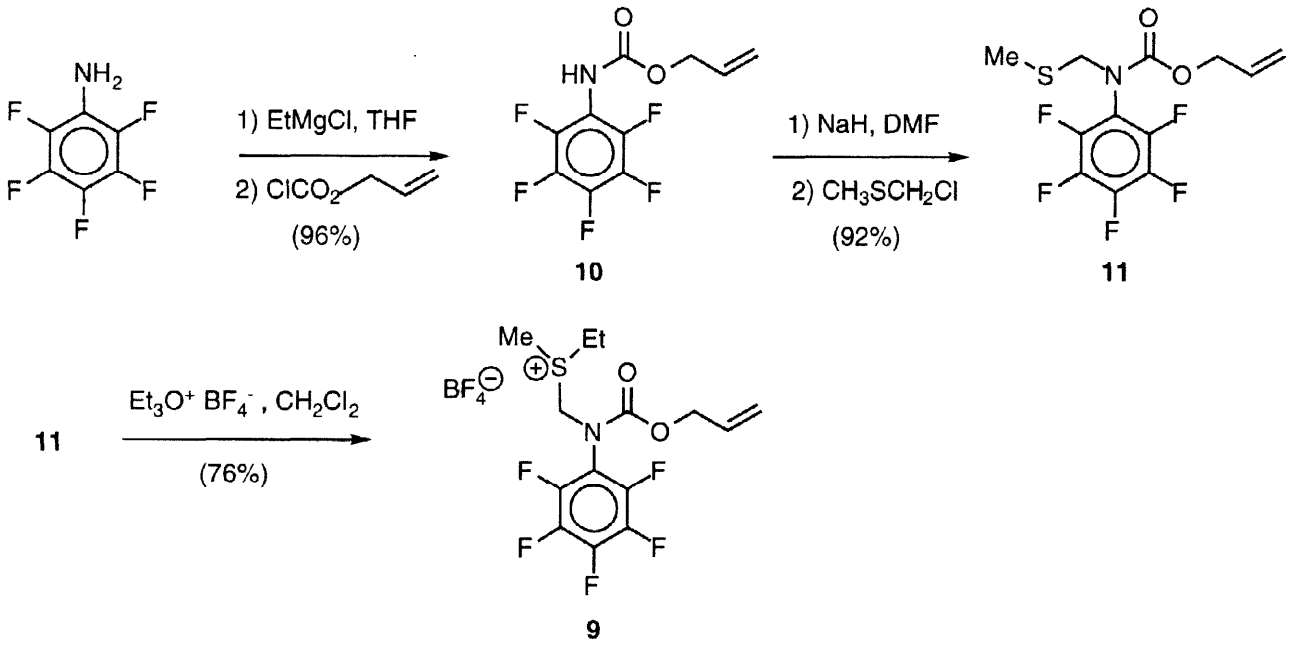
Scheme 1

8a (scheme 1). Compound **8a** is rapidly and quantitatively cleaved by the hydrostannolytic procedure. It is very stable in TFA/CH_2Cl_2 1:3 *v/v* with no detectable (NMR) decomposition within 72 h. On the contrary, upon exposure to 20% piperidine in DMF, a rapid transfer of one Alloc group to the piperidine resulted in the formation of *N*-Alloc-piperidine and the conversion of the bis(Allocam) derivative of benzyl mercaptan into its mono(allyloxycarbonyl)-aminomethyl (Allocam) analogue. Since the bis(Allocam) group did not fulfill the double criterion of stability towards trifluoroacetic acid and piperidine, other allylic protections were therefore investigated.[9]

The N-pentafluorophenyl, N-allyloxycarbonyl-aminomethyl (Fam) and N-[2,3,5,6-tetrafluoro-4-(N-piperidino)-phenyl], N'-allyloxycarbonyl-aminomethyl (Fnam) groups: introduction onto thiols.

The next protecting group to be investigated was the *N*-pentafluorophenyl-*N*-allyloxycarbonyl-aminomethyl (Fam) group. It was expected that the electron withdrawing character of the pentafluorophenyl ring, supposedly weaker than that of the Alloc group, would allow sufficient stability in basic medium while at the same time maintaining stability under acidic conditions.

A convenient reagent for introduction of the Fam group onto thiols was found to be the sulfonium salt **9**, itself prepared from commercially available pentafluoroaniline in three steps and 67% overall yield according to scheme 2. Pentafluoroaniline itself is not nucleophilic enough to react with acylating agents but its chloromagnesium salt smoothly condenses with allyl chloroformate to give the *N*-allyloxycarbonyl derivative **10** in virtually quantitative yield. By monitoring the reaction by GC/MS, it was found that the first formed product is the *N*, *N*-bis(Alloc) derivative of pentafluoroaniline. Redistribution of the Alloc groups then takes place between this derivative and unreacted pentafluoroaniline leading to **10**. This process is probably catalysed by $MgCl_2$ present in the reaction medium. Indeed if sodium salt of pentafluoroaniline (obtained by reaction with sodium hydride) is substituted for its chloromagnesium salt, the reaction stops at the bis(Alloc) stage. *N*-Alloc-pentafluoroaniline **10** was converted to its sodium salt by reaction with HNa in DMF and alkylated with chloromethyl methyl sulfide to give the *N*-methylthiomethyl derivative **11**. **11** was, in turn, converted to crystalline methyl, ethyl, *N*-pentafluorophenyl-*N*-allyloxycarbonyl-aminomethyl sulfonium tetrafluoroborate **9** by reaction with triethyloxonium tetrafluoroborate in dichloromethane.

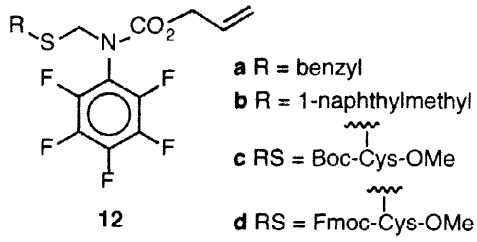


Scheme 2

Sulfonium salt **9** was found to smoothly condense with thiols in dichloromethane in the presence of DIEA. Using this method, the Fam derivatives of benzyl mercaptan **12a**, 1-naphthylmethyl mercaptan **12b**, N^{α}-Boc-cysteine methyl ester **12c** and N^{α}-Fmoc-cysteine methyl ester **12d** were obtained in 90%, 74%, 77% and 70% yield respectively. **12a** was also obtained by alkylation of the sodium salt of **9** with benzyl chloromethyl sulfide.[6]

12a, **12b** and **12d** were completely stable towards TFA. On the contrary, upon exposure to piperidine in DMF, **12a**, **12b** and **12c** undergo a rapid substitution of the *para*-fluorine atom of the phenyl ring by the *N*-piperidino group, leading to *N*-[2,3,5,6-tetrafluoro-4-(*N*'-

piperidino)-phenyl], *N*-allyloxycarbonyl-aminomethyl (Fnam) protected derivatives **13a**, **13b** and **13c**. This reaction occurs in a quantitative and selective way. No Alloc transfer resulting from attack on the carbonyl group could be detected and, as shown by ^{19}F NMR, the fluorine atom in the *para* position is the only one to be displaced.



