Calcd for $C_{27}H_{29}N_3O_6 \cdot {}^1/_2C_6H_6$: C, 67.92; H, 6.04; N, 7.92. Found: C, 67.69; H, 5.88; N, 7.79.

Reaction of the *O*-benzyloxime of benzoin (53, 2.5 mmol, syn and anti isomers) with Ph_3P–DIAD gave 300 mg (38%) of the mono-*O*-benzyloxime of benzil (**54**, mp 59–62 °C), 300 mg (37%) of *syn*-*O*-benzyloxime, and 250 mg (20%) of the adduct with DIAD (**55**, R′ = Pr). **55**: IR (film) 3550 (ν(O—H)), 3420 (ν(N—H)), 1760 (ν(C=O)), 1710 (ν(C=N)) cm^{-1}; NMR ($CDCl_3$) δ 1.0 (m, 6 H), 1.23 (d, 6 H, J = 6 Hz), 4.6 (m, 1 H), 5.0 (septet, 1 H, J = 6 Hz), 5.43 (s, 2 H), 6.4 (br s, 1 H), 6.66 (br d, 1 H, J = 9 Hz), 7.33 (m, 15 H); MS, m/e 558 (M^+), 503, 504, 376.

Reaction of the ethylene ketal of benzoin (56, 2 mmol) with Ph_3P–DIAD gave 170 mg (13%) of **58**, 120 mg (24%) of **57**, and 200 mg (38%) of unreacted substrate **21**. **58**: IR (film) 1750 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 12 H, J = 6 Hz), 3.86 (m, 8 H), 4.78 (septet, 2 H, J = 6 Hz), 5.87 (s, 2 H), 7.23 (m, 10 H). **57**: IR (film) 1690 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 4.22 (br s, 4 H), 7.37 (m, 5 H), 7.6 (m, 3 H), 8.08 (m, 2 H); MS, m/e 254 (M^+).

Reaction of mandelonitrile (59, 5 mmol) with Ph_3P–DEAD provided 400 mg (67%) of **61**: IR (film) 2240 (ν(C≡N)), 1730 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 6.66 (s, 1 H), 7.45 (m, 8 H), 8.07 (m, 2 H); MS, m/e 238 (M + 1), 237 (M^+). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.90. Found: C, 76.17; H, 4.68; N, 6.13. A small amount of another unidentified product was also obtained: IR (film) 2240 (ν(C≡N)), 1760, 1725 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 1.33 (dt, 6 H, J = 7, 3 Hz), 4.2 (2 t, 4 H, J = 7 Hz), 7.5 (m, 3 H), 7.98 (m, 2 H); MS, m/e 345 (M + 1), 344 (M^+), 245.

Reaction of atrolactic acid methyl ester (62, 2 mmol) with Ph_3P–DIAD gave 40 mg (4%) of **64**, 60 mg (8%) of **63**, and 280 mg (78%) of unreacted substrate. **64**: IR (film) 1740 (ν(C=O)) 1760 (sh) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 12 H, J = 6 Hz), 1.95 (s, 3 H), 3.66 (s, 3 H), 4.9 (septet, 2 H, J = 6 Hz), 7.43 (m, 10 H). **63**: IR (film) 3530 (ν(N—H)), 1760, 1730 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 12 H, J = 6 Hz), 1.76 (s, 3 H), 3.76 (s, 3 H), 5.1 (septet, 2 H, J = 6 Hz), 7.33 (m, 3 H), 7.56 (m, 2 H).

Acknowledgment. We are grateful for the support of this research by the NIH. The 300-MHz NMR spectrometer used was made available by grants from the NIH and the University of Notre Dame. Technical assistance was provided by Kathleen Peterson.

Registry No. 1 (R = Et), 1972-28-7; 1 (R = *i*-Pr), 2446-83-5; 2, 603-35-0; D-**7b**, 18668-00-3; DL-**7c**, 37819-25-3; L-**7d**, 18667-97-5; L-**7e**, 3069-50-9; DL-**7f**, 69056-25-3; **8a**, 96-35-5; DL-**8b**, 2155-30-8; D-**8b**, 17392-83-5; DL-**8c**, 108740-81-4; L-**8d**, 24347-63-5; L-**8e**, 17392-84-6; DL-**8f**, 21632-25-7; **11**, 90195-00-9; **12a**, 110271-68-6; **12b**, 110271-69-7; **12c**, 110271-70-0; **12d**, 110271-71-1; **12e**, 110271-72-2; **12f**, 110271-73-3; **13a**, 110271-74-4; **13b**, 110271-75-5; **13c**, 110271-76-6; **13d**, 110271-77-7; **13e**, 110271-78-8; **13f**, 110271-79-9; **14b**, 110271-80-2; **14c**, 110271-81-3; **14e**, 110271-82-4; **14f**, 110271-83-5; **15**, 110271-84-6; **16**, 110271-85-7; **17**, 15255-86-4; **18b**, 110271-86-8; **28** (R = R′ = *i*-Pr), 110271-87-9; **28** (R = H, R′ = *i*-Pr), 110272-03-2; **29**, 110271-88-0; **31**, 771-90-4; **33**, 15206-55-0; **34**, 119-53-9; **35**, 134-81-6; **36** (R′ = Et), 110271-89-1; **36** (R′ = *i*-Pr), 110271-90-4; **37** (R′ = Et), 110271-91-5; **37** (R′ = *i*-Pr), 110271-92-6; **38**, 98-85-1; **39** (R′ = *i*-Pr), 110271-93-7; **41**, 50612-99-2; **42**, 13305-14-1; **43**, 32766-61-3; **44**, 4410-32-6; **45**, 28193-70-6; **46**, 110271-94-8; **47**, 2019-71-8; **48**, 51579-87-4; *anti*-**49**, 574-13-0; *syn*-**49**, 7110-50-1; *anti*-**50**, 574-15-2; **51**, 100-52-7; **52**, 100-47-0; *anti*-**53**, 110271-95-9; *syn*-**53**, 110271-96-0; **54**, 5344-75-2; **55** (R′ = Et), 110271-97-1; **55** (R′ = *i*-Pr), 110271-98-2; **56**, 5694-69-9; **57**, 6252-00-2; **58** (R = *i*-Pr), 110271-99-3; **59**, 532-28-5; **61**, 4242-46-0; **62**, 20731-95-7; **63** (R′ = *i*-Pr), 110272-00-9; **64** (R′ = *i*-Pr), 110272-01-0; H-D-Ala-OH, 338-69-2; H-L-Val-OH, 72-18-4; H-L-Leu-OH, 61-90-5; H-DL-Phe-OH, 150-30-1; H_2NOCH_2Ph, 622-33-3; CbzCl, 501-53-1; Cl_3CCH_2OCOCl, 17341-93-4; CbzN(Me)OCH_2Ph, 110272-02-1; $PhCH(OH)COOH$, 90-64-2; *p*-$MeOC_6H_4CH(OAc)COOMe$, 55538-79-9; $PhCH_2NH_2$, 100-46-9; Me_2NH, 124-40-3; $PhCH(OH)COPh$, 119-53-9; $PhCH_2ONH_2 \cdot HCl$, 2687-43-6; $HOCH_2CH_2OH$, 107-21-1; DL-α-aminobutyric acid, 2835-81-6; mandelic acid succinimido ester, 93799-43-0.

Selective Cleavage of the Allyl and Allyloxycarbonyl Groups through Palladium-Catalyzed Hydrostannolysis with Tributyltin Hydride. Application to the Selective Protection–Deprotection of Amino Acid Derivatives and in Peptide Synthesis

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N-Allyloxycarbonyl (Alloc) derivatives of amines and amino acids are quantitatively and very rapidly converted to free amino compounds by palladium-catalyzed hydrostannolytic cleavage with tributyltin hydride in the presence of a proton donor (acetic acid, *p*-nitrophenol, pyridinium acetate, water). A similar procedure can be used for the deprotection of allyl (All) carboxylates and allyl aryl ethers. Deprotection experiments were performed on various mixed *N*-Alloc and *O*-Bzl, *N*-Z and *O*-All, *N*-Alloc and *O*-*t*-Bu, and *N*-alloc- and *N*-Boc-protected amino acid derivatives. The palladium-catalyzed hydrostannolytic cleavage is fully compatible with the Bzl and Z protecting groups; furthermore the BOC and *t*-Bu groups and the Alloc and All groups appear to be orthogonal. The reliability of the Alloc methodology for temporary protection of the α-amino functions is illustrated by the solid-phase synthesis of the biologically active undecapeptide substance P.

There is always a constant need for new, easy to introduce and selectively removable protecting groups in peptide synthesis. This is especially true in solid-phase methodology where the design of protection schemes with three independent dimensions of orthogonality for N^{α} protection, permanent protection and anchoring linkage

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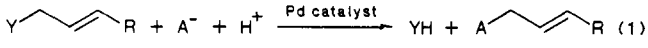
is under active research.[1] In this connection, the allyloxycarbonyl group, as well as other more sophisticated protecting entities with a basic allylic structure, appears to be very promising. The first studies[2] of the allyloxycarbonyl group (Alloc), with regard to protection of amino and hydroxy functions, were carried out in the 1950s, but the lack of specific or straightforward reactions for its removal has for a long time considerably limited its use.[3] Recently, however, following the development of π-allylpalladium chemistry,[4] which offers a new methodology of deprotection, a new impetus has been given to the utilization of allylic systems in protective group chemistry.

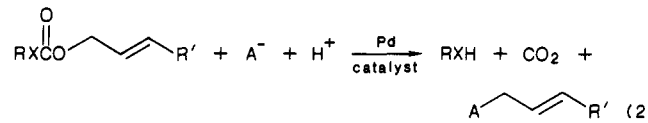
In all the newly proposed methods, the deprotection step involves a palladium-catalyzed transfer of the allyl unit to various nucleophiles (amines, carboxylates, stabilized carbanions) according to general eq 1. Among these nucleophiles must be included formic acid, formate derivatives, and tributyltin hydride which, in the presence of a suitable palladium catalyst, act formally as hydride donors.[5-9]



AH, A⁻ = R_2NH, $(RCO)(R'CO)CH^-$, "H^-"

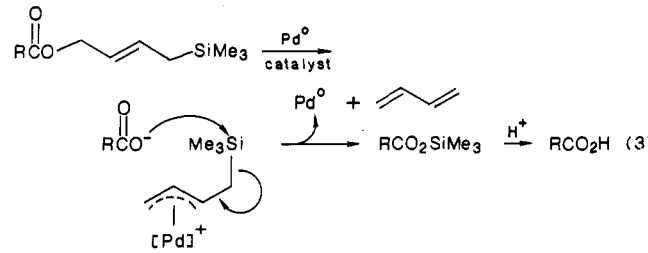
Deprotection of allyloxycarbonyl or cinnamyloxycarbonyl derivatives of alcohols[10,11] or amines[12-18] has been carried out on various polyfunctional molecules including sugars,[11,18] amino acid derivatives,[13-16] and nucleotides[17] (eq 2).

Allyl carboxylates,[6,19,20] phenoxides,[6,12,16] and phosphates[21] have been similarly deprotected (eq 1, Y = RCO_2^-, ArO^-, $(RO)_2P(O)O^-$).

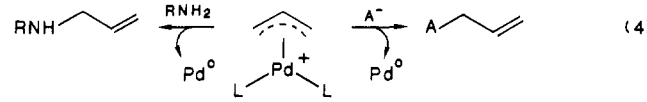


X = O, NH; R' = H, Ph

The cleavage of 4-trimethylsilyl allyl esters[22] is more specifically based on the properties of trimethylsilyl-substituted π-allylpalladium species as evidenced by Trost.[23] In this method, there is no need for any nucleophilic species in the medium as the function to be freed acts as its own deprotecting agent (eq 3).



