50.32 MHz)[24] 13.68 (q), 18.78 (t), 22.61 (t), 23.91 (t), 25.37 (t), 28.33 (t), 30.66 (t), 32.02 (t), 37.74 (t), 41.53 (t), 54.53 (d), 57.93 (s), 211.23 (s), 219.72 (s); exact mass calcd for $C_{14}H_{22}O_2$ 222.1624, found 222.1604.

Equilibration of 12a and 12b. A mixture of spiro diones **12b** and **12a** (10:1, 131 mg) was dissolved in 5 mL of THF and 10 drops of 10% HCl was added. After 48 h at 25 °C, the mixture was diluted with ether and extracted with saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated; purification via elution through a short column of silica gel with 5% ethyl acetate in hexane afforded 110 mg (77%) of **12b** and **12a** (2.3:1 as determined by NMR integration).

Preparation of 12a from 6-*n*-Butyl-7-acetoxyspiro[4.5]-decan-1-one (4). Keto acetate **4**[21] (5.3 mg) was dissolved in 1 mL of methanol containing 10 mg of potassium carbonate. After stirring for 5 h at 25 °C, the saponification was judged to be complete by TLC. The solvent was removed under reduced pressure and the residue purified by passage through a short column of silica gel eluting with 10% ethyl acetate in hexane to yield the corresponding keto alcohol: IR (CCl_4) 3650-3200, 2940 (s), 2860, 1725 (s), 1450, 1155, 900 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 0.8 (t, J = 7 Hz, 3 H), 1.2-1.5 (m, 11 H), 1.54-2.2 (m, 8 H), 2.3 (m, 1 H), 3.3 (m, 1 H).

The above keto alcohol was treated with 7.5 mg of pyridinium chlorochromate and 7.5 mg of anhydrous sodium acetate in 1 mL of dry methylene chloride. After 1 h the reaction mixture was diluted with ether, filtered, and washed with 10% HCl. The organic layer was dried ($MgSO_4$) and evaporated; filtration through a plug of silica gel afforded **12a** identical in all respects (IR, NMR, and TLC) with that prepared from **11**.

Reduction/Oxidation of 12a. Dione **12a** (44 mg, 0.2 mmol) was added to a suspension of 20 mg (0.5 mmol) of $LiAlH_4$ in 2 mL of ether. After 1 h at 25 °C, the excess hydride was destroyed by the addition of $Na_2SO_4 \cdot 10H_2O$. The resulting mixture of diols (four compounds by TLC) was filtered, evaporated, and combined with 60 mg of pyridinium chlorochromate and 60 mg of anhydrous sodium acetate in 2 mL of dry methylene chloride. After 1 h at 25 °C, workup and purification as in the previous experiment gave 16 mg (36%) of a single product whose 250-MHz NMR was identical with authentic **12a**.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant No. 22807. In addition, we thank S. T. Bella of the Rockefeller University for microanalyses and Dr. G. Furst and T. Terwilliger of the University of Pennsylvania spectroscopic facilities for aid in obtaining the high-field NMR and MS spectral data, respectively.

Registry No. **2**, 40709-29-3; **4**, 80090-50-2; **4** (keto alcohol), 88643-14-5; **5a**, 88564-18-5; **5b**, 88643-12-3; **7**, 88564-19-6; **8**, 56459-18-8; **11**, 88564-20-9; **12a**, 88564-21-0; **12b**, 88564-22-1; **13**, 88564-23-2; **15a**, 88564-24-3; **15b**, 88643-13-4; $Cl(CH_2)_3C{\equiv}CH$, 14267-92-6; $Cl(CH_2)_3C{\equiv}CSiMe_3$, 77113-48-5; $I(CH_2)_3C{\equiv}CSiMe_3$, 35761-91-2.

Acid-Stable, Solvolytically Deblocked Amino-Protecting-Groups Applications of the 1,3-Dibromo-2-methyl-2-propyloxycarbonyl (DB-*t*-Boc) Group

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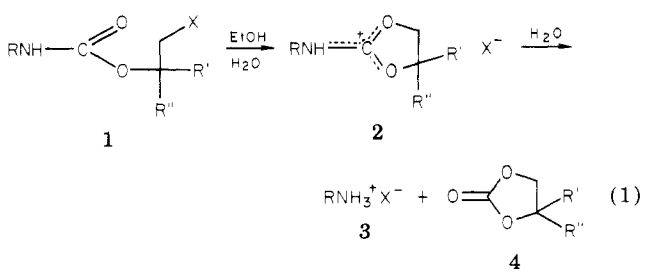
The effects of structure on the ease of solvolytic deblocking of an array of α-halo-*tert*-alkyl carbamates **1** have been studied. The corresponding thiolcarbamates were shown to undergo isomerization and other reactions due to participation of the sulfur atom. 1,1,1,3,3,3-Hexachloro-2-(bromomethyl)-2-propyl carbamates were relatively unreactive toward solvolytic deblocking. On the other hand the 1,3-dibromo-2-methyl-2-propyloxycarbonyl group (DB-*t*-Boc) was easily deblocked by warming in ethanol or methanol and therefore recommended as an acid-stable, solvolytically deblocked amino-protecting group. The key chloroformate **22** was readily synthesized from methallyl chloride by conversion to methallyl bromide followed by reaction with hypobromous acid to give the bromohydrin and treatment of the latter with phosgene. Practical use of the DB-*t*-Boc group was demonstrated by synthesis of the dipeptide phenylalanylleucine.

Only a limited number of amino-protecting groups are known that are deblocked simply by dissolving or warming in an appropriate neutral solvent.[1,2] The first such group reported was the α-bromo-*tert*-butyloxycarbonyl (α-Br-*t*-Boc) group, as in urethane **1** (R = C_6H_5, R′ = R″ = Me, X = Br) which undergoes self cleavage upon warming in methanol or ethanol (eq 1). Application of this protective group in peptide synthesis has been reported by Ohnishi, Sugano, and Miyoshi.[3] For such solvent-sensitive protective groups to be maximally useful, the solvent sensitivity should be narrowly limited so that protection and coupling reactions can be readily carried out in appropriate solvents without fear of premature deblocking. In the case of the α-Br-*t*-Boc system self cleavage does not occur in nonpolar solvents such as chloroform, methylene dichloride, or benzene. In dry dimethyl sulfoxide (Me_2SO) reaction is relatively slow, although self cleavage takes place readily in wet Me_2SO or wet acetonitrile. A deficiency of the α-Br-*t*-Boc group is its moderate sensitivity toward acidic reagents. If a group of this type were far more stable toward acidic conditions, it would lend itself to selective utility[4] in the presence of *t*-Boc and/or other



1 2 3 4 (1)

(1) Carpino, L. A. *Acc. Chem. Res.* **1973**, *6*, 191.
(2) Carpino, L. A.; Parameswaran, K. N.; Kirkley, R. K.; Spiewak, J. W.; Schmitz, E. *J. Org. Chem.* **1970**, *35*, 3291.
(3) Ohnishi, T.; Sugano, H.; Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2603.
(4) For a recent survey regarding the selective deprotection of amino-protecting groups, see: Fauchere, J. L.; Schwyzer, R. "The Peptides"; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1981; Vol. 3, Chapter 5, p 203.

