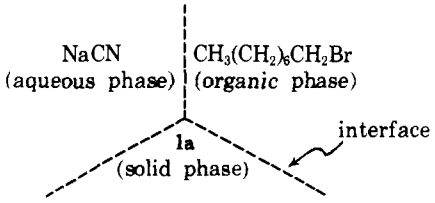
Table I. Cyanide Displacement on 1-Bromo- and 1-Chlorooctane[a]

1-Halooctane	Catalyst	Time, hr	1-Cyanooctane,[b] %
1-Bromooctane		100	0
	1a	4	92
	1b	4	0
1-Chlorooctane		100	0
	1a	24	50[7]
	1b	24	0

[a] The temperature for all reactions was 110°. Product mixtures were analyzed by GLPC. [b] Yields are based on 1-halooctane.

Scheme I



of 1-cyanooctane plus 8% unreacted 1-bromooctane.[6] When the reaction was carried out using unfunctionalized polystyrene (**1b**) in place of **1a** as the catalyst or in the absence of any polymer matrix, 100% of the alkyl bromide remained unchanged. Similar results were obtained with 1-chlorooctane as the substrate (Table I).

In order to ensure that these displacement reactions were, in fact, being catalyzed by the solid phase, the reaction of cyanide ion with 1-bromooctane was repeated but stopped after 0.5 hr so that only a 43% yield of 1-cyanooctane was obtained. A portion of the aqueous phase (0.4 ml) and the organic phase (0.6 ml) was transferred to a second vial, which, along with the original vial, was heated for an additional 2 hr period at 110°. Analysis of the product mixture in the vial containing **1a** showed a 90% yield of 1-cyanooctane. In the absence of **1a**, the yield of 1-cyanooctane remained at 43%.

We have also found that **1a** catalyzes the generation of dichlorocarbene from chloroform solutions placed over aqueous sodium hydroxide. Thus, when α-methylstyrene (0.165 g, 1.4 mmol) dissolved in 2 ml of chloroform was added to 2 ml of a 50% aqueous sodium hydroxide solution containing **1a** (0.1 g) and the mixture was heated for 40 hr at 50°, 1,1-dichloro-2-methyl-2-phenylcyclopropane was produced in 99% yield.[6,8,9] Without **1a** present, a similar reaction afforded less than 0.1% of the dichlorocyclopropane derivative.[10]

A technique recently developed for accelerating aqueous phase-organic phase reactions (phase-transfer catalysis) has proven particularly useful in several synthetic transformations.[11] One practical limitation to this method, however, is that many phase-transfer agents promote stable emulsions which render work-up difficult. The major advantage that triphase catalysis has over phase-transfer catalysis is that the catalyst can be removed from the product mixture by simple filtration.

The detailed nature of the catalytic processes reported herein needs further clarification and we therefore wish to defer mechanistic comments until a later time. Work in progress is aimed at (1) defining resin activity in terms of concentration of ionic groups along the polymer backbone, type of ionic group employed, and degree of swelling of the polymer lattice, and (2) exploring the synthetic utility of this technique.

References and Notes

(1) Supported by the National Science Foundation, Grant No. MPS74-23925.

(2) Anion-exchange resins have previously been found to catalyze certain cyanide displacement reactions: H. B. Copelin and G. B. Crane, U.S. Patent 2779781 (1957). Although such systems bear a resemblance to the triphase catalyzed process reported herein, the fact that these reactions proceed at a significant rate in the absence of suitable resins makes their relationship to triphase catalysis questionable.

(3) Chloromethylated polystyrene was purchased from Bio-Rad Laboratories and was used without further purification.

(4) S. L. Regen and D. P. Lee, *J. Am. Chem. Soc.*, **96**, 294 (1974).

(5) For this system, the polystyrene beads reside at the interface of the organic and aqueous phases.

