
1

THE ROLE OF PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

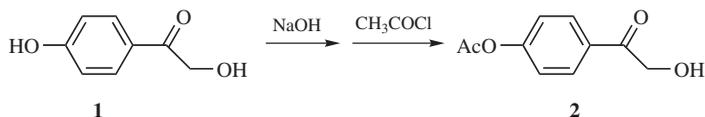
PROPERTIES OF A PROTECTIVE GROUP

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been, and are being, developed for this purpose. A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group. The protective group should form a derivative (without the generation of new stereogenic centers) that can easily be separated from side products associated with its formation or cleavage. The protective group should have a minimum of additional functionality to avoid further sites of reaction. All things considered, no protective group is the best protective group. Currently, the science and art of organic synthesis, contrary to the opinions of some, has a long way to go before we can call it a finished and well-defined discipline, as amply illustrated by the extensive use of protective groups during the synthesis of multifunctional molecules. A greater number of protective group-free syntheses have been accomplished since the last edition of this book, but in some cases this is the result of a suitable target choice rather than a fundamental advance in organic chemistry. Greater control over the chemistry used in the building of Nature's architecturally beautiful and diverse molecular frameworks, as well as unnatural structures, is needed when one considers the number of protection and deprotection

steps often used to synthesize a molecule. Peptides, carbohydrates, and polyketides are among the classes of compounds that still require extensive use of protective groups, whereas the synthesis of alkaloids appears to be less dependent upon protective group use.

HISTORICAL DEVELOPMENT

Since a few protective groups cannot satisfy all these criteria for elaborate substrates, a large number of mutually complementary protective groups are needed and, indeed, are available. In early syntheses, the chemist chose a standard derivative known to be stable to the subsequent reactions. In a synthesis of callistephin chloride, the phenolic -OH group in **1** was selectively protected as an acetate.¹ In the presence of silver ion, the aliphatic hydroxyl group in **2** displaced the bromide ion in a bromoglucoside. In a final step, the acetate group was removed by basic hydrolysis.



Other classical methods of cleavage include acidic hydrolysis (eq. 1), reduction (eq. 2), and oxidation (eq. 3):

- (1) $\text{ArO}-\text{R} \rightarrow \text{ArOH}$
- (2) $\text{RO}-\text{CH}_2\text{Ph} \rightarrow \text{ROH}$
- (3) $\text{RNH}-\text{CHO} \rightarrow [\text{RNHCOOH}] \rightarrow \text{RNH}_3^+$

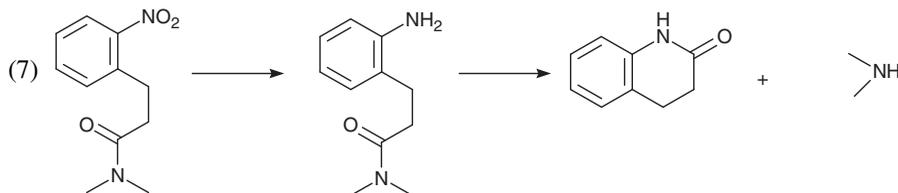
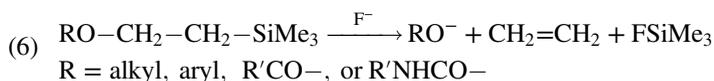
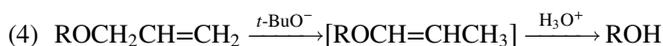
Some of the original work in the carbohydrate area in particular reveals extensive protection of carbonyl and hydroxyl groups. For example, a cyclic diacetonide of glucose was selectively cleaved to the monoacetonide.² A summary³ describes the selective protection of primary and secondary hydroxyl groups in a synthesis of gentiobiose, carried out in the 1870s, as triphenylmethyl ethers.

DEVELOPMENT OF NEW PROTECTIVE GROUPS

As chemists proceeded to synthesize more complicated structures, they developed more satisfactory protective groups and more effective methods for the formation and cleavage of protected compounds. At first, a tetrahydropyranyl acetal was prepared,⁴ by an acid-catalyzed reaction with dihydropyran, to protect a hydroxyl group. The acetal is readily cleaved by mild acid hydrolysis, but formation of this acetal introduces a new stereogenic center. Formation of the 4-methoxytetrahydropyranyl ketal⁵ eliminates this problem.

Catalytic hydrogenolysis of an *O*-benzyl protective group is a mild, selective method introduced by Bergmann and Zervas⁶ to cleave a benzyl carbamate ($>\text{NCO}-\text{OCH}_2\text{C}_6\text{H}_5 \rightarrow >\text{NH}$) prepared to protect an amino group during peptide syntheses. The method has also been used to cleave alkyl benzyl ethers, stable compounds prepared to protect alkyl alcohols; benzyl esters are cleaved by catalytic hydrogenolysis under neutral conditions.

Three selective methods to remove protective groups have received attention: "assisted," electrolytic, and photolytic removal. Four examples illustrate "assisted removal" of a protective group. A stable allyl group can be converted to a labile vinyl ether group (eq. 4)⁷; a β -haloethoxy (eq. 5)⁸ or a β -silylethoxy (eq. 6)⁹ derivative is cleaved by attack at the β -substituent; and a stable *o*-nitrophenyl derivative can be reduced to the *o*-amino compound, which undergoes cleavage by nucleophilic displacement (eq. 7)¹⁰:



The design of new protective groups that are cleaved by "assisted removal" is a challenging and rewarding undertaking.