Most of the processes mentioned above are rather slow. As a result, competing allylamine formation in the deprotection of allyl carbamates may occur due to attack of the free amino function, instead of the trapping agent A^-, on the intermediate π-allyl entity (eq 4).[14,15,17]



Since we first proposed use of π-allylpalladium methodology for removal of the allyloxycarbonyl group,[10] our efforts in this field have mainly focused on the use of tributyltin hydride as the nucleophilic agent. Indeed, tributyltin hydride appears to be a particularly suitable allyl acceptor, both from the point of view of rapidity and specificity, and the palladium-catalyzed hydrostannolytic procedure has been successfully applied to the deprotection of allyl carboxylates,[20] phenoxides,[12,16] carbonates,[10] and carbamates.[16]

We present here a detailed study of the catalytic hydrostannolytic cleavage of allyl carbamates and its applications to the selective deprotection of various amino acid derivatives. Finally, the reliability of the method is illustrated by the solid-phase synthesis of an undecapeptide (substance P) which utilizes the allyloxycarbonyl group for the temporary protection of the terminal α-amino groups. Part of the results presented here have already been briefly reported in a preliminary paper.[16]

Results and Discussion

Palladium-Catalyzed Hydrostannolytic Deprotection of Allyl Carbamates. In this study, the allylic carbamate of benzylamine 1 was used as the model substrate.

The addition of tributyltin hydride (1.2 equiv) to a solution of 1 in various solvents in the presence of catalytic amounts (2%) of tetrakis(triphenylphosphine)palladium(0) or dichlorobis(triphenylphosphine)palladium(II) brings about immediate gas evolution with concomitant formation

(1) (a) Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, *107*, 4936. (b) Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*, 2nd ed.; Pierce Chemical Company: Rockford, IL, 1984. (c) Merifield, R. B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 799. An orthogonal system is defined as "a set of completely independent classes of protecting groups, such that each class of groups can be removed in any order and in the presence of all other classes" (ref 1a).

(2) (a) Stevens, C. M.; Watanabe, R. *J. Am. Chem. Soc.* **1950**, *72*, 725. (b) Boissonas, R. A.; Preitner, G. *Helv. Chim. Acta* **1953**, *36*, 875.

(3) For deprotection of allyl carboxylates and allyloxycarbonyl derivatives of alcohols and amines with $Hg(OAc)_2$/KSCN and with $Ni(CO)_4$, see, respectively: Corey, E. J.; Marcus, A. T. *Tetrahedron Lett.* **1977**, 2081. Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3223. For deprotection of allyl carboxylates with Me_2CuLi, see: Ho, T.-L. *Synth. Commun.* **1978**, *8*, 15. Selective cleavage of allyl groups, especially of allyl ethers and allylamines, has been achieved through base-promoted or transition-metal-catalyzed migration of the double bond to the vinylic position and subsequent treatment of the propenyl derivative with acids or the $HgCl_2$/HgO reagent; see, for instance: Oltvoort, J. J.; Van Boechet, C. A. A.; De Koning, J. H.; Van Boom, J. H. *Synthesis* **1981**, 306 and references cited therein. Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Lett.* **1977**, 2591.

(4) (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, 1980; pp 125-132.

(5) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491.

(6) Hey, H.; Arpe, H.-J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 928.

(7) Guibé, F.; Zigna, A. M.; Balavoine, G. *J. Organomet. Chem.* **1986**, *306*, 257, 267.

(8) Four, P.; Guibé, F. *J. Org. Chem.* **1981**, *46*, 4439.

(9) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1982**, *23*, 241.

(10) Guibé, F.; Saint M'Leux, Y. *Tetrahedron Lett.* **1981**, *22*, 3591.

(11) Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 71.

(12) Four, P.; Guibé, F. *Tetrahedron Lett.* **1982**, *23*, 1825.

(13) Kunz, H.; Unvezagt, C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 436.

(14) Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 2449.

(15) Hinoshita, H.; Inomata, K.; Kameda, T.; Kotaki, H. *Chem. Lett.* **1985**, 515.

(16) Guibé, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986**, *27*, 2368.

(17) Hayakawa, Y.; Uchiyama, M.; Kajimo, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2402.

(18) Boullanger, P.; Descotes, G. *Tetrahedron Lett.* **1986**, *27*, 2599.

(19) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.

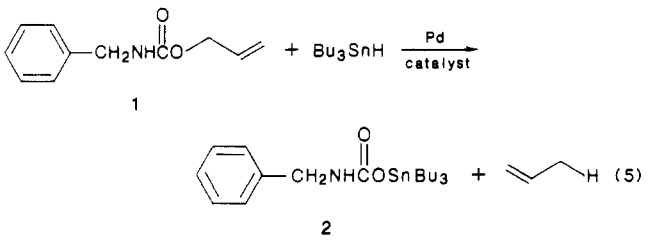
(20) Guibé, F.; Yang, T. X.; Zigna, A. M.; Balavoine, G. *Tetrahedron Lett.* **1985**, *26*, 3559.

(21) Hayakawa, Y.; Uchiyama, M.; Kato, H.; Noyori, R. *Tetrahedron Lett.* **1985**, *26*, 6505.

(22) Mastarlez, H. *J. Org. Chem.* **1984**, *49*, 4094.

(23) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315.

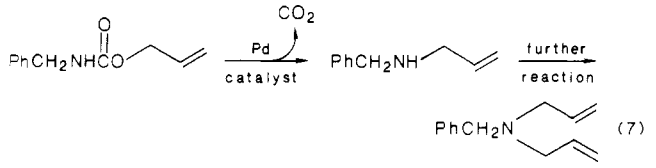
of tributyltin carbamate **2** (ν_{CO} 1640 cm^{-1}, CCl_4). However, in contrast with what we observed in the case of allyl carboxylates[20] or carbonates,[10] reaction 5 was sometimes not complete. Obviously and for reasons which have not



been elucidated, competitive palladium-catalyzed decomposition of tributyltin hydride into hexabutyldistannane[8,12] (eq 6) may occur in some cases, leaving some of the starting allyloxycarbonyl derivative **1** unreacted. The remaining

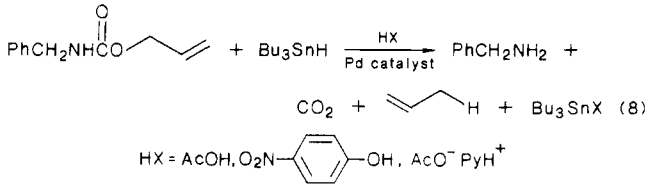
$$2Bu_3SnH \xrightarrow{\text{Pd catalyst}} Bu_3SnSnBu_3 + H_2 \qquad (6)$$

1 is then more slowly (a few hours) transformed into allyl and diallylbenzylamine (eq 7) under the influence of the palladium catalyst, as already reported.[14]



Similar results were observed with the allyloxycarbonyl derivatives of isopropylamine and cyclohexylamine.

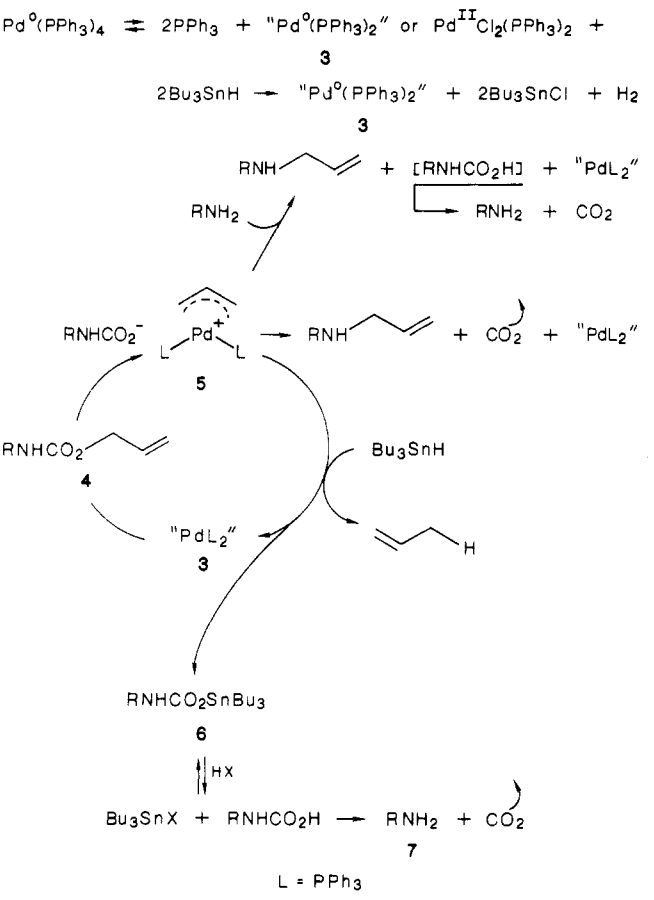
A definite improvement was obtained by carrying out the hydrostannolytic cleavage in the presence of a weakly acidic species (1–1.5 equiv) such as acetic acid, *p*-nitrophenol, or pyridinium acetate. By this procedure, complete removal of the allyl group together with in situ protolysis and decarboxylation of the intermediate tin carbamate was always observed (eq 8). This almost instantaneous re-



action was performed in a great variety of solvents including benzene, toluene, diethyl ether, THF, dichloromethane, acetone, ethyl acetate, and DMF. It was also observed that, in dichloromethane, water could be used, instead of the more acidic species listed above, as the proton donor. Acetonitrile is not a suitable medium for the reaction, due to the insolubility of tributyltin hydride in this solvent.

Probable reaction pathways for the deprotection of allyl carbamates as well as for the competitive formation of allylamines are outlined in Scheme I. As generally assumed for most palladium-catalyzed allylic alkylation reactions, the true catalytic species is believed to be the coordinatively unsaturated bis(triphenylphosphine)palladium(0) complex **3**, which is formed either by ligand dissociation[24] from tetrakis(triphenylphosphine)palladium(0) or upon reduction by tributyltin hydride of dichlorobis(triphenylphosphine)palladium(II). In the catalytic cycle,

Scheme I



$Pd^0(PPh_3)_2$ reacts with the allyl carbamate **4** to give the π-allylpalladium(II) complex **5**; **5** further reacts with tributyltin hydride to produce the tributyltin carbamate **6** and propene with regeneration of the catalyst **3**. Protonolysis and decarboxylation of **6** yields the free amino compound **7**. As already pointed out,[7] tributyltin hydride is, by itself, a very poor nucleophile. The reduction of the π-allyl entity to propene must therefore also involve some activation of the tin–hydrogen bond by the palladium atom (not specified on Scheme I), possibly through the formation of a transient hydridopalladium species.

The formation of allylamine may result either from unimolecular decomposition of the π-allyl complex **5** or from nucleophilic attack of this complex by the free amine which forms in the medium. *The hydrostannolytic process, however, is sufficiently rapid to avoid such side reactions*, and some allylamine can be formed only if some allyl carbamate is left unreacted at the end of the hydrostannolytic process, i.e., only if palladium-catalyzed decomposition of tributyltin hydride (eq 6) competes with palladium-catalyzed hydrostannolytic cleavage of the allyl carbamate. The reason why *the presence of protonic species in the medium efficiently and reproducibly prevents such a possibility* is not clear to us at the moment. It should be noted, however, that a similar effect is observed in the related palladium-catalyzed hydrostannation of α-enones with tributyltin hydride.[12,25]

Selective Deprotection of Allyl and Allyloxycarbonyl Derivatives of Amino Acids. The results concerning the hydrostannolytic cleavage of various representative allyl and allyloxycarbonyl derivatives of amino acids are summarized to Table I. The reactions were

(24) Ugo, R. *Coordination Chemistry Review*, **1968**, *3*, 319. Hartley, F. R. *The Chemistry of Platinum and Palladium*; Applied Science Publishers; London, 1973; pp 30–44.

(25) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477.