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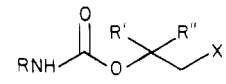
Table I. Solvolysis[a] of 1 in CD_3OD/D_2O ($t_{1/2}$, h)



1

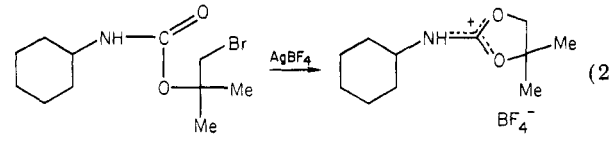
R	R′	R″	X	CD_3OD	CD_3OD/5% D_2O	CD_3OD/10% D_2O
C_6H_5	Me	Me	Br	19	11	9
c-C_6H_{11} [b]	Me	Me	Br	41		6.2
C_6H_5	Me	Me	OTs		1.5	
C_6H_5	Me	Et	Br	10.5	4.3	3.8
p-ClC_6H_4	Me	Et	Br	22.7	7.6	7.3
c-C_6H_{11}	Me	Et	Br	31	11.2	7.4
C_6H_5	Me	Et	OTs		0.4	
C_6H_5	Me	*i*-Pr	Br	6.0	2.8	2.6
p-ClC_6H_4	Me	*i*-Pr	Br	11.1	6.2	5.9
c-C_6H_{11}	Me	*i*-Pr	Br		11.7	
C_6H_5	Et	Et	Br	2.9	1.3	0.9
p-ClC_6H_4	Et	Et	Br	6.8	4.2	2.2
c-C_6H_{11}	Et	Et	Br		7.9	
C_6H_5	R′ = R″ = 		Br		24	

[a] All determinations carried out in NMR tubes at 37 °C by integration of methylene peak of cyclic carbonate; $t_{1/2}$ refers to rate of formation of this product. [b] Obtained in the usual way, mp 71 °C (Skelly B). A polymorphic modification, mp 84 °C, had been obtained previously by Ritter (see ref 5).

acid-sensitive protecting groups.

In the present work we have investigated two approaches leading to the possible development of practical protecting groups of this type. One approach involved examination of the thiol analogues of previously studied derivatives of ordinary alcohols. A second involved taking further advantage of the acid-stabilizing action of additional halogen substitution, which was noted in early work with the α-Br-*t*-Boc function.

A long-term goal of this work was to find a system that is at the same time more stable toward acids but more reactive toward self-cleavage than the α-Br-*t*-Boc group. To this end we first made a general study of some of the factors that affect the speed of the self-cleavage process, especially (a) the nature of the amine moiety, (b) the leaving group, and (c) the bulkiness of the *gem*-dialkyl substituents. As expected, aniline derivatives (e.g., 1; R = C_6H_5, R′ = R″ = Me, X = Br) undergo the self-cleavage more readily than the corresponding *p*-chloroaniline derivatives (see Table I). Reactions were followed by NMR in deuterated methanol to which varying amounts of D_2O were added. Integration of the methylene peaks for 1 and 4 allowed determination of the rate of disappearance and formation of substrate and product, respectively. In these cases spectral examination gave no evidence for formation of an intermediate such as 2. For the *N*-cyclohexyl derivatives (e.g., 1, R = C_6H_{11}, R′ = R″ = Me, X = Br), again as expected, the urethane disappeared more rapidly than the *N*-phenyl analogue[5] although the final products, amine salt 3 and cyclic carbonate 4, were formed more slowly because of the buildup of significant concentrations of intermediate 2. Formation and decay of 2 in the case of various *N*-cyclohexyl systems was readily followed by NMR techniques. The proposed intermediate could in fact be isolated as a stable tetrafluoroborate salt 6 by application of the method of Brugger[6] (eq 2) who reported a

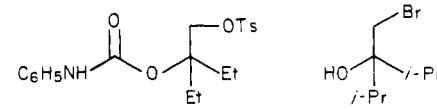


5 6 (2)

similar reaction for the system analogous to 5 but lacking the *gem*-dimethyl groups. Both tetrafluoroborates exhibited characteristic infrared absorption near 1705 cm^{-1} as well as the expected NMR spectrum.

The effect of the leaving group on the solvolytic reactivity of 1 has been reported previously with the expected order being followed (Cl < Br < I). We have now obtained a model tosylate (1, R = C_6H_5, R′ = R″ = Me, X = OTs) and find it to be more reactive than the corresponding bromide by a factor of about 7.

Finally, with regard to the size of the *gem*-dialkyl substituents, it is to be expected that the bulkier the alkyl function the faster the self-cleavage process. Without any such alkyl substitution, no reaction is observed under mild conditions.[7] Changing one or both of the methyl groups to ethyl or isopropyl substituents effects a gradual increase in reactivity. As examples, in the case of 1 (R = C_6H_5, X = Br) the half-lives for solvolysis at 37 °C in CD_3OD–D_2O (90:10) for 1 (R′ = R″ = Me; R′ = Me, R″ = Et; R′ = Me, R″ = *i*-Pr; R′ = R″ = Et) are 9, 3.8, 2.6, and 0.9 h. Tosylate 7 was so sensitive to conversion to aniline that it proved



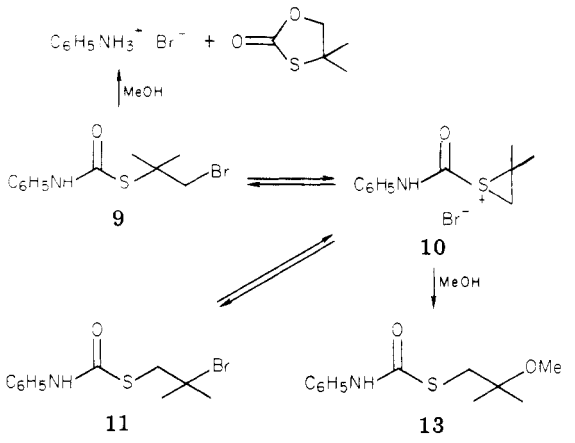
7 8

(5) Preliminary experiments were carried out by Dr. Helmut Ritter at the Organisch-Chemisches Institut, Universität Mainz, who determined that in deuterated methanol at 37 °C the rate of disappearance of starting material followed the order R = c-C_6H_{11} > C_6H_5 > *p*-ClC_6H_4. As described in the present work, more recent studies have revealed the buildup of a stable intermediate in the *N*-cyclohexyl case.

(6) Brugger, M. Dissertation, ETH, Zurich, Switzerland, 1965; Houben-Weyl, Vol. 15/1, p. 101.

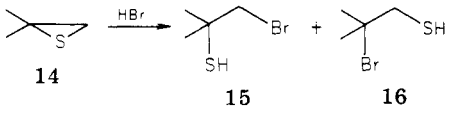
(7) See ref 1, 2, and: (a) Scott, F. L.; Glick, R. E.; Winstein, S. *Experientia* **1957**, *13*, 183. (b) Grimshaw, J. *J. Chem. Soc.* **1965**, 7136. For discussion of the possible origin of the effect of *gem*-dialkyl substitution on cyclization reactions, see: (c) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701. (d) DeTar, D. F. *J. Am. Chem. Soc.* **1980**, *102*, 4505. (e) Galli, C.; Giovannelli, G.; Illuminati, G.; Mandolini, L. *J. Org. Chem.* **1979**, *44*, 1258.