(6) An internal standard (*n*-dodecane) was added to the mixture prior to GLPC analysis. A 6-ft column packed with 5% Carbowax 20M on 80–100 mesh Chromasorb P was employed.

(7) The yield remained unchanged after heating for an additional 24 hr. When the aqueous phase was replaced by a fresh cyanide solution and the reaction mixture heated to 110° for 24 hr, the yield of 1-cyanooctane increased to 64%. It is presumed that the competing hydrolysis of sodium cyanide to sodium formate becomes significant with these longer reaction times.

(8) The yield reported is based on the starting α-methylstyrene.

(9) We are grateful to Professor Michael A. McKinney for his gift of authentic 1,1-dichloro-2-methyl-2-phenylcyclopropane.

(10) Analysis showed that >99% of the starting olefin remained unchanged.

(11) J. Dockx, *Synthesis*, 441 (1973); E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **13**, 170 (1974); E. V. Dehmlow, *Chem. Technol.*, 210 (1975).

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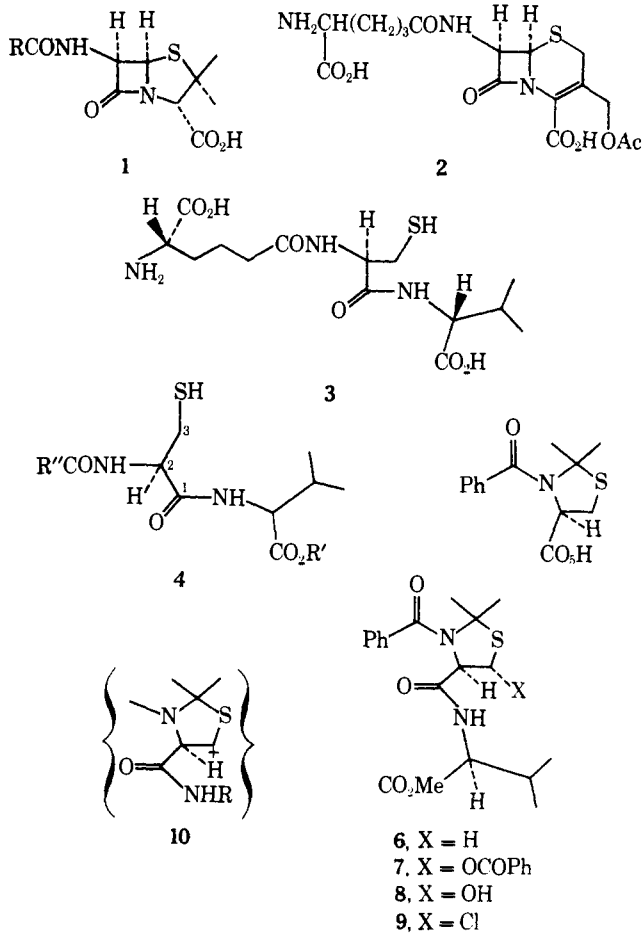
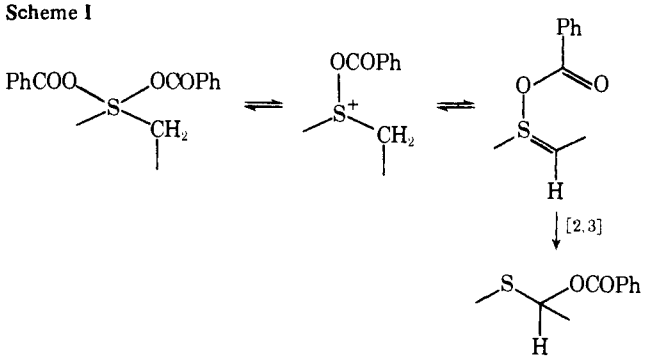
Stereospecific Conversion of Peptides into β-Lactams

Sir:

Evidence has accumulated which supports the hypothesis that the β-lactam antibiotics, penicillin (**1**) and cephalosporin C (**2**), are derived from the so-called Arnstein tripeptide (**3**).[1] In order to achieve this conversion in vitro we have investigated the oxidative chemistry of the cysteinylvaline

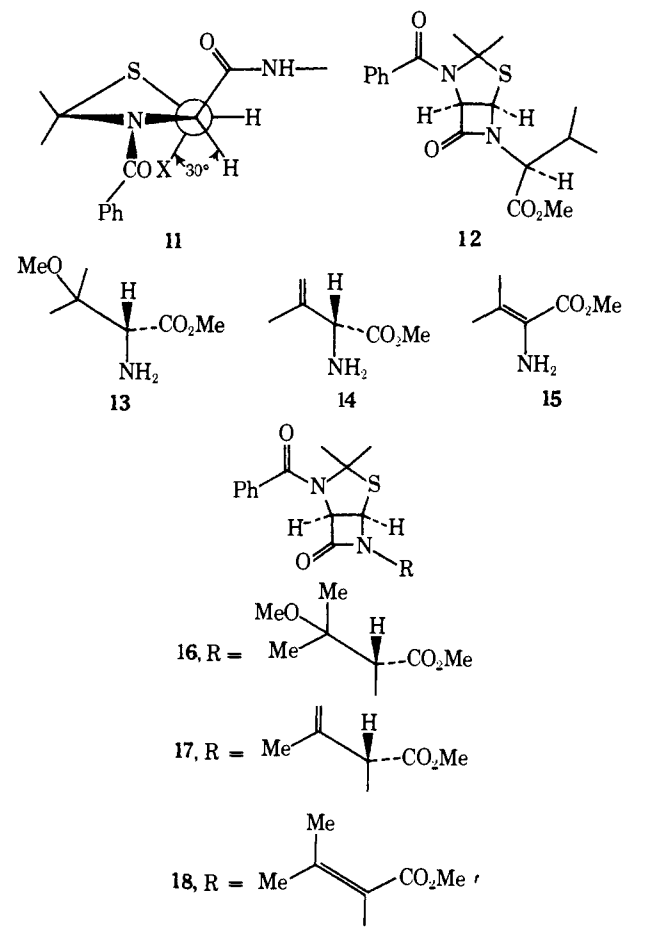


Scheme I



peptide **4** and its derivatives. Since the required oxidation at C3 of the cysteine moiety of **4** necessitated stereospecific removal of one of the C3 hydrogens, rotation around the C2-C3 bond was frozen by use of the known thiazolidine (**5**).[2] Peptide bond formation between **5** and L-valine methyl ester mediated by the reagent EEDQ[3] gave the dipeptide **6**, 58%,[4] mp 147-148°, $[\alpha]^{25}D$ −139.6° (*c* 1, CH_2Cl_2). Stereospecific functionalization at C3 of the cysteine residue in **6** was readily achieved by refluxing with benzoyl peroxide (4 equiv) in CCl_4 (1.5 hr) to provide benzoate **7**, 55%, mp 193-194°, $[\alpha]^{25}D$ 125.3° (*c* 1, CH_2Cl_2); NMR δ 5.1 (1 H, s), 6.55 (1 H, s) (C2, C3 hydrogens, J = 0 Hz). The mechanism of this facile and stereospecific functionalization probably involves the sequence of Scheme I, i.e., an initial formation of sulfurane, followed by a [2,3]-sigmatropic rearrangement of the intermediate ylide.[5] The clean stereochemistry results from shielding of the upper face of the thiazolidine ring by the bulky valine residue. Hydrolysis of the benzoate **7** was achieved in aqueous neutral dioxane at 125° (4 hr) providing the unstable alcohol **8**, 56%: mp 35° dec; NMR δ 4.82 (1 H, s), 5.45 (1 H, s) (C2, C3 hydrogens, J = 0 Hz). Mesylation of **8** with methanesulfonyl chloride and pyridine (CH_2Cl_2, 0°) gave directly the chloride **9**, 62%: mp 136-137.5°, $[\alpha]^{25}D$ −265° (*c* 1, CH_2Cl_2); NMR δ 5.2 (1 H, s), 5.98 (1 H, s) (C2, C3 hydrogens, J = 0 Hz). However this chloride **9** was more easily obtained (95%) by direct treatment of benzoate **7** with hydrogen chloride gas (CH_2Cl_2, 0°). These facile exchange processes which proceed with retention of configuration at C3 of the cysteine moiety presumably involve the cation **10**.[6] The remarkable resistance toward β-elimination in this series requires comment. The coupling constant between hydrogens at C2 and C3 of derivatives **7**–**9** is 0 Hz. This suggests conformation **11** for all of these compounds, in which the C3-X and C2-H bonds are not coplanar and hence resist concerted eliminations. Ring closure of chloride **9** was readily achieved by treatment with NaH (1.1 equiv) in dichloromethane containing tetra-*N*-butylammonium iodide (0.1 equiv)[7] at 25°, to yield the β-lactam **12** as an oil (81%): $[\alpha]^{25}D$ −304.5° (*c* 1, CH_2Cl_2), λ_{max} 1765, 1740 1655 cm^{-1}; NMR δ 5.5 (2 H, AB quartet J = 5.5 Hz) (C2, C3 hydrogens).