Table I. Hydrostannolytic Deprotection of Allyl and Allyloxycarbonyl Derivatives of Amino Acids

entry	protected amino acids[a]	solv/proton donor systems[b]	deprotected amino acids	yields[c] %
1	Alloc-Gly-OH, Alloc-Leu-OH Alloc-Phe-OH, Alloc-Met-OH Alloc-Ser-OH	A	Gly, Leu Phe, Met Ser	90–100
2	Alloc-Gln-OH, Alloc-Pro-OH Alloc-Arg(Ts)-OH Alloc-Lys(Z)-OH, Alloc-Trp-OH	B	Gln, Pro Arg(Ts) Lys(Z), Trp	90–100
3	Alloc-His(Alloc)-OH	C	His	95–100[d]
4	Alloc-Cys(Alloc)-OH	B	Cys	95–100[d]
5	Alloc-Tyr(Alloc)-OH	A,D	Tyr	100
6	Alloc-Tyr(All)-OH	B	Tyr	100
7	Alloc-Phe-*O*-Bzl	A	H-Phe-*O*-Bzl	77[e]
8	Z-Phe-*O*-All	A	Z-Phe-OH	90[f]
9	Alloc-Ser(*t*-Bu)-*O*-*t*-Bu	E	H-Ser(*t*-Bu)-*O*-*t*-Bu	70
10	Alloc-Lys(BOC)-OH	A	Lys(BOC)	73
11	Boc-Lys(Alloc)-OH	A	BOC(Lys)	95
12	Alloc-His(BOC)-OH[g]	B	His[h]	95–100[f]
13	Alloc-His(BOC)-OH[g]	E	His(BOC)	90–100[i]

[a] L Series: Alloc, allyloxycarbonyl; All, allyl; Z, carbobenzyloxy; Bzl, benzyl; BOC, *tert*-butoxycarbonyl. [b] A, CH_2Cl_2/H_2O; B, CH_2Cl_2/AcOH; C, DMF/AcOH; D, AcOEt/AcOH; E, CH_2Cl_2/4-nitrophenol. [c] Isolated yields unless otherwise specified. Crude reactions mixtures were always found, by NMR, IR, and TLC standard, to be free from starting material and from amino acid compounds other than the expected one. [d] Analytical yield (NMR in CF_3CO_2H, anisole as the reference). [e] Isolated as its *p*-toluenesulfonate salt. [f] Analytical yield (NMR). See Experimental Section. [g] Performed on its dicyclohexylammonium salt. See Experimental Section. [h] After further treatment with CF_3CO_2H/CH_2Cl_2. [i] Contaminated with dicyclohexylamine and *p*-nitrophenol. See Experimental Section.

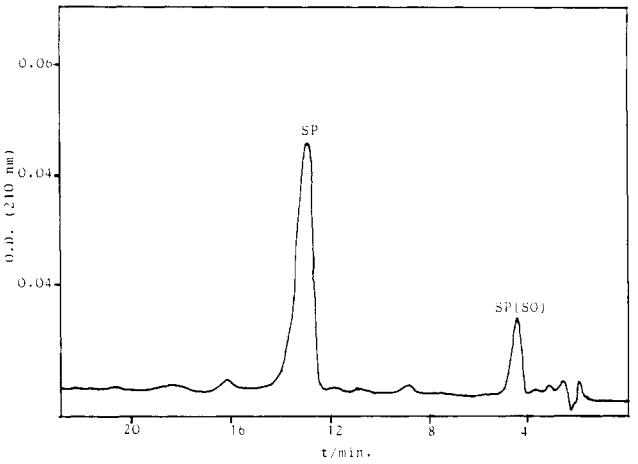


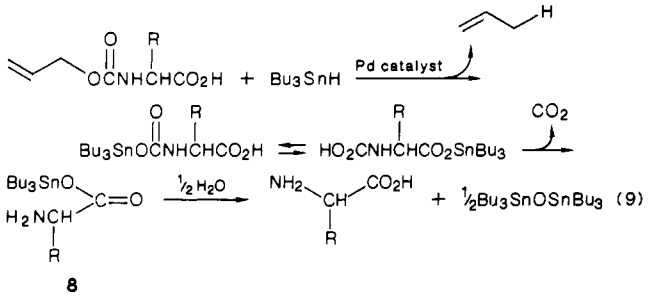
Figure 1. HPLC of crude SP: μ-Bondapak C-1'8 column; isocratic mode 22.2% CH_3CN in 0.25 M triethylammonium phosphate buffer, pH 3.0; injection, 10 μg; flow rate, 1.5 mL/min.

usually run in dichloromethane in the presence of water or acetic acid and under inert atmosphere.[26] $PdCl_2(PPh_3)_2$ was selected as the catalyst, rather than $Pd(PPh_3)_4$, for two reasons: first, it is more readily available and indefinitely air stable; second, unlike the zerovalent $Pd(PPh_3)_4$, the divalent $PdCl_2(PPh_3)_2$, prior to reduction by tributyltin hydride, does not catalyze the decarboxylative rearrangement of allyl carbamates into allylamines (eq 7).

Simple N^{α}-allyloxycarbonyl-protected amino acids were prepared by using allyl chloroformate under Schotten–Baumann conditions as already described.[2a] Other allyl or allyloxycarbonyl derivatives of plurifunctional compounds were prepared by using standard procedures (see Experimental Section).

The hydrostannolytic cleavage of carboxy free N^{α}-allyloxycarbonyl-protected amino acids in moist dichloromethane resulted in the immediate precipitation of the free amino acids. If necessary, most of the dichloromethane was evaporated at the end of the reaction and replaced with moist diethyl ether to ensure complete precipitation of the product. The byproducts of the reaction (hexabutyldistannane, bis(tributyltin) oxide, tributyltin acetate, ...), which are highly or freely soluble in nonpolar solvents, are easy to eliminate. Quasi-quantitative recovery of free analytically pure amino acids was thus obtained from the N^{α}-allyloxycarbonyl derivatives of glycine, leucine, methionine, phenylalanine, serine, proline, glutamine, tryptophan, N^{ϵ}-(benzyloxycarbonyl)lysine and tosylarginine (entries 1 and 2). With 2 equiv of tributyltin hydride, complete deprotection of $N^{\alpha}N^{im}$-bis(allyloxycarbonyl)-histidine, of N^{α},S-bis(allyloxycarbonyl)cysteine, of N,O-bis(allyloxycarbonyl)tyrosine, and of N^{α}-(allyloxycarbonyl)tyrosine *O*-allyl ether was also observed (entries 3–6). In the latter case however the presence of a rather strong acidic species (acetic acid) is necessary to ensure complete removal of the phenolic allyl group. The presence of the thio groups in methionine and in N^{α},S-bis-(allyloxycarbonyl)cysteine did not result in any poisoning of the catalyst.

The deprotection reaction of carboxy-free N^{α}-allyloxycarbonyl amino acid derivatives in the presence of water may be represented by eq 9. The ease of hydrolysis of



the hypothetic intermediate tributyltin amino ester **8** is at first sight surprising but is probably the result of a labilization of the tin–oxygen bond through solvation of the tin atom by the neighboring α-amino group, as already suggested.[27]

The hydrostannolytic cleavage of carboxy protected N^{α}-allyloxycarbonyl amino acid derivatives in moist dichloromethane gives the corresponding tributyltin carbamates (ν_{CO} 1640 cm^{-1}, $CHCl_3$). Conversion to the free

(26) This precaution is not really necessary but avoid the formation of black palladium at the end of the reaction.

(27) Frankel, M.; Gertner, D.; Wagner, D.; Zilkha, A. *J. Org. Chem.* **1965**, *30*, 1596.

amino compounds is immediate upon treatment with acetic acid, *p*-nitrophenol, or pyridinium acetate. Allyl esters are converted to tributyltin carboxylates (ν_{CO} 1650 cm^{-1}, $CHCl_3$), which upon protolysis (TsOH, HCl) yield the free carboxylic acids. N^{α}[((Tributylstannyl)oxy)carbonyl]-phenylalanine benzyl ester and N^{α}-(benzyloxycarbonyl)-phenylalanine tributyltin ester have been isolated by column chromatography and characterized by ^1H NMR and infrared spectroscopy.

The benzyl and benzyloxycarbonyl groups as well as the *tert*-butyl and *tert*-butoxycarbonyl groups are perfectly stable under the conditions of the hydrostannolytic cleavage as shown by the selective deprotection of N^{α}-carbobenzyloxyphenylalanine allyl ester (entry 8), N^{α}-carboallyloxyphenylalanine benzyl ester (entry 7), N^{α}-carboallyloxy-N^{ϵ}-carbobenzyloxylysine (entry 2), N^{α}-carboallyloxy-*O*-*tert*-butylserine *tert*-butyl ester (entry 9), N^{α}-carboallyloxy-N^{ϵ}-(*tert*-butoxycarbonyl)lysine (entry 10), N^{α}-(*tert*-butoxycarbonyl)-N^{ϵ}-carboallyloxylysine (entry 11), and N^{α}-(allyloxycarbonyl)-N^{im}-(*tert*-butyloxycarbonyl)-histidine (entry 13). Conversely the *tert*-butyl and *tert*-butyloxycarbonyl groups in the four latter derivatives could be selectively removed (CF_3CO_2H–CH_2Cl_2) without affecting the allyloxycarbonyl groups. Treatment of (allyloxycarbonyl)benzylamine with CF_3CO_2H–CH_2Cl_2 (1/1) for 48 h did not result in any loss (GC analysis) of the allyloxycarbonyl group. Therefore, the *tert*-butyl and *tert*-butyloxycarbonyl groups and the allyl and allyloxycarbonyl groups appear to be orthogonal. A similar observation has been made by Kuntz and co-workers[13] on different substrates.

The stability of allyl carboxylates or carbamates under various hydrolytic conditions has not yet been investigated but should not be very different from that of benzyl esters. Particularly, as shown by E. Ingold and C. Ingold as early as in 1932,[28] hydrolysis through cleavage of the oxygen–allyl bond is not likely to occur, unless under strongly acidic conditions.

The possibility of racemization at the chiral center during coupling of N^{α}-allyloxycarbonyl-protected amino acid and during hydrostannolytic deprotection has also been investigated. The absence of racemization during the deprotection of N^{α}-(allyloxycarbonyl)-L-methionine was thoroughly checked by gas chromatography analysis on a chiral column after appropriate derivatization[29] of the deprotected amino acid.

Likewise, the dipeptide BOC-L-Leu-L-Met-NH_2 (**9**) obtained via the sequence in eq 10 was found to be diastereoisomerically pure (HPLC, comparison with authentic samples of **9** and of BOC-L-Leu-DL-Met-NH_2).

$$\text{Alloc-L-Met} \xrightarrow[(2)\ NH_3/H_2O]{(1)\ i\text{-BuOCOCl/Et}_3\text{N}} \text{Alloc-L-Met-NH}_2 \xrightarrow[(2)\ \text{BOC-L-Leu-OSu}]{(1)\ Bu_3SnH/Pd} \underset{\mathbf{9}}{\text{BOC-L-Leu-L-Met-NH}_2} \quad (10)$$

Synthesis of an Undecapeptide, Substance P (SP): Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2. In order to check the validity of the N^{α}-allyloxycarbonyl protection strategy, a bioactive peptide, substance P (SP),[30] has been synthetized by solid-phase methodology.[31] The synthesis of SP has been carried out manually starting from a methylbenzhydrylamine resin[32] according to a procedure described previously.[33] A fourfold excess of N^{α}-allyloxycarbonyl-protected amino acids has been used throughout the synthesis. The amino acids were activated by dicyclohexylcarbodiimide–1-hydroxybenzotriazole,[34] with the exception of the two glutamine residues which were introduced as their *p*-nitrophenyl esters. The quasi-instantaneous hydrostannolytic cleavage of the temporary N^{α}-allyloxycarbonyl protecting group was accomplished in dichloromethane in the presence of Bu_3SnH (3.0 equiv), a catalytic amount of $PdCl_2PPh_3$ (0.04 equiv), and 3.5 equiv of acetic acid as the proton donor, per mmole of amino group.[35] After removal of the last N^{α}-allyloxycarbonyl group the peptide was cleaved from the solid support with concomitant removal of the remaining side-chain protecting groups by reacting the peptide resin with hydrogen fluoride. The HPLC profile of the crude SP, reproduced in Figure 1, shows that the only significant impurity seems to be the methionine sulfoxide derivative (SP/SP(SO) = ca. 82/18). After a two-step purification (exchange chromatography on carboxymethylcellulose and partition chromatography) pure SP was obtained in 25% overall yield starting from the amino substitution onto the resin.[36] Its physical parameters, $[\alpha]^{23}_D$, R_f on TLC, HPLC, FAB mass spectrum, and 250-MHz ^1H NMR[37] spectrum, as well as its potencies on isolated guinea pig ileum[38] and on a rat brain synaptosinal preparation[39] were identical with those observed for SP synthesized by using the traditional N^{α}-*tert*-butyloxycarbonyl strategy. Tin content of the peptide after first chromatographic purification, as determined by a very sensitive method involving hydride generation coupled with ICP plasma emission spectroscopy[40] was found not to exceed 1 ppm (±0.5 ppm). A tin content of 7 ppm was found in the crude peptide, before any purification.