Scheme I



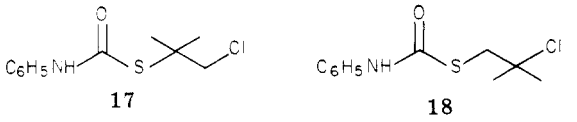
impossible to purify a sample for elemental analysis. Although we were able to synthesize alcohol **8**, its conversion to the corresponding chloroformate or urethane could not be achieved.

In view of the well-known difficulty of separating a cationic center from sulfur,[8] it was considered reasonable that carbamate **9** should be completely stable toward acids and yet still be subject to the self-cleavage process. In fact, due to the incursion of neighboring-group processes involving the sulfur atom, it proved impossible to synthesize a pure sample of **9** (Scheme I). Treatment of isobutylene sulfide **14** with hydrogen bromide gave a mixture of the



two thiols **15** and **16** in the ratio of 60:40. Following distillation the ratio changed to 22:78 and upon standing at room temperature additional isomerization of the tertiary to primary thiol occurred. Similar results have been recorded for the corresponding chloro thiols.[9] Upon treatment of the thiol mixture **15**/**16** (ratio 22:78) with phosgene, a mixture of the corresponding thiolchloroformates (ratio 12:88) was obtained. Treatment of this mixture with aniline gave only the urethane **11** derived from the primary thiol. The urethane **9** derived from the tertiary thiol may be more sterically hindered than **11**.

In the case of the corresponding chloro-substituted thiolcarbamates **17** and **18**, isomerization to the derivative



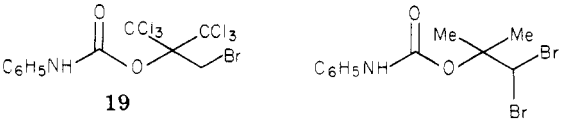
of the primary thiol **18** was less facile and a mixture was obtained containing, according to NMR analysis, 88% **17** and 12% **18**. This mixture exhibited a melting point of 82–84 °C, but when the melt was heated further it suddenly solidified and remelted at 122–125 °C following complete conversion to isomer **18** (mp 126 °C). These structural assignments are based on the expected NMR chemical shift positions of the methylene group when attached to the chloro or bromo substituent on the one hand or the sulfur atom on the other.

(8) Compare: Carpino, L. A.; Terry, P. H.; Crowley, P. J. *J. Org. Chem.* **1961**, *26*, 4336.
(9) Schwartz, N. V. *J. Org. Chem.* **1968**, *33*, 2895.

In spite of the fact that only the carbamate **11** derived from the primary bromo thiol **16** could be isolated, it was thought that if the two isomers were in equilibrium in a solvent such as methanol, the self-cleavage process might well proceed to completion via continuous regeneration of **9** (Scheme I). When a sample of **11** was refluxed in wet methanol for 14 h, 16% conversion to aniline hydrobromide occurred. Even after the solution had been refluxed for 40 h only 16% of the aniline salt could be recovered. NMR examination of the solution after a long reflux in methanol showed that all of the original urethane had been used up. Although soluble products were not isolated, from the NMR data it appeared that the methoxy derivative **13** had been formed. This suggests rapid irreversible methanolysis via sulfonium ion **10** in competition with limited formation of **9** followed by its self-cleavage to give aniline hydrobromide.

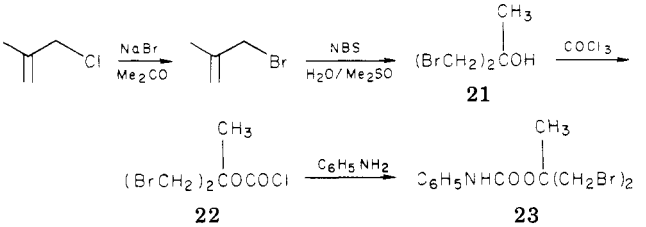
The mixture of the corresponding chloro analogues **17** and **18** upon heating in deuterated methanol at 60 °C gave no aniline hydrochloride although NMR examination showed that both urethanes were consumed in the process. Previously[2] it had been noted that the oxygen analogue of **17** gave 16% aniline hydrochloride after refluxing in ethanol for 1 h. The isomeric oxygen analogue of **18** gave no aniline hydrochloride under the same conditions. Although interesting in themselves, these competing side reactions made it clear that the solvolysis of bromo or chloro thiolcarbamates could probably not be developed into useful systems for amino protection.

The second approach for developing acid-stable systems still subject to solvolytic deblocking involved taking further advantage of the trend previously established with the α-Br-*t*-Boc group in which the dipolar effect of the halogen substituent enhances the acid stability. Perhalo substitution was examined in the case of the model bis(trichloromethyl) urethane **19**, which is exceptionally stable



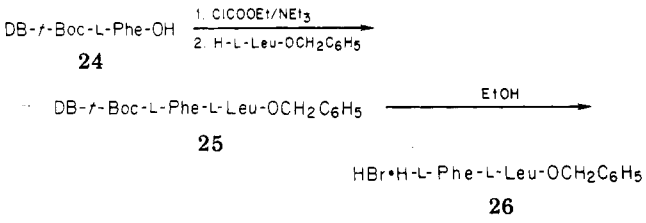
toward acidic reagents. Self-cleavage of **19** in 95% ethanol at reflux for 18 h gave only 40% aniline hydrobromide. This lowered reactivity is attributed to the dipolar effect of the carbon–chlorine bonds, which may destabilize the transition state leading to intermediate **2**. Any expected increase in reactivity due to the increased bulk of the trichloromelthyl vs. the simple methyl substituents must be swamped by this effect. Having previously[2] noted the high acid stability of the *gem*-dibromo urethane **20**, we have now synthesized the isomeric model urethane **23** and found its properties to be ideal for the purpose at hand. Key intermediate alcohol **21** and the corresponding chloroformate **22** were easily synthesized on a large scale from readily available methallyl chloride (Scheme II).

Scheme II



HCl–$MeNO_2$, or HCl–HOAc for at least 24 h. In HBr–$MeNO_2$ for 5 h, no cleavage occurred as shown by quantitative recovery of the carbamate although in HBr–HOAc conversion to aniline hydrobromide took place after several hours. Self-cleavage occurred in CD_3OD–D_2O (95:5) in an NMR tube at 37 °C with a half-life of 4.8 h. The α,α'-dibromo-*tert*-butyloxycarbonyl group (DB-*t*-Boc) is thus significantly more reactive than the monobromo analogue ($t_{1/2}$ = 11 h); and in view of its facile deblocking, marked acid stability, and ease of synthesis of key intermediates, it promises to be of special synthetic utility. The deblocking reaction was conveniently carried out by heating to 50 °C overnight in ethanol, removing solvent, and adding ether to dissolve the cyclic carbonate **4** (R′ = Me, R″ = CH_2Br) and precipitate the desired amine hydrobromide.

