tometer with a 1-mm cell. The progress of the reaction was monitored by disappearance of the band at 2290 cm^{-1} of MNO. Concentrations of MNO for each time interval were obtained by means of a calibration plot (absorbance vs concentration). Rate constants for all the reactions were determined by means of a second-order-kinetics plot using equimolar amounts of both reagents.

Acknowledgment. Support for this work was provided by CICYT (Grant No. PB87-0064) and by CSIC. We are indebted to Prof. V. Gotor and Prof. P. A. Carrupt for assistance in spectral acquisition. Two of us (C.D. and A.M.) gratefully acknowledge the Comunidad de Madrid for doctoral fellowships.

Registry No. **1a**, 79902-01-5; **1b**, 95530-78-2; **1c**, 107607-56-7; **2a**, 873-67-6; **2b**, 2904-57-6; **3a**, 107607-57-8; **3b**, 123075-84-3; **3c**, 107607-59-0; **3d**, 123075-85-4; **3e**, 107607-61-4; **3f**, 123075-86-5; **4a**, 107607-58-9; **4b**, 123075-87-6; **4c**, 123075-88-7; **4d**, 123075-89-8; **4e**, 107607-62-5; **4f**, 123075-90-1; **5a**, 123075-91-2; **5b**, 123075-92-3; **6a**, 123075-93-4; **6b**, 123075-94-5; **7b**, 123075-95-6; **7c**, 123075-96-7; **7d**, 123075-97-8; **8b**, 123163-88-2; **8c**, 123075-98-9; **8d**, 123075-99-0; **9a**, 123076-00-6; **9b**, 123076-01-7; **10a**, 123076-02-8; **10b**, 123076-03-9; benzeneselenenyl bromide, 34837-55-3.

Thioxanthene Dioxide Based Amino-Protecting Groups Sensitive to Pyridine Bases and Dipolar Aprotic Solvents[1,2]

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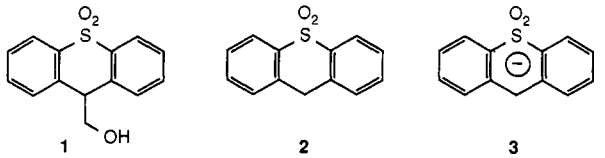
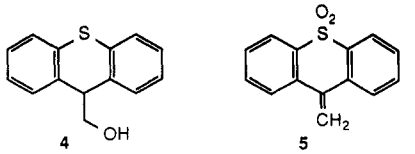
In pursuit of an analogy between fluorine and thioxanthene dioxide, the suitability of the D-TMOC and related functions as base-sensitive amino-protecting groups was examined. Such compounds were found to be cleaved by mild pyridine bases against which the analogous FMOC derivatives are stable. Deblocking gives as a byproduct the methylene sulfone **5** or its adducts with an appropriate secondary deblocking amine. Certain solvents such as DMSO, DMF, etc., were also found to deblock the D-TMOC group, especially on warming, whereas the compounds were stable in ordinary nonpolar solvents (e.g., CH_2Cl_2, benzene, THF). For practical use the D-TMOC function suffers from excessive solvent sensitivity and the low solubility of some derivatives. To overcome this problem *tert*-butyl groups were introduced into the 2,7-positions of the xanthene nucleus. The resulting DBD-TMOC function proved easier to handle in terms of both solubility and reactivity. The key alcohol **12** was synthesized from diphenyl sulfide **13** by *tert*-butylation followed by Friedel–Crafts cyclization using methyl dichloromethyl ether to give a 50–50 mixture of thioxanthene **15** and the corresponding thioxanthone **16**. Without separation of the mixture, oxidation gave a mixture of the dioxides **17** and **18**, and again without separation the mixture was reduced by P/HI to give the desired compound **17** in an overall yield of 60–65%. Formylation of **17** followed by reduction gave **12**, from which urethanes **11** were obtained in the normal manner via the chloroformate. The DBD-TMOC group was stable to strong acids (TFA, HBr–HOAc) but deblocked by catalytic hydrogenolysis as well as via mild bases and warming in dipolar aprotic solvents. Upon deblocking of **11** in DMSO the byproduct **27** separated completely, especially if 3–5% water is present or added subsequently. This process provides a clean solution of the deblocked amine, thus simplifying the use of the DBD-TMOC function in peptide synthesis. An example given is that of leucine enkephalin, in which all coupling steps were effected by acid chlorides and all deblocking steps by warming in DMSO. It was shown with model compounds that coupling could be effected under appropriate conditions without racemization.

In connection with studies aimed at developing a spectrum of base-sensitive amino-protecting groups subject to deblocking under nonhydrolytic conditions by organic bases of varying strengths, of which the FMOC group[3] is currently the most widely used representative, we have examined appropriate urethanes derived from sulfone alcohol **1** largely on the basis of the work of Pagani and associates[4] and the possible relationship between fluorene and the related sulfone **2**. It has been suggested that anion **3** may be subject to special "aromatic" stabilization as a completely conjugated cyclic six π-electron system.[5] Although the exact nature of anion **3** is not clear, the undisputed high kinetic acidity of **2** relative to acyclic analogues inspired our synthesis of alcohol **1** and its urethane derivatives.



Alcohol **1** was obtained by oxidation of known thioxanthyl alcohol **4**, which could be obtained by treatment of thioxanthene with n-butyllithium followed by reaction with paraformaldehyde.[6] Direct hydroxymethylation of



(1) Abstracted in part from the Ph.D. theses of H.-S.G. (1989) and G.-S.T. (1979), University of Massachusetts.

(2) A number of abbreviations are used in this paper. Those for natural amino acids and peptides follow the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature (*J. Biol. Chem.* **1971**, *247*, 997). Other abbreviations are as follows: TFA = trifluoroacetic acid, FMOC = (9-fluorenylmethoxy)carbonyl, DCC = dicyclohexylcarbodiimide, HOBT = *N*-hydroxybenzotriazole, HOSu = *N*-hydroxysuccinimide, PCA = *p*-chloroaniline, Phg = α-phenylglycine, TMOC = [(thioxanthen-9-yl)methoxy]carbonyl, D-TMOC = [10,10,10,10-tetrahydro-10,10-dioxothioxanthen-9-yl)methoxy]carbonyl, DBD-TMOC = 2,7-di-*tert*-butyl-D-TMOC.

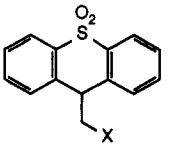
(3) Carpino, L. A. *Acc. Chem. Res.* **1987**, *20*, 401.

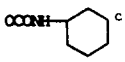
(4) (a) Bradamante, S.; Maiorana, S.; Mangia, A.; Pagani, G. *J. Chem. Soc. B* **1971**, 74. (b) Gaviraghi, G.; Pagani, G. *J. Chem. Soc., Perkin Trans. 2* **1973**, 50.

(5) For additional evidence for d–π interaction in an analogous azasulfone system, see: Fraenkel, G.; Chow, A.; Gallucci, J.; Rizvi, S. Q. A.; Wong, S. C.; Finkelstein, H. *J. Am. Chem. Soc.* **1986**, *108*, 5339.

0022-3263/89/1954-5887$01.50/0

Table I. Characterization of D-TMOC Derivatives and 9-Methylenethioxanthene Sulfone Adducts



compd,[a] X	yield, %	mp, °C (recry solv)	^{1}H NMR,[b] δ	mol formula	anal. data (calcd/found) C	H	N
 [c]	66.4	124 (dec) (Et_2O)	0.7–2.2 (m, 11, C_6H_{11}), 4.4 (br s, 3, CH_2CH), 6.8 (b, 1, NH), 7.4–7.65 (m, 6, aryl), 8.0–8.2 (m, 2, H_4, H_5)	$C_{21}H_{23}NO_4S$	65.45 65.61	5.98 6.11	3.64 3.43
$OCONHCH_2CO_2H$	75	113–4 (EtOH)	3.6 (d, 2, NCH_2), 4.5–4.9 (m, 3, CH_2CH), 6.69 (b, 1, NH), 7.45–7.65 (m, 6, aryl), 7.9–8 (m, 2, H_4, H_5)	$C_{17}H_{15}NO_6S$	56.51 56.47	4.16 4.35	3.88 4.11
$OCONHCH_2COOEt$[d]	94	125–6 (EtOH–Et_2O)	1.23 (t, 3, CH_3), 3.9 (d, 2, NCH_2), 4.2 (q, 2, CH_2O), 4.5 (s, 3, CH_2CH), 5.5 (b, 1, NH), 7.5–7.65 (m, 6, aryl), 8.0–8.2 (m, 2, H_4, H_5)	$C_{19}H_{19}NO_6S$	58.61 58.31	4.88 4.92	
$OCONHC_6H_5$	89	172–3 (EtOH)	4.4–4.9 (m, 3, CH_2CH), 7.0–7.8 (m, 11, aryl), 8.0–8.2 (m, 2, H_4, H_5), 9.75 (s, 1, NH)	$C_{21}H_{17}NO_4S$	66.49 66.61	4.49 4.71	3.69 3.51
NEt_2[e]	92	117–8 (Et_2O)	0.95 (t, 6, CH_3), 2.55 (q, 4, CH_2CH_3), 3.0 (d, 2, CH_2CH), 4.0 (t, 1, CH_2CH), 7.4–7.6 (m, 6, aryl), 8.0–8.2 (m, 2, H_4, H_5)	$C_{18}H_{21}NO_2S$	68.57 68.34	6.67 6.79	4.44 4.31
 [f]	95	148–50 (EtOH)	2.4–2.55 (m, 4, $(CH_2)_2N$), 2.95 (d, 2, $CHCH_2N$), 3.55–3.75 (m, 4, $(CH_2)_2O$), 4.2 (t, 1, CH), 7.4–7.6 (m, 6, aryl), 8.0–8.25 (m, 2, H_4, H_5)	$C_{18}H_{19}NO_3S$	65.65 65.49	5.77 5.62	4.26 4.27
$OCONHC_6H_4Cl$-*p*[g]	78	156–8 (CH_2Cl_2–hexane)	1.3 (s, 18, CMe_3), 4.6 (s, 3, $CHCH_2$), 7.15–8.2 (m, 10, aryl)	$C_{29}H_{32}ClNO_4S$	66.21 66.46	6.13 6.25	2.66 2.55

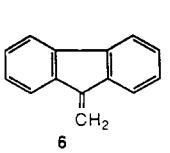
[a] Urethanes derived from simple amines were obtained by addition of the amine *to* a solution of the chloroformate in benzene, ether, or CH_2Cl_2 at 0 °C as described in the Experimental Section for *p*-chloroaniline. Amino acid derivatives were obtained by addition of the chloroformate in dioxane or THF to the amino acid in aqueous $NaHCO_3$. For method see Experimental Section (Phe). Individual differences are noted. [b] Solvent: $CDCl_3$. [c] Also obtained via the reaction of **1** with the corresponding isocyanate. [d] A solution of H_3NCH_2COOEt (+) Cl (–) and D-TMOC-Cl in CH_2Cl_2 was treated at 0 °C with NEt_3. [e] Obtained via reaction of **5** with Et_2NH. [f] Obtained via D-TMOC-PCA and the amine or via method of footnote *e*. [g] 2,7-Di-*tert*-butyl derivative; obtained via isocyanate; IR (KBr) 3320 (NH), 1720 (C=O), 1350, 1150 (SO_2) cm^{-1}.

Table II. Deblocking of D-TMOC-NHR in DMSO-d_6 at 38 °C[a]

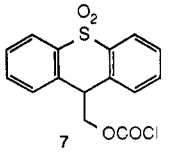
compd, R	$t_{1/2}$, min	compd, R	$t_{1/2}$, min
C_6H_5	240	CH_2CO_2H	120
C_6H_4Cl-*p*	360	CH_2COOEt	60
cyclohexyl	15		

[a] Reactions were carried out in an NMR tube according to the method described in the Experimental Section. Upon completion of the deblocking the spectrum was that of a 1:1 mixture of **5** and the amine.

2 in the same way gave only the methylene sulfone **5**, possibly via dehydration of the desired alcohol under the strongly basic conditions.[7] In contrast to the highly unstable, polymerization-prone[8] fluorene analogue dibenzofulvene **6**, olefin **5** is an easily isolated, stable compound.



