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Allylic Protection of Thiols and Cysteine : I: The Allyloxycarbonylaminomethyl Group

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Abstract: *S*-allyloxycarbonylaminomethyl derivatives of thiols in general and cysteine in particular are readily deprotected by palladium catalysed hydrostannolysis with tributyltin hydride in the presence of acetic acid. They are perfectly stable in the basic conditions (piperidine/DMF) of Fmoc group removal but tend to decompose, albeit slowly, in the acidic conditions (TFA/CH_2Cl_2) of *t*-Bu and Boc groups removal. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The allyl (All) and allyloxycarbonyl (Alloc) protecting groups, first introduced in the field of peptide synthesis by Kunz and coworkers[1,2] are, due to their orthogonality with the widely used acid labile *t*-Bu/Boc and base labile Fmoc protecting groups, increasingly popular. [3] They are selectively cleaved under mild conditions through catalytic π–allyl palladium chemistry (Tsuji-Trost reaction) which involves the combination of a palladium(0) catalyst (typically $Pd(PPh_3)_4$) and a nucleophilic species acting as an allyl group scavenger and thereby allowing regeneration of the catalyst from the intermediate π-allyl palladium(II) complex. They have been used for protection either in a temporary or semi-permanent way, of α-amino and α-carboxy groups and of various side-chain reactive functionalities.[3] In addition, allylic linkers have been devised and used in solid-phase peptide synthesis (SPPS).

Use of semi-permanent allylic protections for side-chain reactive functionalities during peptide synthesis seems attractive in several respects, especially as regards the SPPS of fully protected fragments.[4-6] The two main strategies in current use for such syntheses rely on

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temporary Boc/ semi-permanent Bn or temporary Fmoc/semi-permanent *t*-Bu,Boc protection schemes. In the first one, TFA-stable linkers are used, which may be cleaved by bases, nucleophiles or photochemically; in the second one, base stable, highly acid sensitive handles are usually involved. The acidic conditions required for removal of benzylic or *tert*-butylic side-chain protections may bring about various unwanted side-reactions. In that respect, their replacement by allylic protecting groups could constitute an interesting alternative. Besides, the use of allylic side-chain protections could open the way to new possibilities in the choice of handles and of temporary terminal N^{α}-protecting groups. Finally, due to the small size of the allyl group, allylic protected fragments could display better solubilities in polar medium that their benzylic or *tert*-butylic congeners and thereby help alleviate one of the most acute difficulties encountered in fragment condensations.[4-7]

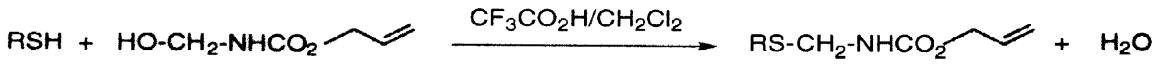
Taking full advantage of allyl-based permanent side chain protection strategy would require having at one's disposal a full array of allylic protecting groups which span the entire set of side chain functionalities of natural aminoacids. This is not yet the case. The allyl group is suitable for protection of the carboxylic groups of aspartic and glutamic acid,[8-10] and the phenolic group of tyrosine[8,11] while the Alloc group may be used for protection of the nitrogen functions of lysine[8,12] or indole.[13] Regiospecific N(π)-protection of the imidazole nucleus of histidine also appears promising.[14] However, neither the allyl nor the allyloxycarbonyl group are suitable for protection of the SH group of cysteine or the OH group of serine and threonine. Indeed, contrary to allyl carboxylates or phenoxides, allyl ethers or thioethers are not cleaved by palladium and the *O*- or *S*-Alloc derivatives of threonine and in particular serine and cysteine are prone, as are most other carbalkoxy derivatives, to undergo intramolecular nucleophilic attack by the neighbouring α-amino function under the basic conditions of Fmoc removal or even during coupling processes.[8]

Recently, we reported, in a preliminary communication,[15] and as a way to circumvent these problems, on the use of the allyloxycarbonylaminomethyl (Allocam) group for specific protection of the thiol group of cysteine. *S*-Allocam derivatives of thiols are cleaved by palladium-catalysed hydrostannolysis with tributyltin hydride. They are perfectly stable in the basic conditions of Fmoc deprotection but only marginally stable under acidic conditions. In the present article, we report in full detail on the Allocam protection of thiols in general and of the sulfhydryl group of cysteine in particular. In the accompanying paper, we report on our further exploratory studies towards the development of more sophisticated, more acid resistant allylic protecting groups derived from the Allocam group by appropriate introduction of electron-withdrawing substituents.

RESULTS AND DISCUSSION

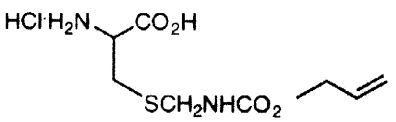
Preparation of S-Allocam derivatives of thiols

S-Allocam derivatives of thiols are conveniently prepared by condensation of thiols with allyl *N*-hydroxymethyl-carbamate in acidic medium (scheme 1). By this method, the *S*-Allocam derivatives of *n*-octyl, benzyl, *p*-bromobenzyl and 1-naphthylmethyl mercaptan were obtained in 70-90% yield after chromatographic purification, and the *S*-Allocam derivative of cysteine was obtained in 95% yield after precipitation as its hydrochloride salt. It should be



Scheme 1

noted that extending unduly the time of these reactions beyond 15-20 min may result in the side-formation of dithioketals, probably as a result of acid catalysed hydrolysis of the thio-Allocam derivatives into thiols and formaldehyde followed by acid catalysed condensation of these two species. The formation of dithioketals was much more pronounced with "simple" thiols than with cysteine. The *S*-Allocam derivative of cysteine **1** was further derivatized into Boc-Cys(Allocam)-OH **2a** or Fmoc-Cys(Allocam)-OH **3a**, by reaction with Boc-ON in the presence of triethylamine or with 9-fluorenylmethyl chloroformate in the presence of bis(trimethylsilyl)acetamide (BSA) respectively. The methyl esters **2b** and **3b** were finally obtained from **2a** and **3a** by alkylation with methyl iodide in the presence of potassium carbonate or by treatment with diazomethane. Finally, the benzylamide derivative **2c** was prepared by DCC/HOBt mediated coupling of **2a** with benzylamine.