In order to demonstrate in a preliminary way the utility of this new protective group, we report here its application to the synthesis of a model depeptide employing a complete three-stage cycle of protection, coupling, and deblocking. Acylation of L-phenylalanine by means of DB-*t*-BocCl gave the protected amino acid **24**, which was ob-



tained as an oil and therefore purified as the corresponding dicyclohexylamine salt.[10] From the salt the free acid was then regenerated[11] and coupled via the mixed anhydride method[3] with L-leucine benzyl ester to give the protected dipeptide **25**. Without purification **25** was warmed in 95% ethanol at 50 °C for 18–20 h or at reflux for 2 h to give the dipeptide hydrobromide **26**.

A racemization test was devised on the basis of the mixed anhydride coupling of DB-*t*-Boc-L-Phe-OH with L-leucine methyl ester, deblocking of the resulting protected dipeptide methyl ester, and subsequent benzoylation. The resulting diastereomeric benzoyl dipeptide esters were analyzed by HPLC techniques[12] on a silica gel column that showed 0.7–1.2% racemization. For the conditions chosen to effect the coupling reaction, this level of racemization was not unexpected.[13] A more refined study of coupling under racemization free conditions[14] as well as an examination of the utility of the DB-*t*-Boc group in more complex systems requiring selective removal of *t*-Boc and/or other acid-sensitive protective groups is underway.

(10) Compare: Klieger, E.; Schröder, E.; Gibian, J. *Liebigs Ann. Chem.* **1961**, *640*, 157.

(11) Regeneration of the protected acid was carried out by treatment of a suspension in ether with dilute hydrochloric acid at room temperature. When a solution of the dicyclohexylamine salt was dissolved in chloroform and treated with a saturated solution of gaseous HCl in THF with slight warming, 50–60% racemization occurred as shown by HPLC analysis of the coupling product obtained from L-leucine methyl ester by the mixed anhydride method.

(12) Carpino, L. A.; Cohen, B. J.; Stephens, K. *J. Am. Chem. Soc.*, submitted for publication.

(13) Compare: Anderson, G. W. "Proc. of the 1st American Peptide Symposium"; Lande, S., Weinstein, B., Ed.; Marcel Dekker: New York, 1970; p 255.

(14) For a thorough discussion of the racemization problem, see: Kemp, D. S. "The Peptides"; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979; Vol. 1, Chapter 7, p 317.

Table II. Solvolysis[a] of 1 (R = C_6H_5, X = Br) in Various Solvents ($t_{1/2}$, h)

R	R′	Me_2SO-d_6	Me_2SO-d_6/5% D_2O	CH_3CN	CH_3CN/20% H_2O
Me	Me	21	3.2	*b*	6.8
Me	Et	12.5	1.3	*b*	3.5
Et	Et	8.2			

[a] All determinations carried out in NMR tubes at 37 °C by integration of methylene peak of cyclic carbonate; $t_{1/2}$ refers to rate of formation of this product. [b] No reaction observed in this solvent.

Experimental Section[15]

General Method for the Preparation of Bromoalkyl Chloroformates. A solution of 3.25 g (0.032 mol) of phosgene in 15 mL of CH_2Cl_2 was cooled to −15 °C under a nitrogen atmosphere. There was then added a solution of 0.016 mol of the appropriate alcohol in 5 mL of CH_2Cl_2 followed by 1.44 g (0.018 mol) of pyridine in 15 mL of CH_2Cl_2. The solution was allowed to warm to room temperature and stirred overnight. Nitrogen was passed through the solution to remove excess phosgene, and the solution was washed successively with ice-cold water, ice-cold 5% $NaHCO_3$, and ice-cold water. After the solution was dried over $MgSO_4$, the solvent was removed by distillation from a water bath with the aid of a water aspirator, and except as noted otherwise, the residue was distilled in vacuo to give the chloroformate, which was examined spectroscopically (IR, NMR) and then used without further purification for conversion to the corresponding carbamate. Three chlorides were prepared: 1-bromo-2-methyl-2-butyl chloroformate [55%, bp 53 °C (0.1 mm)], 1-bromo-2,3-dimethyl-2-butyl chloroformate [62%, bp 34 °C (0.15 mm)], and 3-(bromomethyl)-3-pentyl chloroformate [20%, bp 54 °C dec (0.19 mm)].

General Method for Preparation of Carbamates. A solution of 25 mmol of the appropriate chloroformate in 100 mL of benzene was stirred at room temperature. To the solution was added dropwise over a 30-min period a solution of 50 mmol of the amine in 50 mL of benzene. After stirring for 1 h, the precipitated salt was filtered and washed with a small amount of benzene. The solvent was removed in vacuo (20 mm) at 45 °C from the combined filtrate and washings to leave the carbamate as an oily residue, which was recrystallized from Skelly B. Results are collected in Table III.

General Method for Carbamate Solvolysis. A solution of 0.125 mmol of the carbamate in 0.25 mL of the appropriate solvent was placed in an NMR tube. The tube was placed in the preheater of an NMR instrument at 37 °C and the spectra were taken periodically to monitor the rate of solvolysis. Results are collected in Tables I and II.

1-(Bromomethyl)-1-cyclohexyl Phenylcarbamate. The chloroformate [65%; IR (neat) 1775 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.40–2.55 (br m, 10, ring CH_2), 3.80 (s, 2, CH_2Br)] was obtained by placing the crude residue after removal of solvent in a freezer overnight and filtering from the precipitated alcohol. Attempted distillation gave only decomposition products. The crude chloroformate gave 81% of the carbamate: mp 118 °C; IR (KBr) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.53 (br s, 6, ring CH_2), 2.34 (br s, 4, ring CH_2), 3.98 (s, 2, CH_2Br), 6.75 (br s, 1, NH), 7.06–7.51 (m, 5, C_6H_5).

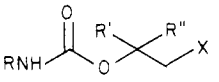
Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.85; H, 5.81; N, 4.49. Found: C, 54.00; H, 5.77; N, 4.34.

1-[(*p*-Tolylsulfonyl)oxy]-2-methyl-2-propyl Phenylcarbamate. A solution of 2.7 g of 2-methyl-1,2-propanediol[16] in

(15) Melting points and boiling points are uncorrected. Infrared spectra were determined on Perkin-Elmer 237B and 727 instruments and NMR spectra on Perkin-Elmer R-12 and Varian A-60 instruments with Me_4Si as internal standard. Elemental analyses were carried out by the University of Massachusetts Microanalytical Laboratory under the direction of Greg Dabkowski. Optical rotations were determined on a Rudolph Autopol-III digital polarimeter and HPLC analyses with an automated Waters system incorporating a Model 720 system controller, Model 730 data module, U6K injector, 45 and 6000A solvent delivery systems, a 441 UV detector, and a Z-module radial compression unit.

(16) Moureu, H.; Dode, M. *Bull. Soc. Chem. Fr.* **1937**, *4*, 281.

