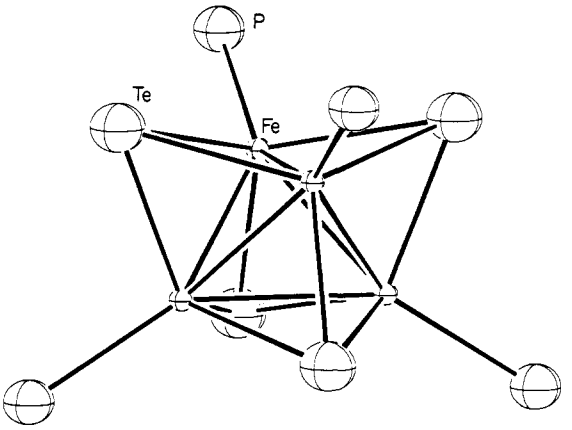

Figure 1. Drawing of the molecular structure of $[(Et_3P)FeTe]_4$. The large circles represent Te atoms, and the small circles Fe atoms. The ethyl groups on the phosphines are omitted for clarity. The molecule is tetrahedrally symmetric. Selected distances (Å): Fe–Fe, 2.623 (4); Fe–Te, 2.609 (1); Fe–P, 2.390 (6). Selected angles (deg): Fe–Fe–Fe, 60.00 (6); $(Fe–Fe–Te)_{small}$, 59.82 (5); $(Fe–Fe–Te)_{large}$, 109.25 (9), Fe–Fe–P, 144.74 (5); Fe–Te–Fe, 60.36 (6); Te–Fe–Te, 112.70 (5).

phosphine ligands bound to the inorganic core (important for the subsequent conversion to extended solids) and in having a lower average oxidation state at iron (2.00+ versus 2.25+). These differences result in the very symmetrical cubic structure of $(Et_3P)_4Fe_4Te_4$ and its shorter Fe–Fe distances (2.623 (4) Å versus 2.847, 2.818 (6), and 2.747 (2) Å in $Cs_7Fe_4Te_8$, $[Fe_4Te_4(SPh)_4]^{3-}$, and $[Fe_4Te_4(TePh)_4]^{3-}$, respectively). It is interesting that in the related compounds, $Fe_4E_4(CO)_{12}$ (E = S, Se)[15] (in which each Fe is in the 2.00+ oxidation state and bears three CO ligands), the Fe_4E_4 cores are only slightly distorted from ideal cubes. They also show substantially larger Fe–Fe distances (3.466 Å, E = S; 3.617 Å, E = Se) than in $(Et_3P)_4Fe_4Te_4$. Assuming that the Te analogue[17c] has a similar structure, it is clear that the additional eight two-electron donors have a dramatic effect on the Fe_4E_4 structure.

We find that heating $[(Et_3P)FeTe]_4$ releases the phosphine and polymerizes the $[FeTe]_4$ unit to form polycrystalline iron tellurides.[18] It is known[5] that stoichiometric FeTe disproportionates to give β-FeTe and ε-FeTe (Fe rich and Te rich, respectively); this is what we observe, powder X-ray diffraction showing both phases.

To summarize, we have found that $Fe(COT)_2$ reacts rapidly with Et_3PTe to give $[(Et_3P)FeTe]_4$. The structure of this cluster shows Fe–Te bonding and suggests Fe–Fe bonding as well. Thermolysis of the cluster gives extended solid iron tellurides; thus the cluster is an allowable chemical intermediate between the molecular reagents and the solid-state products. We are investigating how the properties of the cluster might also be considered intermediate between those of the molecules and of the solid.

Acknowledgment. We gratefully acknowledge P. Trevor for X-ray fluorescence measurements. We are also grateful for helpful discussions with B. Hessen.

Supplementary Material Available: Tables S1 of crystallographic data, S2 of positional and thermal parameters, and S3 of interatomic distances and angles for $(Et_3P)_4Fe_4Te_4$ (5 pages); Table S4 of observed and calculated structure factors for $(Et_3P)_4Fe_4Te_4$ (6 pages). Ordering information is given on any current masthead page.

