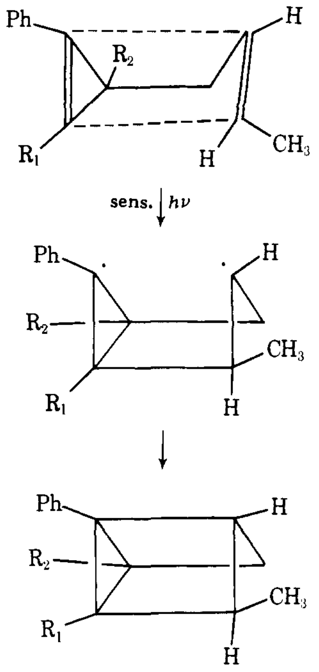
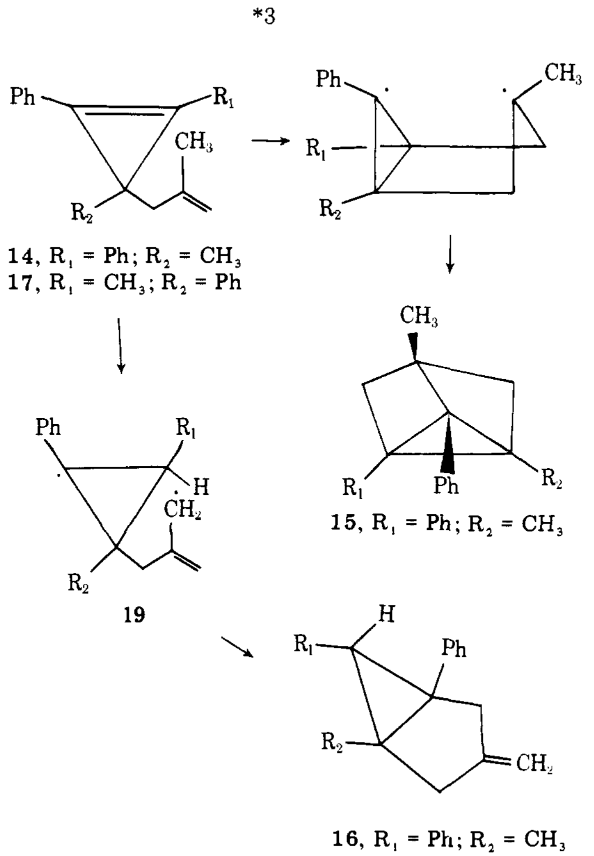


Similar results were encountered with cyclopropene **17**, although, in this case, only one of the two possible bicyclohexanes was produced (ratio of **15**:**18** = 5:3). The formation of the bicyclohexane ring proceeds via an intramolecular hydrogen atom transfer reaction.[14] Both products were equally quenched with added triplet quenchers, thereby indicating that they are both derived from a common triplet state. The regioselectivity exhibited by cyclopropene **17** is undoubtedly related to the fact that hydrogen transfer to the methyl bearing carbon allows maximum delocalization of the radical centers in the resulting diradical intermediate (i.e., **19**).



14, R_1 = Ph; R_2 = CH_3
17, R_1 = CH_3; R_2 = Ph

15, R_1 = Ph; R_2 = CH_3

19

16, R_1 = Ph; R_2 = CH_3
18, R_1 = CH_3; R_2 = Ph

Acknowledgment. We gratefully acknowledge support of this work by the National Cancer Institute (DHEW CA-21471) and the Petroleum Research Fund, administered by the American Chemical Society.

References and Notes

(1) Photochemical Transformations of Small Ring Compounds. 104. For part 103 see Padwa, A.; Loza, R.; Blacklock, T. J. *Tetrahedron Lett.*, 219–222 (1979).

(2) (a) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969,** *8,* 781–853. (b) Hoffmann, R.; Swaminathan, S.; Odell, B. G.; Gleiter, R. *J. Am. Chem. Soc.* **1970,** *92,* 7091–7097. (c) Wright, J. S.; Salem, L. *ibid.* **1972,** *94,* 322–329. (d) Segal, G. A. *ibid.* **1974,** *96,* 7892–7898. (e) Fujimoto, H.; Sugiyama, T. *ibid.* **1977,** *99,* 15–22.