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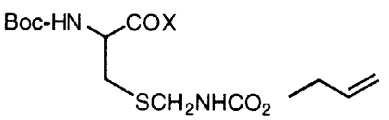
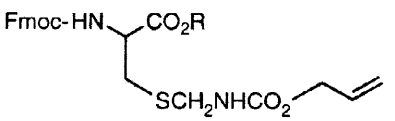


2a X = OH
2b X = OMe
2c X =HNBn



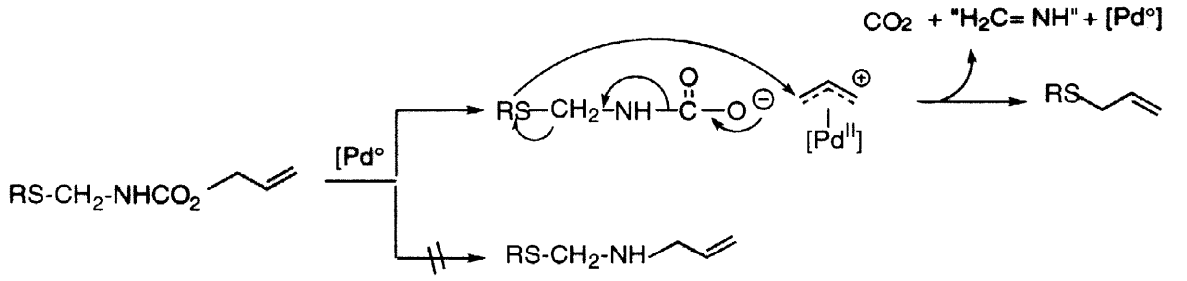
3a R = H
3b R = Me

Palladium-catalysed rearrangement of S-Allocam derivatives of thiols into allyl thioethers.

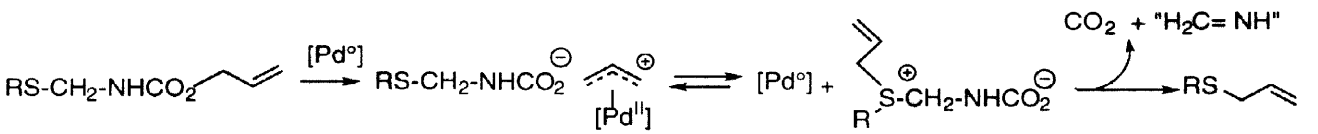
Allyl carbamates generally rearrange quite readily into *N*-allylamines in the presence of palladium(0) catalyst such as $Pd(PPh_3)_4$.[3] It was therefore hoped that a similar decarboxylative rearrangement would take place with the thio-Allocam derivatives, leading to thioaminals. Acyclic thioaminals being easily hydrolysed, a straightforward and selective deprotection method would therefore have been at hand. In the event, we found that *S*-Allocam derivatives do rearrange in the presence of $Pd(PPh_3)_4$, but through a double fragmentation process which leads to allyl thioethers with loss of carbon dioxide and (formally) methylenimine. This reaction appears quite general. For instance, in the presence of 3 mol% of catalyst, total conversion of Boc-Cys(Allocam)-OMe, Boc-Cys(Allocam)-NHBn and Fmoc-Cys(Allocam)-OMe were observed within 4 to 6 h in dichloromethane at 35 °C and the corresponding allyl thioethers Boc-Cys(All)-OMe, Boc-Cys(All)-NHBn and Fmoc-Cys(All)-OMe were isolated, in 63%, 77% and 83% yields respectively.

As proposed in our preliminary communication[15] and represented in scheme 2, a concerted mechanism may be invoked to account for this rearrangement. An alternative pathway may also be envisioned (scheme 3) in which the *S*-allylation step precedes the fragmentation process, thus avoiding the transient formation of anionic thiolato species and the possible

poisoning of catalyst[16] which could ensue. We have already noted, in another context, that allyl carboxylates may indeed transfer, probably in a reversible manner, their allyl group to thioethers in the presence of palladium catalyst, leading to allyl sulfonium species.[17]



Scheme 2



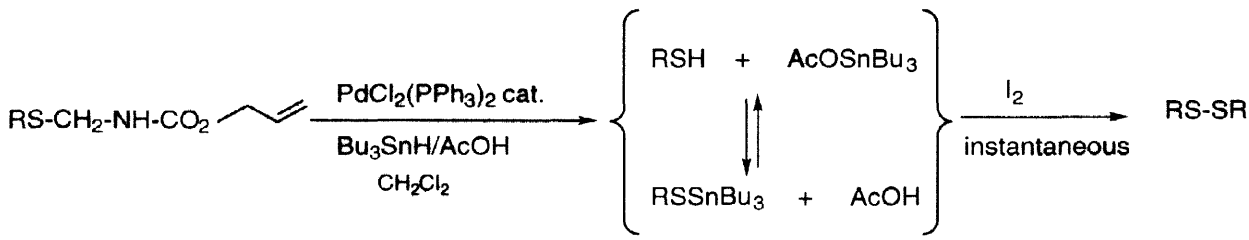
Scheme 3

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

Since *S*-Allocam derivatives of thiols do not rearrange to labile *N*-allylthioaminals but to stable thioallyl ethers in the presence of palladium catalyst, adding a nucleophilic species to the medium appeared necessary in order to trap the π-allyl entity before rearrangement take place. *N,N'*-dimethylbarbituric acid (NDMBA)[18], *N*-trimethylsilylamines[19] and phenylsilane,[20] which have been shown to be efficient allyl group scavengers in the palladium catalysed deprotection of "ordinary" allyl carbamates proved unsuitable in the case of thio-Allocam derivatives. Deprotection reactions were found to stop at an early stage (*ca* 20% deprotection) probably as a result of catalyst poisoning. On the contrary, the ternary system $PdCl_2(PPh_3)_2$/tributyltin hydride/acetic acid[11] was found to lead to rapid (10-15 min) and complete deprotection (TLC, NMR) in all the cases under study. The success of this procedure may reasonably be ascribed to the very high rate of the palladium catalysed hydrostannolytic cleavage and to the presence of acetic acid, both factors which should prevent the formation of the poisonous thiolato species formation (5-10%) of allyl thioether is observed.