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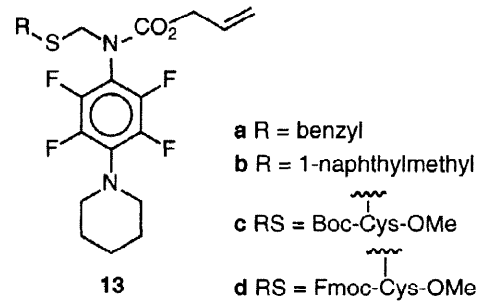
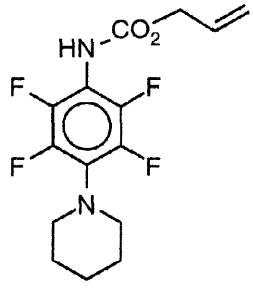


13

Further stability tests showed that the Fnam derivatives **13a**, **13b** and **13c** are perfectly stable in the presence of piperidine. In addition, **13a**, **13b** and **13c** proved to be completely stable towards trifluoroacetic acid. Finally, preliminary experiments indicated that the three Fnam derivatives could readily be deprotected by palladium catalysed hydrostannolysis. On account of these encouraging observations, we decided to further investigate the protection of thiols in general and cysteine in particular by the Fnam group.

Although, as just described above, *S*-Fnam derivatives of thiols are readily prepared from the corresponding *S*-Fallocam derivatives by reaction with piperidine, this method can hardly be used in the case of base labile substrates in general and of Fmoc-cysteine in particular. A method for direct introduction of the Fnam group was therefore highly desirable. While pentafluorophenylaniline proved to be unreactive towards piperidine, its allyloxycarbonyl derivative **10** reacts very selectively, albeit slowly (2 days at room temperature), to give the 4-piperidino-substituted derivative **14** in virtually quantitative yield. Using the reactions described in the pentafluorophenyl series (scheme 2), **14** was further elaborated into the crystalline sulfonium salt **16** in two steps and 68% overall yield *via* alkylation of intermediate *N*-methylthiomethyl derivative **15** with triethyloxonium tetrafluoroborate. This latter reaction was found to take place selectively at sulfur; no concurrent quaternarization of the strongly deactivated piperidino nitrogen atom was detected.



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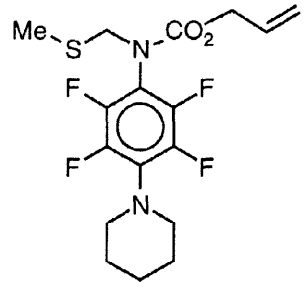

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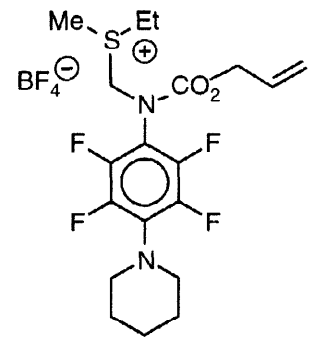
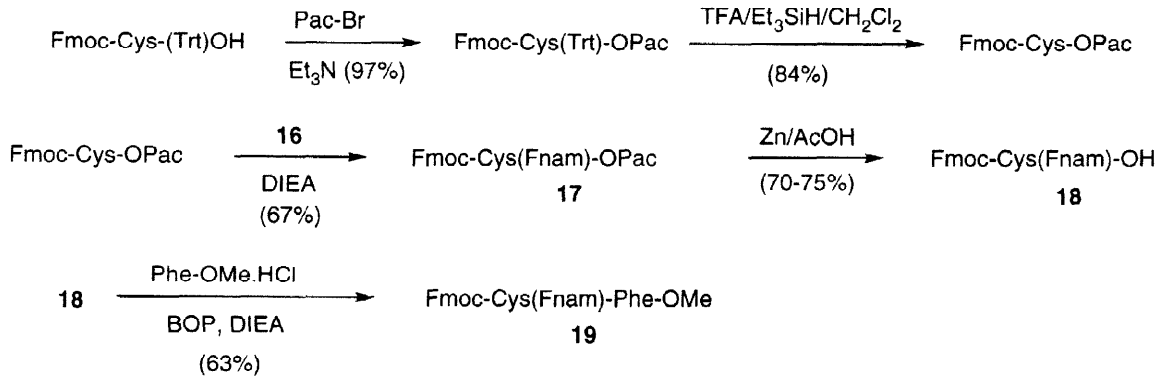


16

Sulfonium salt **16** smoothly reacts with thiols in the presence of DIEA. Several Fnam *S*-protected derivatives were thus prepared, including the Fnam derivatives of 1-naphthylmethyl mercaptan **13b** (84% yield), N^{α}-Boc-cysteine methyl ester **13c** (73% yield)

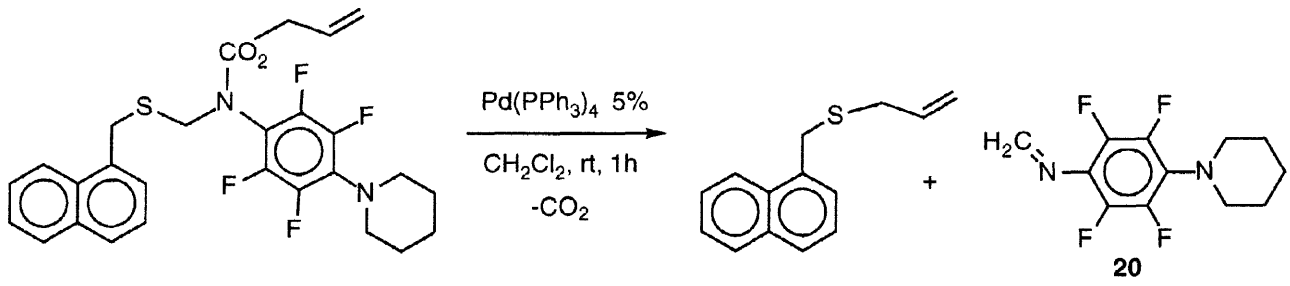
and N^{α}-Fmoc-cysteine methyl ester **13d** (68% yield). Attempts to introduce the Fnam group directly on N^{α}–Fmoc-cysteine by reaction with **16** in the presence of two equivalents of DIEA failed and resulted in the formation of several different products, one of them being the Fnam carboxylic ester of N^{α}-Fmoc-cysteine. Clearly, temporary protection of the carboxyl group was necessary. Accordingly (scheme 3), Fmoc-Cys-(Trt)-OH was condensed with phenacyl bromide (Pac-Br) in the presence of triethylamine to give FmocCys(Trt)-OPac. The trityl group was subsequently removed with TFA in the presence of triethylsilane and the cysteine derivative bearing the free thiol was condensed with **16** in the presence of DIEA to give Fmoc-Cys(Fnam)-OPac **17**. Removal of the phenacyl group with Zn in acetic acid finally led to Fmoc-Cys(Fnam)-OH **18** which was obtained as a foamy solid in 40% overall yield from Fmoc-Cys(Trt)-OH. Also prepared was the dipeptide Fmoc-Cys(Fnam)-Phe-OMe **19** by BOP-mediated coupling of **18** with Phe-OMe·HCl in the presence of DIEA.



Scheme 3

Palladium-catalysed deprotection of S-Fnallocam derivatives of thiols.

In the presence of $Pd(PPh_3)_4$ alone, Fnam derivatives of thiols undergo rearrangement to allyl thioethers, thus behaving like their simple Allocam homologues.[1] For instance, in the presence of 5 mol% of $Pd(PPh_3)_4$ in dichloromethane at room temperature, the Fnam derivative of 1-naphthylmethyl mercaptan is quantitatively converted to 1-naphthylmethyl allyl sulfide within 60 min (scheme 4). Methylenimine **20**, the by-product of the reaction, was fully characterized by NMR and GC/MS.