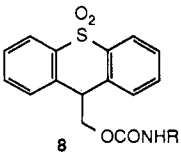
6



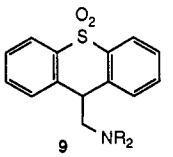
7

Treatment of **1** with phosgene in the absence of base gave [9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthenyl)]methyl chloroformate (D-TMOC-Cl), **7**. Chloroformate **7**, like other representatives of this class of compounds, is stable at room temperature and storable for long periods in the absence of moisture.

Introduction of the D-TMOC group was carried out by slow addition of an amino compound to a cold solution of **7** in benzene, ether, methylene dichloride, or other appropriate solvent. For highly basic aliphatic amines, careful addition was required to avoid premature deblocking of the chloroformate or the desired urethane **8**.



8



9

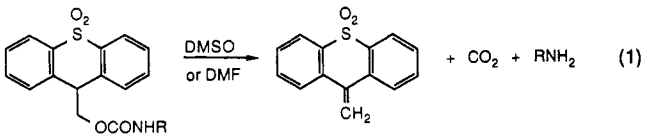
Free amino acids could be acylated in 75–80% yields in water–dioxane mixtures in the presence of sodium bicarbonate. Some of the compounds synthesized are collected in Table I. With urethane **8**, R = C_6H_4Cl-*p*, as a model, it was shown that deblocking of D-TMOC derivatives could be effected by piperidine and similar bases under far milder conditions than those commonly used for the FMOC group, and in marked contrast to the stability of the latter toward pyridine,[9] the D-TMOC function is rapidly cleaved by this base. Interestingly, cleavage by pyridine bases is subject to significant steric influences as shown by the fact that under comparable conditions, pyridine, 2-picoline, and 2,6-lutidine effected complete

(6) Bergmann, E. D.; Rabinowitz, M. *J. Org. Chem.* **1960**, *25*, 828.
(7) For the novel dehydration of the analogous fluorene derivative, see: (a) More O'Ferrall, R. A.; Slae, S. *J. Chem. Soc. B* **1970**, 260. (b) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 268, 274.
(8) (a) Neuenschwander, M.; Vögeli, R.; Fahrni, H.-P.; Lehmann, H.; Ruder, J.-P. *Helv. Chim. Acta* **1977**, *60*, 1073. (b) Kice, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 348.
(9) Carpino, L. A. *J. Org. Chem.* **1980**, *45*, 4250.

deblocking in 0.5, 3, and 12 h, respectively. This order is the inverse of the basicity order (pK_a 5.25, 5.97, 7.14, respectively). Cross-linked poly(4-vinylpyridine) caused no deblocking on being stirred in a swollen state at reflux temperature for 48 h in methylene dichloride.

With secondary amines such as morpholine or piperidine, adducts **9**, analogous to those obtained from FMOC derivatives, are formed. Even hindered noncyclic secondary amines such as diethylamine and the weakly basic imidazole yield adducts, again in contrast to the FMOC case. Some of the adducts prepared are collected in Table I.

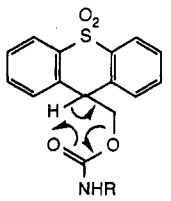
In the course of handling various D-TMOC derivatives it was noted that they exhibited a remarkable instability in certain dipolar aprotic solvents (eq 1). This was first



(1)

noted by accident during attempts to record the NMR spectrum of the glycine derivative in DMSO-d_6 at 37 °C. During the spectral determination free glycine crystallized on the walls of the sample tube. The reaction takes place slowly at room temperature but rapidly at 45–50 °C. The group is stable in refluxing ethanol for 6 h but suffers complete decomposition after 24 h. No degradation is noted in refluxing benzene.

Rough studies of the ease of deblocking in DMSO-d_6 (NMR probe) are collected in Table II and illustrate the importance of the nature of the N substituent in promoting the reaction. The process is expected to be autocatalytic, being promoted by the amine liberated, although the initial reaction may represent an internal elimination (cf. **10**) for

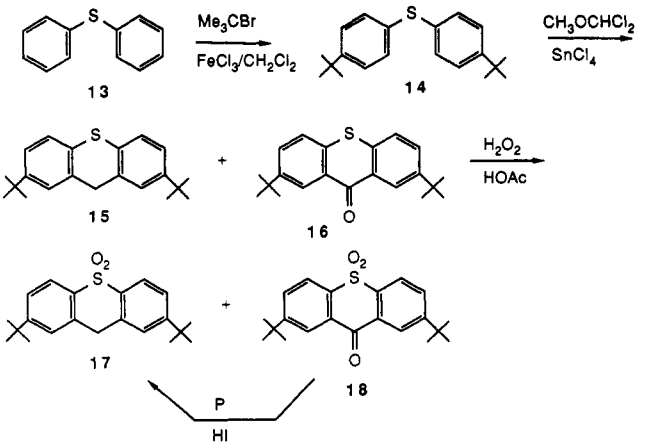


10

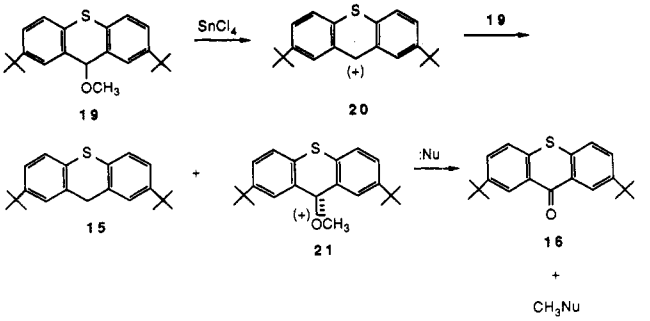
which the transition state is somehow greatly accelerated by dipolar aprotic solvents. The exact nature of this acceleration is not obvious and must be left for further study. The elimination process may be related to the classic acetate pyrolysis reaction, which however normally takes place at very high temperatures (~500 °C).[10] Such reactions are accelerated by any effect that increases the acidity of the β-proton. The same process occurs at the melting point (186 °C in the case of the *p*-chloroaniline derivative). Heating neat at 120 °C requires 12 h for complete decomposition. The presence of traces of basic impurities that might initiate these various reactions was not excluded.

Although the unique properties described for the D-TMOC derivatives implied possible uses as amino protectants, two difficulties hindered the practical realization of this concept: insufficient solubility of some derivatives in ordinary solvents and too rapid spontaneous deblocking in certain cases. Considering that both difficulties might be overcome by electron-donating *tert*-alkyl substitution,[11,12] we began an investigation of such systems. Our

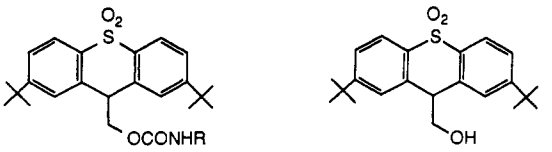
Scheme I



Scheme II



first results concerned the 2,7-di-*tert*-butyl-[10,10,10,10-tetrahydro-10,10-dioxothioxanthen-9-yl)methoxy]carbonyl (DBD-TMOC) system **11**. As a precursor of key alcohol **12**, 2,7-di-*tert*-butylthioxanthene 10,10-dioxide **17** was prepared as outlined in Scheme I.

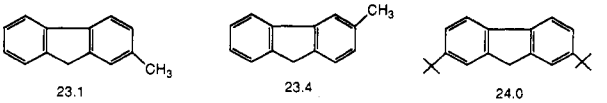


11 **12**

Bis(*tert*-butylphenyl) sulfide[13] **14** was readily prepared by Friedel–Crafts alkylation of diphenyl sulfide in methylene dichloride in the presence of ferric chloride. Upon cyclization with dichloromethyl methyl ether in the presence of the Lewis acid tin(IV) chloride, sulfide **14** gave an approximately 1:1 mixture of 2,7-di-*tert*-butylthioxanthene **15** and the corresponding thioxanthone **16**. In one experiment these compounds were isolated by column

(10) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.

(11) A rough idea of the expected difference in acidity between thioxanthene sulfone and its di-*tert*-butylated derivative can be estimated from the following values given for fluorene (pK_a 22.6) and various alkyl derivatives:



23.1 23.4 24.0

See: (a) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 2867. (b) Streitwieser, A., Jr.; Kaufman, M. J.; Bors, D. A.; Murdoch, J. R.; MacArthur, C. A.; Murphy, J. T.; Shen, C. C. *J. Am. Chem. Soc.* **1985**, *107*, 6983.

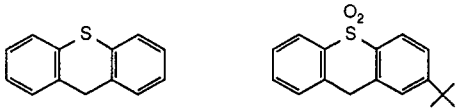
(12) For other examples of the solubility enhancement effected by *tert*-butyl substitution see: Voelter, W.; Müller, J. *Liebigs Ann. Chem.* **1983**, 248.

(13) Franzen, V.; Schmidt, H.-J.; Mertz, C. *Ber.* **1961**, *94*, 2946.

chromatography, but for preparative purposes it was simpler to oxidize the mixture to give the corresponding mixture of sulfones **17** and **18**. Finally the sulfone mixture was reduced by means of red phosphorus and hydriodic acid, thus converting **18** to additional amounts of the desired sulfone **17** (overall yield 60–65%).

An unusual mechanistic aspect of this synthesis is the formation of the 50–50 mixture of **15** and **16** rather than the superficially expected ether **19**. If **19** is an intermediate, it might be expected, in view of the high stability of the xanthylium ion, to undergo a disproportionation-like reaction involving ionization followed by hydride transfer leading eventually to the equimolar mixture of **15** and **16** (Scheme II).

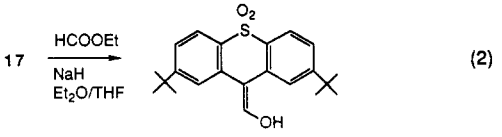
In an alternative route to **17** the mixture of **15** and **16** could first be reduced by the phosphorus/HI technique or by lithium aluminum hydride[14] and the resulting pure sulfide **15** oxidized to **17**. The overall yield was lower (50–55%) by this method due to the final oxidation step, which gave not only **17** but also ketone **18**. Attempts to develop a shorter route to **17** were not successful. For example *tert*-butylation of thioxanthene **22** followed by



22 **23**

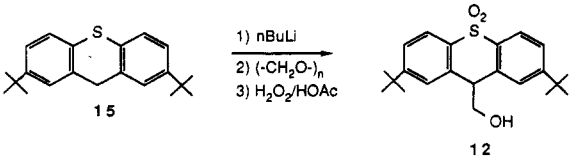
oxidation with hydrogen peroxide gave a mixture from which the mono-*tert*-butyl sulfone **23** was isolated as the major product in 20% yield, whereas the desired di-*tert*-butylated derivative **17** was obtained in only 2% yield.

With adaptation of the method previously used[9] for the synthesis of 9-fluorenemethanol, the key intermediate alcohol **12** was synthesized by treatment of sulfone **17** with



24 (2)

sodium or potassium hydride and ethyl formate in ether–THF (eq 2) followed by reduction of the intermediate aldehyde/vinyl alcohol[15] **24** with sodium borohydride. Alcohol **12** was also synthesized by hydroxymethylation of 2,7-di-*tert*-butylthioxanthene **15** followed by oxidation (eq 3).



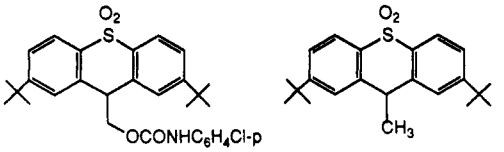
15 **12** (3)

As had been expected, introduction of the 2,7-di-*tert*-butyl substituents into the thioxanthene dioxide nucleus served to increase markedly the solubility of urethanes derived from **12**. Thus DBD-TMOC amino acids were found to be readily soluble in common nonpolar solvents such as methylene dichloride, ether, THF, etc., in contrast to the analogous derivatives of **1**. In addition the presence of the two alkyl substituents made it easier to handle the urethanes without their suffering premature deblocking reactions. It was therefore deemed worthwhile to compare the stability and reactivity of appropriate urethanes with their FMOC analogues. Initial studies were carried out with model urethane **25** (DBD-TMOC-PCA).