(3) (a) Baldwin, J. E. "Pericyclic Reactions", Vol. II, Marchand, A. P.; Lehr, R. E., Eds.; Academic Press: New York, 1977; pp 273–302. (b) Scacchi, G.; Richard, C.; Back, M. H. *Int. J. Chem. Kinet.* **1977,** *9,* 513–524. (c) Scacchi, G.; Back, H. M. *ibid.* **1977,** *9,* 525–534. (d) Bartlett, P. D.; Mallet, J. B. *J. Am. Chem. Soc.* **1976,** *98,* 143–153, and references cited therein. (e) Bartlett, P. D.; Hummel, K.; Elliott, S. P.; Minns, R. A. *ibid.* **1977,** *94,* 2898–2899. (f) Bartlett, P. D.; Cohen, G. M.; Elliott, S. P.; Hummel, K.; Minns, R. A.; Sharts, C. M.; Fukunaga, J. Y. *ibid.* **1972,** *94,* 2899–2902.

(4) The case of Kraft and Koltzenburg[4a] ((a) Kraft, K.; Koltzenburg, G. *Tetrahedron Lett.* **1967,** 4357–4360, 4723–4726) dealing with the stereoselective dimerization of bicyclo[4.2.2]deca-*trans*-3-*cis*-7,9-triene can be attributed to a multistep process involving diradical intermediates.[4b] (b) Padwa, A.; Koehn, W.; Masaracchia, J., Osborn, C. L.; Trecker, D. J. *J. Am. Chem. Soc.* **1971,** *93,* 3633–3638.

(5) Cycloadditions of olefins to allenes,[5a] ketenes[5b] and reactive isocyanates[5c] are known to proceed with very high degrees of stereospecificity, thereby suggesting that cumulative π-bond systems can function more readily as $_{\pi}2_a$ donors than isolated double bonds: (a) Kiefer, E. F.; Okamura, M. Y. *J. Am. Chem. Soc.* **1968,** *90,* 4187–4189. Baldwin J. E.; Roy, U. V. *Chem. Commun.* **1969,** 1225–1226. (b) Brady, W. T.; Hoff, E. F.; Roe, R.; Parry, F. H. *J. Am. Chem. Soc.* **1969,** *91,* 5679–5680. (c) Moriconi, E. J.; Kelly, J. F. *Tetrahedron Lett.*, **1968,** 1435–1438.

(6) (a) Frey, H. M. *Adv. Phys. Org. Chem.* **1966,** *4,* 170–193. (b) Cocks, A. T.; Frey, H. M.; Stevens, I. D. R. *Chem. Commun.* **1969,** 458–459. (c) Baldwin, J. E.; Ford, P. W. *J. Am. Chem. Soc.* **1969,** *91,* 7192.

(7) Cyclopropenes **1, 3, 5,** and **6** were prepared from the reaction of diphenylmethylcyclopropenyl cation with lithio-*tert*-butyl acetate followed by chromatographic separation of the isomeric acetates. Subsequent Dibal reduction, reaction with ethylenetriphenylphosphorane, and chromatographic separation on a silver nitrate column afforded pure samples of the cis and trans olefins. Complete spectroscopic details will be provided in a later publication. Satisfactory spectral and analytical data were obtained for each new compound.

(8) The thermal cycloaddition reactions of cyclopropenes **5** and **6** were carried out to *ca.* 30% conversion since further thermolysis of **8** resulted in a mixture of **5** (9%), **6** (36%), **7** (14%), and **9** (21%).

(9) For some related proton couplings in the tricyclo[2.2.0.0^{2,6}]hexane system, see Ho, C. Y.; Bond, F. T. *J. Am. Chem. Soc.* **1974,** *96,* 7355.

(10) Padwa, A.; Blacklock, T. J. *J. Am. Chem. Soc.* **1978,** *100,* 1321–1323.

(11) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970,** *92,* 2377–2386.

(12) The sensitized irradiation of cyclopropenes **1** and **5** gave rise to a complex mixture of photoproducts which prevented analysis of the stereochemical course of the cycloaddition reaction.

(13) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions", Wiley: New York, 1976.

(14) Padwa, A.; Chiacchio, U.; Hatanaka, N. *J. Am. Chem. Soc.* **1978,** *100,* 3928–3930.