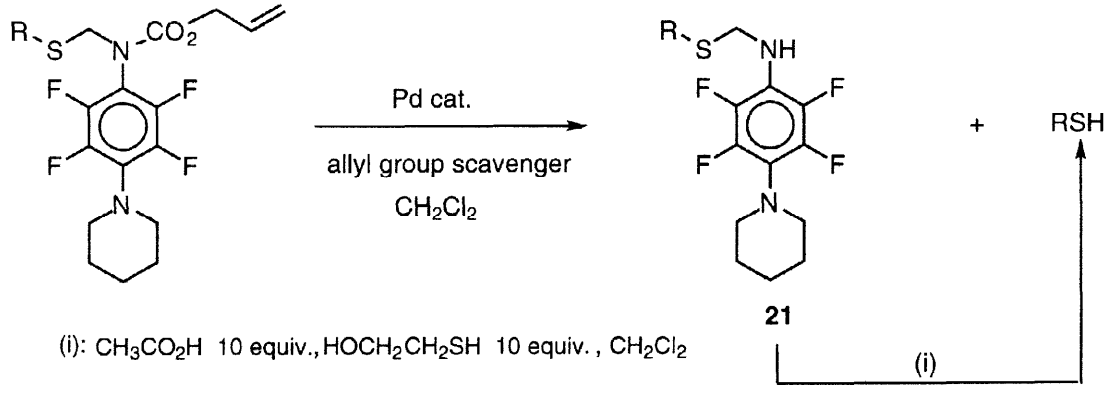
Scheme 4

Proper removal of the Fnam group was first studied on the benzyl and 1-methylnaphthyl derivatives **13a** and **13b**. The reactions, run under an argon atmosphere, were monitored by GC analysis. As already mentioned, cleavage of the Fnam group was readily achieved, within a few minutes, by the palladium catalysed hydrostannolytic procedure, *i.e.* by reaction with tributyltin hydride in dichloromethane in the presence of acetic acid and 5 mol% of $PdCl_2(PPh_3)_2$. No side-formation of allyl thioethers could be detected in either cases and after appropriate treatment of the crude reaction mixtures with iodine[1] and chromatographic purification, dibenzyl disulfide was obtained in 83% yield from **13a** and di(1-naphthylmethyl) disulfide in 77% yield from **13b**.

Deprotection of **13b** was then attempted with $PhSiH_3$[10] or *N,N*-dimethylbarbituric acid[11] as the allyl group scavenger and $Pd(PPh_3)_4$ as the catalyst (3 to 5 mol%). It should be recalled that these two deprotection systems which are very efficient for deprotection of allyl carbamates in general, nevertheless failed in the particular case of S-Allocam derivatives of thiols,[1] probably as a result of poisoning of the catalyst by the thiolato species liberated in the process. To our surprise, deprotection of **13b**, either by $Pd(PPh_3)_4/PhSiH_3$ or by $Pd(PPh_3)_4$/NDMBA was found to go to completion and without side-formation of allyl thioether, within 15 min in the first case and 60 min in the second one. After purification by chromatography, 1-naphthylmethyl mercaptan was isolated in 79% yield by the $PhSiH_3$ method and 85% yield by the NDMBA method.

Deprotection reactions were then tested on the Fnam derivatives of Boc- and Fmoc-CysOMe. Total deallylation was again observed. Most reactions, however, were found to lead not exclusively to the SH-free cysteine derivatives but also and in various amounts, depending on the exact experimental conditions, to thioaminals **21** (scheme 5), resulting from simple removal of the allyloxycarbonyl group.

Thioaminals **21** are fortunately highly acid labile and are cleaved with acetic acid in the presence of mercaptoethanol. By sequential one-pot treatment first with palladium/allyl group scavenger and then with acetic acid/mercaptoethanol, total deprotection was thus achieved with Boc-Cys(Fnam)-OMe, Fmoc-Cys(Fnam)-OMe and dipeptide **19**, as testified by NMR and TLC. The *S*-deprotected cysteine derivatives were then purified by flash chromatography. Some drops in yields were experienced during this operation, due to the difficulty of obtaining pure thiols, free of mercaptoethanol and of its adduct with *N*-[2,3,5,6-tetrafluoro-4-(*N*'-piperidino)-phenyl]-methylenimine **21**. Our results are summarized in table 1.



Scheme 5

Table 1: Palladium catalysed deprotection of Fnam derivatives of thiols

Fnam derivatives	Deprotection methods[a]	Products	Isolated yields
Benzyl-S-Fnallocam	A	(Benzyl-S)$_2$	83%
1-naphthylmethyl-S-Fnam	A	(1 -naphthylmethyl-S)$_2$	77%
1-naphthylmethyl-S-Fnam	B	1 -naphthylmethyl-SH	79%
1-naphthylmethyl-S-Fnam	C	1 -naphthylmethyl-SH	85%
Boc-Cys(Fnam)-OMe	B	Boc-Cys-OMe	90%
Boc-Cys(Fnam)-OMe	C	Boc-Cys-OMe	95%
Fmoc-Cys(Fnam)-OMe	B	Fmoc-Cys-OMe	77%
Fmoc-Cys(Fnam)-OMe	C	Fmoc-Cys-OMe	85%
Fmoc-Cys(Fnam)-Phe-OMe	B	Fmoc-Cys-Phe-OMe	70%

[a] A: $Bu_3SnH/PdCl_2(PPh_3)_2$ followed by treatment with iodine; B: $PhSiH_3/Pd(PPh_3)_4$ followed by treatment with mercaptoethanol/acetic acid; C: NDMBA/$Pd(PPh_3)_4$ followed by treatment with mercaptoethanol/acetic acid.

The fact that, during cleavage by palladium/NDMBA or palladium/$PhSiH_3$, poisoning of the catalyst occurs with the Allocam group but not with the Fnam group deserves an explanation. In the case of the Allocam group, the elimination of methylenimine is believed to be very fast and therefore release of the thiolato species is likely to occur concomitantly with allyl group cleavage. On the other hand, due to the presence of the electron-withdrawing group on nitrogen, fragmentation of the intermediate thioaminal **21** is presumably slower[12] and therefore allyl group cleavage is probably complete before release of substantial amounts of thiolato species.

CONCLUSION

This preliminary work leads us to select the Fnam group as a new potentially useful allylic protecting group for the SH function of cysteine. The reagent **9** for introduction of the Fnam group on thiols is synthesized in four steps from pentafluorophenylaniline in good overall yield. The properties of this new group differ from those of the simple Allocam group in essentially two respects: firstly, the Fnam group is readily removed through palladium catalysis, using, as allyl group scavengers, not only tributyltin hydride but also the easier to handle *N*, *N'*-dimethyl-barbituric acid acid (NDMBA) and $PhSiH_3$. All these conditions are compatible with most other, base labile or acid labile, cysteine protecting group. Secondly, the Fnam group is perfectly stable both under the basic conditions of Fmoc removal and the acidic

conditions of Boc removal. On another hand, it cannot, of course, be expected to be stable in the conditions for removal of the structurally related and widely used acetamidomethyl (Acm) group, which involve catalysis by heavy metal salts ($Hg(OAc)_2$, $AgBF_4$) or oxidative agents such as I_2 or $Tl(TFA)_3$.[13,14]

Further testing of the Fnam group in solid phase peptide synthesis is presently under way. The devising of other protecting entities derived from the Fnam group by replacement of the piperidino substituent by other (especially arylthio) groups, with the aim of obtaining fully cristalline cysteine derivatives is also under study. It should be noted that several attempts to build modified Allocam group starting from electron deficient aniline other than pentafluoroaniline, *i.e.* 4-nitroaniline, 3,5-dichloroaniline and 2,4,5-trichloroaniline, were also made in our laboratory but invariably failed, owing to difficulties encountered at various stages in the synthesis of a suitable reagent for introduction onto thiols.

EXPERIMENTAL SECTION

General.[1]

Only experimental data pertaining to the protection of thiols by the Fam and Fnam groups are reported in this experimental section. Other experimental data may be found in ref [5].