(18) Pyrolysis of $[(Et_3P)FeTe]_4$: Differential scanning calorimetry (DSC) shows an endothermic reaction of this compound at approximately 193 °C. To determine the products of this process, a Pyrex tube was charged with $[(Et_3P)FeTe]_4$ (98 mg, 81 μmol), after which the tube was evacuated (0.1 Torr), sealed, and heated to 280 °C for 18 h. This gave a black solid (61 mg, 102% recovery of Fe and Te). Powder X-ray diffraction showed only β-FeTe and ε-FeTe.[5a]

Automated Synthesis of Peptide C-Terminal Aldehydes

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Peptide C-terminal aldehydes (PAs) are an important class of transition-state analogues, which have drawn considerable attention since their initial discovery as natural products.[1] PAs of various structures are potent inhibitors of the diverse enzymes which are implicated in a wide range of disease states.[2] We report here the development of an automated synthetic technique that dramatically facilitates the preparation of PAs. These peptide analogues represent formidable synthetic targets due to their inherent chemical lability and their multifarious functionalities, which often require orthogonal protection. As part of our program to develop potent selective inhibitors of enzymes, we desired a rapid and efficient general synthesis of PAs. The ready availability of these derivatives would allow for the rational investigation of the structure–activity relationships for peptide analogue based inhibitors of medically relevant enzymes.

The solid-phase method of synthesis has dramatically increased the accessibility of synthetic peptides and oligodeoxynucleotides. In particular, the extension of the solid-phase technique to allow for the automated synthesis of peptides and oligonucleotides has facilitated significant advancement in several areas of science and technology. We chose, therefore, to develop an automatable solid-phase method for the synthesis of PAs.

Of the several strategies for the synthesis of PAs,[3-5] we determined that one was suitable for adaptation to a solid-phase method.[6] This method relies on the protection of the aldehyde function as the stereochemically stable semicarbazone. This method involves the following general steps. The protected amino acid aldehyde semicarbazones are deprotected at the N-terminus and coupled with protected amino acids or protected peptides to give a protected peptide C-terminal semicarbazone. After the desired number of deprotection/coupling cycles are complete, the protected peptide semicarbazone is treated with aqueous acid/formaldehyde to regenerate the aldehyde and cleave it from the solid support. The resulting protected PA can then be deprotected if necessary. This general strategy has been used to prepare PAs in solution[5] and on a *soluble* support.[7] We report here a method that allows for the synthesis of PAs in a way which is fully compatible with conventional peptide synthesizers.

Several approaches were explored for the preparation of amino acid aldehyde semicarbazone resins. The most efficient approach found is shown in Scheme I. This method uses the solution synthesis of the complete semicarbazone carboxylic acid linker **4**. The synthesis of this linker began with the reaction of *tert*-butylcarbazate with carbonyldiimidazole in dimethylformamide (DMF) followed by treatment with *trans*-4-(aminomethyl)-cyclohexanecarboxylic acid benzyl ester[8] (which was prepared in

(1) Aoyagi, T.; Takeuchi, T.; Matsuzaki, A.; Kawamura, M.; Kondo, M.; Hamada, M.; Maeda, K.; Umezawa, H. *J. Antibiot* **1969**, *22*, 283.
(2) Aoyagi, T.; Umezawa, H. In *Proteases and Biological Control*; Reich, E., Rifkin, D. B., Shaw, E., Eds.; Cold Spring Harbor Press: Cold Spring Harbor, 1975; pp 429–454.
(3) Bajusz, S.; Sznell, E.; Bagdy, D.; Barabas, E.; Horvath, G.; Dioszegi, M.; Fittler, Z.; Szabo, G.; Juhasz, A.; Tomori, E.; Szilagyi, G. *J. Med. Chem.* **1990**, *33*, 1729–1735.
(4) Kawamura, K.; Kondo, S.; Maeda, K.; Umezawa, H. *Chem. Pharm. Bull.* **1969**, *17*, 1902.
(5) McConnell, R. M.; Barnes, G. E.; Hoyng, C. F.; Gunn, J. M. *J. Med. Chem.* **1990**, *33*, 86–93.
(6) Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081.
(7) Galpin, I. J.; Beynon, R. J.; Chetland, J.; Mulligan, M. T.; Place, G. A. *Pept.: Struct. Funct., Proc. Am. Pept. Symp., 9th* **1985**, 799–802.