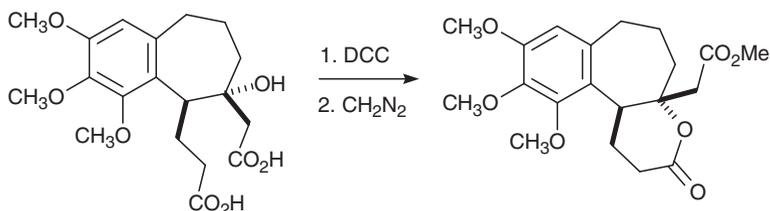
Removal of a protective group by electrolytic oxidation or reduction is useful in some cases. An advantage is that the use and subsequent removal of chemical oxidants or reductants (e.g., Cr or Pb salts; Pt-C or Pd-C) are eliminated. Reductive cleavages have been carried out in high yield at -1 to -3 V (vs. SCE) depending on the group; oxidative cleavages in good yield have been realized at 1.5 – 2 V (vs. SCE). For systems possessing two or more electrochemically labile protective groups, selective cleavage is possible when the half-wave potentials, $E_{1/2}$, are sufficiently different; excellent selectivity can be obtained with potential differences on the order of 0.25 V. Protective groups that have been removed by electrolytic oxidation or reduction are described at the appropriate places in this book; a review article by Mairanovsky¹¹ discusses electrochemical removal of protective groups.¹²

Photolytic cleavage reactions (e.g., of *o*-nitrobenzyl, phenacyl, and nitrophenyl-sulfonyl derivatives) take place in high yield on irradiation of the protected compound for a few hours at 254 – 350 nm. For example, the *o*-nitrobenzyl group, used to protect alcohols,¹³ amines,¹⁴ and carboxylic acids,¹⁵ has been removed by irradiation.

Protective groups that have been removed by photolysis are described at the appropriate places in this book; in addition, the reader may consult five review articles.^{16–20}

One widely used method involving protected compounds is solid-phase synthesis^{21–24} (polymer-supported reagents). This method has the advantage of simple workup by filtration and automated syntheses, especially of polypeptides, oligonucleotides, and oligosaccharides.

Internal protection, used by van Tamelen in a synthesis of colchicine, may be appropriate²⁵:



SELECTION OF A PROTECTIVE GROUP FROM THIS BOOK

To select a specific protective group, the chemist must consider in detail all the reactants, reaction conditions, and functionalities involved in the proposed synthetic scheme. First, he or she must evaluate all functional groups in the reactant to determine those that will be unstable to the desired reaction conditions and require protection. The chemist should then examine reactivities of possible protective groups, listed in the Reactivity Charts, to determine compatibility of protective group and reaction conditions. A guide to these considerations is provided in Chapter 10. (The protective groups listed in the Reactivity Charts in that chapter were the most widely used groups at the time the charts were prepared in 1979 in a collaborative effort with other members of Professor Corey's research group.) Much new technology has been developed since the creation of those tables and thus the user should be aware of that. He or she should consult the complete list of protective groups in the relevant chapter and consider their properties. It will frequently be advisable to examine the use of one protective group for several functional groups (i.e., a 2,2,2-trichloroethyl group to protect a hydroxyl group as an ether, a carboxylic acid as an ester, and an amino group as a carbamate). When several protective groups are to be removed simultaneously, it may be advantageous to use the same protective group to protect different functional groups (e.g., a benzyl group, removed by hydrogenolysis, to protect an alcohol and a carboxylic acid). When selective removal is required, different classes of protection must be used (e.g., a benzyl ether, cleaved by hydrogenolysis but stable to basic hydrolysis, to protect an alcohol, and an alkyl ester, cleaved by basic hydrolysis but stable to hydrogenolysis, to protect a carboxylic acid). One often overlooked issue in choosing a protective group is that the electronic and steric environments of a given functional group will greatly influence the rates of

formation and cleavage. For an obvious example, a tertiary acetate is much more difficult to form or cleave than a primary acetate.

If a satisfactory protective group has not been located, the chemist has a number of alternatives: rearrange the order of some of the steps in the synthetic scheme so that a functional group no longer requires protection or a protective group that was reactive in the original scheme is now stable; redesign the synthesis, possibly making use of latent functionality²⁶ (i.e., a functional group in a precursor form; e.g., anisole as a precursor of cyclohexanone). Or, it may be necessary to include the synthesis of a new protective group in the overall plan or, better yet, design new chemistry that avoids the use of a protective group.

Several books and chapters are associated with protective group chemistry. Some of these cover the area^{27,28}; others deal with more limited aspects. Protective groups continue to be of great importance in the synthesis of three major classes of naturally occurring substances—peptides,²² carbohydrates,²⁴ and oligonucleotides²³—and significant advances have been made in solid-phase synthesis,^{22–24} including automated procedures. The use of enzymes in the protection and deprotection of functional groups has been reviewed.²⁹ Special attention is also called to a review on selective deprotection of silyl ethers.³⁰

SYNTHESIS OF COMPLEX SUBSTANCES: TWO EXAMPLES (AS USED IN THE SYNTHESIS OF HIMASTATIN AND PALYTOXIN) OF THE SELECTION, INTRODUCTION, AND REMOVAL OF PROTECTIVE GROUPS