Table III



1

R	R'	R''	X	yield, %	mp, °C	formula[a]	^{1}H NMR data[b]
C_6H_5	Me	Et	Br	46	65	$C_{12}H_{16}BrNO_2$	0.93 (t, 3, CH_3), 1.55 (s, 3, CH_3), 1.96 (q, 2, CH_2), 3.85 (s, 2, CH_2Br), 6.68 (br s, 1, NH), 7.04-7.48 (m, 5, C_6H_5)
p-ClC_6H_4	Me	Et	Br	53	77	$C_{12}H_{15}BrClNO_2$	0.93 (t, 3, CH_3), 1.55 (s, 3, CH_3), 1.97 (q, 2, CH_2), 3.84 (s, 2, CH_2Br), 6.70 (br s, 1, NH), 7.28 (s, 4, C_6H_4)
c-C_6H_{11}	Me	Et	Br	64	80-80.5	$C_{12}H_{22}BrNO_2$	0.90 (t, 3, CH_3), 1.48 (s, 3, CH_3), 1.97 (q, 2, CH_2), 0.75-2.18 (m, 10, ring CH_2), 3.15-3.65 (br s, 1, ring CH), 3.82 (s, 2, CH_2Br), 4.55 (br s, 1, NH)
C_6H_5	Me	i-Pr	Br	65	66-66.5	$C_{13}H_{18}BrNO_2$	0.92 (d, 3, CH_3), 1.00 (d, 3, CH_3), 1.48 (s, 3, CH_3), 2.57 (sept, 1, CH), 4.02 (s, 2, CH_2Br), 6.66 (br s, 1, NH), 6.94-7.48 (m, 5, C_6H_5)
p-ClC_6H_4	Me	i-Pr	Br	67	86-87	$C_{13}H_{17}BrClNO_2$	0.89 (d, 3, CH_3), 0.97 (d, 3, CH_3), 1.46 (s, 3, CH_3), 2.55 (sept, 1, CH), 3.49 (s, 2, CH_2Br), 6.72 (br s, 1, NH), 7.27 (s, 4, C_6H_4)
c-C_6H_{11}	Me	i-Pr	Br	34	95	$C_{13}H_{24}BrNO_2$	0.87 (d, 3, CH_3), 0.95 (d, 3, CH_3), 1.38 (s, 3, CH_3), 0.82-2.17 (m, 10, ring CH_2), 2.50 (sept, 1, CH), 3.08 (br s, 1, ring CH), 3.97 (s, 2, CH_2Br), 4.56 (br s, 1, NH)
C_6H_5	Et	Et	Br	47	61-62	$C_{13}H_{18}BrNO_2$	0.88 (t, 6, CH_3), 1.99 (q, 4, CH_2), 3.87 (s, 2, CH_2Br), 6.77 (br s, 1, NH), 7.03-7.48 (m, 5, C_6H_5)
c-C_6H_{11}	Et	Et	Br	70	98	$C_{13}H_{24}BrNO_2$	0.87 (t, 6, CH_3), 1.98 (q, 4, CH_2), 0.85-2.38 (m, 10, ring CH_2), 3.5 (br s, 1, ring CH), 3.84 (s, 2, CH_2Br), 4.86 (br s, 1, NH)
C_6H_5	Me	Et	OTs	55	77	$C_{19}H_{23}NO_5S$	0.87 (t, 3, CH_3), 1.42 (s, 3, CH_3), 1.81 (q, 2, CH_2), 2.33 (s, 3, CH_3), 4.34 (s, 2, CH_2O), 6.67 (br s, 1, NH), 7.02-7.30 (m, 5, C_6H_5), 7.22-7.44 (q, 4, C_6H_4)

[a] Elemental analyses for C, H, N were performed on all new compounds and are within ±0.3% of the theoretical values. [b] Taken in $CDCl_3$.

10 mL of pyridine was cooled to 10 °C, and 5.7 g of p-tolylsulfonyl chloride added portionwise so that the temperature did not exceed 20 °C. The solution was stirred at 10–20 °C for 1 h and poured into a mixture of 50 g of ice and 10 mL of concentrated HCl. The mixture was extracted with ether, and the extracts were washed with saturated NaCl and dried ($MgSO_4$). Removal of solvent in vacuo (20 mm) at 55 °C gave 6.1 g (82%) of the tosylate [mp 49–53 °C; NMR ($CDCl_3$) δ 1.18 (s, 6, CH_3), 2.34 (s, 1, OH), 2.41 (s, 3, CH_3), 3.81 (s, 2, CH_2O), 7.30–7.90 (q, 4, C_6H_4)], which was converted in a yield of 79% by the procedure described to the chloroformate [mp 61–63 °C; IR (KBr) 1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.50 (s, 6, CH_3), 2.44 (s, 3, CH_3), 4.13 (s, 2, CH_2O), 7.33–7.91 (q, 4, C_6H_4)]. The carbamate obtained as usual in 81% yield was recrystallized from Skelly B–$CHCl_3$: mp 80 °C: IR (KBr) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.45 (s, 6, CH_3), 2.32 (s, 3, CH_3), 4.23 (s, 2, CH_2O), 6.62 (br s, 1, NH), 7.03–7.33 (m, 5, C_6H_5), 7.22–7.90 (q, 4, C_6H_4).

Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.48; H, 5.83; N, 3.85. Found: C, 59.75; H, 5.90; N, 3.66.

1-[(*p*-Tolylsulfonyl)oxy]-2-methyl-2-butyl phenylcarbamate was obtained in 55% yield as described for the 2-propyl analogue[17] and recrystallized from pentane–benzene: mp 77 °C; IR (KBr) 1708 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.87 (t, 3, CH_3), 1.42 (s, 3, CH_3), 1.81 (q, 2, CH_2C), 2.33 (s, 3, CH_3), 4.34 (s, 2, CH_2O), 6.67 (br s, 1, NH), 7.02–7.30 (m, 5, C_6H_5), 7.22–7.44 (q, 4, C_6H_4).

Anal. Calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71. Found: C, 60.40; H, 6.24; N, 3.51.

1,1,1,3,3,3-Hexachloro-2-(bromomethyl)-2-propyl Phenylcarbamate. A mixture of 19.96 g of 1,1-bis(trichloromethyl)-ethylene oxide[18] in 40 mL of 48% aqueous hydrobromic acid was refluxed for 60 h. The mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate, and extracted with ether. Removal of solvent from the dried ($MgSO_4$) extracts gave after distillation of the residue 22.2 g (88%) of the bromohydrin: bp 115 °C (1.05 mm); NMR ($CDCl_3$) δ 4.26 (br s, 1, OH), 4.51 (s, 2, CH_2Br). Without further purification the bromohydrin was converted by the usual method[2] in 29% yield to the chloroformate [bp 126–133 °C (1.4 mm); IR (neat) 1790 cm^{-1}; NMR ($CDCl_3$) δ 4.97 (s, CH_2Br)] and then to the carbamate [88%; mp 127–128 °C; IR (KBr) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.13 (s, 2, CH_2Br), 7.05 (br s, 1, NH), 7.10–7.58 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_8BrCl_6NO_2$: C, 27.59; H, 1.68; N, 2.93. Found: C, 27.66; H, 1.56; N, 2.64.

Solvolytic Deblocking of 1,1,1,3,3,3-Hexachloro-2-(bromomethyl)-2-propyl Phenylcarbamate. A solution of 0.48 g

(17) The diol precursor was obtained by the method of Sato et al. (Sato, T.; Kaneko, H.; Yamaguchi, S. *J. Org. Chem.* **1980**, *45*, 3778).