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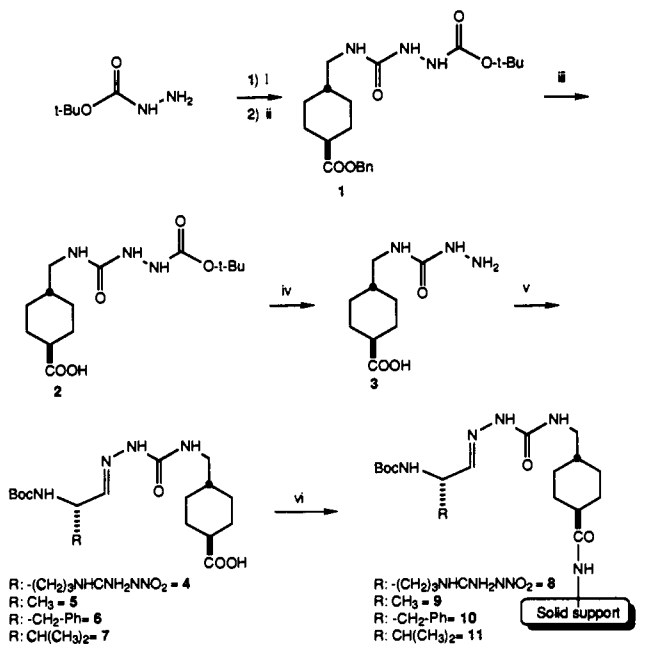
Scheme I[a]



[a] (i) Carbonyldiimidazole/DMF; (ii) *trans*-4-(aminomethyl)cyclohexanecarboxylic acid benzyl ester/triethylamine; (iii) H_2/Pd; (iv) trifluoroacetic acid/0 °C; (v) Boc amino acid aldehyde/NaOAc reflux in ethanol; (vi) MBHA resin/(benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate.

Table I[a,b]

Boc-(D)Leu-Pro-argininal	Boc-(D)Phe-Glu-argininal
Boc-(D)Leu-Ser-argininal	Boc-Ala-Ala-Pro-alaninal
Boc-Asn-Leu-Thr-argininal	Boc-Ala-Ala-Pro-valinal
Boc-Leu-Thr-argininal	Boc-Ala-Ala-Pro-phenylalaninal

[a] The hydroxyl group in the side chains of Boc-Ser-OH, Boc-Thr-OH, and Boc-Tyr-OH was protected as the benzyl ether. The carboxylate in the side chain of Boc-Glu-OH was protected as the benzyl ester. [b] Reference 14.

98% yield from the corresponding acid).[9] The product of this reaction, **1** was hydrogenated, to give crystalline **2** in 75% overall yield. This product was then treated with trifluoroacetic acid (TFA), to give crystalline **3**, in 95% yield. This material was allowed to react with α-Boc-N^g-L-argininal[10] and base, to give pure **4** in 75% yield. Coupling of **4** to the commercially available MBHA resin[11] gave the insoluble support **8**, with a coupling efficiency of 99.9%.[12] This material had all of the physical and chemical properties required for the automated synthesis of PAs. In a similar manner derivatives **5**–**7** gave supports **9** through **10**, which are useful for the preparation of the corresponding peptide aldehydes. Table I shows a few examples of peptide aldehydes prepared via this technique. We found that amino acids containing other functionalities can readily be incorporated into peptide aldehydes. The use of benzyl ether protection for the hydroxyl group and benzyl ester for the carboxyl group allows for the incorporation of Thr, Ser, Tyr, Asp, and Glu into peptide aldehydes, via this technique. A final deprotection by catalytic hydrogenation gives the fully deprotected peptide aldehyde.