^{19}F NMR spectra were recorded in $CDCl_3$ at 235.33 MHz and with C_6F_6 as the external reference.

Note on spectroscopic data concerning Fam and Fnam derivatives of thiols.

Due to the rotational barrier around the C(O)-N bond of the carbamato group, Fam and Fnam derivatives of thiols present two rotameric forms in *ca* 80:20 ratio. The two rotamers are clearly distinct on ^{19}F NMR spectra and they induce a duplication of various peaks in ^{1}H NMR and ^{13}C NMR spectra. Concerning ^{1}H NMR data, the respective attribution of peaks is given only in cases where this can be made without ambiguity. On the other hand, the peaks of minor rotamer are not included in the ^{13}C NMR listings.

N-Pentafluorophenyl-carbamic acid allyl ester ***10.***

A solution of 10 g of pentafluoroaniline in 100 mL of dry THF under an argon atmosphere was cooled in an ice-bath. 27.3 mL (54.6 mmol) of a commercial (Acros) 2 M solution of ethylmagnesium chloride in THF was slowly added. The solution was stirred for 1 h at room temperature and once again cooled to 0 °C. Allyl chloroformate (11.6 mL, 110 mmol) was slowly added and the reaction mixture heated at 50 °C for 24 h. The THF was evaporated and the residue was taken up in 100 mL of diethyl ether. The ethereal solution was washed successively with 50 mL of 10% aqueous citric acid and with water, and dried over $MgSO_4$. After filtration, the ether was evaporated and the solid residue was dried under 0.5 mmHg. 13.94 g (96%) of ***N*-pentafluorophenyl-carbamic acid allyl ester (10)** of 98% purity by GC standard were obtained as a white solid: mp 40 °C; ^{19}F NMR: δ 15.5 (d, J = 22Hz, 2F), 4.81 (t, J = 21.5 Hz, 1F), - 0.85 (t, J = 22 Hz, 2F); ^{1}H NMR: δ 6.98 (broad s, NH), 5.9 (m, 1H), 5.3 (two d (apparent t), 2H, J = 15 Hz and 10 Hz), 4.7 (d, 2H, J = 5.7 Hz, allylic CH_2); ^{13}C NMR: δ 153.7, 142.5, (dm, $^{1}J_{CF}$ = *ca* 320 Hz), 140.7 (dm, $^{1}J_{CF}$ = *ca* 320 Hz), 137.8 (dm, $^{1}J_{CF}$ = *ca* 320

Hz), 131.7, 118.7, 112.3 (sharp m), 67.1; IR($CHCl_3$): 3428 (NH), 1743 (CO), 1650 (C=C) cm^{-1}; GC/MS: 267 (M^+), 209 (20%), 41 (100%), 39 (24%); Anal. Calcd for $C_{10}H_6F_5NO_2$: C: 44.96, H: 2.26, N: 5.23, F: 35.56 Found: C: 44.94, H: 2.18, N: 5.31, F: 34.96.

As indicated in the theoretical section, if the acylation is carried out on the sodium (instead of chloromagnesium) salt of pentafluoroaniline, the product of reaction is **diallyl *N*-pentafluorophenyl-imidodicarbonate**: waxy solid; ^{19}F NMR: δ 16.2 (d, J = 21 Hz, 2F), 8.9 (t, J = 22 Hz, 1F), -0. 29 (t, J = 22 Hz, 2F); ^1H NMR: δ 5.8 (m, 2H), 5.35-5.15 (m, 4H), 4.7 (d, 4H, J = 6 Hz, allylic CH_2); GC/MS: 351 (M^+), 266 (7%), 57 (10%), 41 (100%), 39 (13%).

*N-[2,3,5,6-Tetrafluoro-4-(N'-piperidino)-phenyl]-carbamic acid allyl ester **14**.*

Piperidine (16.0 mL, excess) was added to a solution of 2.6 g (9.8 mmol) of *N*-pentafluorophenyl-carbamic acid allyl ester (**10**) in 70 mL of dry DMF. The resulting solution , of a deep brown colour probably due to partial deprotonation of **10**, was stirred for 3 days at room temperature. The mixture wad concentrated on a Rotovap. The residue was taken up in water (30 mL) and diethyl ether (30 mL). The aqueous phase was decanted and reextraced (3 x 20 mL) with diethyl ether. The organic phases were joined, dried on $MgSO_4$ and evaporated to give a white solid. Recrystallisation from hexane gave 3.1 g (93% yield) of pure product.

***N*-[2,3,5,6-Tetrafluoro-4-(N'-piperidino)-phenyl]-carbamic acid allyl ester (14)**: mp 82 °C; ^{19}F NMR: δ 10.1-10.0 (broad d, J = 19 Hz, 2F), 12.6-12.5 (broad d, 2F, J = 17 Hz); ^1H NMR: δ 6.16 (broad s, NH), 6.0-5.8 (m, 1H), 5.35 (broad d, 1H, J = 17 Hz), 5.25 (broad d, 1H, J= 17 Hz), 5.25 (broad d, 1 H, J = 12 Hz), 4.63 (d, 2H, J = 6.7 Hz), 3.14 (broad peak, 4H), 1.6 (broad peak, 6H); ^{13}C NMR: δ 154.0, 143.2 (dm, $^1J_{CF}$ = 310 Hz, 1F), 142.3 (dm, $^1J_{CF}$ = 310 Hz, 1F), 131.7, 129.8 (sharp m), 118.1, 108.9 (sharp m), 66.3, 52.1, 26.3, 23.8; IR ($CHCl_3$): 3425 (NH), 1735 (CO), 1649 (C=C) cm^{-1}; GC/MS: 332 (M^+), 273 (91%), 247 (88%), 233 (19%), 217 (43%), 191 (21%), 162 (10%), 69 (62%), 57 (44%), 41 (100%); Anal. Calcd for $C_{15}H_{16}F_4N_2O_2$: C: 54.19, H: 4.85, N: 8.43, F: 22.88 Found: C: 53.91, H: 4.90, N: 8.41, F: 23.00.

*N-Pentafluorophenyl, N-methylthiomethyl-carbamic acid allyl ester **11**.*

0.415 g of sodium hydride as a 60% suspension in oil (1.1 equiv. based on *N*-pentafluorophenyl-carbamic acid allyl ester (**10**) was washed with several portions of pentane and then put in suspension in dry DMF (1 mL) under an N_2 atmosphere. **10** (25.8 g, 8.6 mmol) was added and the mixture was magnetically stirred until cessation of gas evolution. Chloromethyl methyl sulfide (870 μL, 10.3 mL) was then added and the reaction mixture was stirred for 2 h at room temperature, then diluted with 20 mL H_2O and extracted three times with 10 mL of diethyl ether. The combined ethereal phases were washed with 10% aqueous citric acid and with water, dried over $MgSO_4$ and evaporated. Pure **11** (2.42 g, 75% yield) was finally obtained after flash chromatogaphy (silica, pentane/diethyl ether).