Synthesis of Himastatin

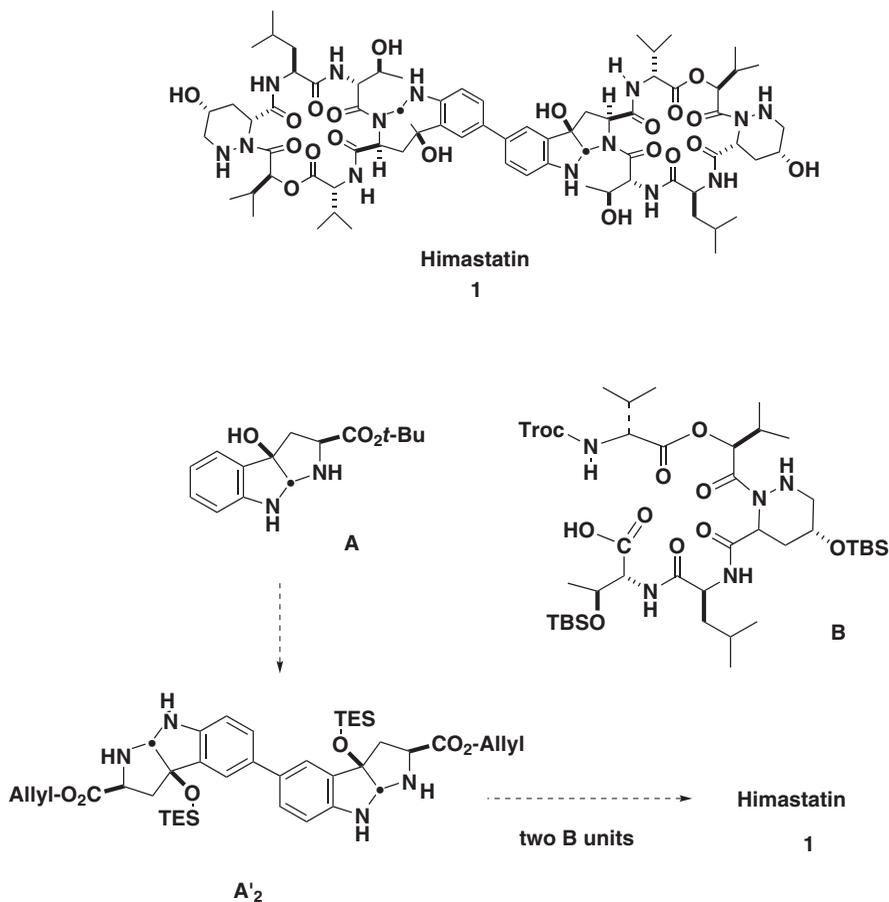
Himastatin, isolated from an actinomycete strain (ATCC) from the Himachal Pradesh State in India and active against Gram-positive microorganisms and a variety of tumor probe systems, is a $C_{72}H_{104}N_{14}O_{20}$ compound, **1**.³¹ It has a novel bisindolyl structure in which the two halves of the molecule are identical. Each half contains a cyclic peptidal ester containing an L-tryptophanyl unit, D-threonine, L-leucine, D-[(R)-5-hydroxy]piperazic acid, (S)-2-hydroxyisovaleric acid, and D-valine. Its synthesis³² illustrates several important aspects of protective group usage.

Synthesis of himastatin involved the preparation of the pyrroloindoline moiety **A**, its conversion to the bisindolyl unit **A'**, synthesis of the peptidal ester moiety **B**, the subsequent joining of these units (**A'** and two **B** units), and cyclization leading to himastatin. The following brief account focuses on the protective group aspects of the synthesis.

Unit A (Scheme 1)

The first objective was the conversion of L-tryptophan into a derivative that could be converted to pyrroloindoline **3**, possessing a *cis* ring fusion and a *syn* relationship of the carboxyl and hydroxyl groups. This was achieved by the conversions shown in Scheme 1. A critical step was e. Of many variants tried, the use of the

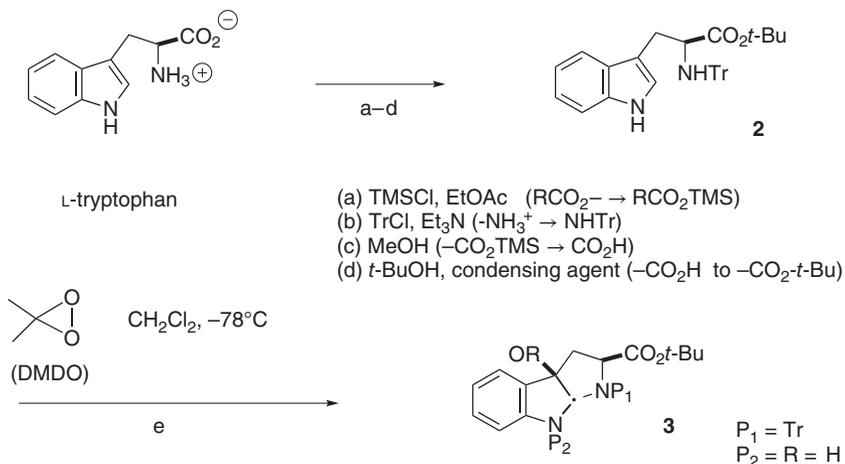
trityl group on the NH_2 of tryptophan and the *t*-butyl group on the carboxyl resulted in stereospecific oxidative cyclization to afford **3** of the desired *cis-syn* stereochemistry in good yield.



Bisindolyl Unit A'_2 (Schemes 2 and 3)

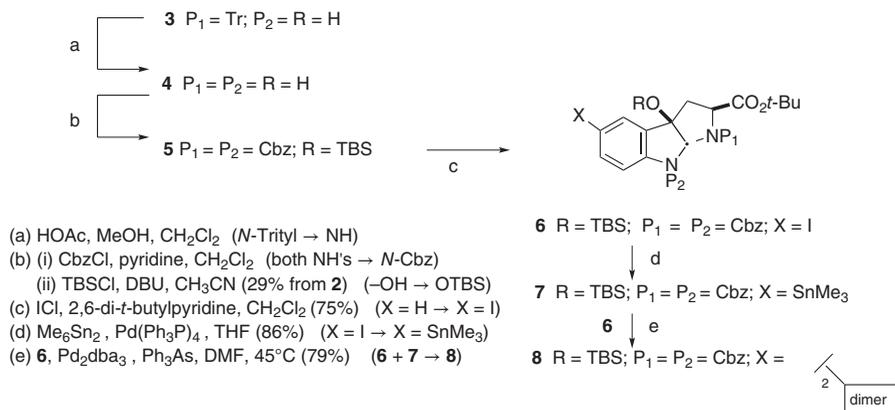
The conversion of **3** to **8** is summarized in Scheme 2. The trityl group (too large and too acid sensitive for the ensuing steps) was removed from N and both N's were protected by Cbz (benzyloxycarbonyl) groups. Protection of the tertiary OH specifically as the robust TBS (*t*-butyldimethylsilyl) group was found to be necessary for the sequence involving the electrophilic aromatic substitution step, **5** to **6**, and the Stille coupling steps (**6** + **7** → **8**).