(18) Stewart, J. M.; Clark, R. L.; Pike, P. E. *J. Chem. Eng. Data* **1971**, *16*, 98.

of the carbamate in 10 mL of 95% ethanol was reluxed for 18 h. Removal of ethanol in vacuo at 55 °C followed by trituration of the residue with ether gave 0.07 g (40.2%) of aniline hydrobromide, identified by comparison of its infrared spectrum with that of an authentic sample. A sample of the carbamate dissolved in MeOH-d_4 in an NMR tube and held at 37 °C in the presence or absence of a catalytic quantity of NaI showed no change after 24 h. The carbamate was also unaffected in trifluoroacetic acid or HBr–$MeNO_2$ at room temperature over a period of 10–20 h.

2-Bromo-2-methyl-1-propyl Phenylthiolcarbamate. A solution of 6.5 g of isobutylene sulfide in 40 mL of CH_2Cl_2 was stirred at room temperature. Into this solution was bubbled 7.4 g (0.09 mole) of hydrogen bromide. The solution warmed slightly during the addition. After the addition was complete the reaction mixture was stirred for 30 min, and the solvent was removed in vacuo at 50 °C to give a pale yellow liquid. An NMR spectrum of the crude thiol showed it to be a mixture of the desired thiol and 2-bromo-2-methylpropanethiol in a ratio of 6:4. The crude material was distilled to give 2.5 g (20%) of a mixture containing 22% of the tertiary thiol and 78% of the primary thiol: bp 52–54 °C (22 mm); IR (neat) 2590, 2533 (SH) cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 3°, CH_3CS) and 1.81 (s, 1°, CH_3CBr) (6 H combined), 1.86 (br s, SH, 1H), 2.98 (d, 1°, CH_2S) and 3.60 (s, 3° (CH_2Br) (2 H combined). This mixture (2.4 g) was added dropwise over a period of 15 min to a solution of 3 g of phosgene in 25 mL of CH_2Cl_2 at −15 °C under N_2. Pyridine (1.12 g) in 15 mL of CH_2Cl_2 was then added over 15 min, and the mixture was stirred at 15 °C for 2 h, warmed to room temperature, and stirred overnight. Nitrogen was bubbled through the solution for 30 min to remove excess phosgene, and the mixture was washed successively with ice-cold water, $NaHCO_3$ solution, and water. Removal of solvent from the dried ($MgSO_4$) solution in vacuo followed by distillation gave 1.64 g (50%) of a mixture of 1-bromo-2-methyl-2-propyl thiolchloroformate and 2-bromo-2-methyl-1-propyl thiolchloroformate (ratio 12:88 by NMR analysis): bp 34 °C (0.03 mm); IR (neat) 1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.56 (s, 1°, CH_3CS) and 1.81 (s, 3°, CH_3CBr) (6 H combined), 3.53 (s, 1°, CH_2S) and 3.80 (s, 3°, CH_2Br) (2 H combined). The mixed thiolchloroformates (1.64 g) in 10 mL of CH_2Cl_2 were stirred at room temperature under N_2, and to the solution was added dropwise over 10 min a solution of 1.32 g of aniline in 5 mL of CH_2Cl_2. The mixture was stirred for 1 h at room temperature, filtered, and concentrated in vacuo to give a residue, which was recrystallized from Skelly B to give 1.48 g (72%) of the 2-bromo-2-methyl-1-propyl carbamate: mp 122–125 °C; IR (KBr) 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.81 (s, 6, CH_3CBr), 3.61 (s, 2, CH_2S), 7.08–7.50 (m, 5, C_6H_5). None of the desired thiolcarbamate derived from the tertiary thiol was isolated. The analytical sample, recrystallized from Skelly B, had mp 126 °C.

Anal. Calcd for $C_{11}H_{14}BrNOS$: C, 45.84; H, 4.90; N, 4.86. Found: C, 45.98; H, 4.81; N, 4.65.

1-Chloro-2-methyl-2-propyl Phenylthiolcarbamate and 2-Chloro-2-methyl-1-propyl Phenylthiolcarbamate. Treatment of 2.7 g of isobutylene sulfide with anhydrous HCl according to the method of Schwartz[9] gave 1.71 g (45%) of the mixed thiols: bp 35–37 °C (18 mm) (ratio 74:26 by NMR analysis); IR (neat) 2565 cm^{-1} (SH); NMR ($CDCl_3$) δ 1.45 (s, 3°, CH_3CS) and 1.65 (s, 1°, CH_3CCl) (6 H combined), 2.03 (br s, 1H, SH), 2.83 (d, 1°, CH_2S), and 3.62 (s, 3°, CH_2Cl) (2 H combined). Reaction of the mixed thiols (74:26) with phosgene as reported for the bromo analogues gave the mixed chlorothiolformates (70:30): bp 57–59° (3.25 mm); IR (neat) 1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.53 (s, 3°, CH_3CS) and 1.64 (s, 1°, CH_3CCl) (6 H combined), 3.40 (s, 1°, CH_2S) and 3.84 (s, 3°, CH_2Cl) (2 H combined). Treatment of the mixed chlorothiolformates with aniline gave in 98% yield a mixture containing according to NMR analysis 68% 1-chloro-2-methyl-2-propyl phenylthiolcarbamate and 32% 2-chloro-2-methyl-1-propyl phenylthiolcarbamate; mp 75–95 °C. After a number of recrystallizations from Skelly B, the ratio was improved to 88:22; mp 82–84 °C. When the melt from this material was heated further it suddenly solidified and then melted a second time at 122–125 °C: IR (KBr) 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.56 (s, 3°, CH_3CS) and 1.65 (s, 1°, CH_3CCl) (6 H combined), 3.48 (s, 1°, CH_2S) and 4.05 (s, 3°, CH_2Cl) (2 H combined), 7.04–7.51 (m, 5 H, C_6H_5). Recrystallization from Skelly B gave an analytical sample, mp 126 °C.

Anal. Calcd for $C_{11}H_{14}ClNOS$: C, 54.20; H, 5.79; N, 5.75. Found: C, 54.46; H, 5.86; N, 5.63.

Solvolytic Deblocking of 2-Bromo-2-methyl-1-propyl Phenylthiolcarbamate. A solution containing 0.1 g (0.34 mmol) of the thiolcarbamate and 1 drop of water in 5 mL of methanol was refluxed for 14 h. The methanol was removed in vacuo and the residue triturated with ether. Filtration gave 0.01 g (16%) of aniline hydrobromide, identified by comparison of its IR spectrum with that of an authentic sample.

α,α′-Dibromo-*tert*-butyl Alcohol. A solution of 67.5 g of methallyl bromide,[19] 18.0 g of water, and 3000 mL of Me_2SO was cooled to 5 °C under N_2. Over a 15-min period, 178 g of NBS was added to the solution with vigorous stirring. During the addition the temperature of the solution spontaneously rose to 45 °C. The mixture was stirred at room temperature for 30 min after the addition of NBS and then quenched with water and extracted with ether. The extracts were washed once with saturated NaCl and dried over $MgSO_4$. After removal of ether in vacuo, the crude alcohol was distilled to give 93.9 g (81%) of the bromohydrin: bp 54 °C (0.3 mm); NMR ($CDCl_3$) δ 1.49 (s, 3, CH_3), 2.52 (s, 1, OH), 3.5 (s, 4, CH_2Br).