The hydrostannolytic procedure leads to a mixture of the thiol, its tributylstannyl salt and minor amounts of disulfide, from which isolation of a well defined deprotected product turned out to be difficult. For the sake of convenience and characterization, after evaporation of

solvent and most acetic acid, the crude reaction mixtures were treated with iodine until persistance of I_2 coloration in order to convert all the thiols or their tin salts into disulfides[21] (scheme 4). These disulfides were then purified from the side-products (catalyst and tin com-



Scheme 4

pounds) by appropriate extractive procedures, described in detail the experimental section, followed by chromatographic purification. In this way, most disulfides and especially the N^{α}-,N'^{α}-bis(Boc)-cystine compounds were obtained in very satisfactory yields as reported in table 1. The lower yield in N^{α}-,N'^{α}-bis(Fmoc)-cystine bis-methyl ester could be the result of partial degradation during iodine treatment.

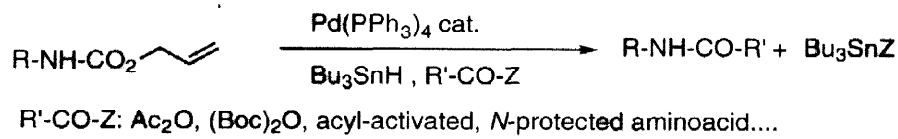
Table 1 Formation of disulfide compounds from hydrostannolytic cleavage of Allocam derivatives of thiols followed by I_2 treatment.

S-Allocam derivatives	Disulfides	Isolated yields
$PhCH_2S$-Allocam	$PhCH_2S$-S-CH_2Ph	72%
(1-Napht)-CH_2S-Allocam[a]	(1-Napht)-CH_2S-SCH_2-(1-Napht)	88%
p-BrPh-CH_2S-Allocam	*p*-BrPh-CH_2S-SCH_2-*p*-BrPh	72%
Boc-Cys(Allocam)-OMe	(Boc-Cys-OMe)$_2$	98%
Boc-Cys(Allocam)-NHBn	(Boc-Cys-NHBn)$_2$	92%
Fmoc-Cys(Allocam)-OMe	(Fmoc-Cys-OMe)$_2$	65%

[a] Napht: naphthyl

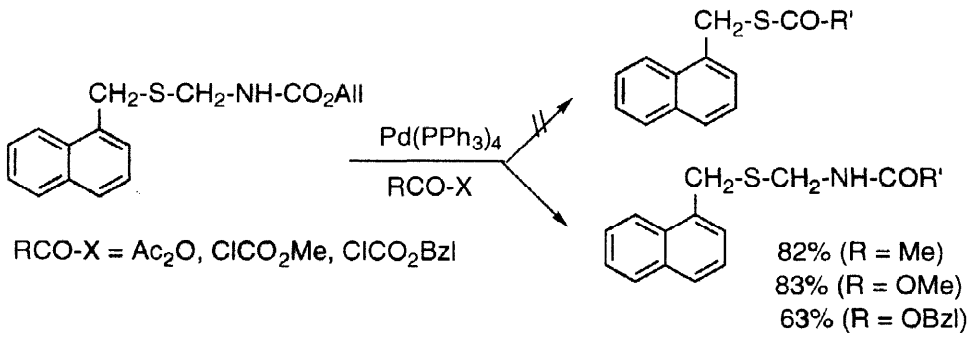
Palladium catalyzed transacylation reactions of S-Allocam derivatives of thiols.

Hiemstra, Speckamp and coworkers have shown[22] that palladium-catalysed hydrostannolytic cleavage of allyl carbamates in general, when conducted in the presence of acylating agents (carboxylic acid anhydrides, acyl chlorides, activated esters) lead to transacylated products, according to scheme 5.



Scheme 5

We have investigated the possible extension of this transacylation methodology to *S*-Allocam compounds. Treatment of the *S*-Allocam derivative of 1-naphthylmethyl mercaptan with palladium catalyst and tributyltin hydride in the presence of acetic anhydride was found to lead to the corresponding *S*-acetamidomethyl compound in 82%. Similar results were obtained with other acylating agents (scheme 6). Noteworthy is the fact that the reaction does not lead



Scheme 6

to the formation of the *S*-acylated compound, a result which stands in contrast with our previous observations concerning the palladium catalysed rearrangement of *S*-Allocam derivatives to thioallyl ethers (*vide supra*). The transacylation procedure also applies to the *S*-Allocam derivatives of cysteine. Thus, from Boc-Cys(Allocam)-NHBn, transacylation products were obtained in 68% yield with Ac_2O and 70% yield with methylchloroformate, and from Fmoc-Cys(Allocam)-OMe 77% of transacylation product were obtained with Ac_2O. An interesting extension of this reaction would have been to use it for the conversion of *S*-Allocam to *S*-Bocam (*S-tert*-butyloxycarbonylaminomethyl) derivative of cysteine. Indeed, the Bocam group, which could constitute a new acid-labile, Fmoc-compatible protection for the sulfhydryl group of cysteine,[23] cannot obviously be introduced onto thiols in the same way as other acylaminomethyl or carbalkoxyaminomethyl groups due to the acidic conditions involved in the corresponding procedures.[24] Accordingly, the hydrostannolytic cleavage of the *S*-Allocam derivatives of first 1-naphthylmethyl mercaptan and then N^{α}-Fmoc-cysteine methyl ester was conducted in the presence of various *tert*-butoxycarbonylating agents, namely di-*tert*-butyl dicarbonate ($(Boc)_2O$), *tert*-butyloxycarbonyl fluoride and *N-tert*-butyloxycarbonyl-4-dimethylaminopyridinium tetrafluoroborate[25] (Boc-DMAP$^+$, BF_4^-) in the presence of

tetrabutylammonium bromide. However, as shown in Table 2, rather disappointing results were obtained, especially in the case of the cysteine derivative for which the yield in Bocam product did not exceed 40%. It is interesting to note that transprotection with Boc-DMAP$^+$, BF_4^- does not take place at all in the absence of tetrabutylammonium bromide, whose role is probably to act as an acceptor of the formal tributyltin cationic entity.

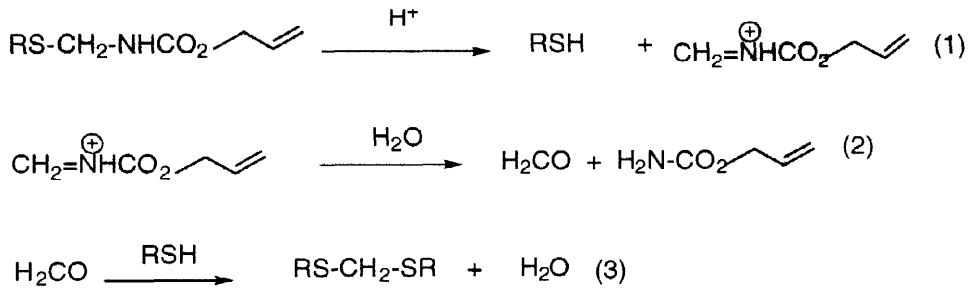
Table 2: Attempted conversion of Allocam derivatives of thiols into **Bocam** derivatives of thiols.