***N*-Pentafluorophenyl, *N*-methylthiomethyl-carbamic acid allyl ester (11)**: Syrup; ^{19}F NMR: two rotamers in *ca* 75/25 ratio: δ 17.55 and 17.0 (two d, J = 21 Hz, (0.25 x 2 and 0.75 x 2) F, 8.0- 7.6 (two overlapping t, 1F) , 0.00 to - 0.3 (two overlapping t, 2F). ^1H NMR: δ 6.05-5.6 (m, 1H), 5.3-5.0 (m, 2H), 4.8 (s, 2H, S-CH_2-N), 4.6-4.48 (two d, (0.25 x 2 and 0. 75 x 2) H, allylic CH_2), 2.2 (s, 3H). ^{13}C NMR δ 154.03, 144.5 (dm, $^1J_{CF}$ = 250 Hz), 141.0 (dm, $^1J_{CF}$ = 260 Hz), 137.7 (dm, $^1J_{CF}$ = 255 Hz), 131.5 , 118.05, 114.6 (sharp m), 67.2, 53.0, 14.2; IR (CCl_4): 1727 (CO), 1645 (C=C) cm^{-1}; GC/MS: 327 (M^+), 61 (27%), 41 (100%); Anal. Calcd for $C_{12}H_{10}F_5NO_2S$: C: 44.04, H: 3.08, N: 4.28 Found: C: 43.88, H: 2.96, N: 4.32.

*N-[2,3,5,6-Tetrafluoro-4-(N'-piperidino)-phenyl], N-methylthiomethyl-carbamic acid allyl ester **15**.*

By a method similar to that described just above for the obtention of **11**, **15** was obtained from *N*-[2,3,5,6-Tetrafluoro-4-(*N'*-piperidino)-phenyl]-carbamic acid allyl ester and chloromethyl methyl sulfide in 83% yield after column chromatography (cyclohexane/AcOEt). **N-[2,3,5,6-Tetrafluoro-4-(N'-piperidino)-phenyl], N-methylthiomethyl-carbamic acid allyl ester (15):** syrup; ^{19}F NMR: two rotamers in *ca* 75/25 ratio; δ 13.94 and 13.4 (two d, J = 17 Hz, (0.25 x 2 and 0.75 x 2) F, 10.0-9.8 (app. t., 2F); ^{1}H NMR: δ 6.1-5.7 (m, 1H), 5.4-5.05 (m, 2H), 4.75 (s, 2H, N-CH_2-S), 4.7 and 4.5 (two d, J = 7 Hz, (0.25 x 2 and 0.75 x 2) H, allylic CH_2), 3.14 (broad peak, 4H), 2.1 (s, 3H), 1.55 (broad peak, 6H); ^{13}C NMR: δ 154.5, 144;5, (dm, $^{1}J_{CF}$ = 250 Hz), 141.8 (dm, $^{1}J_{CF}$ = 240 Hz), 131.75, 131.07 (sharp m), 117.5, 110.9 (sharp m), 66.8, 53.0, 51.9, 26.2, 23.7, 14.1; IR ($CHCl_3$): 1725 (CO), 1649 (C=C) cm^{-1}; GC/MS: 393 (16%), 392 (47%, M^+), 273 (17%), 260 (100%), 259 (47%), 61 (33%), 41 (46%); Anal. Calcd for $C_{17}H_{20}F_4N_2O_2S$: C: 52.03, H: 5.13, N: 7.13 Found: C: 51.97, H:4.99, N: 6.97.

*Preparation of methyl, ethyl, N-pentafluorophenyl, N-allyloxycarbonyl-aminomethyl sulfonium tetrafluoroborate **9**.*

To a solution of *N*-pentafluorophenyl, *N*-methylthiomethyl-carbamic acid allyl ester (6.4g, 16.3 mmol) in dry dichloromethane (60 mL) was added in solid form, with a spatula, triethyloxonium tetrafluoroborate (3.1 g, 16.3 mmol). The reaction mixture was stirred for 8 h at room temperature. The sulfonium salt was precipitated by adding 120 mL of diethyl ether. The precipitate was collected by filtration on a sintered glass, rinsed several times with diethyl ether and dried to give 5.5 g (76%) of a white solid. **Methyl, ethyl, N-penta-fluorophenyl, N-allyloxycarbonyl-aminomethyl sulfonium tetrafluoroborate (9)**: ^{19}F NMR: δ 11.66 (broad peak, 5F); ^{1}H NMR: δ 6.05-5.7 (m, 1H), 5.6 (d, 1H) and 5.4 (d, 1H, AB system, J_{AB} = 18 Hz, N-CH_2-S, 5.3-5.1 (m, 2H, vinylic CH_2), 4.8-4.6 (m, 2H, allylic CH_2), 3.8-3.4 (m, 2H, S-$\underline{CH_2}$-CH_3), 2.95 (s, 3H), 1.5 (t, 3H, S-CH_2-$\underline{CH_3}$); IR ($CHCl_3$): 1738 (CO), 1650 (C=C) cm^{-1}.

*Preparation of methyl, ethyl, N-[2,3,5,6-tetrafluoro-4-(N'-piperidino)-phenyl], N-allyloxy-carbonyl-aminomethyl sulfonium tetrafluoroborate **16**.*

Following the experimental procedure described just above, **16** was prepared from *N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-methylthiomethyl-carbamic acid allyl ester (**15**) and triethyloxonium tetrafluoroborate in 71% yield. **Methyl, ethyl, N-[2,3,5,6-tetrafluoro-4-(N'-piperidino)-phenyl], N-allyloxycarbonyl-aminomethyl sulfonium tetrafluoroborate (16)**: white crystals; ^{19}F NMR: δ 11.8 (broad peak, 4F); ^{1}H NMR: δ 5.9-5.7 (m, 1H), 5.5-5.1 (m, 4H, vinylic CH_2 and N-CH_2-S), 4.6-4.5 (m, 2H), 3.6 (m, 2H, $\underline{CH_2}$-CH_3), 3.2 (broad s, 4H), 2.5 (s, 3H), 1.6 (broad s, 6H), 1.4 (t, 3H, J = 6 Hz); IR ($CHCl_3$): 1736 (CO), 1650 (C=C) cm^{-1}.

General procedure for introduction of the N-pentafluorophenyl, N-allyloxycarbonyl-aminomethyl (Fam) group on thiols. Preparation of ***12a-d.***

To a solution of 0.5 mmol of methyl, ethyl, *N*-pentafluorophenyl, *N*-allyloxycarbonyl-aminomethyl sulfonium tetrafluoroborate (**16**) in 2 mL of dichloromethane was slowly added a solution of the thiol (0.4 mmol) and of diisopropylethylamine (0.45 mmol) in 2 mL of dichloromethane. The reaction was stirred at room temperature overnight. The solvent was evaporated and the residue was taken up in 10 mL of diethyl ether. The ethereal solution was extracted successively with 10% aqueous citric acid and with water. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was finally purified by flash chromatography (silica, pentane/diethyl ether). By this procedure, **12a**, **12b**, **12c** and **12d** were obtained in 90%, 74%, 77% and 70% yield respectively. Most of the time, the preparation of **9** and its further condensation with thiols were combined in a one-pot procedure without intermediate isolation of the sulfonium salt **9**.

***N*-Pentafluorophenyl, *N*-(1-naphtylmethylthio)methyl-carbamic acid allyl ester (12b)**: solid: mp 68 °C; ^{19}F NMR: two rotamers in *ca* 77/23 ratio; major rotamer: δ 17.1 (d, J= 19.5 Hz, 2F), 8.0 (t, J = 21 Hz, 1F), -0.24 (t, 2F); minor rotamer: δ 17.67 (d, J = 19 Hz, 2F), 7.68 (t, J = 22 Hz, 1F), *ca* - 0.03 (t, overlapping with t of major rotamer); ^1H NMR: δ 8.1-7.3 (m, 7H), 6.1-5.7 (m, 1H), 5.4-5.1 (m, 2H), 4.6-4.55 (m, 4H, allylic CH_2 and S-CH_2-N), 4.2 (maj.) and 4.15 (min.) (two s, 2H, ArCH_2); ^{13}C NMR: δ 154.0, 143.9 (dm, $^1J_{CF}$ = 260 Hz), 140.9 (dm, $^1J_{CF}$ = 270 Hz), 137.3 (dm, $^1J_{CF}$ = 260 Hz), 133.9, 132.6, 131.5, 130.8, 128.5, 128.3, 127.5, 126.0, 125.8, 125.0, 123.7, 118.2, 114.5 (sharp m), 67.3, 51.1, 33.4; IR ($CHCl_3$): 1721 (CO), 1650 (C=C) cm^{-1}; GC/MS: 453 (M^+), 186 (24%), 173 (36%), 115 (45%), 41 (79%); Anal Calcd for $C_{22}H_{16}F_5NO_2S$: C: 58.28, H: 3.56, N: 3.09, F: 20.94 Found: C: 57.96, H: 3.61, N: 2.88, F: 20.99.