Anal. Calcd for $C_4H_8Br_2O$: C, 20.71; H, 3.48. Found: C, 20.30; H, 3.29.

α,α′-Dibromo-*tert*-butyl Chloroformate. A solution of 80 g of phosgene in 300 mL of CH_2Cl_2 was cooled to −15 °C under N_2. To the solution was added a solution of 92.8 g of α,α′-dibromo-*tert*-butyl alcohol in 100 mL of CH_2Cl_2 and 32.0 g of pyridine in 200 mL of CH_2Cl_2. The mixture was stirred at −15 °C for 1 h, warmed slowly to room temperature, and stirred overnight. After nitrogen was bubbled through the solution for 30 min, it was washed with ice-cold water twice and dried over $MgSO_4$. Removal of the solvent in vacuo at 50 °C followed by distillation gave 98 g (83%) of chloroformate: bp 78 °C (0.9 mm); IR (neat) 1780 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.79 (s, 3, CH_3), 3.89 (s, 4, CH_2Br).

Anal. Calcd for $C_5H_7Br_2ClO_2$: C, 20.40; H, 2.39. Found: C, 20.33; H, 2.33.

α,α′-Dibromo-*tert*-butyl Phenylcarbamate. To a solution of 2.94 g of α,α′-dibromo-*tert*-butyl chloroformate in 60 mL of benzene was added dropwise 1.7 g of aniline in 20 mL of benzene. The mixture was stirred for 30 min after which the precipitated aniline hydrochloride was filtered and washed with a small amount of benzene. The filtrate and washings were combined and the benzene was distilled in vacuo at 50 °C. The residue was recrystallized from Skelly B to give 1.6 g (45%) of carbamate: mp 58–59 °C; IR (KBr) 1722 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.74 (s, 3, CH_3), 3.80 (s, 4, CH_2Br), 6.71 (br s, 1, NH), 7.06–7.64 (m, 5, C_6H_5). Several recrystallizations from Skelly B gave an analytical sample, mp 59 °C.

Anal. Calcd for $C_{11}H_{13}Br_2NO_2$: C, 37.63; H, 3.73; N, 3.99. Found: C, 37.85; H, 3.67; N, 3.70.

Solvolytic Deblocking of α,α′-Dibromo-*tert*-butyl Phenylcarbamate. (1) A solution of 0.175 g (0.5 mmol) of the carbamate in 2.0 mL of 95% ethanol was allowed to stand at room temperature for 20 h. The ethanol was removed in vacuo at 50 °C and the residue triturated with ether. The precipitate was filtered and washed with ether to give 0.069 g (80%) of aniline hydrobromide, which was identified by comparison of its IR spectrum with that of an authentic sample.

(2) A solution of 0.0439 g (0.12 mmol) of carbamate in 0.25 mL of 95% CD_3OD and 5% D_2O was placed in an NMR tube and the tube was placed in the preheater of an NMR instrument at 37 °C. NMR spectra were taken periodically to monitor the rate of the reaction. After 22 h it was 97% complete ($t_{1/2}$ = 4.8 h).

1,3-Dibromo-2-methyl-2-(propyloxycarbonyl)-L-phenylalanine Dicyclohexylamine Salt. A mixture of 3.3 g (0.02 mol) of L-phenylalanine and 15 mL of 2 N NaOH in 50 mL of THF was cooled to 0 °C. To the mixture was added over a 20-min period a solution of 5.88 g (0.02 mol) of DB-*t*-BocCl in 20 mL of THF. The mixture was stirred for 1 h at 0 °C, acidified with dilute HCl, and extracted with ether. After drying over $MgSO_4$, the solvent was removed in vacuo to give a viscous oil. The oil was dissolved in 75 mL of ether, and a solution of dicyclohexylamine

(19) Brewster, J. J. *J. Am. Chem. Soc.* **1951**, *73*, 366.

in ether (25%) was added dropwise until the solution was slightly basic to pH paper. The precipitate was filtered and washed with ether to give 8.4 g (70%) of the salt. The salt could be purified by dissolving in $CHCl_3$ and filtering the solution into ether to precipitate the salt: mp 220 °C dec; IR (KBr) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90–2.25 (m, 20, cyclohexyl CH_2), 1.64 (s, 3, CH_3), 2.70–3.25 (br s, 2, ring CH), 3.13 (d, 2, CH_2), 3.34 (s, 4, CH_2Br), 5.60 (m, 1, CH), 7.24 (s, 5, C_6H_5), 9.22 (br s, 2, NH). Several additional recrystallizations gave an analytical sample, mp 220 ° dec.

Anal. Calcd for $C_{26}H_{40}Br_2N_2O_4$: C, 51.66; H, 6.67; N, 4.64. Found: C, 51.26; H, 6.58; N, 4.43.

The corresponding D-phenylalanine salt, mp 215 °C dec, was prepared similarly.

Solvolytic Deblocking of DB-*t*-Boc-L-Phe-OH. A suspension of 3 g of DB-*t*-Boc-L-Phe-OH·DCHA salt in 200 mL of ether in a separatory funnel was treated successively with 5–6 100-mL portions of 10% hydrochloric acid with vigorous shaking until all the solid dissolved. The ether layer was then washed with ice water until neutral (three portions), dried over $MgSO_4$; and evaporated to give 1.4 g (70%) of the protected acid as a viscous colorless liquid: $[\alpha]^{16}_{589}$ +31.1° or $[\alpha]^{16}_{546}$ +37.8° (c 1.1, CH_2Cl_2). No method was found to induce crystallization, and therefore 1.0 g of the crude oil was dissolved in 15–20 mL of 95% ethanol and the solution was warmed at 50 °C overnight. Removal of the solvent in vacuo, followed by trituration of the residue with ether, gave a solid, which was filtered and washed with fresh ether to give 0.42 g (72.4%) of L-Phe-OH·HBr, mp 222–224 °C dec. Two recrystallizations from absolute EtOH gave an analytical sample: mp 222–224 °C dec; $[\alpha]^{23}_{589}$ +13.6° or $[\alpha]^{23}_{546}$ +16.9° (c 1, absolute EtOH). This was identified as phenylalanine hydrobromide [mp 222–225 °C dec; $[\alpha]^{16}_{589}$ +14.3° or $[\alpha]^{16}_{546}$ +17.5° (c 1, absolute EtOH)], an authentic sample of which was obtained by shaking the amino acid in ethanol with concentrated HBr, evaporation, and recrystallization from EtOH–Et_2O.

Anal. Calcd for $C_9H_{12}BrNO_2$: C, 43.90; H, 4.88; N, 5.69; Br, 32.52. Found: C, 44.20; H, 5.18; N, 5.60; Br, 32.42.