Conclusion

Allyloxycarbonyl derivatives of amines are deprotected in a highly selective and straightforward manner through palladium-catalyzed hydrostannolytic cleavage of the allyl group.

The specificity of this reaction stems from the fact that tributyltin hydride palladium-catalyzed reduction of organic substrates in general requires a simultaneous activation of both the reducing agent and the electrophile. As a result, only substrates which strongly interact with palladium(0) complexes (essentially acyl chlorides,[8] allyl esters,[9,10,20] and unhindered conjugated enones[12,25]) are susceptible to reaction under these conditions. Toward other substrates, Bu_3SnH remains virtually unreactive at

(28) Ingold, E. H.; Ingold, C. K. *J. Chem. Soc.* **1932**, 756.
(29) El Baba, S.; Poulin, J. C.; Kagan, H. B. *Tetrahedron* **1984**, *40*, 4275.
(30) Von Euler, U. S.; Gaddum, J. H. *J. Physiol. (London)* **1931**, *72*, 74.
(31) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
(32) Stewart, J. M. In *Peptides 1976, Proceedings of the 14th European Peptide Symposium*; Loffet, A., Ed.; Editions de l'Université de Bruxelles: Brussels, 1977; p 285.
(33) Poujade, C.; Lavielle, S.; Chassaing, G.; Marquet, A. *Biochem. Biophys. Res. Commun.* **1983**, *114*, 1109.
(34) Konig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
(35) We had previously established that such conditions led to the model tripeptide, Gly-Leu-Met-NH_2, with a satisfactory yield, after cleavage from the methylbenzydrylamine resin and purification.
(36) This yield is substantially lower than those obtained by use of BOC N^{α} protection[33] (37%) or FMOC N^{α} protection (47% after reduction of the SP sulfoxidde byproduct to SP by dithiothreitol. Arshady, R.; Atherton, E.; Clive, D. L. J.; Sheppard, R. C. *J. Chem. Soc., Perkin Trans 1* **1981**, 538). Optimization of Alloc strategy is currently under work in our laboratories.
(37) Chassaing, G.; Convert, O.; Lavielle, S. *Eur. J. Biochem.* **1986**, *154*, 77.
(38) Poujade, C.; Lavielle, S.; Torrens, Y.; Marquet, A. *Int. J. Peptide Protein Res.* **1983**, *21*, 254.
(39) Viger, A.; Beaujouan, J.-C.; Torrens, Y.; Glowinski, J. *J. Neurochem.* **1983**, *40*, 1030.
(40) Tin analysis was performed by the "Service Central d'Analyse de Vernaison (CNRS)".

room temperature; furthermore, in the presence of the palladium-catalyst, any excess tributyltin hydride is rapidly decomposed (a few minutes) into the completely inert hexabutyldistannane.

In our view, such a specificity strongly recommends the use of the allyloxycarbonyl group and its removal through palladium-catalyzed hydrostannolytic cleavage for the protection–deprotection of amino groups during peptide synthesis. The advantages of this method may be summarized as follows: (1) The allyloxycarbonyl group is easy to introduce by means of the readily available and inexpensive allyl chloroformate. (2) The presence of the allyloxycarbonyl groups on the α-amino function does not induce a special susceptibility to epimerization of the α-chiral center. Apparently, no racemization occurs either during coupling processes or during hydrostannolytic cleavage. (3) Tributyltin hydride is commercially available or may be readily prepared by simple distillation of a mixture of inexpensive polymethylhydrosiloxane and bis(tributyltin) oxides.[41] (4) The catalytic hydrostannolysis of allyl carbamate is a very fast process. The possibility of a competing catalytic conversion of the carbamate into allylamine[14] may thus be confidently dismissed. The fastness of the hydrostannolytic cleavage could also be of interest, should the reaction be used in an automated process. (5) The amount of catalyst needed for the hydrostannolytic process is low (typically 0.02–0.04 equiv) and the reaction tolerates a wide range of solvent including CH_2Cl_2 and DMF. The byproducts of the reaction (hexabutyldistannane, bis(tributyltin) oxide, tributyltin acetate or *p*-nitrobenzoate) are highly or freely soluble in nonpolar solvents and are thus easy to eliminate. (6) The catalytic reaction is not inhibited by the presence of thio functionalities. (7) The hydrostannolytic removal of allyl and allyloxycarbonyl groups is compatible with the presence of the benzyl, benzyloxycarbonyl, *tert*-butyl, and *tert*-butoxycarbonyl groups. Conversely, the *tert*-butyl and *tert*-butoxycarbonyl groups can be removed under standard conditions without affecting the allyl or allyloxycarbonyl groups.

The reliability of the method has been demonstrated by the solid-phase synthesis of the bioactive undecapeptide substance P, in which the allyloxycarbonyl group has been repeatedly used for temporary protection of the α-amino functions.

Further uses of the allyloxycarbonyl and allyl groups, particularly in combination with the orthogonal *tert*-butyl and *tert*-butyloxycarbonyl groups, are currently being investigated in our laboratories. The design of new linking agents for use in solid-phase peptide synthesis, whose breaking would be based on a palladium-catalyzed cleavage reaction, is also under active research.

Experimental Section

General Methods. Melting points were taken on a Reichert Microscop and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 457 instrument. ^1H NMR spectra were obtained at 250 MHz with a Bruker AM 250 instrument and at 90 MHz with a Perkin-Elmer R 32 or a Bruker WM 250 instrument. When necessary, unambiguous assignments were made by decoupling experiments. Chemical shifts are reported in ppm units, by reference to Me_4Si unless otherwise specified. Thin-layer chromatography was carried out on precoated silica gel plates (Merck F-254), usually with the following solvent systems (v/v): eluent A, hexane/pyridine (2/1); eluent B, *n*-BuOH/AcOH/5% ammonia/H_2O (6/1/1/2); eluent C, *n*-BuOH/AcOH/pyridine-/H_2O (15/3/10/12). Spots on TLC chromatograms were detected by UV, iodine, and ninhydrin and by the chlorine/*o*-tolidine reaction. Optical rotations were measured with a Perkin-Elmer Model 241 instrument.

Materials. The DMF for use in peptide synthesis was distilled in the presence of ninhydrin. For other experiments, commercial pure solvents were used without any further purification.

Tributyltin hydride was prepared from polymethylhydrosiloxane (Fluka) and bis(tri-*n*-butyltin) oxide[41] [bp 78–82 °C (0.04 mmHg)]. It was stored at 5 °C under inert atmosphere in a thoroughly washed vessel as recommended by Kochi.[42] In this way, Bu_3SnH could be kept for several months without any appreciable decomposition. The purity of Bu_3SnH may easily be verified in a semiquantitative way (ca. ±10%) by comparison of the relative infrared intensities of the CH bands around 2.900 cm^{-1} and of the Sn–H band at 1810 cm^{-1} (neat, CaF_2 plates).

Tetrakis(triphenylphosphine)palladium(0) was prepared as already described.[8] Dichlorobis(triphenylphosphine)palladium(II) was prepared by dropwise addition of a methanolic solution of Na_2PdCl_4[8] to a magnetically stirred saturated solution of triphenylphosphine (2.2 equiv) in 96% EtOH. The yellow precipitate formed was filtered, washed with water, absolute ethanol, and ether, and dried in vacuo. The yield of $PdCl_2(PPh_3)_2$ was almost quantitative: IR (Nujol mull, ICs plates) 358 cm^{-1} (Pd–Cl).

All the amino acids derivatives used in this study were of L configuration. Simple N^{α}-allyloxycarbonyl-protected amino acids were prepared from the free amino acids by reaction with allyl chloroformate under Schotten-Baumann conditions as already described.[2a] N^{α}-Alloc-N^{ϵ}-Z-Lys, N^{α}-Alloc-N^{ϵ}-BOC-Lys, N^{α}-BOC-N^{ϵ}-Alloc-Lys, and N^{α}-Alloc-N^{ω}-Tos-Arg were similarly prepared from N^{ϵ}-Z-Lys, N^{ϵ}-BOC-*Lys*, N^{α}-BOC-Lys, and N^{ω}-Tos-Arg trifluoroacetate (obtained by trifluoroacetolysis in CH_2Cl_2 of N^{α}-BOC-N^{ω}-Tos-Arg).

The procedure used for the etherification of tyrosine ($CuSO_4$, NaOH, allyl bromide in MeOH) was similar to the one described for the obtention of tyrosine *O*-2,6-dichlorobenzyl ether.[43] The crude tyrosine *O*-allyl ether thus obtained was directly converted to N^{α}-Alloc-Tyr *O*-allyl ether. The overall yield was rather low (ca. 20%), but no effort was made to improve the conditions. The preparation of N^{α}-Alloc-*O*-Alloc-Tyr and N^{α}-Alloc-Lys has already been described.[2a] N^{α}-Alloc-Trp, N^{α},*S*-$Alloc_2$-Cys, N^{α}-Alloc-His, and N^{α},N^{im}-$Alloc_2$-His were prepared by use of allyl chloroformate, following procedures similar to those described for the preparation of N^{α}-Z-Trp,[44] N^{α},*S*-Z_2-Cys,[45] N^{α}-Z-His,[46] and N^{α},N^{im}-Z_2-His.[46] Most allyloxycarbonyl amino acid derivatives are noncrystalline products and were purified and characterized as their dicyclohexylammonium (DCHA) salts.[47]

N^{α}-Alloc-N^{im}-BOC-His. To a solution of 6.9 g (29 mmol) of the sodium salt of N^{α}-Alloc-His in 80 mL of H_2O (pH 8.3–8.4) was slowly added NaOH (4 M) to adjust the pH to 9.5–9.6 (pH meter). Sodium hydrogen carbonate (1.4 g, 16.6 mmol) was then added followed by 45 mL of *tert*-butyl alcohol and 8 mL (7.6 g, 34 mmol) of di-*tert*-butyl dicarbonate (BOC_2). The reaction mixture was magnetically stirred for 2 h at room temperature, upon which it was twice extracted with pentane. The aqueous phase (pH 8.3–8.4) was then acidified to pH 3.3–3.4 with 4 M aqueous citric acid and extracted twice with ethyl acetate. The organic phase was dried over $MgSO_4$, the solvent evaporated on a Rotavap and the residue dried under vacuum (0.1 mmHg) to give 6.39 g (65%) of Alloc-His(BOC)-OH as a white noncrystalline powder. The crude product was directly converted to its dicyclohexylammonium salt in the usual manner.[47]

Physical and Spectroscopic Characteristics of Alloc Derivatives. Unless otherwise reported, DCHA derivatives were recrystallized from $CHCl_3/Et_2O$. All compounds were found to be free (TLC) of other amino acid derivatives. ^1H NMR resonances of the DCHA moiety are not reported except for the DCHA salt of Alloc-Gly.

(41) Hayashi, K.; Iyada, J.; Shuara, I. *J. Organomet. Chem.* **1967**, *10*, 81.

(42) Klinger, R. J.; Mochida, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6626.

(43) Yamashiro, D.; Li, C. H. *J. Am. Chem. Soc.* **1973**, *95*, 1310.

(44) Smith, E. L. *J. Biol. Chem.* **1948**, *175*, 39.