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Reaction of $[Fe(SC_6H_5)_4]^{2-}$ with Organic Trisulfides and Implications Concerning the Biosynthesis of Ferredoxins. Synthesis and Structure of the $[(C_6H_5)_4P]_2Fe_2S_{12}$ Complex

Sir:

The synthesis,[1] structural characterization,[2] and the Mössbauer spectral properties[3] of the tetrahedral $[Fe(SC_6H_5)_4]^{2-}$ complex anion (I) have been reported. The electronic spectra, magnetic properties, and fine and hyperfine parameters as derived from an analysis of the Mössbauer

Table I. Crystal and Refinement Data for $(Ph_4P)_2Fe_2S_{12}$

cell dimensions	$a = 14.907$ (5) Å $b = 15.344$ (4) Å $c = 11.313$ (5) Å $\beta = 91.03°$
space group	$P2_1/n$, $Z = 2$
d_{calcd}, g/cm^3	1.510
d_{obsd},^{a} g/cm^3	1.50 (1)
crystal dimensions, mm	0.18 × 0.04 × 0.26
μ, cm$^{-1\,b}$	92.5
2θ (max), deg	90 (Cu radiation)
reflections used ($F^2 > 3\sigma(F^2)$)	1867
unique reflections	2214
parameters	369
$R_1{}^c$	0.054
$R_2{}^d$	0.081

[a] Determined by flotation in CCl_4-pentane. [b] Absorption correction was applied to the data. [c] $R_1 = \Sigma|\Delta F|/\Sigma|F_o|$. [d] $R_2 = [\Sigma_w(\Delta F)^2/\Sigma_w|F_o|^2]^{1/2}$.

Table II. Selected Structural Parameters in (a) $[Fe_2S_{12}]^{2-}$, (b) $[Fe_2S_2(S_2\text{-}o\text{-xylyl})_2]^{2-}$ (A),[a] and (c) $[Fe_2S_2(S\text{-}p\text{-tolyl})_4]^{2-}$ (B)[a]

	$[Fe_2S_{12}]^{2-}$	A	B
	Bond lengths, Å		
Fe-Fe	2.701 (3)	2.698 (1)	2.691 (1)
Fe-S_1	2.187 (3)	2.185 (2)	2.200 (1)
Fe-S_2	2.323 (3)	2.306 (1)	2.312 (1)
Fe-S_6	2.318 (3)	2.303 (1)	2.312 (1)
Fe-S_1'	2.197 (3)	2.232 (1)	2.202 (1)
S_1-S_1'	3.453 (5)	3.498 (3)	3.483 (3)
S_1-S_2	3.654 (4)	3.732 (2)	3.794 (1)
S_1'-S_2	3.808 (4)	3.736 (2)	3.589 (1)
S_1-S_6	3.634 (4)	3.722 (2)	3.591 (1)
S_2-S_6	3.289 (4)	3.690 (2)	3.816 (1)
	Bond angles, degrees		
S_1-Fe-S_1'	104.0 (2)	104.73 (5)	104.61 (4)
S_1-Fe-S_2	108.2 (2)	112.33 (5)	114.48 (4)
S_1-Fe-S_6	107.5 (1)	112.05 (5)	105.48 (4)
S_1'-Fe-S_2	114.8 (2)	110.78 (5)	105.32 (4)
S_1'-Fe-S_6	114.0 (2)	110.66 (5)	115.81 (4)
Fe-S_1-Fe	76.1 (1)	75.27 (5)	75.39 (4)

[a] After ref 7.

spectra at 4.2 K in high applied magnetic fields[3b] are in excellent agreement with the corresponding values reported for reduced rubredoxin, $(Rd)_{red}$.[4] The structure of $(Rd)_{ox}$ has been determined and the ferric ion in this molecule is found tetrahedrally coordinated by four sulfur atoms from cysteinyl residues on the protein backbone.[5]

There is little doubt that I is a very close analogue of the active center in $(Rd)_{red}$, at least as far as the molecular geometry and electronic energy level structure is concerned. The only other, completely characterized, analogue for $(Rd)_{red}$ that has been reported is the $[Fe(S_2\text{-}o\text{-xylyl})_2]^{2-}$ complex anion.[6] Recently we have initiated a detailed study of the reactivity of the $[M(SC_6H_5)_4]^{2-}$ complexes. The reducing properties and coordination unsaturation of I make this molecule an ideal candidate for oxidative addition reactions. In this communication we report on the reaction of I with organic trisulfides, RSSSR.

The reaction of dibenzyl trisulfide (II) with the tetraphenylphosphonium salt, Ph_4P^+, of I in boiling acetonitrile is rapid and the violet $[F_2S_2(SPh)_4]^{2-}$ dimer[7] (III) is formed and crystallizes on cooling as the Ph_4P^+ salt in 68% yield. Reaction of I with 5 equiv of the trisulfide results in the formation of the dark red brown $[Fe_2S_{12}]^{2-}$ anion (IV), which crystallizes from hot CH_3CN upon the addition of ether as the Ph_4P^+ salt in 75% yield. Anal. Calcd for $Fe_2S_{12}C_{48}H_{40}P_2$: C, 49.01; H, 3.40; S, 32.67; Fe, 9.50. Found: C, 49.00; H, 3.36; S, 31.60; Fe, 9.35.