D-Phenylalanyl-L-leucine Methyl Ester Hydrobromide. A suspension of 3.02 g of DB-*t*-Boc-D-Phe-OH·DCHA in 200 mL of ether was treated successively with 6–7 100-mL portions of 10% HCl. Eventually the solid dissolved completely, and the ether solution was washed with ice-cold water. Evaporation of the dried ($MgSO_4$) ether solution gave 2.0 g (95%) of the crude protected acid as a colorless oil, which was dissolved in 35 mL of chloroform. The solution was cooled to −15 °C, and 0.6 g of triethylamine was added followed by 0.54 g of ethyl chloroformate. The mixture was stirred for 15 min, and a solution of 0.87 g of L-leucine methyl ester in 20 mL of chloroform was added dropwise over 15 min, keeping the temperature at −10 to −5 °C. The mixture was stirred at 0–10 °C for 1 h and then washed successively with dilute HCl, 5% $NaHCO_3$, and water. After drying ($MgSO_4$), removal of solvent in vacuo gave an oil, which was dissolved in 75 mL of 95% EtOH and the solution warmed at 50 °C overnight. Removal of EtOH gave an oil, which was triturated with ether to give the crude peptide hydrobromide. Recrystallization from acetone–ether gave 1.13 g (60%) of the pure hydrobromide; mp 172–174 °C (lit.[20] mp 171–173 °C); $[\alpha]^{16}_{589}$ −98.9° or $[\alpha]^{16}_{546}$ −117.9° (c 3.5, 1 N HCl) (lit.[20] $[\alpha]_D$ −89.7°).

L-Phenylalanyl-L-leucine Benzyl Ester Hydrobromide. This compound was prepared as described for H-D-Phe-L-Leu-OMe·HBr. Recrystallization from methanol and ether gave 1.7 g (51%) of the dipeptide hydrobromide: mp 166–167 °C; $[\alpha]_D$ −15.3 ± 1.0° (c 2.8, 95% ethanol); IR (KBr) 1718, 1670 cm^{-1} (C=O). Several additional recrystallizations from methanol and ether gave an analytical sample, mp 167 °C.

Anal. Calcd for $C_{22}H_{29}BrN_2O_2$: C, 58.80; H, 6.50; N, 6.24. Found: C, 58.52; H, 6.70; N, 6.09.

Racemization Test.[12] DB-*t*-Boc-L-Phe-OH·DCHA (0.72 g) was coupled with H-L-Leu-OMe by the method described above. Following removal of solvent in vacuo, all of the residual oil was warmed in 10 mL of 95% EtOH at 50 °C overnight. After removal of solvent in vacuo the residual oil was dissolved in 10 mL of chloroform and an equal volume of saturated sodium bicarbonate solution added. The mixture was stirred vigorously and 0.2 mL of benzoyl chloride added. After being stirred for 5 min, 0.3 mL of *N*-methylpiperazine was added, the mixture was stirred for 5 min, and the organic phase was washed with 5% hydrochloric acid, saturated $NaHCO_3$ and water. Evaporation of the dried ($MgSO_4$) solution gave a residue, which was examined by HPLC on a Waters Radial Pak 10-μm silica column (0.8 × 10 cm) using 3% 2-propanol in hexane as the mobile phase. Retention times (min) for the two diastereomeric benzoyl dipeptide esters were 14.9–15.1 (L,L) and 19.1–19.4 (D,L). Triplicate analyses showed 0.54–0.81% of the D,L diastereomer. Since the starting L-phenylalanine was contaminated by 0.2%[21] of the D enantiomer, the loss of chirality in the four-step sequence of protection, coupling, deblocking, and benzoylation amounted to 0.34–0.61%.

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Registry No. 1 (R = C_6H_5; R′ = R″ = Me; X = Br), 88476-23-7; 1 (R = C_6H_5; R′ = R″ = Me; X = OTs), 88476-25-9; 1 (R = C_6H_5; R′ = Me; R″ = Et; X = Br), 88476-26-0; 1 (R = *p*-ClC_6H_4; R′ = Me; R″ = Et; X = Br), 88476-27-1; 1 (R = c-C_6H_{11}, R′ = Me, R″ = Et, X = Br), 88476-28-2; 1 (R = C_6H_5, R′ = Me, R″ = Et, X = OTs), 88476-29-3; 1 (R = C_6H_5; R′ = Me; R″ = *i*-Pr; X = Br), 88476-30-6; 1 (R = *p*-ClC_6H_4; R′ = Me; R″ = *i*-Pr; X = Br), 88476-31-7; 1 (R = c-C_6H_{11}; R′ = Me; R″ = *i*-Pr; X = Br), 88476-32-8; 1 (R = C_6H_5; R′ = R″ = Et; X = Br), 88476-33-9; 1 (R = *p*-ClC_6H_4; R′ = R″ = Et; X = Br), 88476-34-0; 1 (R = c-C_6H_{11}; R′ = R″ = Et; X = Br), 88476-35-1; 1 (R′ = R″ = Me; X = OTs) chloroformate, 88476-51-1; 1 (R′ = Me; R″ = Et; X = Br) chloroformate, 88476-62-4; 1 (R′ = Me; R″ = *i*-Pr; X = Br) chloroformate, 88476-63-5; 1 (R′ = R″ = Et; X = Br) chloroformate, 88476-64-6; 1 (R′ = Me; R″ = Et; X = OTs) chloroformate, 88476-65-7; **5**, 88476-24-8; **11**, 88476-37-3; **11** thiolchloroformate, 88476-55-5; **14**, 3772-13-2; **15**, 88476-38-4; **16**, 88476-39-5; **17**, 88476-40-8; **17** chlorothiolformate, 88476-56-6; **18**, 88476-41-9; **18** chlorothiolformate, 88476-57-7; **19**, 88476-42-0; **19** chloroformate, 88476-53-3; **21**, 88476-43-1; **22**, 88476-44-2; **23**, 88476-45-3; (L)-**24**, 88476-46-4; (D)-**24**, 88476-59-9; (L)-**24** dicyclohexylamine salt, 88476-58-8; (D)-**24** dicyclohexylamine salt, 88476-60-2; **25**, 88476-47-5; **26**, 88476-48-6; L-Phe-OH·HBr, 53917-00-3; H-D-Phe-L-Leu-OMe·HBr, 3860-80-8; L-Leu-OMe, 2666-93-5; H-L-Leu-$OCH_2C_6H_5$, 1738-69-8; $C_6H_5NH_2$, 62-53-3; 1-(bromomethyl)-1-cyclohexyl phenylcarbamate, 88476-36-2; 1-(bromomethyl)-1-cyclohexyl chloroformate, 88476-49-7; 2-methyl-1,2-propanediol, 558-43-0; 2-methyl-1,2-propanediol tosylate, 88476-50-0; 1,1-bis(trichloromethyl)ethylene oxide, 30822-13-0; 1,1-bis(trichloromethyl)ethylene oxide bromohydrin, 88476-52-2; 1-bromo-2-methyl-2-propyl thiolchloroformate, 88476-54-4; 3-chloro-2-methylpropane-2-thiol, 16621-44-6; 2-chloro-2-methylpropanethiol, 16621-45-7; methallyl bromide, 1458-98-6; L-phenylalanine, 63-91-2; D-phenylalanine, 673-06-3; D-phenylalanyl-L-leucine methyl ester, 88476-61-3; 4-chloroaniline, 106-47-8; cyclohexanamine, 108-91-8.

(20) Pravda, Z.; Poduska, K.; Blaha, K. *Collect. Czech. Chem. Commun.* **1964**, *29*, 2626.

(21) The chiral purity of the phenylalanine was determined[12] by the method of Gil-Av et al. (Gil-Av, E.; Tisbee, A.; Hare, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 5115).