The TBS group then had to be replaced (two steps, Scheme 3: a and b) by the more easily removable TES (triethylsilyl) group to permit deblocking at the last step in the synthesis of himastatin. Before combination of the bisindolyl unit with the peptidal ester unit, several additional changes in the state of protection at the two

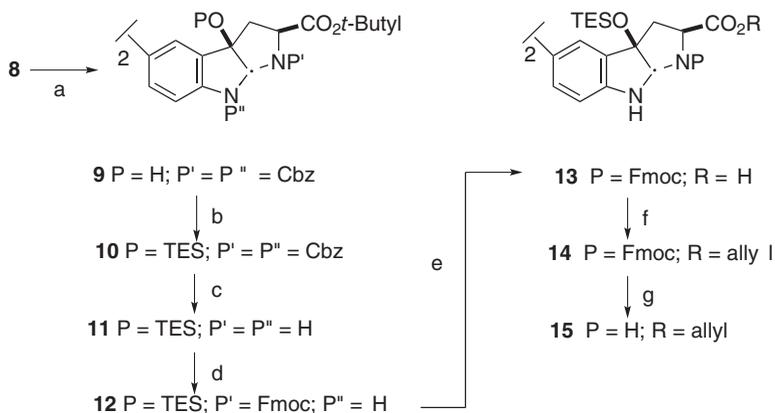


Scheme 1

nitrogens and the carboxyl of **8** were needed (Schemes 2 and 3). The Cbz protective groups were removed from both N's and the more reactive pyrrolidine N was protected as the Fmoc (fluorenylmethoxycarbonyl) group. At the carboxyl, the *t*-butyl group was replaced by the allyl group. [The smaller allyl group was needed for the later condensation of the adjacent pyrrolidine nitrogen of **15** with the threonine carboxyl of **24** (Scheme 5); also, the allyl group can be cleaved by the $\text{Pd}(\text{Ph}_3\text{P})_4\text{-PhSiH}_3$ method, conditions under which many protective groups (including, of course, the other protective groups in **25**; see Scheme 6) are stable.] Returning to Scheme 3, the Fmoc groups on the two equivalent pyrrolidine N's were then removed, affording **15**.



Scheme 2

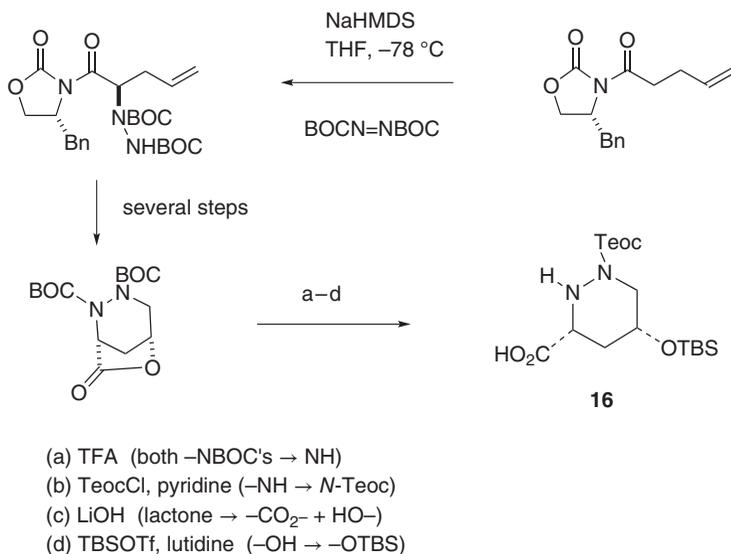


- (a) TBAF, THF (91%) (TBSO- → HO-)
 (b) TESCl, DBU, DMF (92%) (HO- → TESO-)
 (c) H₂, Pd/C, EtOAc (100%) (both *N*-Cbz's → NH)
 (d) Fmoc-HOSU, pyridine, CH₂Cl₂ (95%) (NH → NF moc)
 (e) TESOTf, lutidine, CH₂Cl₂ (-CO₂-*t*-Bu → -CO₂H)
 (f) allyl alcohol, DBAD, Ph₃P, CH₂Cl₂ (90% from **12**) (-CO₂H → -CO₂-allyl)
 (g) piperidine, CH₃CN (74%) (NF moc → NH)

Scheme 3

Peptidal Ester Unit B (Schemes 4 and 5)

Several of these steps are common ones in peptide synthesis and involve standard protective groups. Attention is called to the 5-hydroxypiperazine. Its synthesis (Scheme 4) has the interesting feature of the introduction of the two nitrogens in protected form as BOC (*t*-butoxycarbonyl) groups in the same step. Removal of the BOC groups and selective conversion of the nitrogen furthest from the carboxyl group into the *N*-Teoc (2-trimethylsilylethoxycarbonyl) group, followed by hydrolysis of the lactone and TBS protection of the hydroxyl, afforded the piperazine acid entity **16** in a suitable form for combination with dipeptide **18** (Scheme 5). Because of the greater reactivity of the leucyl -NH₂ group of **18** in comparison to the piperazyl -N_αH group in **16**, it was not necessary to protect this piperazyl NH in the condensation of **18** and **16** to form **19**. In the following step (**19** + **20** → **21**), this somewhat hindered piperazyl NH is condensed with the acid chloride **20**. Note that the hydroxyl in **20** is protected by the Fmoc group—not commonly used in hydroxyl protection. A requirement for the protective group on this hydroxyl was that it be removable (for the next condensation: **21** + Troc-*D*-valine **22** → **23**) under conditions that would leave unaltered the -COO-allyl, the *N*-Teoc, and the OTBS groups. The Fmoc group (cleavage by piperidine) met this requirement. Choice of the Troc (2,2,2-trichloroethoxycarbonyl) group for *N*-protection of valine was based on the requirements of removability, without affecting OTBS and OTES groups, and stability to the conditions of removal of allyl from -COO-allyl [easily met by use of Pd(Ph₃P)₄ for this deblocking].