***N*$^{\alpha}$-*tert*-Butoxycarbonyl-*S*-(*N*-pentafluorophenyl, *N*-allyloxycarbonyl)-aminomethyl-cysteine methyl ester (Boc-Cys(Fam)-OMe, 12c)**: syrup; ^{19}F NMR: two rotamers in 77/23 ratio; major rotamer: δ 17.1 (d, J = 22.8 Hz, 1-F, *o*-F), 16.9 (d, J = 22.7 Hz, 1F, *o'*-F), 7.94 (t, J = 20.5 Hz, 1F), -0.13 to -0.35, broad m, 2F); minor rotamer: δ 17.9 (d, 1F, *o*-F), 17.27 (d, 1F, *o'*-F), 7.85 (t, 1F), - 0.13 to -0.35 (broad m, 2F); ^1HNMR: δ 6.0-5.6 (m, 1H), 5.4 (broad d, 1H, NH), 5.25-5.05 (m, 2H), 4.9-4.6 (m, 3H, C^{α} H and S-CH_2-N), 4.52 (d, J = 7 Hz, 2H, allylic CH_2), 3.7 (s, 3H), 3.2-2.8 (m, ABX System, J_{AB} = 14 Hz, J_{AX} = 5 Hz, J_{BX} = 8 Hz, 2H, $C^{\beta}H_2$), 1.43 (s, 9H); ^{13}C NMR: δ 171.1, 155.0, 153.9, 144.5 (dm, $^1J_{CF}$ = 250 Hz), 140.8 (dm, $^1J_{CF}$ = 240 Hz), 133.5 (dm, $^1J_{CF}$ = 260 Hz), 131.3, 118.3, 114.5 (sharp m), 79.9, 67.4, 53.1, 52.4, 51.5, 33.0, 28.0; IR ($CHCl_3$): 3435 (NH), 1717 (broad, CO ester and carbamate), 1650 (C=C) cm^{-1}; HRMS (EI): Calcd for $C_{25}H_{32}F_4N_3O_6S$: 514.1196 Found: 514.1202.

***N*$^{\alpha}$-9-Fluorenylmethoxycarbonyl-*S*-(*N*-pentafluorophenyl, *N*-allyloxycarbonyl)-aminomethyl-cysteine methyl ester (Fmoc-Cys(Fam)-OMe, 12d)**: syrup; ^{19}F NMR: two rotamers in 80/20 ratio; major rotamer: δ 17.16 (d, J = 23 Hz, 1F, *o*-F), 16.9 (d, J = 23 Hz, 1F, *o'*-F), 8.46 (t, J = 22 Hz, 1F), -0.16 to -0.35, broad m, 2F); minor rotamer: δ 18.0 (d, J = 22Hz, 1F, *o*-F), 17.3 (d, 1F, *o'*-F), 8.16 (t, 1F), -0.16 to -0.34 broad m, 2F); ^1H NMR: δ 7.75 (d, 2H, J = 8 Hz), 7.6-7.2 (m, 6H), 6.0-5.7 (m, 2H, vinylic CH and NH), 5.4-5.1 (m, 2H, vinylic CH_2), 4.9-4.6 (m, 5H, allylic CH_2, N-CH_2-S and $C^{\alpha}H$), 4.4 (d, 2H, J = 6 Hz, Fmoc CH_2), 4.25 (t, 1H, Fmoc C^9H), 3.7 (s, 3H), 3.2-2.9 (m, ABX System, J_{AB} = 14 Hz, J_{AX} = 5 Hz, J_{BX} = 8Hz, 2H, $C^{\beta}H_2$); ^{13}C NMR (carbons of the fluoroaromatic ring were not visible, due to insufficient accumulation): δ 171.1, 155.9, 155.7, 143.6, 141.2, 131.3, 127.6, 126.9, 125.0, 119.8, 118.5, 114.5, 67.1, 66.7, 54.0, 52.6, 51.6, 46.9, 32.4; MS (electrospray/PI): 637.2 (M+1), 659.2 (M+Na, 100%), 675.2

(M+K, 13.7%).HRMS (electrospray/PI): Calcd for $C_{30}H_{25}F_5N_2O_6S$: (M+Na) 659.1255 Found 659.1251.

Conversion of S-(N-pentafluorophenyl, N-allyloxycarbonyl)-aminomethyl derivatives of mercaptans into the corresponding S-[[N-2,3,5,6-tetrafluoro-4-(N'-piperidino)-phenyl], N-allyloxycarbonyl]-aminomethyl derivatives in the presence of piperidine.

The *S*-(*N*-pentafluorophenyl, *N*-allyloxycarbonyl)-aminomethyl derivative (0.5 mmol) was dissolved in 6 mL of DMF, and 2 mL of piperidine was added to this solution. The reaction which could be conveniently monitored by TLC analysis, was allowed to proceed at room temperature for 4 h. The reaction mixture was concentrated on a Rotovap, diluted with 30 mL of water and then extracted with diethyl ether (3 x 20 mL), each ether portion being washed with water. The desired product was finally obtained after drying over $MgSO_4$ of the combined ethereal phases, filtration, evaporation of the solvent and, if necessary, chromatographic purification.

General procedure for introduction of the N-[2,3,5,6-tetrafluoro-4-(N'-piperidino)-phenyl], N-allyloxycarbonyl-aminomethyl group on thiols. Preparation of ***13a-d.***