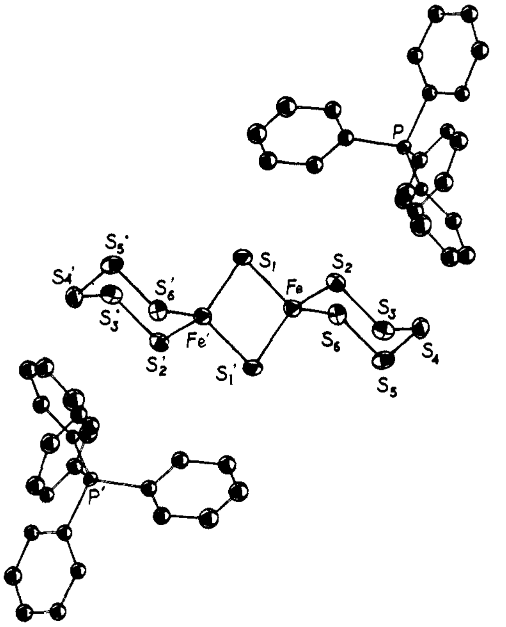

Figure 1. Structure and labeling of the $Fe_2S_{12}{}^{2-}$ anion of the $(Ph_4P)_2Fe_2S_{12}$ "salt". Thermal ellipsoids as drawn by ORTEP (C. K. Johnson, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965) represent the 50% probability surfaces.

The high yield of the product and the absence in the mass spectrum of II of higher polysulfides, $RS(S)_xSR$, other than a trace of $RS(S)_2SR$, suggested that $Fe_2S_{12}{}^{2-}$ forms via a very efficient reaction between III and II.[8]

The visible spectrum of IV (600 sh, 445 nm (ϵ 37 800), 370 (31 700)) is similar to, but distinctly different from, that of III or other iron-sulfur complexes with the Fe_2S_2 core.[6] Cyclic voltammetry of IV in DMF with Bu_4NClO_4 as supporting electrolyte showed no well-defined reduction characteristics and an irreversible oxidation wave at +0.43 V vs. SCE. The Mössbauer spectrum of the diamagnetic IV is similar to that of other dimeric complexes with the same Fe_2S_2 core.[6]

Crystal and refinement data for $(Ph_4P)_2Fe_2S_{12}$ are shown in Table I. Intensity data were collected from a well-formed crystal on a Picker-Nuclear FACS-I automatic diffractometer using a θ-2θ scan technique. The structure was solved by conventional Patterson and Fourier techniques and has been refined by full-matrix, least-squares techniques. The structure (Figure 1) shows the $Fe_2S_{12}{}^{2-}$ anion containing two, tetrahedrally coordinated, iron(III) ions bridged by two sulfides to form the Fe_2S_2 core. The remaining two coordination sites on each of the two iron atoms are occupied by the two unusual $S_5{}^{2-}$ bidentate chelates. The $S_5{}^{2-}$ anion, although not a common ligand, occurs as a bidentate chelate in $[PtS_{15}]^{2-}$ [9] and $Ti(Cp)_2S_5$.[10] The former complex undergoes reduction with CN^- and affords the $[PtS_{10}]^{2-}$ complex.[11] A structure determination of the $[PtS_{15}]^{2-}$ [12] complex shows the PtS_5 "ring" unit in the chair conformation, not unlike the conformation found for the FeS_5 "ring" in the present structure. Other structural details for the $S_5{}^{2-}$ ligands in IV are very similar to those reported for the same ligands in $[PtS_{15}]^{2-}$.[12] Selected structural parameters in the $[Fe_2S_{12}]^{2-}$ anion[13] are shown in Table II and are compared with corresponding values in the structures of the $[Fe_2S_2(S_2\text{-}o\text{-xylyl})_2]^{2-}$ and $[Fe_2S_2(S\text{-}p\text{-tolyl})_4]^{2-}$ anions.[7] Both of these complexes are successful analogues for the active sites in the oxidized forms of the two-iron ferredoxins.[6]