Entry	*S*-Allocam derivatives	S-Bocam derivatives	*tert*-Butoxycarbonylating agents	Yields[a]
1	(1-Napht)-CH_2S-Allocam[b]	(1-Napht)-CH_2S-Bocam	$(Boc)_2O$	76%
2	*ibid*	*ibid*	Boc-F	59%
3	*ibid.*	*ibid.*	Boc-DMAP$^+$ BF_4^-	0%
4	*ibid.*	*ibid.*	Boc-DMAP$^+$ BF_4^- + Bu_4N^+ Br^-	64%
5	Fmoc-Cys(Allocam)-OMe	Fmoc-Cys(Bocam)-OMe	$(Boc)_2O$	45%[c]
6	*ibid.*	*ibid.*	Boc-F	40%[c]

[a]isolated yield; [b] Napht: naphthyl; [c]*ca* 50% of SH free Fmoc-Cys-OMe is also formed.

Stability of S-Allocam derivatives of thiols in basic or acidic media.

S-Allocam derivatives of thiols are indefinitely stable in a 20% dichloromethane solution of piperidine. On the contrary, in TFA/CH_2Cl_2 1/3 *v/v*, and at room temperature the Allocam derivative of benzyl mercaptan slowly decomposed. NMR analysis of the crude reaction mixture after 15 h showed the presence of 70% of unchanged Allocam compound. The almost exclusive decomposition product was identified as the dithioketal Bzl-CH_2-Bzl. Its formation, made possible by the presence of adventitious water, may be explained on the basis of eqs 1-3of scheme 7.



Scheme 7

The stability under similar conditions of *S*-Allocam derivatives of cysteine was studied on N^{α}-Fmoc-*S*-Allocam-cysteine (Fmoc-Cys(Allocam)-OH). The following percentages of decomposition were observed , based on HPLC analysis, in TFA/CH_2Cl_2 1/3 *v/v* at 25 °C: 3.4% (3 h), 10.3% (20 h), 16 % (45 h). The product from this decomposition, whose identity has not been determined, was found to display the characteristic UV absorbance of the fluorene chromophoric group but did not exhibit the characteristic NMR peak of the -S-CH_2-S group of dithioketal.

EXPERIMENTAL SECTION

General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or in other solvents as indicated, at 250 MHz and 63 MHz respectively. Chemical shifts are quoted in ppm relative to TMS. All solvents were dried and freshly distilled under a nitrogen atmosphere. All manipulations involving palladium catalysts were carried out under an argon atmosphere. All compounds descibed in this study displayed satisfactory analytical and spectroscopic data, but only the data for the more significant compounds are reported here.

Preparation of allyl carbamate H_2N-CO_2All.

In a two-necked round-bottom flask equipped with a mechanical stirrer and a dropping funnel were placed 250 mL of toluene and 40 mL of allyl chloroformate. The flask was cooled in an ice-water bath and 90 mL of 32% NH_3/H_2O was added dropwise under agitation while maintaining the temperature of the reaction mixture close to 5 °C. The reaction was further stirred at room temperature for 1 h. The organic phase was then decanted and dried over $MgSO_4$. The toluene was evaporated and the residue was distilled to give 31.54 g (78% yield) of allyl carbamate as a liquid: bp 106 °C/22mmHg; ^{1}H NMR: δ 5.8-6.0 (m, 1H), 5,30 (broad s, 2H, NH_2), 5.25 (two d (app. t), J = 13Hz and 7 Hz, 2H), 4.55 (d, J = 7 Hz, 2H); ^{13}C NMR: δ 157.2, 132.4, 117.5, 65.4; IR (CCl_4): 3356 (NH), 3206 (NH), 1703 (CO), 1649 (C=C) cm^{-1}; GC/MS: 102, 57, 41, 39; Anal. Calcd for $C_4H_7NO_2$: C: 47.52, H: 6.97, N: 13.85 Found: C: 47.25, H: 6.70, N: 13.69.

Preparation of N-hydroxymethyl carbamic acid allyl ester $HOCH_2$-NH-CO_2All.

In a Schlenk tube placed in an oil bath, were introduced 10 g (0.1 mol) of allyl carbamate, 3 g of paraformaldehyde (1 equiv.) and 0.05 g of $Ba(OH)_2$ under an inert atmosphere. The temperature of the bath was progressively raised to 60 °C upon which the reaction mixture became limpid. The reaction was allowed to proceed at 60 °C for one additional hour during which a new precipitate formed . After cooling, the precipitate was collected on a sintered glass, washed with several small portions of diethyl ether and finally recrystallised from toluene.Yield: 8 g (68%); mp 57 °C; ^{1}H NMR: δ 6.0-5.8 (m, 1H), 5.15-5.45 (two d, J= 13 Hz and 5 Hz), 4.70 (broad t, 2H, $\underline{CH_2}OH$), 4.60 (d, allylic CH_2, J = 5 Hz); ^{13}C NMR: δ 157.2, 132.4, 117.7, 66.4, 65.4; IR (nujol): 3360, 1710 (CO) cm^{-1}; Anal. Calcd for $C_5H_9NO_3$: C: 45.79, H: 6.91, N: 10.68 Found: C: 45.92, H: 6.88, N: 10.67.