To a solution of 0.5 mmol of methyl, ethyl, *N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-allyloxycarbonyl-aminomethyl sulfonium tetrafluoroborate **16** in 2 mL of dichloromethane was added dropwise a solution of 0.4 mmol of thiol and 0.45 mmol of diisopropylethylamine in 2 mL of dichloromethane. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was taken up in diethyl ether. The ethereal solution was washed with water, with 10% aqueous citric acid and again with water. After drying over $MgSO_4$, the solvent was evaporated and the residue was flash chromatographed (silica, hexane/AcOEt). Most of the time, the preparation of **16** and its further condensation with thiols were combined in a one-pot procedure without intermediate isolation of the sulfonium salt.
***N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-(1-naphthylmethylthio)methyl-carbamic acid allyl ester (13b)**: 84% yield; syrup; ^{19}F NMR: two rotamers in *ca* 77/23 ratio; major rotamer: δ 14.0 (d, J = 17 Hz, 2F), 10.2 (d, J = 17 Hz, 2F); minor rotamer: δ 14.5 (d, J = 17.5 Hz, 2H), 10.25 (d, J = 17.5 Hz, 2H); ^1H NMR: δ 8.1 (d, J = 9 Hz, 1H), 7.9 (d, J = 9 Hz, 1H), 7.8 (d, J = 10 Hz, 1H), 7.6-7.4 (m, 4H), 6.0-5.8 (m, 1H), 5.4-5.15 (m, 2H), 4.85 and 4.75 (two s, (0.77 x 2 and 0.23 x 2) H, S-CH_2-N), 4.65 (d, 2H, allylic CH_2), 4.3 and 4.2 (two s, (0.77 x 2 and 0.23 x 2) H, Ar-CH_2), 3.2 (broad peak, 4H), 1.6 (broad peak, 6H); ^{13}C NMR: δ 154.7, 144.6 (dm, $^1J_{CF}$ = 250 Hz), 142.2 (dm, $^1J_{CF}$ = 250 Hz), 133.9, 133.2, 131.9, *ca* 131 (sharp m), 128.7, 128.2, 127.4, 126.1, 125.7, 125.2, 123.8, 118.9, 117.8, 111.0 (sharp m), 67.1, 52.2, 51.9, 33.1, 26.4, 24.0; GC/MS: 519 (M^+), 518 (61%), 260 (96%), 259 (53%), 141 (100%), 115(38%), 41 (76%). Anal. Calcd for $C_{27}H_{26}F_4N_2O_2S$: C: 62.54, H: 5.05, N: 5.40 Found C: 62.66, H: 4.98, N: 5.50.
***N*$^{\alpha}$-*tert*-Butoxycarbonyl-*S*-[*N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], N-allyloxycarbonyl]-aminomethyl-cysteine methyl ester (Boc-Cys(Fnam)-OMe, 13c)**: 73 % yield; syrup; ^{19}F NMR: two rotamers in *ca* 80/20 ratio; major rotamer: δ 13.8 (d, J = 21 Hz, 1F, *o*-F),13.55 (d, J = 21 Hz, 1F, *o'*-F), 10.3-10.1 (m, 2F); minor rotamer: δ 14.35 (d, J = 22 Hz, 1F, *o*-F), *ca* 13.8 (1F, *o'*-F, masked by major rotamer), 10.3-10.1 (m, 2F); ^1H NMR: δ 6.1-5.65 (m, 1H), 5.4 (broad d, 1H, NH), 5.3-5.1 (m, 2H), 4.85-4.65 (m, AB system, J_{AB} = 14 Hz, S-CH_2-N), 4.7- 4.6 (m, 1H, $C^{\alpha}H$), 4.55 (d, J = 5 Hz, allylic CH_2), 3.7 (s, 3H), 3.2 (broad peak, 4H),

3.2-2.85 (m, ABX system, J_{AB} = 14 Hz, J_{AX} = 5 Hz, J_{BX} = 7Hz, 2H, $C^{\beta}H_2$), 1.6 (broad peak, 6H), 1.4 (s, 3H); ^{13}C NMR: δ 171.2, 155.1, 154.6, 145.2 (dm, $^{1}J_{CF}$ = 250 Hz), 142.0 (dm, $^{1}J_{CF}$ = 250 Hz), 131.3 (sharp m), 131.6, 117.7, 110.6 (sharp m), 79.8, 67.0, 53.2, 52.7, 52.3, 51.9, 31.1, 28.0, 26.2, 23.8; HRMS (EI): Calcd for $C_{25}H_{32}F_4N_3O_6S$: 579.2026 Found: 579.2019; Anal Calcd for $C_{25}H_{32}F_4N_3O_6S$: C: 51.81, H: 5.74, N: 7.25 Found: C: 51.73, H: 5.64, N: 7.24.

N^{α}-9-Fluorenylmethoxycarbonyl-*S*-[*N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-allyloxycarbonyl]-aminomethyl-cysteine methyl ester (Fmoc-Cys(Fnam)-OMe, 13d): 68% yield; syrup, ^{19}F NMR: two rotamers in *ca* 80/20 ratio; major rotamer: δ 13.85 (d, J = 21 Hz, 1F, *o*-F), 13.5 (d, J = 21 Hz, 1F, *o'*-F), 10.45-10.3 (m, 2F); minor rotamer: δ 14.4 (d, J = 20 Hz, 1F, *o*-F), *ca* 13.85 (1F, *o'*-F, masked by major rotamer), 10.4-10.3 (m, 2F); ^{1}H NMR: δ 8.2-7.8 (8H), 6.05 (broad d, 1H, NH), 6.1-5.7 (m, 1H), 5.4-5.1 (m, 2H, vinylic CH_2), 4.98 and 4.75 (two d, AB system, J_{AB} = 19 Hz, S-CH_2-N), 4.7-4.6 (m, 3H, $C^{\alpha}H$ and allylic CH_2), 4.4 (d, 2H, Fmoc CH_2), 4.2 (m, 1H, Fmoc $C^{9}H$), 3.8 (s, 3H), 3.15 (broad peak, 4H), 3.1-2.9 (m, 2H, $C^{\beta}H_2$), 1.6 (broad peak, 6H); ^{13}C NMR: δ 170.9, 155.7, 154.7, 144.2 (dm, $^{1}J_{CF}$ = 250 Hz), 143.5, 141.7 (dm, $^{1}J_{CF}$ = 230 Hz), 141.0, 131.5, 130.4 (sharp m), 127.4, 126.8, 124.9, 119.7, 118.9, 117.75, 110.6 (sharp m), 67.1, 66.9, 54.1, 52.4, 51.9, 51.6, 46.8, 32.6, 26.2, 23.7: HRMS (EI): Calcd for $C_{35}H_{35}F_4N_3O_6S$: 701.2182 Found: 701.2177.

*Synthesis of N^{α}-9-fluorenylmethoxycarbonyl-S-[N-[2,3,5,6-tetrafluoro-4-(N'-piperidino)-phenyl], N-allyloxycarbonyl]-aminomethyl-cysteine (Fmoc-Cys(Fnam)-OH, **18**)*

Fmoc-Cys(Trt)-OH was converted to its phenacyl ester Fmoc-Cys(Trt)-OPac by reaction with 2-bromoacetophenone (Pac-Br) in the presence of triethylamine following standard procedure.[15] Removal of the trityl group was carried out in TFA/dichloromethane 1/1 (6 mL per mmol of cysteine derivative) in the presence of triethylsilane (2 molar equiv.) and for 1 h at room temperature. The detritylated derivative, obtained in 97% yield, was condensed with the sulfonium salt **16** according to the general procedure already described to give Fmoc-Cys(Fnam)-OPac (**17**) in 70% yield. Removal of the Pac group to give the Fnam derivative of cysteine was carried out in the following way: freshly activated zinc powder (260 mg, 16 equiv.) was added in small portions to a solution of **17** (200 mg, 0.2 mmol) in 5 mL of acetic acid. The reaction mixture was further stirred for 2 h at room temperature and then filtrated. The remaining Zn was washed several times with dichloromethane. The organic filtrates were combined and washed successively with a 0.1 N aqueous HCl solution and with brine. After drying and evaporation, the residue was purified by flash chromatography on silica (AcOEt/AcOH 100:1 as the eluent). After repeated coevaporations with toluene in order to completely eliminate acetic acid, 106 mg (77% yield) of N^{α}-9-fluorenylmethoxycarbonyl, *S*-[*N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl]-*N*-allyloxycar-bonyl]-aminomethyl-cysteine were obtai-ned as a waxy solid which could not be properly recrystallised.

N^{α}-9-Fluorenylmethoxycarbonyl-*S*-trityl-cysteine phenacyl ester (Fmoc-Cys(Trt)-OPac): foamy solid. ^{1}H NMR: δ 7.9-7.2 (m, 28H), 5.45 (broad d, 1H, NH), 5.3 (s, 2H), 4.5-4.4 (m, 3H, $C^{\alpha}H$ and Fmoc CH_2), 4.25 (t, 1H, Fmoc $C^{9}H$), 2.92 (d, 2H, $C^{\beta}H_2$).