Scheme 4

Himastatin 1 (Scheme 6)

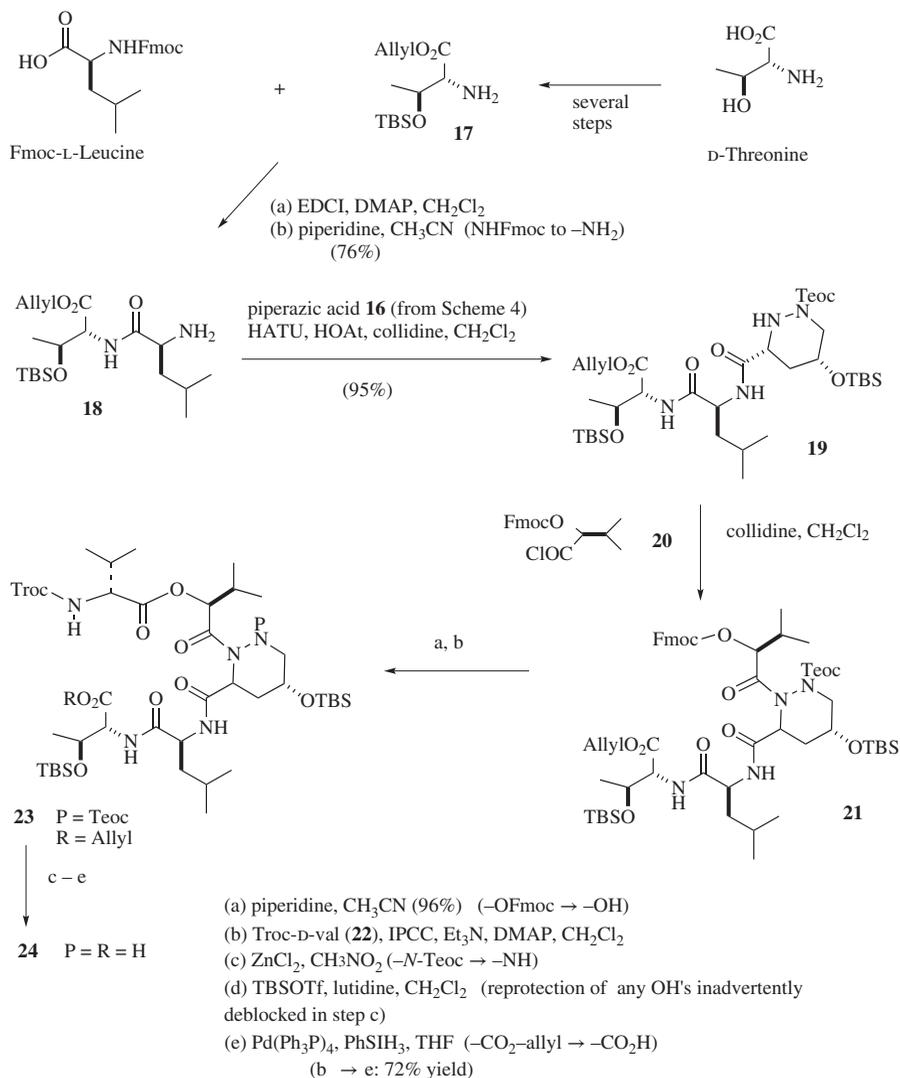
Of special importance to the synthesis was the choice of condensing agents and conditions.³³ HATU-HOAt³⁴ was of particular value in these final stages. Condensation of the threonine carboxyl of **24** (from Scheme 5) with the pyrrolidine N's of the bisindolyl compound **15** (from Scheme 3) afforded **25**. Removal of the allyl groups from the tryptophanyl carboxyls and the Troc groups from the valine amino nitrogens, followed by condensation (macrolactamization), gave **27**. Removal of the six silyl groups (the two quite hindered TES groups and the four, more accessible, TBS groups) by fluoride ion afforded himastatin.

Synthesis of Palytoxin Carboxylic Acid

Palytoxin carboxylic acid, C₁₂₃H₂₁₃NO₅₃, Figure 1 (R¹-R⁸=H), derived from palytoxin, C₁₂₉H₂₂₃N₃O₅₄, contains 41 hydroxyl groups, one amino group, one ketal, one hemiketal, and one carboxylic acid, in addition to some double bonds and ether linkages.

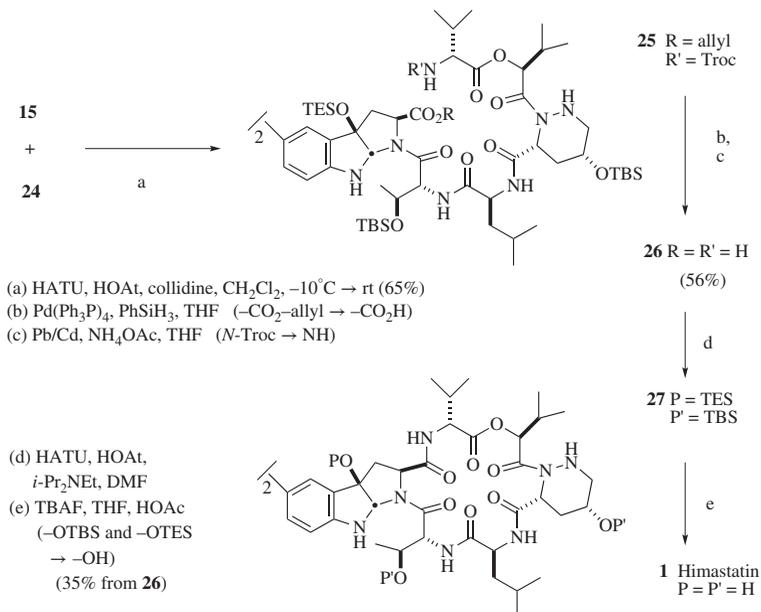
The total synthesis³⁵ was achieved through the synthesis of eight different segments, each requiring extensive use of protective group methodology, followed by the appropriate coupling of the various segments in their protected forms.