(45) Berger, A.; Noguchi, J.; Katchalski, E. *J. Am. Chem. Soc.* **1956**, *78*, 4483.

(46) Patchornik, A.; Berger, A.; Katchalski, E. *J. Am. Chem. Soc.* **1957**, *79*, 6418.

(47) Matsuda, F.; Itoh, S.; Hattori, N. *Tetrahedron* **1985**, *41*, 3625.

Alloc-Gly DCHA salt: mp 120–120.5 °C; IR ($CHCl_3$) 1710 cm^{-1}, (Nujol mull) 3260 (NH), 1715 (CONH), 1640 cm^{-1} (CO_2^-); ^1H NMR (90 MHz, $CDCl_3$) δ [allyl group resonances] 6.05–5.55 (m, 1 H, internal, vinylic H), 5.30–4.95 (m, 2 H, terminal vinylic H), 4.44 (br d, J = 6 Hz, 2 H, allylic H), [other resonances] 5.35 (br peak, 1 H, NH), 3.57 (d, 2 H, J = 7 Hz, α-CH_2), 3.00–2.6 (m, 2 H), and 2.0–1.0 (m, 20 H, dicyclohexylammonium CH). Anal. Calcd for $C_{18}H_{32}N_2O_4$: C, 63.50; H, 9.45; N, 8.23. Found: C, 63.55; H, 9.26; N, 8.27.

Alloc-Leu DCHA salt: mp 124–126 °C; $[\alpha]^{20}_D$ −2.14° (*c* 2.0, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ [allyl group resonances] 6.10–5.65 (m, 1 H), 5.4–5.0 (m, 2 H), 4.50 (d, 2 H, J = 6 Hz), [other resonances] 5.50 (v br d, 1 H, NH), 4.1–3.95 (m, 1 H, α-CH), 0.90 and 0.82 (2 d, J = 7 Hz, 6 H, methyl groups) [other resonances masked by DCHA]. Anal. Calcd for $C_{22}H_{40}N_2O_4$: C, 66.63; H, 10.17; N, 7.06. Found: C, 66.56; H, 10.00; N, 7.15.

Alloc-Ser DCHA salt: mp 138–139 °C; $[\alpha]^{20}_D$ +12.3° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.02–5.83 (m (ddt centered at 5.93 ppm), 1 H, internal vinylic H), 5.32 (dd, J_{trans} = 17 Hz, J_{gem} = 0.5–1 Hz, 1 H, *Z* terminal vinylic H), 5.22 (dd, J_{cis} = 10 Hz, J_{gem} = 0.5–1 Hz, 1 H, *E* terminal vinylic H) [other resonances] ca. 5.8 (br, 1 H, NH), 4.08 (br q, 1 H, α-CH), 3.94 (dd, 1 H), and 3.72 (br dd, 1 H, diastereotopic methylene protons H^1,H^2, J_{gem} = 11 Hz, $J_{H1,H\alpha}$ = 5–6 Hz, $J_{H2,H\alpha}$ = ca. 10 Hz).

Alloc-Met DCHA salt: mp 120–120.5 °C; $[\alpha]^{20}_D$ +27.0° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.05–5.84 (m, 1 H), 5.33 (dd, J_{trans} = 17 Hz, J_{gem} = 0.5–1 Hz, 1 H), 5.22 (dd, J_{cis} = 10 Hz, J_{gem} = 0.5–1 Hz, 1 H), 4.6 (d, J = 5 Hz, 2 H), [other resonances] 5.8 (d, J = 7 Hz, NH), 4.5 (br q, 1 H, α-CH), 3.1–2.8 (m, 2 H, CH_2S), 2.6–2.3 (m, CH_2), 2.5 (s, 3 H, SCH_3). Anal. Calcd for $C_{21}H_{38}N_2O_4S$: C, 60.83; H, 9.24; N, 6.54. Found: C, 60.73; H, 8.98; N, 6.78.

Alloc-Phe DCHA salt: mp 133–134 °C; $[\alpha]^{20}_D$ +42.4° (*c* 1.0, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ [allyl group resonances] 6.15–5.7 (m, 1 H), 5.4–5.1 (m, 2 H), 4.55 (d, J = 6 Hz, 2 H), [other resonances] 7.3–7.2 (m, 5 H), 5.55 (br d, 1 H, NH), 4.3 (q, J = 7 Hz, 1 H, α-CH), 3.2 (d, J = 7 Hz, 2 H, benzylic H). Anal. Calcd for $C_{25}H_{38}N_2O_4$: C, 69.74; H, 8.90; N, 6.51. Found: C, 69.73; H, 8.88; N, 6.64.

Alloc-Pro DCHA salt: mp 122–123 °C; $[\alpha]^{20}_D$ −34.6° (*c* 1.0, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ [allyl group resonances] 6.2–5.65 (m, 1 H), 5.45–5.0 (m, 2 H), 4.55 (br d, J = 6 Hz, 2 H), [other resonances] 4.2 (v br t, 1 H, α-CH), 3.65–3.45 (m, 2 H, δ-CH_2) [other resonances masked by DCHA]. Anal. Calcd for $C_{21}H_{36}N_2O_4$: C, 66.28; H, 9.54; N, 7.36. Found: C, 66.59; H, 9.33; N, 7.73.

Alloc-L-Gln (recrystallized from AcOEt): mp 96–97 °C; $[\alpha]^{20}_D$ −17.15° (*c* 1.0, DMF); IR (Nujol mull) 3445, 3345, 3222 (NH), 1725, 1695 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$/DMSO-d_6 (1/1)) δ [allyl group resonances] 5.81–5.61 (m, 1 H), 5.30 (dd, J_{trans} = 17 Hz, J_{gem} = 0.5–1 Hz, 1 H), 5.19 (dd, J_{cis} = 10 Hz, J_{gem} = 0.5–1 Hz, 1 H), 4.54 (d, J = 5 Hz, 2 H), [other resonances] 7.03 and 6.22 (2 s, (1 + 1) H, NH_2), 6.71 (br d, $J \approx$ 8 Hz, 1 H, α-NH), 4.15 (br sext, 1 H, α-CH), 2.30 (t, J = 8.5 Hz, 2 H, γ-CH_2), 2.2–2.1 (m, 1 H), and 2.1–1.9 (m, 1 H, diastereotopic β-methylene protons). Anal. Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.6. Found: C, 46.85; H, 6.41; N, 12.01.

Alloc-Trp (recrystallized from CH_2Cl_2): mp 120–121 °C; $[\alpha]^{20}_D$ −34.2° (*c* 1.0, DMF); ^1H NMR (250 MHz, DMSO-d_6/$CDCl_3$ (1/1)) δ [allyl group resonances] 6.00–5.80 (m, 1 H), 5.30 (dd, J_{trans} = 17 Hz, J_{gem} = 0.5–1 Hz, 1 H), 5.20 (dd, J_{cis} = 10 Hz, J_{gem} = 0.5 Hz 1 H), 4.46 (d, J = 5.5 Hz, 2 H), [other resonances] 7.59 (d, J = 7.5 Hz, 1 H, indolyl H^4), 7.39 (d, J = 7.5 Hz, 1 H, indolyl H^7), 6.96–7.21 (m, 4 H, indolyl H^1, H^2, H^5, H^6), 4.4 (apparent sext, ddt, $J_1 \approx J_2 \approx$ 8 Hz, J_3 = 4.5 Hz, 1 H, α-CH), 3.30 (dd) and 3.15 (dd) (*ABX* system, J_{AB} = 14 Hz, J_{AX} = 4 Hz, J_{BX} = 8 Hz, (1 + 1) H, diastereotopic β-methylene H). Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.60; N, 9.72. Found: C, 62.23; H, 5.65; N, 9.43.

Alloc-Cys(Alloc) DCHA salt (recrystallized from AcOEt/pentane): mp 105–107 °C; $[\alpha]^{20}_D$ −0.13 (*c* 3.0, $CHCl_3$); IR ($CHCl_3$) 1722 (C=O, amide and thiocarbonate), 1633 cm^{-1} (CO_2^-); ^1H NMR (250 MHz, $CDCl_3$) δ [allyl groups resonances] 6.06–5.79 (m, 2 H, internal vinylic H), 5.42–5.12 (m, (4 peaks), 4 H, terminal vinylic H), 4.64 (br d, J = 5 Hz, 2 H) and 4.58 (v br d, 2 H, allylic H), [other resonances] ca. 5.85 (br, 1 H, NH), 4.30 (br, 1 H, α-CH), 3.65 (br dd) and 3.38 (br dd) ((1 + 1) H, *ABX* system, J_{AB} = 12 Hz, J_{AX} and J_{BX} undetermined, diastereotopic β-methylene H). Anal. Calcd for $C_{23}H_{38}N_2O_6S$: C, 58.70; H, 8.14; N, 5.95. Found: C, 58.77; H, 8.02; N, 5.74.

Alloc-His(BOC) DCHA salt (recrystallization from AcOEt/pentane): mp 126–127 °C; $[\alpha]^{20}_D$ +25.5° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 1750 (C=O, BOC), 1710 (C=O, Alloc), 1630 cm^{-1} (CO_2^-); ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.02–5.8 (m, 1 H), 5.30 (d, J_{trans} = 17 Hz, 1 H), 5.18 (d, J_{cis} = 10 Hz, 1 H), 4.58 (d, J = 5 Hz, 2 H), [other resonances] 7.95 (s, 1 H, imidazolyl H^2), 7.2 (s, 1 H, imidazolyl H4), ca. 5.94 (br peak, NH), 4.33 (m (apparent q), 1 H, α-CH), 3.20 (dd) and 3.07 (dd) (*ABX* system, J_{AB} = 15 Hz, $J_{AX} \approx J_{BX} \approx$ 9 Hz, (1 + 1) H, diastereotopic methylene H), 1.62 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{27}H_{44}N_4O_6$: C, 62.28; H, 8.52; N, 10.76. Found: C, 62.24; H, 8.68; N, 10.83.

Alloc-His(Alloc) (recrystallized from benzene/pentane): mp 89–90 °C; $[\alpha]^{20}_D$ +125.0° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1770 (C=O, N^{im}-Alloc), 1710 cm^{-1} (C=O, CO_2H, and N^{α}-Alloc); ^1H NMR (25 MHz, $CDCl_3$) δ [allyl groups resonances] 6.07–5.87 (m, 2 H, internal vinylic H), 5.55–5.18 (m (6 peaks), 4 H, terminal vinylic H), 4.89 (d, J = 6 Hz, 2 H, presumably allylic H of N^{im}-Alloc), 4.60 (d, J = 5.5 Hz, 2 H, presumably allylic H of N^{α}-Alloc), [other resonances] 8.30 (s, 1 H, imidazolyl H2), 7.30 (s, 1 H imidazolyl H4), 5.65 (br d, J = 6 Hz, 1 H, NH), ca. 4.6 (α-CH, masked by allylic H), 3.36 (dd) and 3.22 (dd) (*ABX* system, J_{AB} = 15 Hz, J_{AX} = 4 Hz, J_{BX} = 5 Hz, (1 + 1) H, diastereotopic β-methylene H). Anal. Calcd for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30; N, 13.00. Found: C, 52.13; H, 5.42; N, 12.83.

Alloc-Tyr(Alloc) (recrystallized from EtOH/H_2O): mp 105–106 °C; $[\alpha]^{20}_D$ +54.12° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1750, 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] (a) 6.08–5.92 (m (ddt centered at 6.05 ppm) 1 H), 5.43 (dd, J_{trans} = 17 Hz, J_{gem} = 0.5–1 Hz, 1 H), 5.35 (dd, J_{cis} = 10 Hz, J_{gem} = 0.5–1 Hz, 1 H), 4.75 (d, J = 6 Hz, 2 H), (b) 5.98–5.81 (m (ddt centered at 5.9 ppm), 1 H), 5.35–5.18 (m, 2 H, terminal vinylic H), 4.58 (d, J = 5 Hz, 2 H), [other resonances] 7.2 (A_2B_2 system, J_{AB} = 8 Hz, 4 H), ca. 5.85 (br, NH), 4.70 (br q, 1 H, α-CH), 3.18 (*ABX* system J_{AB} = 12 Hz, $J_{AX} = J_{BX}$ = 7 Hz, 2 H, benzylic H). Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.54; H, 5.67; N, 4.10.