Preparation of Allocam derivatives of "simple" mercaptans

Allocam derivative of benzyl mercaptan (*N*-benzylthiomethyl-carbamic acid allyl ester): In a Schlenk tube equipped with a magnetic stirring bar and a rubber septum and under an argon atmosphere, 1.70 g (13.7 mmol) of benzylmercaptan were dissolved in 10 mL of trifluoroacetic acid. With a syringe, were then introduced 2 g (15.2 mmol) of *N*-hydroxymethyl carbamic acid allyl ester dissolved in 10 mL of dichloromethane. The reaction mixture was further stirred for 10 min. and then evaporated on a Rotovap. Purification of the residue by flash chromatography (silica, cyclohexane/AcOEt 4:1) gave 3.24 g (90%) of Allocam derivative of benzyl mercaptan as an oil. ^{1}H NMR: δ 7.4-7.2 (m, 5H), 6.0-5.8 (m, 1H), 5.45-5.15 (two d, J = 13 Hz and 7 Hz, 2H), 4.60 (d, J = 5 Hz, 2H), 4.30 (d, J = 7 Hz, S-CH_2-N), 3.80 (s, 2H); ^{13}C NMR: δ 157.2, 137.3, 132.4, 129.1, 128.0, 127.2, 117.7, 66.4, 65.4 ; IR(CCl_4): 3455 (NH), 1733 (C=O), 1649 (C=C). Anal. Calcd for $C_{12}H_{15}NO_2S$: C: 60.73, H: 6.37, N: 5.90 Found: C: 60.59, H: 6.50, N: 5.88.

When the reaction time was extended to 2 h, the dibenzylthioketal of formaldehyde $PhCH_2SCH_2SCH_2Ph$ was found to be the main product of reaction and was isolated in 30% yield after recrystallization from EtOH/H_2O; mp 45 °C ; ^{1}H NMR: δ 7.4-7.1 (m, 10 H), 3.85 (s, 4H), 3.35 (s, 2H); ^{13}C NMR: δ 137.2, 129.4, 127.3, 63.7, 34.2; Anal. Calcd for $C_{15}H_{16}$ S: C: 69.18, H: 6.19, S: 24.62 Found: C: 69.40, H: 6.06, S: 24.45; GC/MS : 261 (36%), 260 (M^+), 91 (100%).

The Allocam derivatives of *n*-octyl mercaptan (oil, bp 122-124/0.01 mmHg), *p*-bromobenzyl mercaptan (oil, purified by chromatography) and 1-naphtylmethyl mercaptan (oil, purified by chromatography) were prepared according to the same experimental procedure.

*Preparation of S-Allocam cysteine hydrochloride (HCl·H-(L)-Cys(Allocam)-OH, **1**)*

A suspension of 2.67 g (15.26 mmol) of (L)-cysteine hydrochloride in 20 mL of anhydrous TFA was placed under an argon atmosphere in a first Schlenk tube equipped with a magnetic stirring bar. In a second Schlenk tube was introduced under an argon atmosphere a solution of 2 g (15,26 mmol) of *N*-hydroxymethyl carbamic acid allyl ester in 20 mL of anhydrous CH_2Cl_2 under argon. The content of this second tube was then added, under magnetic stirring, into the first one through a cannula. The reaction mixture was further stirred at room temperature until it became limpid (*ca* 10 min).The solvent and most TFA were then evaporated and the residue was taken up in 50 mL of ethanol. To the ethanolic solution, were then added 6 mL of 4N aqueous HCl. The solvent was evaporated and the solid residue was triturated and rinsed several times with diethyl ether. After drying, 4.02 g of **HCl·H-(L)-Cys(Allocam)-OH** (92%) were collected as a white foamy solid: ^{1}H NMR (200 MHz, DMSO-d^6): δ 6.0-5.8 (m, 1H), 5.15-5.35 (two d (app. t), J = 13 Hz and 7 Hz, 2H), 4.5 (d, J = 5Hz, 2H), 4.15-4.35 (two dd, ABX system, J_{AB} = 14 Hz, J_{BX} = J_{AX} = 6.6 Hz, 2H, S-CH_2-N), 4.10 (broad t, 1H, $C^{\alpha}H$), 2.9-3.2 (two dd, ABX system, J_{AB} = 12 Hz, J_{AX} = 4.8 Hz, J_{BX} = 6 Hz, 2H); TLC (silica, n-butanol/AcOH/ H_2O 4: 1: 5): R_f = 0.21; $[\alpha]_D^{20}$ = - 15.6 (*c* 1, H_2O); Anal. Calcd for $C_8H_{15}NO_4SCl$: C: 35. 49, H: 5.58, N: 10.34 Found: C: 35.58, H: 5.71, N: 10.08.

Preparation of N^{α}-tert-butoxycarbonyl-S-Allocam-(L)-cysteine (Boc-Cys(Allocam)-OH, 2a) and of its dicyclohexylammonium salt.

2 g (7.4 mmol) of HCl·H-(L)-Cys(Allocam)-OH and 2.25g (3 equiv.) of triethylamine were introduced in 15 mL of water. 15 mL of dioxane and 3.6 g (14.8 mmol) of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON) were then added. The reaction mixture which became homogeneous after 1 h was further stirred at room temperature for two additional hours. 40 mL of water and 60 mL of dioxane were added. The aqueous phase was washed with AcOEt and then acidified to *ca* pH 2 with 1N aqueous H_2SO_4. This acidic solution was extracted twice with AcOEt and the organic phases were washed with water and brine. After drying and evaporation of the solvent, 2.13 g of crude Boc-Cys(Allocam)-OH were collected as a syrup. TLC (silica, $CHCl_3$/MeOH/AcOH 85:10:5): R_f 0.41; TLC (reverse phase: DC-Fertigplatten RP-18, acetonitrile/H_2O 1:1): R_f 0.18; ^1H NMR: δ 6.0 (broad s, 1H, NH), 5.8-6.0 (m, 1H, vinylic CH), 5.6 (broad peak, NH) 5.3 (two broad d, 2H, vinylic CH_2), 4.58 (m, 3H, allylic CH_2 and $C^{\alpha}H$), 4.35 (broad d, 2H, N-CH_2-S), 3.13-3.08 (dd, ABX system, J_{AB} = 12 Hz, J_{AX} = 4.8 Hz, J_{BX} = 6 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR: δ 171.5, 156.2, 155.7, 132.3, 117.9, 80.5, 66.0, 54.0, 53.35, 44.1, 33.4, 28.2.

The crude Boc-Cys(Allocam)-OH was converted to its dicyclohexylammonium salt [24] which was recrystallized from pentane/AcOEt: white solid; yield 70%; mp 218-222°C; ^1H NMR: δ 6.4 (broad t, 1H, Alloc NH), 6.0-5.85 (m, 1H), 5.71 (broad d, 1H, Boc NH), 5.3 (two d (app. t), J =13 and 7 Hz), 4.55 (d, J= 5Hz, allylic CH_2), 4.3 (d, 2H, S-CH_2-N), 4.15 (broad q, 1H, $C^{\alpha}H$), 3.1 (broad d, $C^{\beta}H_2$), 1.45 (s, 9H); dicyclohexylammonium moiety, 2.9 (m, 2H), 2.0-1.1 (several multiplets, 20 H); $[\alpha]_D^{20}$ = +26.6 (*c* 1, DMF); Anal. Calcd for $C_{26}H_{46}N_3O_6S$: C: 58.11, H: 8.97, N: 8.13 Found: C: 58.18, H: 8.67, N: 8.25.