Table III. Deblocking of DBD-TMOC-PCA in Dimethyl Sulfoxide[a]

solvt	temp, °C	time	deblocking, %
DMSO	25	19 h	50
DMSO	50	4.5 h	100
DMSO	75	20 min	100
DMSO-d_6	25	19 h	20
DMSO-d_6	50	4.5 h	80
DMSO-d_6	75	20 min	>90
DMSO/0.5% H_2O	50	8 h	100
DMSO/1% H_2O	50	5 h	100

[a] A solution of 50 mg of the urethane in 0.3 mL of the solvent was maintained at the temperature indicated. The reaction was monitored by changes in the *tert*-butyl protons of **27** and the amino group of PCA against the NH and *tert*-butyl peaks for the urethane. Upon completion of the reaction byproduct **27** separates from the solution at room temperature.



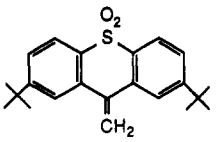
25 **26**

Urethane **25** was unaffected by acidic reagents. Thus, under conditions which readily deblock the benzyloxycarbonyl group, in HBr–HOAc[16] over a period of 3 days at room temperature, the DBD-TMOC group was not attacked. On the other hand, the DBD-TMOC function was deblocked by catalytic transfer hydrogenolysis[17] under conditions similar to those used for the Z- and FMOC groups. For example, treatment of urethane **25** with ammonium formate in the presence of a palladium catalyst in methanol–methylene dichloride for 14 h completely consumed the carbamate with 9-methyl derivative **26** being formed as byproduct from the sulfone moiety.

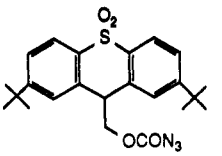
Significantly the DBD-TMOC group is stable in solvents such as chloroform, methylene dichloride, tetrahydrofuran, and 1,4-dioxane. In hydroxylic solvents such as methanol or ethanol, compound **25** can be recovered unchanged after being refluxed for 36 h. Stability was also noted in refluxing acetone or methylene dichloride as well as acetic acid at room temperature. Although more stable than the corresponding derivative of **1** in DMSO compound **25** nevertheless undergoes facile deblocking upon warming to 50–75 °C. Rough rates were measured under various conditions by carrying out the reaction in an NMR tube. Results are summarized in Table III. In DMSO-d_6 the deblocking rate was slower than in reagent grade DMSO, possibly due to contamination by some impurity in one or the other of these solvents. The presence of small amounts of water in the DMSO had only a small influence on the deblocking rate.

A remarkable and unexpected result of considerable practical interest was the fact that after completion of the deblocking process in DMSO, the byproduct methylene sulfone **27** had separated almost completely. Simple filtration provides a solution containing only the desired amine. TLC monitoring of the filtrate shows only a trace of **27**, but if ca. 3% water is present during deblocking or added later, none of the sulfone is detected. It is curious that in comparison with the parent system the precursor

(14) Mustafa, A.; Hilmy, M. K. *J. Chem. Soc.* **1952**, 1343.
(15) For a discussion of the keto–enol tautomerism of the analogous 9-formylfluorene for which the enol form is also favored see: Harcourt, M. P.; More O'Ferrall, R. A. *Bull. Soc. Chim. Fr.* **1988**, 407.
(16) Ben-Ishai, D. *J. Org. Chem.* **1954**, *19*, 62.
(17) (a) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929. (b) Carpino, L. A.; Tunga, A. *J. Org. Chem.* **1986**, *51*, 1930.



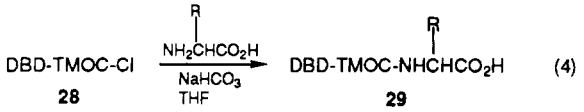
27



30

tert-butylated urethanes are more soluble in DMSO and other solvents, whereas the situation is reversed for the two methylene sulfones. This phenomenon could provide an important practical advantage in using the DBD-TMOC group for peptide chain elongation and segment condensation.[18]

To make preliminary investigations regarding applications to peptide coupling, the synthesis of the simple pentapeptide leucine enkephalin was initiated as a first model. It was found that chloroformate **28** reacted readily



DBD-TMOC-Cl (**28**) $\xrightarrow[NaHCO_3,\ THF]{NH_2CHCO_2H}$ DBD-TMOC-NHCHCO$_2$H (**29**) (4)

in THF solution with free amino acids in the presence of sodium carbonate or bicarbonate at 0 °C to give amino acid derivatives **29** in good yield (eq 4). In contrast to FMOC amino acids, DBD-TMOC amino acids are only slightly soluble in weakly alkaline solution. For example when the two-phase method[19] was applied to the phenylalanine derivative, 90% of the product was obtained from the organic phase and only 10% from the aqueous phase after acidification. All of the FMOC derivative is obtained from the aqueous phase. Presumably the two *tert*-butyl groups greatly increase the hydrophobic character of these compounds.

Certain oligomeric side products are often detected when FMOC amino acids are synthesized by reaction of 9-fluorenylmethyl chloroformate and amino acids.[20] For phenylalanine and α-phenylglycine these impurities, if present in the DBD-TMOC case, were easily removed by simple recrystallization or column chromatography. However, in the case of DBD-TMOC-Gly-OH, impurities present were difficult to remove from the desired protected amino acid by such simple techniques, and an alternate synthetic method was examined. With a view to avoiding the expected side products, the corresponding di- or tripeptides, the *tert*-butyl ester of glycine was substituted for the free amino acid with subsequent cleavage of the ester via 25% CF_3CO_2H/CH_2Cl_2. Other pure protected amino acids were also prepared by this method.

In the FMOC case an alternate method to avoid the formation of oligopeptides involves the use of an active ester[20a,b] or the azidoformate.[20c] However in the DBD-TMOC case attempts to use azide **30** failed. Such attempts gave only methylene sulfone **27** due to facile elimination.

When acid-sensitive amino-protecting groups are used in peptide synthesis, the employment of acid chlorides as coupling agents is not generally possible. This is unfortunate since acid chlorides are among the most reactive acylating agents and generally require among the shortest coupling times for peptide bond formation. In contrast, results for the DBD-TMOC group parallel those recently described for the FMOC case.[19]

DBD-TMOC amino acid chlorides, which are stable crystalline reagents capable of being stored at room temperature for extended periods, are readily synthesized by refluxing the corresponding protected amino acids in methylene dichloride with an excess (10 equiv) of thionyl chloride. Alternatively the acid chlorides can be prepared under very mild conditions at 0 °C in the presence of amide catalysts such as tetramethylurea.[21] Acid chlorides synthesized in the course of the present model studies are described in Table IV and the Experimental Section. Coupling reactions of DBD-TMOC amino acid chlorides with amino acid esters could be carried out via either two- or one-phase methods, the former involving a weak inorganic base such as sodium bicarbonate in the aqueous layer. No deblocking product, sulfone **27**, was found while using the two-phase method. A small amount of the free acid which resulted from hydrolysis of the amino acid chloride could readily be removed by recrystallization or column chromatography.

Coupling reactions were also carried out in the presence of organic bases in homogeneous solution. The coupling of DBD-TMOC-Phg-Cl with alanine methyl ester hydrochloride in THF using a variety of organic bases was studied. A weak base was selected to avoid premature deblocking and racemization. Although the sterically hindered 2,6-di-*tert*-butylpyridine (pK_a = 3.58) does not deblock the DBD-TMOC group, coupling is too slow to be practical with this base. On the other hand, coupling with alanine methyl ester in the presence of the hindered base, diisopropylethylamine, occurs in high yield (85%) at 0 °C for 10 min. If in this case the coupling time is extended to 30 min, a small amount of deblocking occurs. Although tetramethylurea (pK_a = 2) gave no coupling product, the nonbasic acid scavenger propylene oxide[22] gave the dipeptide in 50% yield over a period of 20 min. Aside from the use of acid chlorides in these reactions, the DCC coupling technique, especially in the presence of HOBt, was successfully used.

Although urethane amino-protecting groups generally protect against racemizaton, in the case of the DBD-TMOC function the strong electron-withdrawing inductive effects of the thioxanthene sulfone moiety might be expected to lead to greater loss of chirality than comparable BOC, Z, or FMOC derivatives. These expectations were examined by using a quick NMR test for gross racemization which involves coupling via the α-phenylglycine derivative.[23] When DBD-TMOC-Phg-Cl was treated with alanine methyl ester via the two-phase acid chloride technique at 0 °C (30 min), no significant racemization (<1%) was observed. On the other hand, the same reaction carried out at room temperature (3 min) gave 33%

(18) Attention has often been called to the difficulty of obtaining free N-terminal peptide segments uncontaminated by tertiary bases or other extraneous materials. See: (a) Bodanszky, M. *Int. J. Pept. Protein Res.* **1985**, *449*, 460. (b) Bodanszky, M.; Tolle, J. C.; Gardner, J. D.; Walker, M. D.; Mutt, V. *Int. J. Pept. Protein Res.* **1980**, *16*, 402.

(19) Upon treatment of the free amino acid with DBD-TMOC-Cl (**28**) in a manner analogous to the coupling of FMOC amino acid chlorides. See Carpino L. A.; Cohen, B. J.; Stephens, K. E.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732.

(20) (a) Tessier, M.; Albericio, F.; Pedroso, E.; Grandas, A.; Eritja, R.; Giralt, E.; Granier, C.; Rietschoten, J. *Int. J. Pept. Protein Res.* **1983**, *22*, 125. (b) Sigler, G. F.; Fuller, W. D.; Chaturvedi, N. C.; Goodman, M.; Verlander, M. *Biopolymers* **1983**, *22*, 2157; (c) Laptsanis, L.; Milias, G.; Froussios, K.; Kolovos, M. *Synthesis* **1983**, 671.

(21) Compare Castellvi, J. C.; Coll, A. P. *Afinidad* **1987**, *44*, 333.

(22) Pirkle, W. H.; Alessi, D. M.; Hyun, M. H.; Pochapsky, T. C. *J. Chromatogr.* **1987**, *398*, 203.

(23) Carpino, L. A. *J. Org. Chem.* **1988**, *53*, 875.

Table IV. Characterization of DBD-TMOC-Amino Acid Chlorides

compd[a] (AA)	yield, %	mp, °C	α_D, deg (T, °C)	^{1}H NMR,[b] δ
Phe	76	125	+12.7 (20) (c 0.3, CH_2Cl_2)	1.3 (s, 18, CMe_3), 3.2 (m, 2, $CH_2C_6H_5$), 4.4–4.6 (m, 4, CH_2CH, NCHCO), 5.2 (m, 1, NH), 7.1–8.1 (m, 11, aryl)
Gly	72	72–5		1.3 (s, 18, CMe_3), 4.4 (d, 2, CH_2), 4.6 (m, 3, CH_2CH), 5.5 (m, 1, NH), 7.2–8.2 (m, 6, aryl)
Tyr(Bn)	70	89–92	+19.5 (19) (c 1.2, CH_2Cl_2)	1.3 (s, 18, CMe_3), 3.2 (m, 2, CH_2Ar), 4.4 (m, 3, CH_2CH), 4.6 (m, 1, NCHCO), 5.0 (s, 2, OCH_2), 5.2 (m, 1, NH), 6.8–8.2 (m, 15, aryl)

[a] In each case about 1 mmol of the acid was refluxed with 10 mmol of $SOCl_2$ in 25 mL of CH_2Cl_2 for 30 min, and the solution worked up as given for the Phg analogue in the Experimental Section. The data presented came from samples precipitated once from CH_2Cl_2 by addition of hexane. Each sample was tested by addition to MeOH and TLC spotting which with elution by 40% EtOAc in Skelly B showed only the methyl ester (no spot at origin due to the free acid). All samples showed IR absorption (KBr) at 3400–3450 (NH), 1800 (ClC=O), 1720–1730 (NC=O), 1300 and 1150 (SO_2) cm^{-1}. [b] Solvent: $CDCl_3$.