Alloc-Tyr(All) (recrystallized from EtOH/H_2O): mp 97–97.5 °C; $[\alpha]^{20}_D$ +60.25° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] (a) 6.13–5.97 (m (ddt centered at 6.05 ppm), 1 H), 5.41 (dd, J_{trans} = 18 Hz, J_{gem} = 0.5–1.0 Hz, 1 H), 5.29 (dd, J_{cis} = 10 Hz, J_{gem} = 0.5–1.0 Hz, 1 H), 4.65 (d, J = 5 Hz, 2 H), (b) 5.96–5.77 (m (ddt centered at 5.87 ppm), 1 H), 5.34–5.12 (m, 2 H), 4.56 (d, J = 5 Hz, 2 H), [other resonances] 7.08 (d, J = 8.5 Hz, 2 H) and 6.85 (d, J = 8.5 Hz, 2 H, Ar H), ca. 5.85 (br s, NH), 4.63 (br q, 1 H, α-CH), 3.09 (*ABX* system, J_{AB} = 11 Hz, $J_{AX} = J_{BX}$ = 8 Hz, 2 H, benzylic CH_2). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.66; H, 6.33; N, 4.55.

Alloc-Lys(Z) DCHA salt: mp 121–122 °C; $[\alpha]^{20}_D$ +7.55° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 1712 cm^{-1}, (Nujol mull) 3345, 3245, 1705, 1695, 1628 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.0–5.82 (m, 1 H), 5.30 (br d, J_{trans} = 17 Hz, 1 H), 5.19 (d, J_{cis} = 10 Hz, 1 H), 4.58 (d, J = 5 Hz, 2 H), [other resonances] 7.4–7.22 (m, 5 H, Ar), 5.75 (br d, J = 6–7 Hz, NH Alloc), 5.1 (s, 2 H, CH_2Ph), ca. 5.0 (v br, 1 H, NH-Z), 4.01 (br q, 1 H, α-CH), 3.15 (br q, 2 H, ϵ-CH_2). Anal. Calcd for $C_{30}H_{47}N_3O_6$: C, 66.04; H, 8.68; N, 7.70. Found: C, 65.90; H, 8.06; N, 7.94.

BOC-Lys(Alloc) DCHA salt (recrystallized from AcOEt/hexane): mp 114.5–116 °C; $[\alpha]^{20}_D$ +8.21° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 1705 cm^{-1} br; ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.01–5.82 (m, 1 H), 5.30 (br d, J_{trans} = 18 Hz, 1 H), 5.20 (br d, J_{cis} = 10 Hz, 1 H), 4.55 (br d, J = 5 Hz, 2 H), [other resonances] 5.52 (d, J = 7 Hz, 1 H, NHBoc), ca. 5.18 (v br, NHAlloc), 3.94 (br q, 1 H, α-CH), 3.17 (br q, 2 H, ϵ-CH_2), 1.47 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{27}H_{49}N_3O_6$: C, 63.37; H, 9.65; N, 8.21. Found: C, 62.96; H, 9.57; N, 8.18.

Alloc-Lys(BOC) DCHA salt: mp 136 °C; $[\alpha]^{20}_D$ +9.46° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 1712 cm^{-1} br s; ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.03–5.85 (m, 1 H), 5.32 (dd, J_{trans} = 18 Hz, J_{gem} 0.5–1.0 Hz, 1 H), 5.18 (dd, J_{cis} = 10 Hz, J_{gem} = 0.5–1.0 Hz, 1 H), 4.56 (d, J = 6 Hz, 2 H), [other resonances] 5.78 (br d, $J \approx$ 6–7 Hz, 1 H, NHAlloc), 4.72 (br peak, 1 H, NHBoc),

4.02 (br q, 1 H, α-CH), 3.12 (br q, 2 H, ε-CH_2), 1.46 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{27}H_{49}N_3O_6$: C, 63.37; H, 9.65; N, 8.21. Found: C, 63.33; H, 9.59; N, 8.17.

Lys(Alloc) (recrystallized from H_2O): mp 230 °C dec; $[\alpha]^{20}_D$ +9.0 (*c* 1.0, H_2O/CO_3K_2 8%); ^1H NMR (250 MHz, DMSO-d_6) δ [allyl group resonances] 6.00–5.80 (m, 1 H), 5.27 (d, J_{trans} = 16 Hz, 1 H), 5.15 (d, J_{cis} = 10 Hz, 1 H), 4.43 (d, *J* = 5 Hz, 2 H), [other resonances] 7.20 (v br t, 1 H, NH), 3.08 (br t, 1 H, α-CH), 2.94 (br q, *J* = 7 Hz, ε-CH_2), 1.69 (m, 1 H), 1.57 (m, 1 H), 1.6–0.8 (m, 4 H). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.42; H, 7.94; N, 11.93.

Alloc-Arg(Ts) DCHA salt: mp 116 °C; $[\alpha^{20}_D$ +4.4° (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 5.98–5.78 (m, 1 H), 5.30 (br d, J_{trans} = 17 Hz, 1 H), 5.18 (br d, J_{cis} = 10 Hz, 1 H), 4.53 (d, *J* = 5 Hz, 2 H), [other resonances] 7.73 (d, *J* = 7.5 Hz, 2 H) and 7.23 (d, *J* = 7.5 Hz, 2 H) (Ar H), 3.18 (m, 2 H, δ-CH_2), 2.42 (s, 3 H, CH_3); TLC R_f (B) 0.69, R_f(C) 0.68.

N^α-Alloc-Phe Benzyl Ester. This derivative was obtained by esterification with benzyl alcohol of the DCHA salt of N^α-Alloc-Phe following essentially the recent procedure of Matsuda[47] and co-workers for the synthesis of amides from carboxylic acids.

To a stirred solution of Alloc-Phe DCHA salt (430 mg, 1.0 mmol) and pyridine (102 mg, 1.3 mmol) in CH_2Cl_2 (2 mL) was added $SOCl_2$ (143 mg, 1.2 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for 1 min. A solution of 185 mg of (dimethylamino)pyridine (1.5 mmol) and 97 mg (0.90 mmol) of benzyl alcohol was then added to the mixture, which was further stirred at room temperature for 45 min. After brine had been added to the mixture, the product was extracted with AcOEt. The organic layer was washed successively with HCl (3 N) and NaOH (1 N) and dried over SO_4Mg. Evaporation of the solvent in vacuo gave a crude product, which was purified by flash chromatography on silica (hexane/AcOEt (3/1)). 260 mg of N^α-Alloc-Phe benzyl ester (yield 76%) was thus obtained as a colorless oil. **N^α-Alloc-Phe-*O*-Bzl**: IR (CCl_4) 1740–1725 v br s, 1645 cm^{-1} vw (C=C); ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.00–5.80 (m, 1 H), 5.35–5.12 (m, 2 H), 4.55 (d, *J* = 5 Hz, 2 H), [other resonances] 7.42–7.18 (m, 10 H), ca. 5.2 (br peak, 1 H, NH), 5.15 (s, 2 H, OCH_2Ph), 4.71 (br q, *J* = 7 Hz, 1 H, α-CH), 3.11 (d, *J* = 7 Hz, 2 H, α-CCH_2Ph). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.76; H, 6.24; N, 4.13. Found: C, 70.32; H, 6.46; N, 4.13.

N^α-Z-Phe Allyl Ester. By the same procedure, 7.5 g (74% yield) of crude N^α-Z-Phe allyl ester was obtained from 9 g (30 mmol) of N^α-Z-Phe and 2.09 g (36 mmol) of dry allyl alcohol. Recrystallization from $EtOH/H_2O$ gave 5.2 g (51% yield) of pure compound as white crystals. **N^α-Z-Phe-*O*-All**: mp 60–60.5 °C; IR (CCl_4) 1727 br, 1650 cm^{-1} vw (C=C); ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.0–5.75 (m, 1 H), 5.36–5.18 (m, 2 H), 4.55 (d, *J* = 5 Hz, 2 H), [other resonances] 7.45–7.20 (m, 10 H), 5.10 (s, 2 H, OCH_2Ph), 4.70 (br q, *J* = 7 Hz, 1 H, α-CH), 3.13 (m, 2 H, CCH_2Ph). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.76; H, 6.24; N, 4.13. Found: C, 70.76; H, 6.46; N, 4.13.

N^α-Alloc-Ser(*t*-Bu) *tert*-Butyl Ester. N^α-Alloc-Ser(*t*-Bu)-*O*-*t*-Bu was prepared from N^α-Alloc-Ser by following the *tert*-butylation procedure of Schroder.[48] In a flask fitted with a rubber septum, 2.3 g of Alloc-Ser (12.2 mmol) was dissolved in 20 mL of CH_2Cl_2 under argon atmosphere. The solution was cooled at −10 °C. H_2SO_4 (0.2 mL, 3.7 mmoles) was added, followed by 20 mL of isobutylene, added in four portions with a syringe prechilled at −30 °C. Care was taken to exclude moisture during all these operations.

The reaction mixture was stirred for 1 h at −10 °C and then kept at 0 °C overnight. The reaction mixture was then poured into 100 mL of ca. 1 N aqueous citric acid partially neutralized with 1.15 mL of NaOH (4 N, 4.6 mmol). The organic layer was decanted and the aqueous phase reextracted once with CH_2Cl_2. After drying over $MgSO_4$ and evaporation of the solvent, the crude product was purified by flash chromatography on silica (AcOEt/hexane (1/8)) to yield 2.4 g (67% yield) of pure oily Alloc-Ser(*t*-Bu)-*O*-*t*-Bu: $[\alpha]^{20}_D$ +13.0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1715 s, 1645 cm^{-1} w; ^1H NMR (250 MHz, $CDCl_3$) δ [allyl group resonances] 6.02–5.84 (m, 1 H), 5.31 (d, J_{trans} = 17 Hz, 1 H), 5.21 (d, J_{cis} = 10.5 Hz, 1 H), 4.58 (d, *J* = 6 Hz, 2 H), [other resonances] 5.6 (v br d, 1 H, NH), 4.38–4.33 (br m, 1 H, α-CH), 3.78 (dd, 1 H) and 3.54 (dd, 1 H, diastereotopic methylene H1,H2, J_{gem} = 9.5 Hz, $J_{H1,H\alpha}$ = 3.5 Hz, $J_{H2,H\alpha}$ = 4 Hz), 1.45 (s, 9 H, CO_2-*t*-Bu), 1.13 (s, 9 H, O-*t*-Bu). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.77; H, 9.03; N, 4.75. Found: C, 59.53; H, 8.95; N, 4.75.

Palladium-Catalyzed Hydrostannolysis of (Allyloxycarbonyl)benzylamine. In a Schlenk tube equipped with a magnetic bar and fitted with a rubber septum, 190 mg of (allyloxycarbonyl)benzylamine (1 mmol), 14 mg of $PdCl_2(PPh_3)_2$ (0.02 mmol), and 135 μL of acetic acid (2.4 mmol) were dissolved in 20 mL of CH_2Cl_2 under argon atmosphere. The pale lemon yellow color of the solution was then characteristic of the presence of the palladium(II) complex. With a syringe, 300 μL of Bu_3SnH (ca. 1.1 mmol) was then *rapidly and in one portion* added to the stirred solution. A slightly exothermic reaction with vigorous gas evolution immediately ensued.

At the end of the reaction (a few minutes) the golden yellow color of the reaction mixture is typical of the presence of palladium(0) species in the medium (on standing in oxygen-containing atmosphere, formation of black palladium gradually occurs). An aliquot portion of the solution was diluted in CCl_4, the CCl_4 solution extracted with aqueous sodium hydrogen carbonate to eliminate any acetic acid in excess and dried. IR analysis showed a complete disappearance of the carbonyl band at 1720 cm^{-1} and its replacement by the strong carbonyl absorption of tributyltin acetate at 1740 cm^{-1}.