By starting this same sequence with the D-amino acid esters **13** and **14**[8] and also the dehydrovaline ester **15**, it was possible to obtain all three β-lactam containing peptides **16**, **17**, and **18**. The conversion of these latter substances into the naturally occurring β-lactam antibiotics is in progress.[9]



Acknowledgments. We thank the National Science Foundation, the National Institutes of Health, Eli Lilly and Co., Hofmann La Roche, and Merck & Co. for financial support. We also acknowledge helpful discussions with the research staff of Eli Lilly & Co.

References and Notes

(1) (a) E. P. Abraham, "Biosynthesis and Enzymic Hydrolysis of Penicillins and Cephalosporins", University of Tokyo Press, Tokyo, 1974. (b) Recently the incorporation of radiolabeled tripeptide **3** into penicillin N was reported, P. A. Fawcett, J. J. Usher, and E. P. Abraham, "Proceedings of Second International Symposium on Genetics of Industrial Microorganisms", Aug 1974, Sheffield, England, K. D. MacDonald, Ed., Academic Press, New York, N.Y., 1975.
(2) J. C. Sheehan and D-D. H. Yang, *J. Am. Chem. Soc.*, **80**, 1158 (1958). The classic synthesis of cephalosporin C by Woodward and his collaborators involves a similar activation at C3 of cysteine. However, that sequence is not a peptide to β-lactam conversion, as described here. Cf. R. B. Woodward, *Science*, **153**, 487 (1966).
(3) B. Belleau and G. Malek, *J. Am. Chem. Soc.*, **90**, 1651 (1968).
(4) Reported yields refer to *isolated*, chromatographically pure substances. All new compounds have satisfactory combustion analyses and/or mass spectra.
(5) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 538 (1968).
(6) Participation in **10** of the neighboring amide linkage is possible and would also contribute to the high stereospecificity of these reactions.
(7) This is an example of phase transfer catalysis between a solid and liquid phase.
(8) Synthesized in these laboratories by J. E. Baldwin and S. B. Haber, unpublished results.
(9) Professor Y. Kishi has informed us that he has made β-lactams from 2-substituted cysteinyl derivatives by similar base catalyzed closures, personal communication.
(10) Chapin Fellow, 1974–1975.

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Protonation of Phosphorus Trihalides

Sir:

While protonation of phosphorus in $PR_{3-n}(OR')_n$ systems is readily accomplished in strong acid,[1-5] the evidence for the formation of HPX_3^+ cations is limited to a tentative