Preparation of N^{α}-9-fluorenylmethyloxycarbonyl-S-Allocam- (L)-cysteine (Fmoc-Cys(Allocam)-OH, 3a).

1 g of HCl·H-(L)-Cys(Allocam)-OH was put in suspension in 10 mL of dry THF under an argon atmosphere. To this solution was added in one portion 3.6 mL (4 equiv.) of *N,O*-bis(trimethylsilyl)acetamide (BSA) and the reaction mixture was stirred for 1 h at room temperature. 0.9 g of 9-fluorenylmethyloxycarbonyl chloride in solution in 5 mL of THF were added. The reaction mixture was further stirred at room temperature for 15 h. The solvent was removed on a Rotovap and the residue was partitioned between 10 mL of diethyl ether and 10mL of saturated aqueous $NaHCO_3$ The ethereal phase was discarded. The aqueous phase was acidified to *ca* pH 3 with aqueous HCl and extracted three times with 20 mL portions of AcOEt. The organic phase was washed with water and dried on $MgSO_4$. The solvent was evaporated and the residual solid residue was recrystallised in ether/hexane. 1.12 g (66% yield) of Fmoc-Cys(Allocam)-OH were collected as a white solid: mp 138-140°C; ^1H NMR: δ 7.8 (d, J = 8 Hz, 2H, Fmoc group), 7.65 (d, J = 5.5 Hz, 2H, Fmoc group), 7.5-7.3 (m, 4H, Fmoc group), 6.15 (d, 1H, Fmoc NH), 6.0-5.8 (m, 1H), 5.5 (t, 1H, Alloc NH), 5.36-5.18 (two d (app. t), J = 13 and 7 Hz), 4.7-4.6 (m, 4H, allylic and Fmoc CH_2 group), 4.4 (m, 3H, $C^{\alpha}H$ and N-CH_2-S), 4.2 (t, 1H, Fmoc C^9H group), 3.1 (two dd, ABX system, J_{AB} = 12 Hz, J_{AX} = 4.8 Hz, J_{BX} = 6 Hz); TLC (silica, EtOH/ MeOH/AcOH 3: 1: 0.1): R_f 0.40; TLC (silica, EtOH/ $CHCl_3$ 1: 3): R_f 0.17; TLC (reverse phase: DC-Fertigplatten RP-18, acetonitrile/H_2O 2:1): R_f 0.63; $[\alpha]_D^{20}$ = - 35.9 (*c* 1, DMF); Anal. Calcd for $C_{23}H_{24}N_2O_6S$: C: 58.11, H: 8.97, N: 8.13. Found: C: 58.18, H: 8.67, N: 8.25.

*Preparation of N^{α}-tert-butoxycarbonyl-S-Allocam- (L)-cysteine methyl ester (Boc-Cys (Allocam)-OMe, **2b**) and of N^{α}-9-fluorenylmethyloxycarbonyl-S-Allocam-(L)-cysteine methyl ester (Fmoc-Cys(Allocam)-OMe, **3b**).*

General procedure: To a suspension of 15 mmol of the carboxylic acid in 20 mL of diethyl ether, an ethereal solution of diazomethane was added in small portions until persistance of a yellow coloration. After 15 min, diazomethane in excess was destroyed with a few drops of acetic acid. After evaporation of the solvent the methyl ester was purified by recrystallisation in acetonitrile/water or by flash chromatography with cyclohexane/AcOEt as the eluant.

N^{α}-*tert*-Butoxycarbonyl-S-Allocam-(L)-cysteine methyl ester (Boc-Cys(Allocam)-OMe): syrup; ^{1}H NMR: δ 6.0-5.8 (m, 1H), 5.7 (d, 1H, BocNH), 5.45 (t, 1H, Alloc NH), 5.4-5.2 (two d (app. t), J = 13 and 7 Hz, 2H) 4.55 (m and d, 3H, C$^{\alpha}$H and allylic CH_2), 4.3 (d, 2H, S-CH_2-N), 3.7 (s, 3H), 3.1 (two dd, ABX system, J_{AB} = 12 Hz, J_{AX} = 4.8 Hz, J_{BX} = 6 Hz), 1.4 (s, 9H); ^{13}C NMR: δ 171.1, 156.2, 155.1, 134.3, 118.4, 80.0, 66.2, 54.3, 52.2, 44.1, 33.3, 28.2 ; $[\alpha]_D^{20}$ = + 23.2 (*c* 1, $CHCl_3$); Anal. Calcd for $C_{14}H_{24}N_2O_6S$: C: 49.96, H: 6.71, N: 7.77. Found: C: 49.93, H: 6.86, N: 7.55 .

N^{α}-9-fluorenylmethyloxycarbonyl-S-Allocam- (L)-cysteine methyl ester (Fmoc-Cys(Allocam)-OMe): white solid; mp 117-119 °C; ^{1}H NMR δ 7.8 (d, J = 8 Hz, 2H, Fmoc); 7.65 (d, J = 5.5 Hz, 2H, Fmoc), 7.5-7.3 (m, 4H, Fmoc), 6.15 (d, 1H, Fmoc NH), 6.0-5.8 (m, 1H), 5.5 (t, 1H, Alloc NH), 5.36-5.18 (two d (app. t), J = 13 and 7 Hz), 4.7-4.6 (m, 4H, Fmoc CH_2 and allylic CH_2); 4.4 m, 3H, C$^{\alpha}$H and S-CH_2-N), 4.2 (t, 1H, Fmoc C^{9}H), 3.75 (s, 3H), 3.1 (two dd, ABX system, J_{AB} = 12 Hz, J_{AX} = 4.8 Hz, J_{BX} = 6 Hz); ^{13}C NMR: δ 171.2, 155.4, 143.7, 141.3, 132.6, 128.8, 127.3, 125.5, 120.4, 118.7, 67.2, 66.9, 54.3, 52.6, 47.7, 44.9, 33.3; $[\alpha]_D^{20}$ = + 3.4 (*c* 1, $CHCl_3$); Anal. Calcd for $C_{24}H_{26}N_2O_6S$: C: 61.21, H: 5.56, N: 5.95 Found: C: 61.01, H: 5.42, N: 5.75.