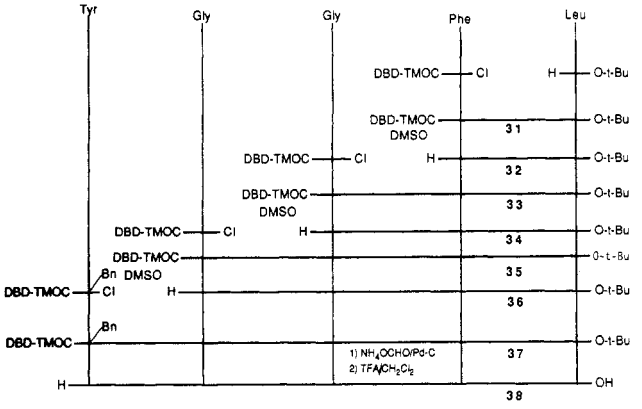


Figure 1.

of the DL diastereomer. No racemization occurs with FMOC-α-phenylglycine chloride under similar conditions at room temperature. Under one-phase conditions in the presence of diisopropylethylamine at −10 °C (10 min) no racemization was noted. With the DCC technique at −10 °C (14 h) use of HOBt led to no detectable racemization, whereas 6–8% of the DL form was noted with HOSu as additive.

A more sensitive HPLC test[24] involving coupling of DBD-TMOC-Phe-Cl with leucine methyl ester by the two-phase technique or DCC coupling in the presence of HOBt showed no detectable amount of the DL-dipeptide (<0.1%) in either case. These results show that under appropriate conditions coupling reactions involving DBD-TMOC-protected amino acids can be carried out safely. With this demonstration, the synthesis of a simple model peptide, leucine enkephalin **38**, was undertaken. The sequence of reactions used in the synthesis is shown in Figure 1. Synthesis began with a sample of **31** which had been synthesized in connection with prior racemization studies by two-phase coupling at 0 °C for 30 min. Subsequent steps were carried out without isolation of the deblocked intermediates and using only quick flash chromatography to obtain the protected compounds. For example, the protected dipeptide **31** was warmed at 60–70 °C in DMSO for 50 min. After removal of methylene sulfone **27** the filtrate was treated directly with 10 volumes of methylene dichloride, 10% sodium bicarbonate solution, and the DBD-TMOC derivative of glycyl chloride. The crude protected tripeptide **33** was deblocked similarly although a longer time was required (16 h). In addition, following filtration to remove **27**, the DMSO solvent was removed in vacuo prior to the next acylation so as to minimize hydrolysis of the acid chloride since it was noted that the presence of significant amounts of DMSO during the two-phase acylation process enhanced the undesired hydrolysis of the acid chloride. The pentapeptide **37** was made similarly. In this case the prior deblocking step required 10 h for completion.

Finally **37** was deblocked first by catalytic transfer hydrogenolysis to remove both the DBD-TMOC and benzyl ether functions and second by 50% TFA in methylene dichloride to remove the *tert*-butyl group. The resulting pentapeptide **38** was shown to be identical with an authentic sample according to comparison of physical properties and spectral data. It was also shown that the peptide isolated was not contaminated by any significant quantity of the corresponding D-Phe[4]-leucine enkephalin diastereomer which can readily be separated from the normal isomer by an HPLC technique.

Conclusion. This work has shown that the DBD-TMOC group can be used in the synthesis of a simple peptide with the sequential deblocking step involving only warming in the neutral solvent DMSO. This novel technique could be useful in the case of sequences for which acidic or basic reagents are contraindicated or for systems where bases (e.g., pyridine) milder than those normally used for the FMOC system might be advantageous. Side reactions involving diketopiperazine, pyroglutamic acid, or succinimide formation might be ameliorated or eliminated. DBD-TMOC protection might also be useful in connection with segment condensation. Thus synthesis of an appropriate segment via FMOC or *t*-BOC α-protection could be followed by introduction of only the final N-terminal amino acid as the DBD-TMOC derivative. The resulting protected segment could then be used to obtain a solution of the free N-terminal unprotected segment in DMSO or DMF. It remains to be seen whether the sluggishness observed during the solvolytic removal of the DBD-TMOC function on passing from the di- to the tri- and tetrapeptide derivatives is a general phenomenon.

Experimental Section

Instrumentation and General Procedures. Melting points obtained in open capillary tubes with a Mel-Temp apparatus and boiling points were uncorrected. Infrared spectra were determined on Perkin-Elmer Model 237B, 1310, 1420, or 1600 FT spectrometers, and ^{1}H NMR spectra on Perkin-Elmer R-12 (60 MHz) or Varian XL-200 (200 MHz) or XL-300 (300 MHz) instruments with Me_4Si as internal standard. For racemization tests based on NMR analysis sensitivities were 60 MHz (2–3%) and 300 MHz (~1%). Elemental analyses were carried out by the University of Massachusetts Microanalytical Laboratory under the direction of Greg Dabkowski. Thin-layer chromatography was performed on aluminum-backed Merck silica gel 60 F254 plates. Separations by flash chromatography were achieved with Merck silica gel 9385 (230–400 mesh). Optical rotations were determined on a Rudolph Autopol-III digital polarimeter using quartz cells and HPLC analyses with a Waters automated system incorporating a Model 721 system controller; M730 data module, U6K injector, 710B

(24) Carpino, L. A.; Rice, N. W.; Mansour, E. M. E.; Triolo, S. A. *J. Org. Chem.* **1984**, *49*, 836.

Wisp, 510 and 6000A pumps, Z-Module radial compression units, and a 441 absorbance detector.

9-(Hydroxymethyl)thioxanthene 10,10-Dioxide (1). Thioxanthene was converted to 9-(hydroxymethyl)thioxanthene 4 by the method of Bergmann[6] except that commercial *n*-butyllithium was used. To a solution of 20 g of **4** in 50 mL of acetic acid was slowly added 50 g of 30% H_2O_2 (100% excess). The mixture was stirred overnight at room temperature, diluted with 150 mL of water, and filtered to give 14 g (61.4%) of the crude dioxide, mp 218–220 °C. Recrystallization from nitromethane–chloroform (1:4) gave 12 g (52.6%) of the pure sulfone alcohol, mp 219 °C; IR (KBr) 1310, 1160 cm^{-1} (SO_2); ^1H NMR (DMSO-d_6) δ 3.85 (d, 2, CH_2O), 4.4 (t, 1, CH), 5.5 (s, 1, OH), 7.5–7.65 (m, 6, aryl), 7.9–8.2 (m, 2, H_4, H_5).

Anal. Calcd for $C_{14}H_{12}O_3S$: C, 64.61; H, 4.62; S, 12.31. Found: C, 64.42; H, 4.72; S, 12.33.

9-Methylenethioxanthene 10,10-Dioxide (5). Into a 500-mL round-bottomed flask fitted with a magnetic stirrer and a reflux condenser were introduced 20 g of thioxanthene 10,10-dioxide (**2**) and 200 mL of anhydrous ether (distilled over $LiAlH_4$). A current of dry N_2 was passed through the solution, the flask was cooled to −15 °C with dry ice–acetone, and 60 mL of *n*-butyllithium (2.0 M, in *n*-hexane) and 40 mL of anhydrous ether were added. The solution was stirred at −15 °C for 30 min, and 6 g of paraformaldehyde (dried over concentrated H_2SO_4 for 24 h) added at −15 °C. The mixture was refluxed for 35 min, cooled, and treated with ice and dilute (25%) H_2SO_4. Filtration gave 17 g of the olefin, mp 214–217 °C. Extraction of the aqueous filtrate with chloroform gave an additional 2 g of crude olefin. The combined solid (19 g, 90.5%) was recrystallized from chloroform to give 17.5 g (83.3%) of the pure methylene sulfone, mp 212–213 °C; ^1H NMR ($CDCl_3$) δ 6.02 (s, 2, $=CH_2$), 7.65 (m, 6, aryl), 8.1 (m, 2, H_4, H_5).

Anal. Calcd for $C_{14}H_{10}O_2S$: C, 69.42; H, 4.13; S, 13.22. Found: C, 69.47; H, 4.16; S, 13.24.

D-TMOC-Cl (7). A solution of 5.7 g of phosgene in 100 mL of CH_2Cl_2 was cooled in an ice bath, and 10 g of **1** was added slowly with stirring. The solution was stirred in the ice bath for 1 h and stored for an additional 4 h at the same temperature. Removal of solvent and excess phosgene under reduced pressure gave an oil which soon solidified. Recrystallization from anhydrous ether gave 9.5 g (76.6%) of the chloroformate as colorless crystals, mp 158 °C (dec); IR ($CHCl_3$) 1780 (C=O), 1310, 1160 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 4.5–4.9 (m, 3, $CHCH_2$), 7.6 (m, 6, aryl), 8.15 (m, 2, H_4, H_5).

Anal. Calcd for $C_{15}H_{11}ClO_4S$: C, 55.81; H, 3.42. Found: C, 56.01; H, 3.62.

D-TMOC-PCA (8, R = C_6H_4Cl-*p*). To a solution of 3.2 g of **7** in 200 mL of benzene was added dropwise with stirring and cooling in an ice bath 2.6 g of *p*-chloroaniline dissolved in 25 mL of benzene. The mixture was stirred in the ice bath for 30 min and at room temperature for 1 h and then treated with 5 mL of H_2O. After this was stirred for another 10 min, filtration gave 3.9 g (94%) of the crude carbanilate, mp 187–189 °C. Recrystallization from ethanol gave 3.6 g (87%) of the pure urethane, mp 189 °C; IR ($CHCl_3$) 3400, 3350 (NH), 1720 (C=O), 1300, 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 4.2–4.6 (m, 3, $CHCH_2$), 7.15–7.35 (d, 4, aryl amine), 7.45–7.65 (m, 6, aryl), 7.9–8.0 (m, 2, H_4, H_5), 9.8 (s, 1, NH). The same compound was obtained by treatment of alcohol **1** with *p*-chlorophenyl isocyanate.

Anal. Calcd for $C_{21}H_{16}ClNO_4S$: C, 60.94; H, 3.87; N, 3.39; S, 7.74; Cl, 8.59. Found: C, 60.72; H, 4.00; N, 3.37; S, 7.71; Cl, 8.56.

D-TMOC-Phe-OH. To a solution of 2 g of phenylalanine in 30 mL of 10% $NaHCO_3$ and 10 mL of dioxane was added slowly with stirring and ice bath cooling a solution of 3.9 g of D-TMOC-Cl in 20 mL of dioxane. The mixture was stirred in the ice bath for 1 h and at room temperature for another 2 h, poured into 300 mL of H_2O, and extracted with ether. The aqueous layer was cooled in an ice bath and acidified with concentrated HCl. The oily precipitate was collected and recrystallized from CH_2Cl_2 to give 4.5 g (82.4%) of the pure material, mp 75 °C (dec); $[\alpha]^{28}_D$ +6.5 (c = 1.5, EtOAc); IR ($CHCl_3$) 3550, 3300 (NH and OH), 1730 (C=O), 1310, 1160 (SO_2); ^1H NMR ($CDCl_3$) δ 3.15–3.3 (m, 2, CH_2), 4.4–4.7 (m, 4, CH_2CH, CHN), 6.59 (b, 1, NH), 7.25–7.75 (m, 11, aryl), 7.9–8.1 (m, 2, H_4, H_5), 12.5 (b, 1, OH).

Anal. Calcd for $C_{24}H_{21}NO_6S$: C, 63.86; H, 4.66. Found: C, 63.71; H, 5.11.

Piperidine Cleavage of D-TMOC-PCA. A solution of 1 g of D-TMOC-PCA in 10 mL of piperidine was stirred at room temperature for 30 min and then poured into 250 mL of cold water. The precipitated solid was filtered, and the filtrate extracted with ether. Evaporation of the dried ($MgSO_4$) ether extracts gave 0.27 g (89%) of *p*-chloroaniline, mp 73 °C, identified by mixture melting point and comparison of its IR spectrum with that of an authentic sample. The solid (0.75 g, 95%) precipitated from the original aqueous solution was recrystallized from ether to give 0.7 g (89%) of *N*-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthenyl)methyl]piperidine, mp 127–128 °C; IR ($CHCl_3$) 1310, 1170 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.4–1.6 (m, 6, $CH_2CH_2CH_2$), 2.3–2.5 (m, 4, CH_2NCH_2), 2.9 (d, 2, CH_2N), 4.2 (t, 1, CH), 7.5 (m, 6, aryl), 8.0–8.2 (m, 2, H_4, H_5). The same compound was obtained by treatment of **5** with piperidine. For other derivatives see Table I.

Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.72; H, 6.42; N, 4.28; S, 9.79. Found: C, 69.67; H, 6.62; N, 4.19; S, 9.92.

Imidazole Cleavage of D-TMOC-PCA. A solution of 1 g of D-TMOC-PCA and 1 g of imidazole in 20 mL of CH_2Cl_2 was stirred at room temperature for 4 h. The solvent was evaporated to dryness, and the residue washed with 50 mL of hot water. The aqueous washings were concentrated in vacuo to about 2 mL and cooled in a refrigerator to give 0.14 g (46%) of *p*-chloroaniline, mp 72–73 C, identified by mixture melting point and IR spectral comparison with an authentic sample. The original water-insoluble residue was recrystallized from ethanol to give 0.7 g (93%) of the imidazole adduct of **5** as colorless prisms, mp 167–168 °C; ^1H NMR ($CDCl_3$) δ 4.4–4.6 (m, 3, $CHCH_2$), 7–7.6 (m, 9, aryl + imidazole), 8–8.2 (m, 2, H_4, H_5).

Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.81; H, 4.52; N, 9.03. Found: C, 65.50; H, 4.71; N, 8.75.

Deblocking of D-TMOC-PCA by Pyridine Bases. In a 25-mL round-bottomed flask a mixture of 2 g of D-TMOC-PCA and 20 mL of pyridine was stirred at room temperature. At 5-min intervals a sample was removed to test for completeness of deblocking by monitoring the decrease of the carbonyl band at 1730 cm^{-1} in the IR spectrum and the signal for the $CHCH_2$ group at δ 4.5 in the ^1H NMR spectrum. Reaction was complete within 30 min. A separate run led to the isolation of 95% of pure **5**, mp 219 °C, and 93% of pure *p*-chloroaniline, mp 72 °C. Under the same conditions 2-picoline and 2,6-lutidine required 3 and 12 h to effect complete deblocking.

Solvolytic Deblocking of D-TMOC-PCA. A solution of 40 mg of the urethane in 0.5 mL of CD_3SOCD_3 in an ^1H NMR tube was maintained at 38 °C, and the rate of deblocking followed by the increase in intensity of peaks at δ 6.0 due to the olefinic protons of **5** and those at δ 5.0 due to the amino group of *p*-chloroaniline and the decrease of those at δ 4.2–4.5 and 9.7 due to the urethane ($CHCH_2$ and NH groups, respectively). The half-life was about 6 h, and complete reaction required 18 h. Results for a variety of compounds are collected in Table I. On a preparative scale, a solution of 1 g of D-TMOC-PCA in 15 mL of DMSO was heated in a water bath at 40 °C. After 18 h the mixture was poured into 300 mL of water. Filtration gave 0.55 g (94%) of **5**, mp 218–219 °C.

Solvolytic Deblocking of D-TMOC-Gly-OH in DMSO. A solution of 1 g of D-TMOC-Gly-OH in 10 mL of DMSO was stirred at 40 °C for 8 h. A precipitate that gradually separated was filtered and washed with a little ethanol and ether to give 0.15 g (75%) of a colorless solid, mp 262 °C, which was identified as glycine by comparison of its IR and NMR spectra with those of an authentic sample. The DMSO filtrate, added to 150 mL of cold water, gave 0.64 g (96%) of **5**, mp 219–220 °C.

Bis(4-*tert*-butylphenyl) Sulfide (14). To a solution of 83.2 mL (0.5 mol) of phenyl sulfide and 4.1 g (0.025 mol) of ferric chloride in 100 mL of methylene chloride was added a solution of 172 mL (1.5 mol) of *tert*-butyl bromide and 120 mL of methylene chloride with mechanical stirring. The mixture was refluxed for 72 h and washed twice with 150-mL portions of 10% HCl, twice with 150-mL portions of water, twice with 150-mL portions of 5% NaOH, twice with 150-mL portions of water, and finally with 150 mL of saturated NaCl solution. Drying over $MgSO_4$ and removal of solvent gave a pink–yellow solid which was recrystallized from MeOH to give 118 g (80%) of the sulfide, mp 78–79 °C (lit.[13] mp 83–83.5 °C); ^1H NMR ($CDCl_3$) δ 1.25 (s, 18, CMe_3),

7.3 (m, 8, aryl); IR (KBr) 3080, 1600, 1500, 1410, 1370 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}S$: C, 80.4; H, 8.78; S, 10.74. Found: C, 80.67; H, 9.15; S, 10.55.

2,7-Di-*tert*-butylthioxanthene (15). Method A. A solution of 12.8 mL (0.11 mol) of tin(IV) chloride and 10.1 mL (0.11 mol) of dichloromethyl methyl ether in 60 mL of methylene chloride was cooled at 0 °C under nitrogen. To the pink solution was added dropwise 15 g (0.05 mol) of **14** in 60 mL of methylene chloride with stirring. The red solution was stirred at room temperature for 12 h. The reaction mixture was poured into 80 g of ice water slowly, and the organic layer was washed with water, 10% $NaHCO_3$, and water and dried over $MgSO_4$. Removal of solvent by means of a rotary evaporator gave 14 g of a yellow oil which was a 1:1 mixture of **15** and **16**. Without any attempt to separate the two products, the mixture was reduced directly. A solution of 15 g of the mixture, 15 mL of 57% hydriodic acid, and 15 g of red phosphorus in 120 mL of propionic acid was refluxed for 48 h, cooled, and diluted with 300 mL of H_2O. The residue was filtered and treated with $CHCl_3$ to remove red phosphorus. After filtration the filtrate was washed with H_2O, 10% $Na_2S_2O_3$, and H_2O and finally dried over $MgSO_4$. After removal of solvent by rotary evaporation the residue was recrystallized from MeOH to give 12.5 g (81%) of the sulfide, mp 152–154 °C; ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 3.85 (s, 2, CH_2), 7.25–7.5 (m, 6, aryl); IR (KBr) 3080, 1620, 1460, 1400, 1370 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}S$: C, 81.23; H, 8.44; S, 10.33. Found: C, 81.45; H, 8.61; S, 10.24.

Method B. The red oil obtained as described above from 12 g of bis(4-*tert*-butylphenyl) sulfide was dissolved in 100 mL of dry ether, and the solution added dropwise over 15 min to a suspension of 2.5 g of lithium aluminum hydride in 100 mL of dry ether while cooling in an ice bath. The mixture was refluxed for 3 h and cooled, and excess hydride destroyed by means of saturated ammonium chloride solution. The ether layer was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and evaporated to a white solid which was recrystallized from CH_2Cl_2–hexane to give 9.0 g (72%) of the thioxanthene as white crystals, mp 152–154 °C, identified by comparison of melting point and spectral properties with the sample prepared in method A above.

2,7-Di-*tert*-butylthioxanthenone (16). The 1:1 mixture of **15** and **16** was obtained as described above from 12 g of **14**, 100 mL of CH_2Cl_2, 21 g of $SnCl_4$, and 9.27 g of α,α-dichloromethyl methyl ether. The crude red oil was chromatographed on silica gel. Elution by means of hexane–ethyl acetate (95/5) removed 4.6 g (37%) of **15** (see above), after which there was obtained 4.65 g (37%) of **16**, which was recrystallized from hexane–CH_2Cl_2 as yellow crystals, mp 176–178 °C; ^1H NMR ($CDCl_3$) δ 1.35 (s, 18, CH_3), 7.5 (m, 4, aryl), 8.75 (d, 2, CHCCO).

Anal. Calcd for $C_{21}H_{24}OS$: C, 77.73; H, 7.46; S, 9.88. Found: C, 77.83; H, 7.58; S, 9.75.

2,7-Di-*tert*-butylthioxanthene 10,10-Dioxide (17). Method A. The oil obtained from 38.5 mL (0.33 mole) of tin(IV) chloride, 30.5 mL (0.33 mol) of dichloromethyl methyl ether in 180 mL of methylene chloride and 50 g (0.05 mole) of **14** in 180 mL of methylene chloride obtained as described above was oxidized by dissolving in 300 mL of acetic acid and adding slowly 200 mL of 30% H_2O_2. The mixture was refluxed for 4 h, cooled, and diluted with 500 mL of H_2O to give a yellowish solid which proved to be a mixture of **17** and **18**. Without isolation of the components of the mixture it was reduced directly. A solution of 52 g of the sulfone mixture, 51 mL of 57% hydriodic acid, and 48 g of red phosphorus in 400 mL of propionic acid was refluxed for 48 h, cooled, and diluted with 800 mL of H_2O. The residue was filtered and treated with $CHCl_3$ to remove red phosphorus. After filtration the filtrate was washed with H_2O, 10% $Na_2S_2O_3$, and H_2O and then dried over $MgSO_4$. After removal of solvent by rotary evaporation the residue was recrystallized from MeOH to give 41 g (71%) of the pure sulfone, mp 190–191 °C; ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 4.25 (s, 2, CH_2), 7.35–8.1 (m, 6, aryl); IR (KBr) 3070, 1600, 1460, 1320, 1150 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_2S$: C, 73.64; H, 7.65; S, 9.35. Found: C, 73.44; H, 7.40; S, 9.44.

Method B. To a solution of 5 g of 2,7-di-*tert*-butylthioxanthene in 30 mL of acetic acid was added slowly 20 mL of 30% H_2O_2, and the mixture refluxed for 4 h. After cooling, dilution with 120 mL of H_2O gave a yellowish solid which was recrystallized from MeOH to give 4.8 g (88%) of the pure sulfone, mp 190–191 °C, identified by spectral comparison with the sample prepared as described in method A.

2-*tert*-Butylthioxanthene 10,10-Dioxide (23). To a solution of 5 g (25 mmol) of thioxanthene and 11.7 mL (100 mmol) of *tert*-butyl bromide in 110 mL of nitromethane was added, in small portions and at intervals of 20 min, 14 g (100 mmol) of anhydrous aluminum chloride with stirring and cooling in an ice bath. The reaction mixture was heated at 45–55 °C for 24 h, allowed to cool to room temperature, and poured into a solution of 30 g of crushed ice and 15 mL of concentrated HCl. Undissolved material was filtered, and the filtrate extracted twice with 150-mL portions of CH_2Cl_2. The organic phase was washed with 50% HCl and H_2O. After drying over $MgSO_4$ and removal of solvent there was obtained 5.5 g of a dark oil. The oil was dissolved in 70 mL of acetic acid, 20 mL of 30% H_2O_2 added slowly, and the mixture refluxed for 4 h. After cooling, the solution was poured into 120 mL of H_2O to give 5 g of dark oil. The oil was extracted four times with 50-mL portions of hot hexane. Evaporation of solvent gave 3 g of a yellow oil which was mixed with 6 g of zinc dust and 30 mL of acetic acid, and the mixture was treated in small portions with 2 mL of concentrated HCl. After this was heated for 30 minutes, an additional 2 mL of concentrated HCl was added, the mixture refluxed for 8 h and cooled, and the filtrate diluted with 100 mL of H_2O to give 2.7 g of yellow oil. Column chromatography on silica gel (230–400 mesh, 100 g) with elution by 25% EtOAc–hexane gave 1.3 g (20%) of the mono-*tert*-butyl product. The analytical sample was recrystallized from EtOH, mp 102–104 °C; ^1H NMR ($CDCl_3$) δ 1.3 (s, 9, CMe_3), 4.25 (s, 2, CH_2), 7.35–8.2 (m, 7, aryl); IR (KBr) 3080, 1475, 1330, 1120 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}SO_2$: C, 71.30; H, 6.34; S, 11.20. Found: C, 71.53; H, 6.46; S, 10.76.