The choice of protective groups to be used in the synthesis of each segment was based on three aspects: (a) the specific steps chosen to achieve the synthesis of each segment; (b) the methods to be used in coupling the various segments, and (c) the conditions needed to deprotect the 42 blocked groups in order to liberate palytoxin carboxylic acid in its unprotected form. (These conditions must be such that the



Scheme 5

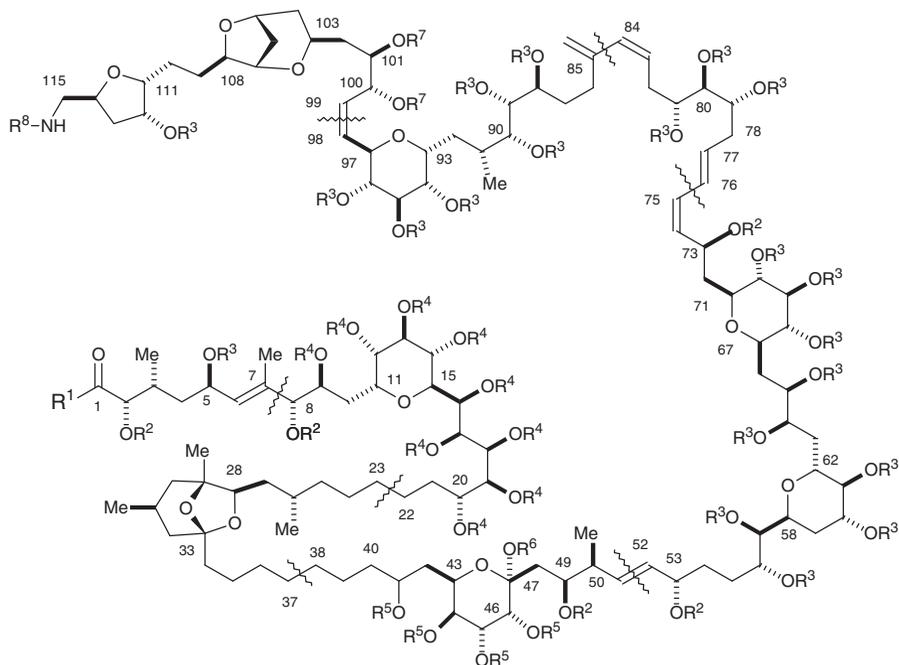
functional groups already deprotected are stable to the successive deblocking conditions.) Kishi's synthesis employed only eight different protective groups for the 42 functional groups present in the fully protected form of palytoxin carboxylic acid (Figure 1, **1**). A few additional protective groups were used for "end group" protection in the synthesis and sequential coupling of the eight different segments. The synthesis was completed by removal of all of the groups by a series of five different methods. The selection, formation, and cleavage of these groups are described below.



Scheme 6

For the synthesis of the C.1–C.7 segment, the C.1 carboxylic acid was protected as a methyl ester. The C.5 hydroxyl group was protected as the TBS ether. This particular silyl group was chosen because it improved the chemical yield and stereochemistry of the Ni(II)/Cr(II)-mediated coupling reaction of segment C.1–C.7 with segment C.8–C.51. Nine hydroxyl groups were protected as *p*-methoxyphenylmethyl (MPM) ethers, a group that was stable to the conditions used in the synthesis of the C.8–C.22 segment. These MPM groups were eventually cleaved oxidatively by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

The C.2 hydroxyl group was protected as an acetate, since cleavage of an MPM ether at C.2 proved to be very slow. An acetyl group was also used to protect the C.73 hydroxyl group during synthesis of the right-hand half of the molecule (C.52–C.115). Neither an MPM nor a TBS ether was satisfactory at C.73: DDQ cleavage of an MPM ether at C.73 resulted in oxidation of the *cis*–*trans* dienol at C.78–C.73 to a *cis*–*trans* dienone. When C.73 was protected as a TBS ether, Suzuki coupling of segment C.53–C.75 (in which C.75 was a vinyl iodide) to segment C.76–C.115 was too slow. In the synthesis of segment C.38–C.51, the C.49 hydroxyl group was also protected at one stage as an acetate, to prevent benzoate migration from C.46. The C.8 and C.53 hydroxyl groups were protected as acetates for experimental convenience. A benzoate ester, more electron withdrawing than an acetate ester, was used to protect the C.46 hydroxyl group to prevent spiroketalization of the C.43 and C.51 hydroxyl groups during synthesis of the C.38–C.51 segment. Benzoate protection of the C.46 hydroxyl group also increased the stability of the C.47 methoxy group (part of a ketal) under acidic cleavage



- 1: $R^1 = \text{OMe}$, $R^2 = \text{Ac}$, $R^3 = (t\text{-Bu})\text{Me}_2\text{Si}$, $R^4 = 4\text{-MeOC}_6\text{H}_4\text{CH}_2$, $R^5 = \text{Bz}$,
 $R^6 = \text{Me}$, $R^7 = \text{acetonide}$, $R^8 = \text{Me}_3\text{SiCH}_2\text{CH}_2\text{OCO}$
 2: (Palytoxin carboxylic acid): $R^1 = \text{OH}$, $R^2\text{--}R^8 = \text{H}$

Figure 1. Palytoxin carboxylic acid.

conditions. Benzoates rather than acetates were used during the synthesis of the C.38–C.51 segment, since they were more stable and better chromophores in purification and characterization.

Several additional protective groups were used in the coupling of the eight different segments. A tetrahydropyranyl (THP) group was used to protect the hydroxyl group at C.8 in segment C.8–C.22, and a *t*-butyldiphenylsilyl (TBDPS) group for the hydroxyl group at C.37 in segment C.23–C.37. The TBDPS group at C.37 was later removed by $\text{Bu}_4\text{N}^+\text{F}^-/\text{THF}$ in the presence of nine MPM groups. After the coupling of segment C.8–C.37 with segment C.38–C.51, the C.8 THP ether was hydrolyzed with pyridinium *p*-toluenesulfonate (PPTS) in methanol–ether, 42°C, in the presence of the bicyclic ketal at C.28–C.33 and the cyclic ketal at C.43–C.47. (As noted earlier, the resistance of this ketal to these acidic conditions was due to the electron-withdrawing effect of the benzoate at C.46.) A cyclic acetonide (a 1,3-dioxane) at C.49–C.51 was also removed by this step and had to be reformed (acetone/PPTS) prior to the coupling of segment C.8–C.51 with segment C.1–C.7. After coupling of these segments to form segment C.1–C.51, the new hydroxyl group at C.8 was protected as an acetate, and the acetonide at C.49–C.51 was, again, removed

without alteration of the bicyclic ketal at C.28–C.33 or the cyclic ketal at C.43–C.47, still stabilized by the benzoate at C.46.