*Preparation of N^{α}-tert-butoxycarbonyl-S-Allocam- (L)-cysteine benzylamide (Boc-Cys(Allocam)-NHBn, **2c**).*

1.5 mmol of Boc-Cys(Allocam)-OH was dissolved in 10 mL of dry DMF together with 1.5 mmol of benzylamine and 1.5 mmol of HOBt. The solution was cooled to 0 °C and 1 equiv. of dicyclohexylcarbodiimide (DCC) was added. The reaction mixture was stirred first for 1 h at 0 °C and then for 4 h at room temperature. The precipitated dicyclohexylurea was filtered off and the filtrate was evaporated under 0.5 mmHg. The residue was taken up in 20 mL of AcOEt and the organic phase was washed successively with aqueous solutions of citric acid and of HCO_3Na, and dried over $MgSO_4$. After chromatography with cyclohexane/AcOEt as the eluent, Boc-Cys(Allocam)-NHBn was isolated in 50% yield as a waxy solid. ^{1}H NMR: δ 7.3 (m, 5H), 7.2 (t, NH), 6.1 (t, NH), 6.0-5.8 (m, 1H), 5.6 (d, NH), 5.2 (dd (app. t), 1H), 4.6-4.1 (m, 7H), 2.9 (m, 2H), 1.45 (s, 9H). ^{13}C NMR: δ 170.9, 156.2, 155.5, 137.5, 132.2, 131.7, 128.2, 127.2, 117.3, 79.7, 65.4, 53.3, 43.1, 42.75, 33.2, 28.0; Anal. Calcd for $C_{24}H_{26}N_2O_6S$: C: 56.72, H: 6.90, N: 9.92, S: 7.57. Found: C: 56.65, H: 6.83, N: 9.77, S: 7.35.

Palladium catalysed conversion of thio-Allocam derivatives into allyl thioethers.

General procedure: A solution containing 0.5 mmol of Allocam derrivative of thiol and 0.04 mmol. of $Pd(PPh_3)_4$ in 5 mL of DCM was placed under an argon atmosphere in a Schlenk tube equipped with a magnetic stirring bar. The reaction, monitored by TLC was allowed to

proceed at room temperature until completion (5 to 8 h). The solvent was then evaporated and the residue purified by flash chromatography on silica with cyclohexane/AcOEt as the eluent.
Boc-Cys(All)-OMe : 68% yield, oil; ^{1}H NMR: δ 5.75 (m, 1H); 5.4 (d, 1H, NH): 5.15 (m, 2H), 4.5 (broad q, 1H, $C^{\alpha}H$), 3.75 (s, 3H), 3.15 (d, 2H, J = 7.5 Hz, allylic CH_2), 2.9 (m, 2H, ABX system, $C^{\beta}H_2$), 1.45 (s, 9H); ^{13}C NMR δ 171.5, 155.0, 133.55, 117.7, 79.93, 53.0 ,52.4, 35.0, 32.7; 28.2; $[\alpha]_D^{20}$ = -18.4 (*c* 1, CH_2Cl_2) ; Anal. Calcd for $C_{12}H_{21}NO_4S$: C: 52.34, H: 7.69, N: 5.09, S: 11.64 Found: C: 52.65, H: 7.83, N: 5.77, S: 11.55.
Fmoc-Cys(All)-OMe 83% yield, white solid: ^{1}H NMR: δ 7.8 (d, 2H, Fmoc ArH),7.6 (d, 2H, Fmoc ArH), 7.4 (m, 4H, Fmoc ArH), 5.75 (m, 1H), 5.7 (m, 1H, NH), 5.1 (m, 2H), 4.6 (broad q, 1H, $C^{\alpha}H$), 4.4 (d, 2H, Fmoc-CH_2), 4.2 (t, 1H, Fmoc-C^9H), 3.8 (s, 3H), 3.2(d, 2H, J = 7Hz, allylic CH_2), 2.8 (m, ABX system, 2H, $C^{\beta}H_2$) ; ^{13}C NMR: δ 171.2, 155.6, 143.6, 141.2, 133.5, 127.6, 126.9, 124.9, 119.9, 117.8, 67.1, 53.4, 52.5, 46.9, 35.1, 32.7; Anal. Calcd for $C_{22}H_{23}NO_4S$: C: 66.47, H: 5.83, N: 3.52, S: 8.06 Found: C: 66.31, H: 5.75, N: 3.37, S: 7.96.

Palladium catalysed hydrostannolytic deprotection of S-Allocam derivatives of thiols

General method: A solution of 50 mmol of S-Allocam derivative, 3 molar equiv. of acetic acid and 0.04 molar equiv. of $PdCl_2(PPh_3)$ in 4 mL of CH_2Cl_2 was placed under an argon atmosphere in a Schlenk tube equipped with a magnetic stirring bar and fitted with a rubber septum cap. To this solution was added dropwise, through a syringe and over a period of *ca* 5 min, 2.2 equiv. of tributyltin hydride. The reaction mixture was stirred for a further 30 min. at room temperature although the deprotection reaction was found, by TLC, to be usually complete within 10 min.