After evaporation of the solvent, ^1H NMR analysis ($CDCl_3$ containing a small amount of acetic acid for better resolution) of the crude reaction products indicated a quantitative yield in benzylamine acetate (based on the integration of benzylic protons at 4.0 ppm, anisole as the reference). Similar results were obtained in the following solvent–proton donor systems: benzene/AcOH, AcOEt/AcOH, DMF/AcOH, DMF/AcO^-PyH^+, CH_2Cl_2/H_2O.

Palladium-Catalyzed Hydrostannolysis of Simple N^α-Allyloxycarbonyl Derivatives of Amino Acids. In a typical experiment, 349 mg (1 mmol) of N^α-Alloc-*O*-Alloc-Tyr in 20 mL of CH_2Cl_2 was treated as described above, with 600 μL (ca. 2.2 mmol) of Bu_3SnH in the presence of 14 mg of $PdCl_2(PPh_3)_2$ and 100 μL of H_2O with vigorous magnetic stirring. Unprotected tyrosine immediately precipitated out of the solution.

The reaction mixture was concentrated to about one-third of its volume; the precipitate was collected by filtration, washed with several portions of ether, and dried. A quantitative yield of analytically pure tyrosine was obtained. A similar procedure (using 1.1–1.2 equiv of Bu_3SnH per allyl group to be cleaved) was followed for the deprotection of other N^α-allyloxycarbonyl protected amino acids. In some cases CH_2Cl_2 was evaporated at the end of the reaction and replaced by wet diethyl ether to ensure complete precipitation of the free amino acid.

Hydrostannolytic Deprotection of N^α-(Allyloxycarbonyl)phenylalanine Benzyl Ester. N^α-Alloc-Phe-*O*-Bzl (260 mg, 0.77 mmol) in 8 mL of CH_2Cl_2 was reacted in the usual way with 220 μL of Bu_3SnH (ca. 0.85 mmol) in the presence of $PdCl_2(PPh_3)_2$ (11 mg, 0.016 mmol) and H_2O (80 μL). After 10 min, IR analysis (CCl_4) of an aliquot showed the presence of two strong carbonyl bands at 1728 (CO_2Bzl) and 1638 cm^{-1} ($NHCO_2SnBu_3$). Total conversion of the starting material was evidenced by the absence of any residual absorption at 1700 cm^{-1}. After evaporation of the solvent, no signals characteristic of allyl groups could be detected by ^1H NMR analysis of the crude reaction mixture.

The crude product was purified by column chromatography on silica gel. Various tin impurities were first eluted with cyclohexane/ether (80/20) and N^α-[((tributylstannyl)oxy)carbonyl]phenylalanine benzyl ester was collected, upon elution with ethyl acetate, as an oil (330 mg, 74% yield): IR (CCl_4) 1740 (CO_2Bzl), 1640 cm^{-1} ($NHCO_2SnBu_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.4–7.1 (m, 10 H), 5.1 (s, 2 H, OCH_2Ph), 3.75 (br t, *J* = 8 Hz, α-CH), 3.0 (*ABX*, J_{AB} = 15 Hz, $J_{AX} = J_{BX}$ = 7 Hz, 2 H, CCH_2Ph), 2.6–0.9 (m, 27 H, Bu_3Sn).

In another experiment, CH_2Cl_2 was evaporated after completion of the hydrostannolytic cleavage and the residue taken up in about the same volume of diethyl ether. A saturated solution of *p*-toluenesulfonic acid (2.1 equiv) in diethyl ether was then added, upon which immediate gas evolution (CO_2) and precipitation

(48) Shroder, E. *Justus Liebigs Ann. Chem.* **1936**, 670, 127.

occurred. The ethereal mixture was concentrated to about half of its volume, the precipitate was collected by filtration, washed repeatedly with diethyl ether and identified by comparison with an authentic sample as the tosylate of phenylalanine benzyl ester (77% yield).

By TLC analysis only phenylalanine benzyl ester (R_f = 0.77; EtOH (96%)/NH_3–H_2O (25%), 4/1) could be detected in the filtrate.

Hydrostannolytic Deprotection of N^{α}-(Benzyloxycarbonyl)phenylalanine Allyl Ester. To a magnetically stirred solution of 338 mg (1 mmol) of Z-Phe-All and 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ in 10 mL of CH_2Cl_2 under argon atmosphere, 300 μL (ca. 1.1 mmol) of tributyltin hydride was added with a syringe over a period of about 2 min. After 10 min, IR analysis (CCl_4) of an aliquot showed two carbonyl bands at 1720 (NH–CO_2CH_2Ph) and 1650 cm^{-1} (CO_2SnBu_3); the absence of any residual absorption at 1750 cm^{-1} indicated a complete conversion of starting material. No allyl ^1H NMR signals were detected in the crude reaction mixture.

Column chromatography on silica using hexane and then diethyl ether as the eluents yielded 420 mg (70% yield) of N^{α}-(benzyloxycarbonyl)phenylalanine tributyltin ester as a waxy solid: IR (CCl_4) 1723 (NH–CO_2CH_2Ph), 1652 cm^{-1} (CO_2SnBu_3); ^1H NMR (90 MHz) δ 7.45–7.1 (m, 10 H), 5.38 (v br s, 1 H, NH), 5.1 (s, 2 H, OCH_2Ph), 4.1 (br q, J = 8 Hz, α-CH), 3.13 (br d, J = 7 Hz, 2 H, α-CCH_2Ph), 1.9–0.8 (m, 27 H, Bu_3Sn).

In another experiment, the crude reaction mixture was twice extracted with aqueous 10% HCl and both acidic washings reextracted once with dichloromethane. The combined organic fractions were dried over $MgSO_4$ and the solvent evaporated. An analytical yield of 90% in N^{α}-(benzyloxycarbonyl)phenylalanine was determined by ^1H NMR spectroscopy (based on the integration of the benzylic protons of the benzyloxycarbonyl group, anisole as the reference).

TLC analysis of the reaction mixture before or after extraction with aqueous HCl did not allow the detection of amino acid derivatives other than the expected N^{α}-(benzyloxycarbonyl)-phenylalanine (R_f(A) 0.24) and its tributylstannyl ester.

Hydrostannolytic Deprotection of N^{α}-(Allyloxycarbonyl)-*O*-*tert*-butylserine *tert*-Butyl Ester. The hydrostannolytic cleavage was performed on 300 mg (1 mmol) of Alloc-Ser (*t*-Bu)-*O*-*t*-Bu, by using 14 mg (0.01 mmol) of $PdCl_2(PPh_3)_2$, 300 μL (ca. 1 mmol) of Bu_3SnH in 25 mL of CH_2Cl_2 containing 280 mg (2 mmol) of *p*-nitrophenol as the proton donor. After completion of the reaction, only one carbonyl band at 1715 cm^{-1} (CO_2-*t*-Bu) was detected by IR analysis (CCl_4). As the two carbonyl bands of starting material closely overlap, the total conversion of starting material was verified by TLC analysis [Alloc-Ser(*t*-(Bu)-*O*-*t*-Bu: R_f = 0.55 (AcOEt/hexane, 1/4].

The organic phase was extracted by an aqueous solution of citric acid (ca. 3 equiv). The aqueous phase was then brought to alkaline pH (pH 9) with 4 N sodium hydroxide and extracted repeatedly with diethyl ether. After drying over $MgSO_4$ and evaporation of the solvent, 204 mg (70% yield) of analytically pure Ser(*t*-Bu)-*O*-*t*-Bu[49] was obtained: TLC, R_f 0.27 (AcOEt/MeOH, 9/1); IR (CCl_4) 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.50 (*ABX* pattern, J_{AB} = 9 Hz, J_{AX} = 5 Hz, J_{BX} = 4 Hz, 2 H, α-CCH_2), 3.38 (br t, 1 H, α-CH), 1.82 (br s, NH_2), 1.40 (s, 9 H), 1.10 (s, 9 H).

Trifluoroacetolysis of N^{α}-(Allyloxycarbonyl)-*O*-*tert*-butylserine *tert*-Butyl Ester. Alloc-Ser(*t*-Bu)-*O*-*t*-Bu (300 mg, 1 mmol) was reacted with CF_3CO_2H (25 mL) in CH_2Cl_2 (25 mL) for 6 h at room temperature. The solvent and trifluoroacetic acid were evaporated first on a rotary evaporator and then under 0.1 mmHg for 30 min. Analytically pure Alloc-Ser was obtained quantitatively: TLC, R_f(B) 0.58, R_f(C) 0.71.

Hydrostannolytic Deprotection of N^{α}-(Allyloxycarbonyl)-N^{ϵ}-(*tert*-butyloxycarbonyl)lysine. The hydrostannolytic reaction was carried out in 25 mL of wet (100 μL of H_2O) CH_2Cl_2 on 330 mg (1 mmol) of Alloc-Lys(BOC) with the usual amount of Bu_3SnH (1.1 equiv) and catalyst (0.02 equiv). After evaporation of about $^4/_5$ of the solvent, the precipitate formed during the reaction was collected by filtration, washed with a small volume of CH_2Cl_2, and dried. Crystalline N^{ϵ}-BOC-Lys (180 mg), identical with an authentic sample (Fluka), was obtained (73% yield).

The filtrate was concentrated and analyzed by NMR and IR spectroscopy. No allyl ^1H NMR signals were detected, but a weak residual absorption at 1640 cm^{-1} (tin carboxylate) was visible in the infrared spectrum. N^{ϵ}-BOC-Lys was the only amino acid derivative detected by TLC analysis in the filtrate (the solvent systems B and C instantly hydrolyze the corresponding tin ester). TLC characteristics are reported in the paragraph dealing with trifluoroacetolysis of BOC-Lys(Alloc).

Hydrostannolytic Deprotection of N^{α}-(*tert*-Butoxycarbonyl)-N^{ϵ}-(allyloxycarbonyl)lysine. The experimental procedure already used for the hydrostannolytic deprotection of N^{α}-Alloc-N^{ϵ}-BOC-Lys was followed. In the present case, however, no precipitation occured during the reaction. After evaporation of CH_2Cl_2, the oily residue was taken up in a mixture of approximately 1/1 (v/v) of $CDCl_3$ and DMSO-d_6. No allylic signals could be detected by ^1H NMR spectroscopy.

Analytical yield of N^{α}-BOC-Lys was found to be 95% (based on the integration of the *tert*-butyl group protons, anisole as the reference). Total and selective conversion of the starting material to N^{α}-BOC-Lys was confirmed by TLC analysis.

Trifluoroacetolysis of N^{α}-(Allyloxycarbonyl)-N^{ϵ}-(*tert*-butoxycarbonyl)lysine. N^{α}-Alloc-N^{ϵ}-BOC-Lys (130 mg, 0.4 mmol) was reacted with 5 mL of trifluoroacetic acid in 5 mL of CH_2Cl_2. After 2 h, complete and selective deprotection (TLC) to N^{α}-Alloc-Lys had occurred. After elimination of the solvent and of trifluoroacetic acid by evaporation on a rotary evaporator and then under 0.05 mmHg of pressure for 12 h, N^{α}-Alloc-Lysine trifluoroacetate was obtained as a very hygroscopic solid: $[\alpha]^{20}_D$ +15.2° (*c* 1.0, H_2O–Na_2CO_3 (8%)); ^1H NMR (250 MHz) [Alloc-Lys CF_3CO_2H salt ($CDCl_3$)] δ [allyl group resonances] 6.05–5.82 (m, 1 H), 5.32 (d, J_{trans} = 17 Hz, 1 H) and 5.16 (d, J_{cis} = 10 Hz, 1 H), 4.52 (d, J = 5 Hz, 2 H), [others resonances] 4.01 (v br sext, α-CH), 2.95–2.80 (m, 2 H, $CH_2NH_3^+$), 1.8–1.0 (m, 6 H, internal CH_2 groups), [Alloc-Lys (H_2O/CO_3K_2)] δ (by reference to DOH frequency assumed to be at 4.60 ppm) [allyl group resonances] 5.9–5.65 (m, 1 H) 5.15 (d, J_{trans} = 17 Hz, 1 H) and 5.02 (d, J_{cis} = 10 Hz, 1 H), 4.48 (d, J = 5 Hz, 2 H), [other resonances] 3.85–3.65 (m, 1 H, α-CH), 2.72 (t, J = 7.5 Hz, 2 H, CH_2NH_2), 1.65–1.35 (m, 4 H, β-CH_2 and δ-CH_2), 1.30–1.10 (m, 2 H, γ-CH_2).