The synthesis of segment C.77–C.115 from segments C.77–C.84 and C.85–C.115 involved the liberation of an aldehyde at C.85 from its protected form as a dithioacetal, $\text{RCH}(\text{SEt})_2$, by mild oxidative deblocking ($\text{I}_2/\text{NaHCO}_3$, acetone, water) and the use of the *p*-methoxyphenyldiphenylmethyl (MMTr) group to protect the hydroxyl group at C.77. The C.77 MMTr ether was subsequently converted to a primary alcohol (PPTS/MeOH– CH_2Cl_2 , rt) without affecting the 19 TBS ethers or the cyclic acetonide at C.100–C.101.

The C.100–C.101 diol group, protected as an acetonide, was stable to the Wittig reaction used to form the *cis* double bond at C.98–C.99, and to all of the conditions used in the buildup of segment C.99–C.115 to fully protected palytoxin carboxylic acid (Figure 1, **1**).

The C.115 amino group was protected as a trimethylsilylethyl carbamate ($\text{Me}_3\text{SiCH}_2\text{CH}_2\text{OCONHR}$), a group that was stable to the synthesis conditions and cleaved by the conditions used to remove the TBS ethers.

Thus, the 42 functional groups in palytoxin carboxylic acid (39 hydroxyl groups, one diol, one amino group, and one carboxylic acid) were protected by eight different groups:

1 methyl ester	–COOH
5 acetate esters	–OH
20 TBS ethers	–OH
9 MPM ethers	–OH
4 benzoate esters	–OH
1 methyl “ether”	–OH of a hemiketal
1 acetonide	1,2-diol
1 $\text{Me}_3\text{SiCH}_2\text{CH}_2\text{OCO}$	–NH ₂

The protective groups were then removed in the following order by the five methods listed below:

1. To cleave MPM ethers: DDQ/*t*-BuOH– CH_2Cl_2 –phosphate buffer (pH 7.0), 4.5 h.
2. To cleave the acetonide: 1.18 *N* HClO₄–THF, 25°C, 8 days.
3. To hydrolyze the acetates and benzoates: 0.08 *N* LiOH/H₂O–MeOH–THF, 25°C, 20 h.
4. To remove TBS ethers and the carbamoyl ester ($\text{Me}_3\text{SiCH}_2\text{CH}_2\text{OCONHR}$): $\text{Bu}_4\text{N}^+\text{F}^-$, THF, 22°C, 18 h → THF–DMF, 22°C, 72 h.
5. To hydrolyze the methyl ketal at C.47, no longer stabilized by the C.46 benzoate: HOAc–H₂O, 22°C, 36 h.

This order was chosen so that DDQ treatment would not oxidize a deprotected allylic alcohol at C.73, and so that the C.47 hemiketal would still be protected (as the ketal) during basic hydrolysis (step 3).

So, the skillful selection, introduction, and removal of a total of 12 different protective groups have played a major role in the successful total synthesis of palytoxin carboxylic acid (Figure 1, 2).

1. A. Robertson and R. Robinson, *J. Chem. Soc.*, 1460 (1928).
2. E. Fischer, *Ber.*, **28**, 1145–1167 (1895), see p. 1165.
3. B. Helferich, *Angew. Chem.*, **41**, 871 (1928).
4. W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).
5. C. B. Reese, R. Saffhill, and J. E. Sulston, *J. Am. Chem. Soc.*, **89**, 3366 (1967).
6. M. Bergmann and L. Zervas, *Chem. Ber.*, **65**, 1192 (1932).
7. J. Cunningham, R. Gigg, and C. D. Warren, *Tetrahedron Lett.*, 1191 (1964).
8. R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).
9. P. Sieber, *Helv. Chim. Acta*, **60**, 2711 (1977).
10. I. D. Entwistle, *Tetrahedron Lett.*, 555 (1979).
11. V. G. Mairanovsky, *Angew. Chem., Int. Ed. Engl.*, **15**, 281 (1976).
12. See also M. F. Semmelhack and G. E. Heinsohn, *J. Am. Chem. Soc.*, **94**, 5139 (1972).
13. S. Uesugi, S. Tanaka, E. Ohtsuka, and M. Ikehara, *Chem. Pharm. Bull.*, **26**, 2396 (1978).
14. S. M. Kalbag and R. W. Roeske, *J. Am. Chem. Soc.*, **97**, 440 (1975).
15. L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978).
16. V. N. R. Pillai, *Synthesis*, 1–26 (1980).
17. P. G. Sammes, *Q. Rev. Chem. Soc.*, **24**, 37–68 (1970), see pp. 66–68.
18. B. Amit, U. Zehavi, and A. Patchornik, *Isr. J. Chem.*, **12**, 103–113 (1974).
19. V. N. R. Pillai, *Org. Photochem.*, **9**, 225–323 (1987).
20. V. Zehavi, *Adv. Carbohydr. Chem. Biochem.*, **46**, 179–204 (1988).
21. (a) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963); (b) P. Hodge, *Chem. Ind. (London)*, 624 (1979); (c) C. C. Leznoff, *Acc. Chem. Res.*, **11**, 327 (1978); (d) *Solid Phase Synthesis*, E. C. Blossey and D. C. Neckers, Eds., Halsted, New York, 1975; (e) *Polymer-Supported Reactions in Organic Synthesis*, P. Hodge and D. C. Sherrington, Eds., Wiley-Interscience, 1980. A comprehensive review of polymeric protective groups by J. M. J. Fréchet is included in this book. (f) D. C. Sherrington and P. Hodge, *Synthesis and Separations Using Functional Polymers*, Wiley-Interscience, New York, 1988.
22. **Peptides:** (a) *Methods in Molecular Biology*, Vol. **35: Peptide Synthesis Protocols**, M. W. Pennington and B. M. Dunn, Eds., Humana Press, Totowa, NJ, 1994, pp. 91–169; (b) *Synthetic Peptides*, G. Grant, Ed., W. H. Freeman & Co., New York, 1992; (c) *Novabiochem 97/98, Catalog*, Technical Section S1–S85 (this section contains many useful details on the use and manipulation of protective groups in the amino acid–peptide area); (d) J. M. Stewart and J. D. Young, *Solid Phase Peptide Synthesis*, 2nd ed., Pierce Chemical Company, Rockford, IL, 1984; (e) E. Atherton and R. C. Sheppard, *Solid Phase Peptide Synthesis. A Practical Approach*, Oxford–IRL Press, New York, 1989; (f) *Innovation and Perspectives in Solid Phase Synthesis: Peptides, Polypeptides and Oligonucleotides. Collected Papers, First International Symposium: Macro-*