9-(Hydroxymethyl)-2,7-di-*tert*-butyl-10,10-dioxythioxanthene (12). Method A. A solution of 4.8 g of **17** in 8 mL of dry THF and 80 mL of dry ether was cooled in an ice bath under nitrogen. To the solution was added 1.68 g (35 mmol) of 50% NaH in oil with stirring. After addition was complete, the solution was warmed to room temperature and refluxed for 30 min. A solution of 10.5 mL (140 mmol) of ethyl formate in 20 mL of ether was added dropwise. After the mixture had been refluxed for 4 h, it was cooled to room temperature and small chips of ice were added to decompose excess NaH. The resulting solution was poured into 120 mL of ice water. The aqueous solution was extracted three times with 40-mL portions of ether and three times with 40-mL portions of Skelly B and acidified to Congo Red with 5% H_2SO_4. The precipitate was dissolved in 200 mL of EtOAc, washed with 5% $NaHCO_3$, H_2O, and saturated NaCl solution, and dried over $MgSO_4$. After removal of solvent by rotary evaporation, the viscous residue was dissolved in 240 mL of methanol and treated over 4–5 min with 4 g of sodium borohydride. During this period gas evolution and spontaneous warming occurred. The solution was stirred at room temperature for 3 h. After dilution with 560 mL of water, the solution was treated with 300 mL of 5% H_2SO_4 and stirred at room temperature for 1 h. Filtration followed by washing with water gave a white solid which was recrystallized from CH_2Cl_2–hexane to give 3.2 g (60%) of the alcohol, mp 200–202 °C; ^1H NMR ($CDCl_3$) δ 1.35 (s, 18, CMe_3), 3.95–4.4 (m, 3, $CHCH_2$), 7.3–8.2 (m, 6, aryl); IR (Nujol) 3550–3400 (OH), 1300, 1140 (SO_2) cm^{-1}.

Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.87; H, 7.51; S, 8.59. Found: C, 70.99; H, 7.91; S, 8.40.

Method B. To a solution of 10 g of 9-(hydroxymethyl)-2,7-di-*tert*-butylthioxanthene in 50 mL of acetic acid was added slowly 25 g of 30% H_2O_2, and the mixture heated at 100 °C for 4 h. Cooling, dilution with 200 mL of water, and filtration gave 7 g of the crude sulfone. Recrystallization from CH_2Cl_2–hexane gave 6 g (55%) of the sulfone as white crystals, mp 200–203 °C, identified by comparison of physical and spectral properties with the sample prepared in method A.

9-(Hydroxymethyl)-2,7-di-*tert*-butylthioxanthene. To a solution of 15 g of 2,7-di-*tert*-butylthioxanthene (**15**) in 150 mL of dry THF cooled to −75 °C was added dropwise 20 mL of *n*-butyllithium solution (2.45 M). A deep red color developed. After stirring at −75 °C for 30 min, 5 g of paraformaldehyde was added slowly. The mixture was then allowed to warm to room

temperature and refluxed for 30 min. Completion of the reaction was signalled by discharge of the red color. The mixture, which contained a grey precipitate, was cooled and decomposed with ice and 25% H_2SO_4. Extraction of the aqueous layer with CH_2Cl_2, followed by washing of the extracts with H_2O, 5% $NaHCO_3$, H_2O, and saturated NaCl solution, drying ($MgSO_4$), and evaporation gave an oily material which was purified by chromatography on silica gel by elution with hexane–ethyl acetate (95/5). The alcohol was obtained as a white solid, mp 158–159 °C.

Anal. Calcd for $C_{22}H_{28}OS$: C, 77.64; H, 8.13; S, 9.41. Found: C, 77.72; H, 8.52; S, 9.28.

DBD-TMOC-Cl. To a solution of 5 g of phosgene in 150 mL of dry THF was slowly added, with stirring, 8.7 g of **12** while cooling in an ice bath. The solution was then stirred in the ice bath for 2 h and at room temperature for 4 h. Excess phosgene was removed by a stream of N_2, and THF evaporated to a white solid which upon recrystallization from ether gave 8.85 g (87%) of the chloroformate as white crystals, mp 200–201 °C (dec); ^1H NMR ($CDCl_3$) δ 1.35 (s, 18, CH_3), 4.7 (m, 3, $CHCH_2$), 7.6 (m, 4, aryl), 8.1 (d, 2, $CHCSO_2$).

Anal. Calcd for $C_{23}H_{27}ClO_4S$: C, 63.51; H, 6.26; S, 7.37. Found: C, 63.68; H, 6.48; S, 7.08.

DBD-TMOC-N_3 (30). To a solution of 0.07 g (1.08 mmol) of NaN_3 in 1 mL of H_2O was added slowly a solution of 0.3 g (0.69 mmol) of DBD-TMOC-Cl in 1.5 mL of acetone with stirring in an ice bath. The mixture was stirred in the ice bath for 2 h and at room temperature for 2 h. The solid was filtered, washed with water, and recrystallized from CH_2Cl_2–hexane to give 0.25 g (82%) of the azide, mp 142–143 °C; ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 4.5–4.85 (m, 3, CH_2CH), 7.5–8.2 (m, 6, aryl); IR (KBr) 2240 (N_3), 1750 (C=O), 1310, 1150 (SO_2) cm^{-1}.

Anal. Calcd for $C_{23}H_{27}N_3O_4S$: C, 62.57; H, 6.16. Found: C, 62.14; H, 6.51.

9-Methylene-2,7-di-*tert*-butyl-10,10-dioxythioxanthene (27). A solution of 1 g of DBD-TMOC-PCA and 8 mL of dimethyl sulfoxide was heated in a sand bath with the temperature being kept at 60–70 °C, for 45 min. The mixture was poured into 50 mL of water. Filtration gave 0.67 g (91%) of a white solid which was recrystallized from EtOH–EtOAc to give 0.55 g (82%) of the olefinic sulfone, mp 245–246 °C; ^1H NMR ($CDCl_3$) δ 1.35 (s, 18, CMe_3), 6.05 (s, 2, $=CH_2$), 7.45–8.2 (m, 6, aryl); IR (KBr) 1650 (C=C), 1600, 1480 (aryl), 1300, 1160 (SO_2).

Anal. Calcd for $C_{22}H_{26}O_2S$: C, 74.54; H, 7.39; S, 9.04. Found: C, 74.48; H, 7.61; S, 9.19.

Deblocking of DBD-TMOC-PCA in Dimethyl Sulfoxide. A solution of approximately 50 mg of DBD-TMOC-PCA in 0.3 mL of ordinary dimethyl sulfoxide was placed in an NMR tube. The rate of cleavage was estimated by the increase in intensity of the peaks due to the *tert*-butyl proton of methylene sulfone **27** at δ 1.35 and those of the amino group of *p*-chloroaniline at δ 5.1 and by the decrease in intensity of peaks due to the NH group of the urethane moiety at δ 9.8 and the *tert*-butyl group at δ 1.3 for DBD-TMOC-PCA. After completion of the deblocking process, the byproduct **27** precipitated from the solution at room temperature. From NMR and TLC analysis it was shown that the methylene sulfone could be completely precipitated from DMSO solution by adding about 3% water. NMR analysis was used in estimation of the crude deblocking rates for other solvent systems. Results are collected in Table III.

Stability of DBD-TMOC-PCA in Hydrogen Bromide–Acetic Acid. Hydrogen bromide gas was led from a gas tank into a graduated cylinder which was cooled with dry ice to collect a measured amount of HBr. The concentration of the HBr–AcOH used in the test was 6.7 M. A solution of 50 mg of DBD-TMOC-PCA in 3 mL of the HBr–AcOH solution was stirred at room temperature for 4 days and diluted with 15 mL of water. After filtration the precipitate was washed with water to give 40 mg of a pink–yellow solid which was identified by NMR analysis as recovered starting material, mp 152–156 °C.

DBD-TMOC-Phe-O-*t*-Bu. To a solution of 0.12 g (0.46 mmole) of H-Phe-O-*t*-Bu·HCl in 5 mL of 10% $NaHCO_3$ was added slowly 0.2 g (0.46 mmole) of DBD-TMOC-Cl in 5 mL of THF with stirring in an ice bath. The mixture was stirred at 0 °C for 20 min and diluted with 15 mL of ether. The organic layer was washed with 7 mL of water, 7 mL of 5% HCl, and 7 mL of water and dried over $MgSO_4$. After removal of solvent a white solid was obtained which was recrystallized from EtOAc–Skelly B to give 0.22 g (77%) of the *tert*-butyl ester, mp 162–164 °C (dec); $[\alpha]^{19}_D$ = +10.5° (*c* 0.2, EtOAc); ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 1.4 (s, 9, $OCMe_3$), 3–3.2 (d, 2, $CH_2C_6H_5$), 4.4–4.6 (m, 4, $CHCH_2$ and CH (Phe)), 7.15–8.2 (m, 11, aryl); IR (KBr) 3400 (NH), 1720 (C=O), 1360, 1150 (SO_2) cm^{-1}.

Anal. Calcd for $C_{36}H_{45}O_6NS$: C, 69.76; H, 7.32; N, 2.26. Found: C, 69.70; H, 7.39; N, 2.16.

DBD-TMOC-Phe-OH. Method A. To a solution of 0.38 (2.3 mmol) of phenylalanine in 15 mL of 10% Na_2CO_3 was slowly added 1 g (2.3 mmol) of DBD-TMOC-Cl in 15 mL of THF while cooling in an ice bath. After stirring at 0 °C for 2 h, the whole solution was acidified with concentrated HCl to Congo Red with vigorous stirring. The solution was extracted three times with 15-mL portions of EtOAc. The organic solution was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. After removal of solvent the crude product was recrystallized from 20% EtOAc–Skelly B to give 0.9 g (70%) of the protected phenylalanine, mp 193–195 °C (dec); $[\alpha]^{20}_D$ = +14.4° (*c* 1, EtOAc); ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 3.05–3.25 (d, 2, $CH_2C_6H_5$), 4.4–4.6 (m, 4, $CHCH_2$ and NCHCO), 5.4 (m, 1, NH), 7.2–8.2 (m, 11, aryl); IR (KBr) 3400, 3300 (br s, NH and OH), 1730 (C=O), 1310, 1160 (SO_2) cm^{-1}.

Anal. Calcd for $C_{32}H_{37}O_6NS$: C, 68.18; H, 6.62; N, 2.48. Found: C, 68.29; H, 6.75; N, 2.40.

Method B. A solution of 1 g (0.3 mmol) of DBD-TMOC-Phe-O-*t*-Bu in 40 mL of 25% CF_3CO_2H–CH_2Cl_2 was stirred at room temperature overnight. After removal of solvent under reduced pressure, the crude product was recrystallized from EtOAc–Skelly B to give 0.66 g (72%) of the protected phenylalanine, mp 193–195 °C. The properties of the acid agreed with those given in method A.

DBD-TMOC-Phg-OH. To a solution of 0.2 g (1.3 mmol) of α-phenylglycine in 10 mL of 10% Na_2CO_3 was slowly added 0.5 g (1.2 mmol) of DBD-TMOC-Cl in 10 mL of THF in an ice bath. Workup as given for the phenylalanine analogue gave 0.51 g (80%) of the protected α-phenylglycine, mp 207–208 °C; $[\alpha]^{20}_D$ = +73° (*c* 1, EtOAc); ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 4.4–4.6 (br s, 3, $CHCH_2$), 5.4 (d, 1, NCHCO), 5.8 (m, 1, NH), 7.3–8.2 (m, 11, aryl); IR (KBr) 3300 (NH and OH), 1720 (C=O), 1350, 1150 (SO_2) cm^{-1}.

Anal. Calcd for $C_{31}H_{35}O_6NS$: C, 67.74; H, 6.42; N, 2.55. Found: C, 67.65; H, 6.53; N, 2.50.

DBD-TMOC-Gly-OH. To a solution of 0.5 g (3.2 mmol) of H-Gly-O-*t*-Bu·H_3PO_3 in 18 mL of $NaHCO_3$ was added slowly 0.9 g (2.2 mmol) of DBD-TMOC-Cl in 18 mL of THF with stirring in an ice bath. The remainder of the process followed that given for the Phe analogue. The crude *tert*-butyl ester was then cleaved by TFA as also described for the Phe derivative. There was obtained 0.8 g (80%) of the protected glycine, mp 130–132 °C; ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 3.9–4.1 (d, 2, NCH_2CO), 4.5–4.7 (m, 3, CH_2CH), 5.6 (m, 1, NH), 7.5–8.2 (m, 6, aryl); IR (KBr) 3450 (NH and OH), 1700 (C=O), 1300, 1150 (SO_2).