Conversion of the crude deprotection product to disulfide: Aside from the catalyst, the by-products of the hydrostannolytic procedure are tributyltin acetate and hexabutyldistannane, the latter one resulting from the palladium catalysed decomposition of tributyltin hydride in excess.[11] After evaporation of dichloromethane and acetic acid in excess, short column chromatography (silica, cyclohexane/AcOEt as the eluent) allowed the elimination of hexabutyldistannane ($R_f \approx 1$) and of the catalyst. After evaporation of the solvents, the chromatographed product was taken up in CCl_4 and treated dropwise with a CCl_4 solution of iodine until persistence of iodine colour. The oxidation process may be also carried out before chromatographic purification, in which case more iodine is necessary as hexabutyldistannane is also oxidized to Bu_3SnI. In the case of the cystine derivatives which are insoluble in hydrocarbon solvents, the crude reaction mixture from oxidation was concentrated under vacuum, the residue was taken up in 9/1 *v/v* CH_3CN/H_2O and repeatedly extracted (x 6) with pentane, which allowed the complete elimination of all tin by-products.[27] In this way , the methyl ester and benzylamide of Boc-cystine were obtained in pure form. The Fmoc cystine methyl ester was further purified by flash column chromatography (silica, cyclohexane/AcOEt as the eluent). In the case of arylmethyl disulfides which are soluble in hydrocarbon solvents, the reaction mixture from iodine oxidation was concentrated on a Rotovap, taken up in diethyl ether and treated with an excess of a concentrated aqueous solution of KF to convert Bu_3SnI, which tails on chromatography, into Bu_3SnF.[28] The precipitated Bu_3SnF was then filtered off, the organic phase was concentrated and flash chromatographed on silica.
N^{α},N'^{α}-(bis) Boc-cystine bis-methyl ester: 98% yield; white solid, mp 100-102 °C; ^{1}H NMR: δ 5.5 (d, J = 6 Hz, 2H, NH x 2), 4.6 (broad q, 2H, $C^{\alpha}H$ x 2), 3.74 (s, 6H), 3.2 (d, 4H, $C^{\beta}H_2$ x 2), 1.45 (s, 18H); ^{13}C NMR: δ 171.4, 155.2, 80.4, 53.0, 52.8, 41.4, 28.45; $[\alpha]_D^{20}$ = + 65.5 (*c* 1, CH_2Cl_2); Anal. Calcd for $C_{18}H_{32}O_8N_2S_2$: C: 46.14, H: 6.88 , N: 5.98, S: 13.68 Found: C:46.23, H: 6.90, N: 5.82, S: 13.48.

N^{α},N'^{α}-(bis) Fmoc-cystine bis-methyl ester: 65% yield; white solid; ^{1}H NMR: δ 7.8 (d, 4H, Ar-H), 7.6 (m, 4H, Ar-H), 7.35 (m, 8H, Ar-H), 5.8 (d, J = 8 Hz, 2H, NH x 2), 4.65 (broad q, 2H, $C^{\alpha}H$ x 2), 4.4 (m, 4H, Fmoc CH_2 x 2), 4.2 (t, 2H, Fmoc C^9H x 2), 3.7 (s, 6H), 3.2 (d, J = 6 Hz, 4H, $C^{\beta}H_2$ x 2);^{13}C NMR: δ 170.85, 155.75, 143.8, 141.4, 127.8, 127.15, 125.1, 120.1, 67.3, 53.4, 52.9, 47.2, 41.2; $[\alpha]_D^{20}$ = + 23.1 (*c* 1, CH_3CN); Anal. Calcd for $C_{38}H_{36}O_8N_2S_2$: C: 64.03, H: 5.09, N: 3.93, S: 8.99 Found: C: 63.91, H: 5.35, N: 3.90, S: 8.66.

Transacylation of S-Allocam derivatives of thiols

Transacylation with Ac_2O, typical procedure: 0.5 mmol of the S-Allocam derivative of 1-naphtylmethyl mercaptan were dissolved together with 10^{-3} mmol (2 mol%) of $Pd(PPh_3)_4$ and 2 mmol (4 equiv.) of Ac_2O in 5 mL of dichloromethane in a Schlenk tube under an argon atmosphere. 1.1 mmol of tributyltin hydride was then added in one portion. The reaction mixture was stirred for 2 h at room temperature. The solvent was then evaporated and the residue was flash chromatographed (silica, dichloromethane/methanol 98/2)

Transacylation with methyl and benzyl chloroformate: Transacylations with methyl and benzyl chloroformate were conducted in a similar manner using 2 equiv. of acylating agent.

Transprotection of S-Allocam derivatives into Bocam derivatives, general procedures:

(a) with di-tert-butyl dicarbonate ($(Boc)_2O$): the S-Allocam derivative (0.7 mmol) was dissolved in 5 mL of dichloromethane under an argon atmosphere. To this solution were added 2 mmol of $(Boc)_2O$, 4 x 10^{-5} mmol of $Pd(PPh_3)_4$ (2 mol%) and then 1.1 mmol. of tributyltin hydride in one portion. The reaction mixture was allowed to proceed for 2 h at room temperature and under magnetic stirring. The solvent was evaporated and the residue was flash chromatographed.

(b) with tert-butyloxycarbonyl fluoride: to a solution of 0.5 mmol of Allocam derivative in 5 mL of dichloromethane under argon atmosphere were added 0.76 mL of a 44.2% w/w solution of Boc-F in dimethoxyethane (2.5 mmol), 0.01 mmol of $Pd(PPh_3)_4$ and finally 1.1 mmol of tributyltin hydride in one portion. The reaction mixture was further stirred at room temperature for 2 h and the solvent was evaporated. The residue was finally flash chromatographed on silica.

*(c) with 1-tert-butyloxycarbonyl-4-dimethylamino-pyridinium tetrafluorobora*te: to a solution of 0.5 mmol of Allocam derivative in 5 mL of dichloromethane under an argon atmosphere were added 2 mmol of Boc-DMAP$^+$, BF_4^- [23], 1 mmol of tetabutylammonium bromide and finally 1.1 mmol of tributyltin hydride in one portion. The reaction was allow to proceed for 3 hr at room temperature and then worked up in the usual manner.
N^{α}-9-fluorenylmethoxycarbonyl-*S*-(*N-tert*-butyloxycarbonylaminomethyl)-cysteine methyl ester (Fmoc-Cys(Bocam)-OMe); yields: see table 2; waxy solid : ^{1}H NMR: δ 7.8 (d, 2H,), 7.6 (m, 2H), 7.35 (m, 4H), 6.2 (d, 1H, NH), 5.3 (t, 1H, NH), 4.6 (q, J = 5 Hz, 1H, $C^{\alpha}H$), 4.4 (m, 3H, S-CH_2-N and Fmoc C^9H), 4.2 (m, 2H, Fmoc CH_2), 3.75 (s, 3H), 3.0 (two dd, ABX system, J_{AB} = 14 Hz, J_{AX} = 7 Hz, J_{BX} = 5 Hz, 2H, $C^{\beta}H_2$), 1.45 (s, 9H). ^{13}C NMR: δ 171.2, 155.9, 155.5, 143.7, 141.1, 127.6, 127.0, 125.0, 119.8, 80.2, 67.1, 54.4, 52.5, 47.0, 43.5, 32.6, 28.1 ; Anal. Calcd for $C_{25}H_{30}N_2O_6S$: C: 61.71, H: 6.2, N: 5.75, S: 6.6. Found: C: 61.53, H: 6.18, N: 5.64, S: 6.72 .

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