- Organic Reagents and Catalysts*, R. Epton, Ed., SPCC, UK, 1990; *Collected Papers, Second International Symposium*, R. Epton, Ed., Intercept Ltd, Andover, UK, 1992; (g) V. J. Hruby and J.-P. Meyer, "The Chemical Synthesis of Peptides," in *Bioorganic Chemistry: Peptides and Proteins*, S. M. Hecht, Ed., Oxford University Press, New York, 1998, Chapter 2, pp. 27–64.
23. **Oligonucleotides:** (a) S. L. Beaucage and R. P. Iyer, *Tetrahedron*, **48**, 2223 (1992), **49**, 1925 (1993), **49**, 6123 (1993), **49**, 10441 (1993); (b) J. W. Engels and E. Uhlmann, *Angew. Chem., Int. Ed. Engl.*, **28**, 716 (1989); (c) S. L. Beaucage and M. H. Caruthers, "The Chemical Synthesis of DNA/RNA," in *Bioorganic Chemistry: Nucleic Acids*, S. M. Hecht, Ed., Oxford University Press, New York, 1996, Chapter 2, pp. 36–74.
24. **Oligosaccharides:** (a) S. J. Danishefsky and M. T. Bilodeau, *Angew. Chem., Int. Ed. Engl.*, **35**, 1380 (1996); (b) P. H. Seeberger and S. J. Danishefsky, *Acc. Chem. Res.*, **31**, 685 (1998); (c) P. H. Seeberger, M. T. Bilodeau, and S. J. Danishefsky, *Aldrichim. Acta*, **30**, 75 (1997); (d) J. Y. Roberge, X. Beebe, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **120**, 3915 (1998); (e) B. O. Fraser-Reid et al., "The Chemical Synthesis of Oligosaccharides," in *Bioorganic Chemistry: Oligosaccharides*, S. M. Hecht, Ed., Oxford University Press, New York, 1999, Chapter 3, pp. 89–133; (f) K. C. Nicolaou et al., "The Chemical Synthesis of Complex Carbohydrates," in *Bioorganic Chemistry: Oligosaccharides*, S. M. Hecht, Ed., Oxford University Press, New York, 1999, Chapter 4, pp. 134–173.
25. **Oligosaccharides:** E. E. van Tamelen, T. A. Spencer, Jr., D. S. Allen, Jr., and R. L. Orvis, *Tetrahedron*, **14**, 8 (1961).
26. D. Lednicer, *Adv. Org. Chem.*, **8**, 179–293 (1972).
27. (a) See H. Kunz and H. Waldmann, "Protecting Groups," in *Comprehensive Organic Synthesis*, B. M. Trost, Ed., Pergamon Press, Oxford, UK, 1991, Vol. **6**, pp. 631–701; (b) P. J. Kocienski, *Protecting Groups*, George Thieme Verlag, Stuttgart/New York, 1994; (c) *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum Press, New York/London, 1973.
28. (a) *Organic Syntheses*, Wiley-Interscience, New York, Collect. Vols. I–IX, 1941–1998, 75, 1997; (b) *Synthetic Methods of Organic Chemistry*, W. Theilheimer, Ed., S. Karger, Basel, Vols. **1–52**, 1946–1997; (c) *Methoden der Organischen Chemie* (Houben-Weyl), E. Müller, Ed., George Thieme Verlag, Stuttgart, Vols. 1–21f, 1958–1995; (d) *Spec. Period. Rep.: General and Synthetic Methods*, Royal Society of Chemistry, Vols. **1–16**, 1978–1994; (e) *The Chemistry of Functional Groups*, S. Patai, Ed., Wiley-Interscience, Vols. **1–51**, 1964–1997.
29. (a) H. Waldmann and D. Sebastian, *Chem. Rev.*, **94**, 911 (1994); (b) *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*, K. Drauz and H. Waldmann, Eds., VCH, 1995, Vol. **2**, pp. 851–889.
30. T. D. Nelson and R. D. Crouch, *Synthesis*, 1031 (1996).
31. (a) K.-S. Lam, G. A. Hesler, J. M. Mattel, S. W. Mamber, and S. Forenza, *J. Antibiot.*, **43**, 956 (1990); (b) J. E. Loet, D. R. Schroeder, B. S. Krishnan, and J. A. Matson, *J. Antibiot.*, **43**, 961 (1990); (c) J. E. Leet, D. R. Schroeder, J. Golik, J. A. Matson, T. W. Doyle, K. S. Lam, S. E. Hill, M. S. Lee, J. L. Whitney, and B. S. Krishnan, *J. Antibiot.*, **49**, 299 (1996); (d) T. M. Kamenecka and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, **37**, 2993 (1998).
32. T. M. Kamenecka and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, **37**, 2995 (1998). We thank Professor Danishefsky for providing us with preprints of the himastatin communications (Refs. 31d and 32).

33. (a) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, **97**, 2241 (1997); (b) A. Ehrlich, H.-U. Heyne, R. Winter, M. Beyermann, H. Haber, L. A. Carpino, and M. Bienert, *J. Org. Chem.*, **61**, 8831 (1996).
34. HOAt, 7-aza-1-hydroxybenzotriazole; HATU (CAS Registry No. 148893-10-1), *N*-[(dimethylamino)(3*H*-1,2,3-triazolo(4,5-*b*)pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate, previously known as *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. [Note: Assignment of structure to HATU as a guanidinium species rather than as a uronium species—that is, attachment of the $(\text{Me}_2\text{NC}=\text{NMe}_2)^+$ unit to N_3 of 7-azabenzotriazole 1-*N*-oxide instead of to the *O*—is based on X-ray analysis (Ref. 33b).]
35. R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter, Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J.-I. Uenishi, J. B. White, and M. Yonaga, *J. Am. Chem. Soc.*, **111**, 7530–7533 (1989). See also *J. Am. Chem. Soc.*, **111**, 7525–7530 (1989).