Anal. Calcd for $C_{25}H_{31}NO_6S$: C, 63.41; H, 6.60; N, 2.96. Found: C, 63.39; H, 6.59; N, 2.94.

DBD-TMOC-Tyr(Bn)-OH. To a solution of 0.6 g (2.3 mmol) of *O*-benzyltyrosine hydrochloride in 20 mL of 10% Na_2CO_3 was slowly added 1 g (2.3 mmol) of DBD-TMOC-Cl in 20 mL of THF while cooling in an ice bath. Workup as described for the phenylalanine analogue gave 0.9 g of colorless oil. Column chromatography on silica gel (230–400 mesh, 20 g) with elution by 40% EtOAc–Skelly B gave 0.6 g (40%) of the protected tyrosine as a colorless oil, $[\alpha]^{20}_D$ = +15.6° (*c* 0.7, EtOAc); ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 3.1 (d, 2, $CH_2C_6H_5$), 4.5 (m, 4, $CHCH_2$ and NCHCO), 4.95 (s, 2, $OCH_2C_6H_5$), 5.2 (m, 1, NH), 7.2–8.2 (m, 15, aryl); IR (KBr) 3400–3100 (br s, NH and OH), 1720 (C=O), 1310, 1150 (SO_2) cm^{-1}.

Anal. Calcd for $C_{39}H_{43}O_7NS$: C, 69.93; H, 6.47; N, 2.09. Found: C, 69.88; H, 6.63; N, 1.98.

DBD-TMOC-Phg-Cl. To a solution of 0.22 g (0.4 mmol) of DBD-TMOC-Phg-OH in 8 mL of dry methylene chloride was added 0.3 mL (4 mmol) of thionyl chloride. The mixture was refluxed for 30 min under nitrogen and cooled to room temperature, and solvent and excess thionyl chloride were removed under reduced pressure to give a yellow residue which was redissolved in ether or CH_2Cl_2 and precipitated by addition of hexane.

Filtration gave 0.16 g (70%) of the acid chloride as a yellow solid, mp 147–150 °C, $[\alpha]^{21}_D$ = +92.7° (c 0.3, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 4.4–4.5 (m, 3, CH_2CH), 5.55 (d, 1, NCHCO), 5.65 (m, 1, NH), 7.3–8.2 (m, 11, aryl); IR (KBr) 3300 (NH), 1800, 1720 (C=O), 1300, 1150 (SO_2) cm^{-1}. Other acid chlorides were prepared similarly: see Table IV. Generally the crude acid chlorides were characterized by their ^1H NMR and IR spectra and not purified for elemental analysis.

Preparation of DBD-TMOC-Phg-Cl in the Presence of TMU under Mild Conditions. To a solution of 0.08 mL (0.36 mmol) of tetramethylurea in 3 mL of methylene chloride was added 0.048 mL (0.36 mmol) of thionyl chloride at −5 to −10 °C. After this was stirred for 10 min at this temperature, 0.1 g (0.18 mmole) of DBD-TMOC-Phg-OH was added. The resulting mixture was stirred under nitrogen at −5 to −10 °C for 5 min and at 0 °C for 30 min. Solvent and excess thionyl chloride were removed under reduced pressure to give a yellow oil. A small amount of the crude acid chloride was added to methanol. Spotting on a TLC plate followed by elution with 40% EtOAc–Skelly B showed no residue of the free acid but only the corresponding methyl ester (R_f = 0.52). The structure of the crude acid chloride was established by its reaction with H-Ala-OMe·HCl in the presence of diisopropylethylamine to give the expected dipeptide methyl ester (76%), mp 184–185 °C (crude), 188–189 °C (pure). See below for characterization.

DBD-TMOC-Phe-Leu-*O*-*t*-Bu (31). Method A. Acid Chloride Coupling. To a solution of 0.21 g (0.94 mmol) of H-Leu-O-*t*-Bu·HCl in 6 mL of 10% $NaHCO_3$ was added a solution of 0.5 g (0.86 mmol) of DBD-TMOC-Phe-Cl in 6 mL of THF while cooling in an ice bath with vigorous stirring. The reaction mixture was stirred at 0 °C for 30 min and diluted with 10 mL of EtOAc, and the organic layer was washed with H_2O, 5% HCl, and H_2O. After drying over $MgSO_4$ removal of solvent gave 0.5 g of white solid. The crude solid was chromatographed on silica gel (230–400 mesh, 20 g) with elution by 40% EtOAc–Skelly B to give 0.45 g (71%) of the dipeptide. The sample was recrystallized from EtOAc–Skelly B, mp 140–142 °C; $[\alpha]^{20}_D$ = −7.2° (c 0.5, EtOAc); ^1H NMR ($CDCl_3$) δ 0.8–1 (d, 6, CMe_2), 1.3–1.5 (m, 30, two CMe_3, $OCMe_3$ and CH_2CH(Leu)), 2.95–3.15 (d, 2, $CH_2C_6H_5$), 4.4–4.6 (m, 4, CH_2CH and NCHCO), 5.4 (m, 1, NH), 6.2 (m, 1, NH), 7.15–8.2 (m, 11, aryl); IR (KBr) 3500–3400 (NH), 1740 (C=O), 1370, 1150 (SO_2) cm^{-1}.

Anal. Calcd for $C_{42}H_{56}N_2O_7S$: C, 68.82; H, 7.70; N, 3.82. Found: C, 68.64; H, 7.71; N, 3.82.

Method B. DCC Coupling. Free ester H-Leu-O-*t*-Bu (0.15 g, 0.75 mmol) was obtained from the corresponding hydrochloride by treatment with saturated potassium carbonate, extraction with ether, washing with water, drying over $MgSO_4$, and removal of solvent. The resulting colorless oil was treated with a solution of 0.3 g (0.53 mmol) of DBD-TMOC-Phe-OH in 8 mL of THF, followed by addition of 0.11 g (0.53 mmol) of DCC at −15 °C. The solution was stirred at −15 °C for 1 h and at room temperature for 2 h, solvent removed, and the residue redissolved in EtOAc. Dicyclohexylurea was removed by filtration, and the filtrate washed with 10% $NaCO_3$, H_2O, 5% HCl, and H_2O and dried over $MgSO_4$. Removal of solvent gave a white solid which was recrystallized from EtOAc–Skelly B to give 0.2 g (51%) of the *tert*-butyl ester of the dipeptide, mp 140–142 °C, identified by spectral comparison with a sample made as described under method A above.

NMR-Visualized Racemization Test. Coupling of DBD-TMOC-Phg-OH with H-Ala-OMe. A. Acid Chloride Based Two-Phase Technique. To a solution of 50 mg (0.26 mmol) of H-Ala-OMe·HCl in 2 mL of 10% $NaHCO_3$ was added slowly a solution of 0.1 g (0.17 mmol) of DBD-TMOC-Phg-Cl in 3 mL of THF in an ice-water bath with vigorous stirring. The reaction mixture was stirred at 0 °C for 30 min and poured into 10 mL of EtOAc. The organic layer was washed with H_2O, 5% HCl, and H_2O and dried over $MgSO_4$. Removal of solvent gave 85 mg of the protected dipeptide DBD-TMOC-Phg-Ala-OMe, mp 173–175 °C. The crude dipeptide, examined without purification by ^1H NMR analysis, showed less than 1% of the DL diastereomer. When the same acylation was carried out at room temperature for 3 min, about 33% of the DL form was observed. The crude LL product was recrystallized from EtOAc–Skelly B to give 73 mg (61%) of the protected dipeptide, mp 188–189 °C; $[\alpha]^{19}_D$ = +33.4° (c 1, EtOAc); H NMR ($CDCl_3$) δ 1.3 (s, 21, two CMe_3 and CH_3), 3.66 (s, 3, OCH_3), 4.5 (m, 4, CH_2CH and CH(Ala)), 5.2 (m, 1, CH(Phg)), 6.1 (m, 1, NH), 6.3 (m, 1, NH), 7.2–8.2 (m, 11, aryl); IR (KBr) 3300 (NH), 1730 (C=O), 1300, 1150 (SO_2) cm^{-1}.

Anal. Calcd for $C_{35}H_{42}N_2O_7S$: C, 66.22; H, 6.67; N, 4.41. Found: C, 66.01; H, 6.57; N, 4.39.

B. Acid Chloride Based One-Phase Technique. A solution of 24 mg (0.17 mmol) of H-Ala-OMe·HCl, 0.064 mL (0.37 mmol) of diisopropylethylamine, and 4 mL of THF was stirred for 1 min, and 100 mg (0.17 mmol) of DBD-TMOC-Phg-Cl was added to the solution while cooling in an ice-water bath. The reaction mixture was stirred at 0 °C for 10 min, diluted with 5 mL of EtOAc, washed with H_2O, 5% HCl, H_2O, and 10% $NaHCO_3$, and dried over $MgSO_4$. Removal of solvent gave 90 mg (75.6%) of the crude dipeptide which was examined without purification for the DL diastereomer (<2–3%) by ^1H NMR analysis. The sample was recrystallized from EtOAc–Skelly B. Spectral properties and melting point of the dipeptide agreed with those given previously for the same compound made via the two-phase technique.

C. DCC-HOSu or DCC-HOBt Technique. Free methyl alaninate (0.03 g, 0.18 mmol) was obtained from H-Ala-OMe·HCl by treatment with saturated sodium carbonate solution, extraction with ether, washing with water, drying over $MgSO_4$, and removal of solvent. The resulting oil was treated with a solution of 0.1 g (0.18 mmol) of DBD-TMOC-Phg-OH in 3 mL of THF and 0.02 g (0.18 mmol) of *N*-hydroxysuccinimide or 0.025 g (0.18 mmol) of *N*-hydroxybenzotriazole. To the mixture was added 0.03 g (0.18 mmol) of DCC while cooling in an ice-water bath under nitrogen. The resulting solution was stored in a freezer overnight and at room temperature for 4 h, solvent removed, and the residue redissolved in EtOAc. Dicyclohexylurea was removed by filtration, and the filtrate was washed with 10% $NaHCO_3$, H_2O, 5% HCl, and H_2O and dried over $MgSO_4$. Removal of solvent gave about 80% of the crude dipeptide which was examined without purification for the DL diastereomer by ^1H NMR analysis (6–8% for HOSu, less than 2–3% for HOBt).

HPLC-Based Racemization Test. Coupling of DBD-TMOC-Phe-OH with H-Leu-OMe. A. Acid Chloride Based Two-Phase Technique. To a solution of 0.12 g (0.6 mmol) of H-Leu-OMe·HCl in 6 mL of 10% $NaHCO_3$ was added slowly 0.3 g (0.5 mmol) of DBD-TMOC-Phe-Cl in 6 mL of THF while cooling in an ice bath with vigorous stirring. The reaction mixture was stirred at 0 °C for 30 min and poured into 12 mL of EtOAc, and the organic phase washed with H_2O, 5% HCl, and H_2O. Drying over $MgSO_4$ and removal of solvent in vacuo gave 0.3 g (84%) of the protected peptide DBD-TMOC-Phe-Leu-OMe, as a white solid: ^1H NMR ($CDCl_3$) δ 0.8–1 (d, 6, CMe_2), 1.3–1.45 (m, 21, two CMe_3 and CH_2CH(Leu)), 3.1 (d, 2, $CH_2C_6H_5$), 3.7 (s, 3, OCH_3), 4.5 (m, 4, CH_2CH and NCHCO), 5.5 (m, 1, NH), 6.4 (m, 1, NH), 7.2–8.2 (m, 11, aryl); IR (Nujol) 3300 (NH), 1730 (C=O), 1300, 1150 (SO_2) cm^{-1}.

Without any purification, 100 mg (0.14 mmol) of the crude dipeptide was dissolved in 1.2 mL of DMSO. The solution was stirred at 60–70 °C for 40 min. Completion of the reaction was monitored by TLC analysis. After completion of the deblocking the solution was cooled in an ice bath for 10 min, 0.1 mL of H_2O added, and the mixture filtered to remove the methylene sulfone. Removal of solvent gave a white solid which was dissolved in 3 mL of CH_2Cl_2 and converted to the *N*-benzoyl derivative as described previously.[24] HPLC analysis showed no detectable amount of the DL isomer (<0.1%).