The synthesis of the $[Fe_2S_2(SC_6H_5)_4]^{2-}$ dimer anion from $Fe(SC_6H_5)_4{}^{2-}$ and a RSSSR trisulfide has important implications regarding the enzymatic biosynthesis of the metal centers in the two-iron ferredoxins, particularly since certain trisulfides seem to be present in some biological systems. The generation of thiocystine, CySSSCy, from the reaction of cystine with the unstable cysteine hydropersulfide has been noted.[14] The latter is obtained enzymatically by the action of cysteine desulfhydrase on cystine.[15]

The reconstitution of parsley apoferredoxin in the presence of rhodanese (thiosulfate-cyanide sulfur transferase), dithiothreitol, and thiosulfate[16] suggests that the sulfur transferase activity of rhodanese also could be involved in ferredoxin biosynthesis. The equilibrium (eq 1) that describes the "sulfur-rich" rhodanese ($\mathrm{E\cdot S_2}$) action on dihydrolipoate has been reported.[17]

$$\mathrm{E\cdot S_2 + 2lip(SH)_2 \rightleftarrows 2lipS_2 + 2HS^- + 2H^+ + E} \qquad (1)$$

In the course of formation of lipoate, $\mathrm{lipS_2}$, a chromophore was observed and assumed to be an organic persulfide intermediate. Whether this intermediate, with a hydropersulfide functional group, lip(SH)(SSH), undergoes further reaction with lipoate (eq 2) with formation of a cyclic lipoate trisulfide remains to be established. Such a reaction, however, would be analogous to the reaction reported to occur between CySSH and CySSCy[14] (eq 3). A suggestion is advanced, that linear or cyclic trisulfides, upon reduction, may serve as sources for inorganic sulfide. A synthesis of cyclic trithiothreitol was undertaken to examine the ability of this molecule to act as an oxidizing agent for the $\mathrm{[Fe(SC_6H_5)_4]^{2-}}$ complex. Trithiothreitol[18] reacts readily with $\mathrm{[Fe(SC_6H_5)_4]^{2-}}$ in DMF to form $\mathrm{[Fe_2S_2(SC_6H_5)_4]^{2-}}$, which was obtained in good yields and characterized by comparison with an "authentic" sample.[7]

$$\mathrm{lip(SH)(SSH) + lipS_2 \rightarrow lipS_3 + lip(SH)_2} \qquad (2)$$

$$\mathrm{CySSH + CySSCy \rightleftarrows CySSSCy + CySH} \qquad (3)$$

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Supplementary Material Available. Observed structure factors for $\mathrm{[(C_6H_5)_4P]_2Fe_2S_{12}}$ (9 pages). Ordering information is given on any current masthead page.

References and Notes

(1) D. G. Holah and D. Coucouvanis, *J. Am. Chem. Soc.*, **97**, 6917 (1975).
(2) D. Coucouvanis, D. Swenson, N. C. Baenziger, D. G. Holah, A. Kostikas, A. Simopoulos, and V. Petrouleas, *J. Am. Chem. Soc.*, **98**, 5721 (1976).
(3) (a) A. Kostikas, V. Petrouleas, A. Simopoulos, D. Coucouvanis, and D. G. Holah, *Chem. Phys. Lett.*, **38**, 582 (1976); (b) N. Sfarnas, A. Simopoulos, A. Kostikas, and D. Coucouvanis, unpublished work.
(4) C. E. Johnson, *J. Phys.* (*Paris*), **35**, C1-S7 (1974).
(5) K. D. Watenpaugh, L. C. Sieker, J. R. Herriot, and L. H. Jensen, *Acta Crystallogr., Sect. B*, **29**, 943 (1973).
(6) R. H. Holm and J. A. Ibers in "Iron Sulfur Proteins", Vol. 3, W. Lovenberg, Ed., Academic Press, New York, 1977, Chapter 7, and references therein.
(7) J. J. Mayerle, S. E. Denmark, B. V. De Pamphilis, J. A. Ibers, and R. H. Holm, *J. Am. Chem. Soc.*, **97**, 1032 (1975).
(8) The nature of this reaction is presently under study.
(9) K. A. Hofmann and F. Höchtlen, *Chem. Ber.*, **36**, 3090 (1903).
(10) H. Köpf, B. Block, and M. Schmidt, *Chem. Ber.*, **101**, 272 (1968).
(11) A. E. Wickenden and R. A. Krause, *Inorg. Chem.*, **8**, 779 (1969).
(12) P. E. Jones and L. Katz, *Acta Crystallogr., Sect. B*, **25**, 745 (1969).
(13) The strictly inorganic $\mathrm{Fe_2S_{12}{}^{2-}}$ anion undergoes interesting sulfur abstraction reactions with triphenylphosphine which are presently under study.
(14) T. W. Szczepkowski and J. L. Wood, *Biochim. Biophys. Acta*, **139**, 469 (1967).
(15) D. Cavallini, B. Mondovi, C. De Marco, and A. Scioscia-Santoro, *Enzymologia*, **24**, 253 (1962).
(16) U. Tomati, R. Matarese, and G. Federici, *Phytochemistry*, **13**, 1703 (1974).
(17) M. Villarejo and J. Westley, *J. Biol. Chem.*, **238**, 4016 (1963).
(18) A white crystalline solid of the composition $\mathrm{C_4H_6O_2S_3}$ was obtained by the reaction of dithiothreitol with $\mathrm{SCl_2}$ in ether. Analytical and NMR spectra data are consistent with the formulation of this molecule as a trisulfide.