Trifluoroacetolysis of N^{α}-(*tert*-Butoxycarbonyl)-N^{ϵ}-(allyloxycarbonyl)lysine. By the same procedure, N^{ϵ}-Alloc-Lys was selectively and quantitatively obtained as its trifluoroacetate salt. Spectroscopic characteristics of N^{ϵ}-Alloc-Lys has already been described above (see Physical and Spectroscopic Characteristics of Alloc Derivatives).

TLC data: N^{α}-Alloc-N^{ϵ}-BOC-Lysine, R_f(A) 0.31; N^{α}-BOC-N^{ϵ}-Alloc-Lysine, R_f(A) 0.25; N^{α}-BOC-Lys, R_f(B) 0.28, R_f(C) 0.51; N^{ϵ}-BOC-Lys, R_f(B) 0.36, R_f(C) 0.58; N^{α}-Alloc-Lys R_f(B) 0.22, R_f(C) 0.44; N^{ϵ}-Alloc-Lysine, R_f(B) 0.30, R_f(C) 0.54.

Hydrostannolytic Deprotection of the DCHA Salt of N^{α}-(Allyloxycarbonyl)-N^{im}-(*tert*-butyloxycarbonyl)-histidine. The hydrostannolytic deprotection was performed by starting from 156 mg (0.31 mmol) of Alloc-His(BOC) DCHA salt in CH_2Cl_2 (7 mL) and by use of 120 μL of Bu_3SnH (ca. 0.45 mmol), 40 μL of acetic acid (0.7 mmol), and 7 mg of $PdCl_2(PPh_3)_2$ (0.01 mmol).

After completion of the reaction, the solvent was evaporated, and the residue was taken up in 6 mL of a mixture 1/1 (v/v) of trifluoroacetic acid and fresh dichloromethane. After 3 h, complete deprotection of the intermediate N^{im}-BOC-His had occurred. An analytical yield of 95–100% of histidine trifluoroacetate was determined by ^1H NMR spectroscopy in CF_3CO_2H after evaporation of dichloromethane (based on the integration of imidazole ring protons, anisole as the reference).

In another experiment, the hydrostannolytic procedure was carried out as above except that *p*-nitrophenol (97 mg, 0.7 mmol) was used instead of acetic acid as the proton donor. After completion of the reaction, IR analysis ($CHCl_3$) of an aliquot showed a complete disappearance of the carbonyl band of the Alloc moiety (1710 cm^{-1}) while the carbonyl absorption at 1750 cm^{-1} (BOC moiety) was retained. After evaporation of the solvent, the residue was washed with diethyl ether (2 × 5 mL). TLC analysis of the yellow residual solid showed that N^{im}-BOC-His was the only amino acid derivative present, to the exclusion of histidine and of

(49) Callahan, F. H.; Anderson, G. W.; Paul, R.; Zimmerman, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 201.

N^{α}-Alloc-N^{im}-BOC-His. No amino acid derivatives could be detected in the ethereal washings.

TLC data: N^{im}-BOC-His, R_f(B) 0.28, R_f(C) 0.60; N^{α}-Alloc-N^{im}-BOC-His, R_f(B) 0.55, R_f(C) 0.74; His, R_f(B) 0.04, R_f(C) 0.12; DCHA R_f(B) 0.77, R_f(C) 0.76; *p*-nitrophenol, R_f(B) 0.93, R_f(C) 0.85.

By ^{1}H NMR, the solid residue (110 mg) was found to contain ca. 60% of N^{im}-BOC-His (97% of theoretical amount), 25% of dicyclohexylamine, and 15% of *p*-nitrophenol (molar proportions). No further purification was attempted.

His(BOC): ^{1}H NMR (250 MHz, D_2O, pD ca. 7.5) δ (by reference to DOH frequency assumed to be at 4.60 ppm) 8.00 (s, 1 H, imidazolyl H2), 7.20 (s, 1 H, imidazolyl H4), 3.79 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1 H, α-CH), 2.98 (dd, 1 H) and 2.84 (dd, 1 H) (*ABX* system J_{AB} = 15 Hz, J_{AX} = 5 Hz, J_{BX} = 8 Hz), 1.48 (s, 9 H, *t*-Bu). In this solution, N^{im}-BOC-His is slowly hydrolyzed to histidine and *tert*-butyl alcohol ($t_{1/2}$ ca. 120 min).

Hydrostannolytic Deprotection of N^{α}-(Allyloxycarbonyl)-L-methionine and Determination of Optical Purity. N^{α}-(Allyloxycarbonyl)methionine was hydrostannolyzed in the usual way in wet dichloromethane. After completion of the reaction, the organic layer was extracted with a small excess of aqueous HCl (6 N). After evaporation of the aqueous phase under 0.5 mmHg, 4 mg of the solid residue was treated as follows in a one-pot procedure:[29] (1) 4 mL of *i*-PrOH/HCl (6%), 100 °C, 1 h; (2) vacuum-drying; (3) $(CF_3CO)_2O$ (0.2 mL)/CH_2Cl_2 (1 mL) at room temperature for 1 h; (4) vacuum-drying and dissolution in 1 mL of acetone.

Chiral GC analysis was performed on an Erba Science apparatus equipped with a 50-m fused silica capillary column coated with XE-60-(*S*)-valyl-(*S*)-α-phenylethylamide (Chrompack) with temperature programming (100 °C + 5 °C/min). No D-methionine derivative (<0.1%) could be detected on the chromatogram. Blank analysis performed on DL-methionine and on the hydrostannolytic products of N^{α}-(allyloxycarbonyl)-DL-methionine showed equal proportions of the two enantiomers.

Synthesis of BOC-Leu-L-Met-NH_2 and BOC-Leu-DL-Met-NH_2 (9). Alloc-Met-NH_2 was synthesized from Alloc-Met according to a procedure described for BOC-Met-NH_2.[50] Alloc-Met (160 mg, 0.69 mmol) was dissolved in 4 mL of anhydrous tetrahydrofuran and cooled to −15 °C. To this solution were added triethylamine (100 μL, 1 equiv) and then isobutyloxycarbonyl chloride (95 μL, 1 equiv). After 2 min, 45 μL of 34% aqueous ammonia (1.1 equiv) was added. After 1 h, the reaction mixture was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 5% $NaHCO_3$ and water. The extract was dried over $MgSO_4$ and the solvent removed in vacuo to yield 100 mg of Alloc-Met-NH_2 as an oil (63%). The Alloc protecting group was removed as described in a typical experiment. N^{α}-BOC-Leu-*O*-Succ (180 mg, 1.1 equiv) was coupled in DMF to the crude Met-NH_2. The mixture was stirred at room temperature for 15 h, after the pH had been adjusted to 8.0 with *N*-methylmorpholine. Usual workup yielded crude BOC-Leu-Met-NH_2, which was compared with an authentic sample of BOC-Leu-Met-NH_2 obtained by the BOC strategy[51] (TLC, NMR, and HPLC). BOC-Leu-DL-Met-NH_2 was obtained by the same procedure starting from DL-Alloc-Met. The mixture of diastereoisomers was resolved by HPLC (μ-Bondapak C-18 column, iso 30% acetonitrile in 0.25 M triethylammonium phosphate buffer pH 3.0): t_R 19.5 (LL) and 20.7 min (LD).

Synthesis of Substance P. Methylbenzhydrylamine resin[32] (1.85 g, substitution 0.40 mequiv/g of resin) was used as the solid support. N^{α}-amino group and side-chain functional group protection consisted of allyloxycarbonyl for the N^{α}-amino group and benzyloxycarbonyl for the Lys (Z) and tosyl for the guanidinium of Arg(Tos). All the amino acids from the C-terminal pentapeptide were activated by the dicyclohexylcarbodiimide-1-hydroxybenzotriazole (DCCI-1-HOBt[34]) in dimethylformamide dichloromethane (1:9); the N^{α}-Alloc-Gln residues were coupled as their *p*-nitrophenyl ester in DMF. Finally, all the amino acids from the N-terminal tetrapeptide were activated by the DCCI-1-HOBt in dimethylformamide–dichloromethane (9:1). The coupling efficiency was monitored by the Kaiser test.[52] The N^{α}-alloc protective group was removed by adding to the peptide–resin a solution of $PdCl_2(PPh_3)_2$ (0.04 equiv) and 3.5 equiv/mmol of amino group linked to the resin, of CH_3COOH in dichloromethane (3 mL/g of resin). The deprotection was completed in less than 5 min after addition of Bu_3SnH (3 equiv). The resin was then washed according to the following scheme: (1) methylene chloride wash (3×); (2) 1:9 (v/v) triethylamine–methylene chloride neutralization (2×); (3) methylene chloride wash (2×); (4) methanol wash (3×); (5) methylene chloride wash (3×). After removal of the last N^{α}- protecting group, the resin was dried in vacuo and the protected peptide resin was treated with 1.5 mL of anisole, 0.25 mL of diethyl disulfide, and and 10 mL of hydrogen fluoride per gram of peptide resin for 0.5 h at −20 °C and for 0.5 h at 0 °C. The resin was first washed with 1:1 diethyl ether–chloroform, and then the peptide was eluted with 1:9 acetic acid–water. Lyophilization of the extract gave 625 mg of crude substance P containing, as estimated by HPLC, 60% of SP and 13% of SP sulfoxide. The HPLC conditions were as follows: μ-Bondapak C-18 column; 0.25 M triethylammonium phosphate buffer pH 3.0, 1.5 mL/min, isocratic 22.2% acetonitrile in TEAP buffer, 13.5 min.

This crude product was purified by CM-32 carboxymethylcellulose (Whatman) cation-exchange chromatography (1.5 cm × 15 cm), using a linear gradient (400 mL of 1:1 0.01 M NH_4OAc (pH 4.5)–acetonitrile; 400 mL of 0.4 M NH_4OAc (pH 6.5)); 320 mg yields 200 mg. Final purification was achieved by partition chromatography on Sephadex G-25 F (Pharmacia) with the solvent system 1-butanol–acetic acid–water, (4:1:5). The chromatographic fractions were monitored by TLC and pooled to yield 110 mg of SP and 17 mg of SP sulfoxide: TLC, R_f 0.20 (1-butanol–pyridine–acetic acid–water, (5:5:1:4)); $[\alpha]^{23}_D$ −81° (*c* 1.0, 10% acetic acid); HPLC (iso, 22.2% acetonitrile in TEAP buffer, 13.5 min, minimum purity 99%). Anal. Found: Arg, 0.95; Pro, 1.98; Lys, 0.97; Glu, 2.05; Phe, 2.07; Gly, 1.00; Leu, 1.03; Met, 0.91. FAB mass spectrometry, MH^+ m/z 1361; 250-MHz ^{1}H NMR (dimethyl sulfoxide).[37]

Biological Potencies of Substance P. The binding potency of substance P was measured on rat brain synaptosomes as described previously.[39] The IC_{50} value was found to be identical with that observed for substance P obtained by conventional methods: 6.4×10^{-10} M; this result is the mean of three independent experiments run in triplicate. The bioactivity of substance P was estimated on the isolated guinea pig ileum bioassay,[38] $ED_{50} = 7.5 \times 10^{-10}$ M.

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(50) Izeboud, E.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 1.

(51) Lavielle, S.; Chassaing, G.; Beaujouan, J.-C.; Torrens, Y.; Marquet, A. *Int. J. Peptide Protein Res.* **1984**, *24*, 480.

(52) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.