B. DCC-HOBt Technique. The coupling procedure followed that described for the Phg analogue. Deblocking, *N*-benzoylation, and HPLC analysis followed the method described under A. No detectable amount of the DL isomer (<0.1%) was observed.

DBD-TMOC-Gly-Phe-Leu-O-*t*-Bu (33). A solution of 0.72 g (0.98 mmol) of DBD-TMOC-Phe-Leu-O-*t*-Bu and 7.5 mL of dimethyl sulfoxide was heated in an oil bath with the temperature maintained at 60–70 °C for 50 min. To the solution was added 1 mL of water, the mixture cooled in an ice bath, and the precipitate filtered. Examination of the NMR spectrum showed the precipitate to be methylene sulfone **27**, mp 242–244 °C. TLC analysis showed the filtrate to contain none of the sulfone. To the filtrate which contained the free dipeptide was added 72 mL of CH_2Cl_2, 8 mL of 10% $NaHCO_3$, and 0.49 g (0.98 mmol) of DBD-TMOC-Gly-Cl with vigorous stirring at 0 °C for 30 min. The

aqueous phase was separated, and the organic layer was washed with H_2O, 5% HCl, and H_2O. Drying over $MgSO_4$, removal of solvent, and column chromatography on silica gel (230–400 mesh, 20 g) with elution by 40% EtOAc–Skelly B gave 0.61 g (78%) of the crude protected tripeptide: ^1H NMR ($CDCl_3$) δ 0.9 (d, 6, CMe_2), 1.3 (m, 30, two CMe_3, $OCMe_3$ and CH_2CH(Leu)), 2.95–3.15 (d, 2, $CH_2C_6H_5$), 3.9 (s, 2, CH_2(Gly)), 4.4 (m, 1, CH(Leu)), 4.5 (s, 3, CH_2CH), 4.7 (m, 1, CH(Phe)), 5.5 (m, 1, NH), 6.7 (m, 1, NH), 7.15–8.2 (m, 11, aryl). An analytically pure sample was not obtained, the crude tripeptide being used directly in the next step.

DBD-TMOC-Gly-Gly-Phe-Leu-*O*-*t*-Bu (35). A solution of 0.3 g (0.38 mmol) of the crude tripeptide **33** and 4 mL of dimethyl sulfoxide was heated in an oil bath with the temperature maintained at 60–70 °C for 16 h. To the solution was added 0.5 mL of water, the mixture cooled in an ice bath, and the precipitate filtered. The filtrate was diluted with 20 mL of EtOAc and washed three times with 10-mL portions of water, the extracts were dried over $MgSO_4$, and solvent was removed in vacuo to give the crude free tripeptide **34**. A solution of the free tripeptide and 0.19 g (0.38 mmol) of DBD-TMOC-Gly-Cl in 8 mL of CH_2Cl_2 was stirred in the presence of 4 mL of 10% $NaHCO_3$ at 0 °C for 30 min. The aqueous phase was separated, and the organic layer was washed with H_2O, 5% HCl, and H_2O. Drying over $MgSO_4$, removal of solvent, and column chromatography on silica gel (230–400 mesh, 15 g) with elution by EtOAc gave 0.22 g (69%) of the crude protected tetrapeptide: ^1H NMR ($CDCl_3$) δ 0.9 (d, 6, CMe_2), 1.3–1.5 (m, 30, CMe_3, $OCMe_3$ and CH_2CH(Leu)), 2.95–3.15 (d, 2, $CH_2C_6H_5$), 3.9 (s, 4, two CH_2(Gly)), 4.4 (m, 1, CH(Leu)), 4.5 (br s, 3, CH_2CH), 4.7 (m, 1, CH(Phe)), 5.7 (m, 1, NH), 6.7 (m, 1, NH), 6.8 (m, 1, NH), 7.15–8.2 (m, 11, aryl). An analytically pure sample was not obtained, the crude tetrapeptide being used directly in the next step.

DBD-TMOC-Tyr(Bn)-Gly-Gly-Phe-Leu-O-*t*-Bu (37). A solution of 0.12 g (0.14 mmol) of the crude tetrapeptide **35** and 1.5 mL of dimethyl sulfoxide was heated in an oil bath with the temperature maintained at 75–80 °C for 10 h. To the solution was added 0.2 mL of water, the mixture cooled in an ice bath, and the precipitate filtered. The filtrate was diluted with 15 mL of EtOAc and washed three times with 7-mL portions of water, the extracts were dried over $MgSO_4$, and solvent was removed in vacuo to give the free crude tetrapeptide **36**. A solution of the free tetrapeptide and 0.098 g (0.14 mmol) of DBD-TMOC-Tyr-(Bn)-Cl in 3 mL of CH_2Cl_2 was stirred in presence of 1.5 mL of 10% $NaHCO_3$ at 0 °C for 30 min. The aqueous phase was separated, and the organic layer was washed with H_2O, 5% HCl, and H_2O. Drying over $MgSO_4$, removal of solvent, and chromatography (230–400 mesh, 10 g) with elution by EtOAc gave a white solid which was recrystallized from MeOH–CH_2Cl_2 to give 0.063 g (41%) of the crude protected pentapeptide, $[\alpha]^{19}_D = -7°$ (*c* 0.6, EtOAc); ^1H NMR ($CDCl_3$) δ 0.9 (d, 6, CMe_2), 1.3–1.5 (m, 30, CMe_3, $OCMe_3$ and CH_2CH(Leu)), 2.95–3.2 (d, 4, two CH_2Ar(Phe, Tyr)), 4–4.3 (m, 5, two CH_2(Gly), CH(Tyr)), 4.5–4.8 (m, 5, CH_2CH, CH(Phe), CH(Leu)), 4.93 (s, 2, $OCH_2C_6H_5$), 5.2 (m, 1, NH), 6.2 (m, 1, NH), 6.7 (m, 1, NH), 6.8–8.2 (m, 21, aryl, NH).

Anal. Calcd for $C_{62}H_{77}N_5O_{11}S$: C, 67.68; H, 7.05; N, 6.36. Found: C, 67.49; H, 6.93; N, 6.36.

Leucine Enkephalin (38). To a solution of 40 mg (0.036 mmol) of DBD-TMOC-Tyr(Bn)-Gly-Gly-Phe-Leu-O-*t*-Bu in a mixture of 3 mL of CH_2Cl_2 and 3 mL of CH_3OH were added 20 mg of palladium acetate, 20 mg of 10% Pd/C, and 80 mg of ammonium formate. After this was stirred at room temperature for 16 h, the catalyst was filtered, and solvent removed. The residue was redissolved in 5 mL of EtOAc, and the solution washed with saturated NaCl solution to remove excess ammonium formate. Drying over $MgSO_4$ and removal of solvent gave a solid. A solution of the solid and 0.04 mL (0.38 mmol) of anisole in 4 mL of 50% CF_3COOH–CH_2Cl_2 was stirred at room temperature for 8 h. Removal of solvent under reduced pressure gave a solid which was dissolved in MeOH and precipitated with ether to give 14 mg (57.5%) of the pentapeptide TFA salt as a white solid, mp 152–154 °C (lit.[17a] mp 155–158 °C, and lit.[25] mp 158–165 °C); TLC R_f = 0.48 ($CHCl_3$–MeOH–H_2O 10:5:1); HPLC t_R = 9.20–9.26 min (MeOH–H_2O–CF_3COOH 50:50:0.1) (authentic sample t_R = 9.26 min;[26] D-Phe[4]-leucine enkephalin, t_R = 16.66 min,[26] was shown to be absent); ^1H NMR (DMSO-d_6) δ 0.9 (m, 6, CMe_2), 1.45–1.70 (m, 3, CH_2CH), 2.6–2.8, 2.9–3.1 (m, 4, CH_2(Tyr and Phe)), 3.6 (m, 1, CH(Tyr)), 3.70 (m, 4, two CH_2(Gly)), 4.2 (m, 1, CH(Leu), 4.45 (m, 1, CH(Phe)), 6.7, 7.0 (d, 4, aryl(Tyr)), 7.2 (m, 1, NH(Tyr), 7.25 (m, 5, aryl(Phe)), 8.1 (m, 2, two NH(Gly[3] and Leu)), 8.3 (d, 1, NH(Phe)), 8.7 (br s, 1, NH(Gly)). The NMR spectrum was superimposable on that recorded by Garbay-Jaureguiberry and co-workers.[27] The treatment described served to remove deblocking byproduct **26**, mp 163–165 °C; ^1H NMR ($CDCl_3$) δ 1.3 (s, 18, CMe_3), 1.78 (d, 3, CH_3), 4.25 (m, 1, CH), 7.2–8.2 (m, 6, aryl).

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Registry No. **1**, 123167-89-5; **2**, 3166-16-3; **4**, 17394-18-2; **5**, 40020-77-7; **5** (imidazole adduct), 123168-20-7; **7**, 123167-90-8; **8** (R = 4-ClC_6H_4), 123167-91-9; **9** (R = Et), 123168-05-8; **9** (NR_2 = piperidino), 123167-92-0; **9** (NR_2 = morpholine), 123168-06-9; **12**, 93962-29-9; **13**, 139-66-2; **14**, 52908-55-1; **15**, 93962-27-7; **15** (9-hydroxymethyl), 93962-28-8; **16**, 93962-26-6; **17**, 123167-93-1; **18**, 123167-94-2; **22**, 261-31-4; **23**, 123167-95-3; **24**, 123167-96-4; **25**, 93962-30-2; **26**, 123167-97-5; **27**, 93962-36-8; **28**, 93962-31-3; **30**, 123167-98-6; **31**, 93962-34-6; **33**, 123167-99-7; **34**, 82362-19-4; **35**, 93962-35-7; **36**, 77426-98-3; **37**, 123168-00-3; **38**·TFA, 73563-78-7; 4-ClC_6H_4NCO, 104-12-1; 4-$ClC_6H_4NH_2$, 106-47-8; $MeOCHCl_2$, 4885-02-3; H-Gly-OH, 56-40-6; HCOOEt, 109-94-4; H-Phe-OH, 63-91-2; H-Gly-OEt·HCl, 623-33-6; H-Phe-Leu-OBu-*t*, 28635-78-1; (c-C_6H_{11})NH_2, 108-91-8; (c-C_6H_{11})NCO, 3173-53-3; (D-TMOC)-NH(c-C_6H_{11}), 123168-01-4; (D-TMOC)-Gly-OH, 123168-02-5; (D-TMOC)-Gly-OEt, 123168-03-6; (D-TMOC)NHPh, 123168-04-7; (D-TMOC)-Phe-OH, 123168-07-0; H-Phe-OBu-*t*·HCl, 15100-75-1; H-Phg-OH, 2935-35-5; H-Gly-OBu-*t*·H_3PO_3, 71666-98-3; H-Tyr-(Bn)-OH·HCl, 123168-08-1; (DBD-TMOC)-Phe-OBu-*t*, 123168-09-2; (DBD-TMOC)-Gly-OBu-*t*, 123168-10-5; (DBD-TMOC)-Phe-OH, 93962-32-4; (DBD-TMOC)-Phg-OH, 123168-11-6; (DBD-TMOC)-Gly-OH, 123168-12-7; (DBD-TMOC)-Tyr(Bn)-OH, 123168-13-8; (DBD-TMOC)-Phg-Cl, 123168-14-9; (DBD-TMOC)-Phe-Cl, 123168-15-0; (DBD-TMOC)-Gly-Cl, 123168-16-1; (DBD-TMOC)-Tyr(Bn)-Cl, 123168-17-2; H-Ala-OMe·HCl, 2491-20-5; H-Leu-OBu-*t*·HCl, 2748-02-9; H-Leu-OBu-*t*, 21691-53-2; H-Ala-OMe, 10065-72-2; H-Leu-OMe-HCl, 7517-19-3; (DBD-TMOC)-Phg-OMe, 123168-18-3; (DBD-TMOC)-Phg-Ala-OMe, 123183-63-1; (DBD-TMOC)-Phe-Leu-OMe, 123168-19-4; H-Phe-Leu-OMe, 38155-19-0; Bz-Phe-Leu-OMe, 118474-25-2.

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