N^{α}-9-Fluorenylmethoxycarbonyl-cysteine phenacyl ester (Fmoc-Cys-OPac): glassy solid; ^{1}H NMR: δ 7.9-7.22 (13 H), 6.0 (broad d, 1H, NH), 5.5 (d, 1H) and 5.2 (d, 1H, AB system, J_{AB} = 16 Hz, Pac CH_2), 4.95 (dt, 1H, $C^{\alpha}H$), 4.4 (d, J = 7 Hz, 2H, Fmoc CH_2), 4.28 (t, J = 7 Hz, 1H, Fmoc $C^{9}H$), 3.4-3.2 and 3.1-2.9 (two m, ABXY system, $C^{\beta}H_2$), 2.1 (t, J = 8.8 Hz, SH); ^{13}C NMR δ 191.2, 169.5, 155.6, 143.6, 141.0, 134.0, 128.7, 127.5, 126.9, 124.9, 119.8, 66.9, 66.5, 54.7, 46.8, 27.2; HRMS (EI): Calcd for $C_{26}H_{23}NO_5S$: 461.1297 Found: 461.1298.

N^{α}-9-Fluorenylmethoxycarbonyl-*S*-[*N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-allyloxycarbonyl]-aminomethyl-cysteine phenacyl ester (Fmoc-Cys(Fnam)-OPac, 17): off-white solid; mp 68 °C; ^{19}F NMR: two rotamers in *ca* 80/20 ratio; major rotamer: δ 14.1 (broad d, 1F, *o*-F), 13.5 (broad d, 1F, *o'*-F), 10.5-10.3 (broad m, 2F); minor rotamer: δ 14.55, 1F, *o*-F), *ca* 13.5 (1F, *o'*-F, masked by major rotamer), 10.5-10.3 (broad m, 2F); ^{1}H NMR: δ 8.0-7.1 (m, 13 H), 6.1 (broad d, 1H, NH), 6.0-5.7 (m, 1H), 5.5-4.95 (m, 4H, Pac CH_2 and vinylic CH_2), 4.95-4.5 (m, 3H, S-CH_2-N and allylic CH_2), 4.45-4.3 (m, 3H, Fmoc CH_2 and $C^{\alpha}H$), 4.25 (m, 1H, Fmoc $C^{9}H$), 3.38 (dd, 1H, A proton of an ABX system, other peaks of $C^{\beta}H_2$ masked by piperidino group), 3.2 (broad peak, 4H), 1.6 (broad peak, 6H).

N^{α}-9-Fluorenylmethoxycarbonyl-*S*-[*N*-[2,3,5,6-tetrafluoro-4-(*N'*-piperidino)-phenyl], *N*-allyloxycarbonyl]-aminomethyl-cysteine (Fmoc-Cys(Fnam)-OH, 18): waxy solid; ^{19}F NMR: two rotamers in *ca* 80/20 ratio; major rotamer: δ 13.95 (broad d, 1H, *o*-F), 13.6 (broad d, 1F, *o'*-F), 10.7-10.05 (broad m, 2F); minor rotamer: δ 14.55 (broad d, 1F, *o*-F), *ca* 14.0 (1F, o'-F, masked by major rotamer), 10.7-10.05 (broad m, 2F); ^{1}H NMR: δ 8.0-7.1 (m, 8H), 6.1 (broad d, 1H, NH), 6.1-5.6 (m, 1H), 5.3-5.0 (m, 2H), 4.9-4.5 (m, 5H, allylic CH_2, $C^{\alpha}H$ and S-CH_2-N), 4.4 (m, 2H, Fmoc CH_2), 4.2 (m, 1H, Fmoc $C^{9}H$), 3.2 (broad peak, 4H), 3.2-2.9 (m, partially masked by piperidino group, $C^{\beta}H_2$), 1.6 (broad peak, 6H); ^{13}C NMR: δ 170.1, 155.8, 155.5, 147.35 (dm, $^{1}J_{CF}$ = 260 Hz), 141.2 (dm, $^{1}J_{CF}$ = 260 Hz), 141.15, 131.7, 131.3 (sharp m), 127.6, 126.9, 125.1, 119.9, 118.3, 112.2 (sharp m), 67.4, 67.1, 55.1, 52.03, 47.0, 31.5, 26.7, 26.3, 23.8; $[\alpha]_D^{20}$ = - 19.9 (*c* 1, $CHCl_3$); MS (electrospray): 688.0 (20%, M+1), 710.0 (100%, M+Na), 726.0 (2%, M+K); Anal. Calcd for $C_{34}H_{33}F_4N_3O_6S$: C: 59.38, H: 4.80, N: 6.11, F: 11.06 Found: C: 60.15, H: 5.02, N: 6.34, F: 10.93.

*Synthesis of the dipeptide Fmoc-Cys(Fnam)-Phe-OMe **19**.*

Fmoc-Cys(Fnam)-Phe-OMe was synthesized by BOP-mediated coupling of Fmoc-Cys(Fnam)-OH with HCl·H-Phe-OMe following standard procedure.[16] From 100 mg (0.145 mmol) of Fmoc-Cys(Allocam)-OH, 62 mg (50% yield) of Fmoc-Cys(Fnam)-Phe-OMe was obtained after purification by flash chromatography. White solid; ^{19}F NMR: major rotamer δ 14.11 (broad d, 1F, *o*-F), 12.8 (broad d, 1F, *o'*-F), 10.5-10.3 (broad m, 2F); ^{1}H NMR: δ 7.8-7.0 (m, 13 H), 6.1-5.7 (m, 3H, NH and vinylic CH), 5.4-4.2 (several multiplets, 11H), 3.7 (s, 3H), 3.2 (m, 8H), 1.55 (broad peak, 6H); MS (electrospray/PI): 849.2 (M+1, 100%).

Deprotection of Fam and Fnam derivatives of thiols.

By the system $PdCl_2(PPh_3)_2/Bu_3SnH/AcOH$: This procedure has already been described [1].

By the system $Pd(PPh_3)_4$/N,N'-dimethylbarbituric acid (NDMBA). Typical procedure: In a Schlenk tube and under an argon atmosphere, a mixture of NDMBA (85.6 mg, 0.55 mmol) and $Pd(PPh_3)_4$ (10.5 mg, 0.009 mmol) is dissolved in 1 mL of degassed dichloromethane. A solution of 0.27 mmol of protected thiol in degassed dichloromethane is then syringed into the Schlenk tube. The reaction mixture is stirred for 2 h at room temperature. 190 μL (2.7 mmol) of mercaptoethanol and 154 μL (2.7 mmol) of acetic acid are added, and the reaction mixture is further stirred for 5 h. The dichloromethane is evaporated and the residue is taken up in diethyl ether. The organic phase is extracted with 10% aqueous citric acid and with water, dried on $MgSO_4$ and evaporated.The deprotected thiol is finally purified by flash chromatography.

An inverse addition procedure, *i.e.* addition of *first* NDMBA and then $Pd(PPh_3)_4$ to a dichloromethane solution of protected thiol may as well be utilized.

By the system $Pd(PPh_3)_4/PhSiH_3$:This procedure is similar to the $Pd(PPh_3)_4$/NDMBA procedure. 2 mol of $PhSiH_3$ and 0.05 mol of catalyst are used for 1 mol of protected thiol.

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9. It should be noted however that the bis(Alloc)am derivatives of benzyl mercaptan is stable in dichloromethane solution in the presence of tertiary amines such as triethylamine, DIEA or N-methylmorpholine which are currently used in the neutralization steps of SPPS according to the Boc temporary protection strategy. The bis(Alloc)am group therefore appears compatible with Boc chemistry. It may be introduced on thiols by alkylation with diallyl *N*-chloromethyl-imidodicarbonate which may itself be prepared by treating the corresponding methylthiomethyl derivative **8b** with SO_2Cl_2.[5]
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