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Peptide Synthesis in Water and the Use of Immobilized Carboxypeptidase Y for Deprotection

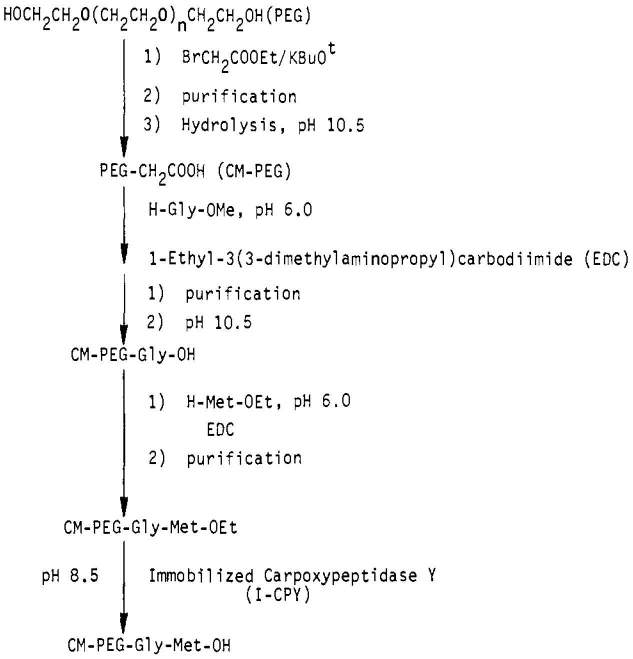
Sir:

We report here a method for peptide synthesis in aqueous systems in which coupling and deblocking are carried out at pH 6 and 8.5, respectively (Scheme I). Water-soluble carbodiimide and amino acid ethyl esters are used to elongate the chain from the carboxyl end (Scheme II). The removal of the ethyl ester blocking group is accomplished by treatment with immobilized carboxypeptidase Y (CPY) at pH 8.5 and room temperature. The bound enzyme is removed by filtration and the filtrate used directly for the addition of the next amino acid. Peptides were grown on carboxymethyl-poly(ethylene glycol)-glycylmethionine (CM-PEG-Gly-Met). The use of this handle provides solubility for the growing chain and permits facile release of finished peptide using CNBr.[1] The advantages of a polymeric handle have been pointed out by Mutter et al., who used underivatized PEG in synthesis of peptides by extension of the amino terminus in organic solvents.[2] The preparation of chemically and optically pure H-Leu-Phe-Leu-OEt is illustrated below.

CPY is an exopeptidase from yeast with a very broad specificity.[3] The enzyme also has esterase activity. An important point for this study is that the pH optima for the peptidase and esterase activities are quite different. In preliminary studies, we demonstrated the absence of peptidase activity in the time required to deblock Z-Leu-Phe-OEt. Immobilization of the enzyme on CL-Sepharose does not appear to perturb the pH profiles of the enzyme.[5] It is also significant that a D-amino acid at the C terminus or the penultimate position prevents ester hydrolysis by CPY. This feature assures optical purity of the final product.

PEG (14 g, mol wt 6000-7000, MCB) and potassium *tert*-butoxide (10 g, Aldrich) were dissolved in *tert*-butyl alcohol (150 mL) by warming to 40 °C. Ethyl bromoacetate (5 mL) was added over a period of 10 min. After we stirred the solution for 2 h, the solvent was evaporated. The residue was dissolved in 100 mL of 1 N NaOH. After 2 h at room temperature, the pH of the mixture was adjusted to 2. The CM-PEG was extracted into $\mathrm{CHCl_3}$ (two 200-mL portions). The organic extract was washed with water and dried with anhydrous

Scheme I. Preparation of the Handle



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