Standard automated Boc protocols[13] and resin **5** can be used to prepare protected PA semicarbazones on supports (with coupling yields that are greater than 98%) and then cleaved with dilute aqueous acid/formaldehyde, to give the protected free PAs in good yield. We have found that PA arginals containing various hydrogen/Pd labile protecting groups (e.g., N^g-nitro, benzyl ether, and benzyl esters) can be deprotected, in a single step, to give the unprotected PAs after purification by reverse-phase HPLC.[14]

In conclusion, we have developed a highly efficient method for the automated synthesis of peptide aldehydes. This method relies on the crystalline heterobifunctional linkers **4**–**7**, which are prepared in greater than 50% overall yield without chromatographic purification. This preformed linker may be attached to resins, such as the 1% cross-linked MBHA polystyrene resin, to give insoluble supports (**8**–**11**) which are suitable for use in conventional peptide synthesizers. We have used this method to prepare over 100 different peptide aldehydes. The investigation of the scope and limitations of this method, and the biological properties of the new synthetic PAs will be the subject of future reports.

Supplementary Material Available: Experimental details for the preparation of **1**–**11** and a general procedure for the synthesis of peptide aldehydes using the novel supports **8**–**11** (10 pages). Ordering information is given on any current masthead page.

(8) To the best of our knowledge, this method for preparing semicarbazides has not previously been reported. It has been observed that amino carbonyl imidazolides decompose at room temperature to give isocyanates; see: Staab, H. A.; Benz, W. *Justus Liebigs Ann. Chem.* **1961**, *648*, 72.
(9) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Robert E. Krieger Publishing Company: Malabar, FL, 1986; Vol. 2, p 942.
(10) We found that this material was best prepared by the method of Fehrentz and Castro; see: Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676. Goel, O. P.; Krolls, U.; Stier, M.; Kesten, S. *Org. Synth.* **1988**, *67*, 69–75.
(11) Pietta, P. G.; Marshall, G. R. *J. Chem. Soc. D* **1970**, 650–651.
(12) Coupling yields and loading of the resin were determined via the method of Kaiser et al.: Kaiser et al. *Anal. Biochem.* **1970**, *34*, 595.
(13) Barany, G.; Merrifield, R. B. Solid-Phase Peptide Synthesis. In *The Peptides*; Academic Press, Inc.: New York, **1980**; Vol. 2, pp 1–284.
(14) All new compounds were characterized by NMR, elemental analysis or mass spectra.

Cross Relaxation without TOCSY: Transverse Rotating-Frame Overhauser Effect Spectroscopy

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Rotating-frame Overhauser effect spectroscopy (ROESY or CAMELSPIN)[1,2] NMR techniques measure transverse nuclear Overhauser enhancements. Transverse magnetization is "locked" by a constant-phase radiofrequency (rf) field about the *y*-axis of the rotating frame, and cross relaxation can occur.[3] Studies of peptides,[4] proteins,[5] nuleic acids,[6-8] and oligosaccharides[9] have used ROESY. The ROE is indispensable when the NOE is weak ($\omega_0\tau_c \approx 1.12$).

An annoying problem in ROESY is *coherent* magnetization transfer by TOCSY[10] that occurs by *J*-coupling pathways[11-14] and is unrelated to cross relaxation. It seemed like an inescapable

* Author to whom correspondence should be addressed.
(1) Bothner-By, A. A.; Stephens, R. L.; Lee, J.-M.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811.
(2) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207.
(3) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect In Structural And Conformational Analysis*; VCH Publishers, Inc.: New York, 1989.
(4) Davis, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 3471.
(5) Matsoukas, J. M.; Bigam, G.; Zhou, N.; Moore, G. J. *Peptides* **1990**, *11*, 359.
(6) Loschner, T.; Engls, J. W. *Nucleic Acids Res.* **1990**, *18*, 5083.
(7) Andre, F.; Demassier, V.; Bloch, G.; Neumann, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 6784.
(8) Bauer, C. J.; Frenkiel, T. A.; Lane, A. N. *J. Magn. Reson.* **1990**, *87*, 144.
(9) Leeflang, B. R.; Bouwstra, J. B.; Kerekgyarto, J.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1990**, *208*, 117.
(10) Braunschweiler, L.; Ernst, R. R. *J. Magn. Reson.* **1983**, *53*, 521.
(11) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 2820.
(12) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 7197.
(13) Neuhaus, D.; Keeler, J. *J. Magn. Reson.* **1986**, *68*, 568.
(14) Bax, A. *J. Magn. Reson.* **1988**, *77*, 134.

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