Synthesis of a Tetrafluoro-Substituted Aryl Azide and Its Protio Analogue as Photoaffinity Labeling Reagents for the Estrogen Receptor

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A tetrafluoro-substituted aryl azide 1 and its protio analogue 2, both photoaffinity labeling reagents for the estrogen receptor, have been prepared by direct coupling of the appropriately substituted 4-azidobenzoyl chloride with the electron rich C-3 of 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 3. This represents a rare example of aryl azide stability under Friedel-Crafts acylation conditions. Alternatively, the protio analogue 2 can also be prepared with the azide functionality masked as a phthaloyl-protected arylamine, and the tetrafluoro analogue 1, by direct displacement of a pentafluoroaryl derivative 20 with NaN_3. Solution photolysis of tetrafluoro-substituted aryl azide (bis-methyl ether) 15 and its protio analogue 16 in toluene at 30 °C results in relatively high yields of products derived from C-H insertion. Both azides 1 and 2 demonstrate favorable relative binding affinity (RBA) (1 = 10%, 2 = 66%, estradiol = 100%) and photoinactivation efficiency (1 = 43%, 2 = 55% at 30 min) for the estrogen receptor (ER). The synthesis of both azides has been modified to accommodate a palladium-catalyzed tritium gas hydrogenolysis of an iodoaryl precursor at a late stage in the synthetic sequence, as will be needed to prepare them in radiolabeled form, and this procedure has been verified by deuteration. This pair of compounds will allow a detailed evaluation of the role that fluorine substitution plays in the photochemistry and photocovalent attachment behavior of aryl azides in a complex biochemical system, the estrogen receptor. The radiosynthesis and further biochemical results will be presented elsewhere.

Introduction

The search for effective and selective photoaffinity labeling (PAL) reagents[1] for the estrogen receptor (ER) has been extensive, but up to now, only partially successful. A variety of aryl azides and diazo ketones, both steroidal (based on estradiol)[2] and nonsteroidal (based on hexestrol),[3] as well as certain ketonic estrogens[4] and nitroanisole derivatives of hexestrol,[5] have been prepared. While some of these compounds exhibit certain favorable labeling characteristics, none of them demonstrate the required combination of high receptor binding affinity and good photocovalent attachment, coupled with the low nonspecific binding necessary for efficient and selective labeling of the ER.[3]

Electron-withdrawing groups are thought to enhance the reactivity of aryl azides,[6] and as such fluorine is especially attractive because of its small steric size. Simple polyfluorinated aryl azides have recently been proposed by Platz and co-workers as PAL reagents, since they demonstrate efficient carbon-hydrogen insertion chemistry upon photolysis even at ambient temperatures (in selected examples), whereas the simple phenyl azide systems yield mostly anilines, azo compounds, and tars.[7,8] Soundararajan and Platz have also found that the number of adducts obtained upon photolysis of polyfluoro aryl azides (in a variety of solvents) tends to increase with increasing number of fluorine atoms present.[9] Similarly, Keana and co-workers have recently reported the synthesis of several polyfluorinated aryl azides as "universal PAL" reagents since, in addition to the highly reactive azide moiety, they contain additional functionalization for further attachment to other molecular systems.[10]

In this paper, we describe the synthesis of a tetrafluoro aryl azide 1 as well as its protio analogue 2 as PAL reagents for the ER. In addition to a photoreactive aryl azide moiety, both of these compounds feature a 3-aroyl-2-arylbenzo[*b*]thiophene molecular skeleton, which, in closely related systems, is known to demonstrate high binding affinity for the ER.[11] Because these two aryl azides are a matched set in terms of fluorine substitution, a comparison of their covalent labeling toward the estrogen receptor may enable a direct evaluation of the effect of fluorine substitution on aryl azide covalent labeling efficiency in a complex, biological system.

Results and Discussion

Synthetic Approach to the Protio Aryl Azide 2. The most logical approach to the 3-aroyl-2-arylbenzo[*b*]-thiophene system is by connection of the C-3 electron-rich center of 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]-thiophene 3 with the carbonyl group of the para-substituted benzoyl derivative. The two precursor fragments are readily prepared. The benzo[*b*]thiophene 3 can be prepared on a multigram scale by an interesting cyclization-rearrangement reaction that is well described.[11,12] The substituted benzoyl portion of the molecule was prepared from 4-aminobenzoic acid, protected as the phthaloyl de-

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(2) (a) Katzenellenbogen, J. A.; Myers, H. N.; Johnson, H. J. *J. Org. Chem.* **1973**, *38*, 3525. (b) Katzenellenbogen, J. A.; Johnson, H. J.; Myers, H. N. *Biochemistry* **1973**, *12*, 4085. (c) Marquet, J.; Cantos, A.; Teixido, M.; Moreno-Manas, M. *Steroids* **1989**, *54*, 441.

(3) Katzenellenbogen, J. A.; Carlson, K. E.; Johnson, H. J.; Myers, H. N. *Biochemistry* **1977**, *16*, 1970.

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(7) (a) Young, M. J. T.; Platz, M. S. *Tetrahedron Lett.* **1989**, *30*, 2199. (b) Leyva, E.; Munoz, D.; Platz, M. S. *J. Org. Chem.* **1989**, *54*, 5938. (c) Leyva, E.; Young, M. J. T.; Platz, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 8307.

(8) For earlier work, see: (a) Banks, R. E.; Madany, E. M. *J. Fluorine Chem.* **1985**, *30*, 211. (b) Banks, R. E.; Prakash, A. *Tetrahedron Lett.* **1973**, *2*, 99. (c) Banks, R. E.; Sparkes, G. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2964. (d) Dunkin, I. R.; Thomson, P. C. P. *J. Chem. Soc., Chem. Commun.* **1982**, 1192.

(9) Soundararajan, N.; Platz, M. S. *J. Org. Chem.* **1990**, *55*, 2034.

(10) (a) Keana, J. F. W.; Cai, S. X. *J. Org. Chem.* **1990**, *55*, 3640. (b) Cai, S. X.; Keana, J. F. W. *Tetrahedron Lett.* **1989**, *30*, 5409. (c) Keana, J. F. W.; Cai, S. X. *J. Fluorine Chem.* **1989**, *43*, 151.

(11) Jones, C. K.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057.

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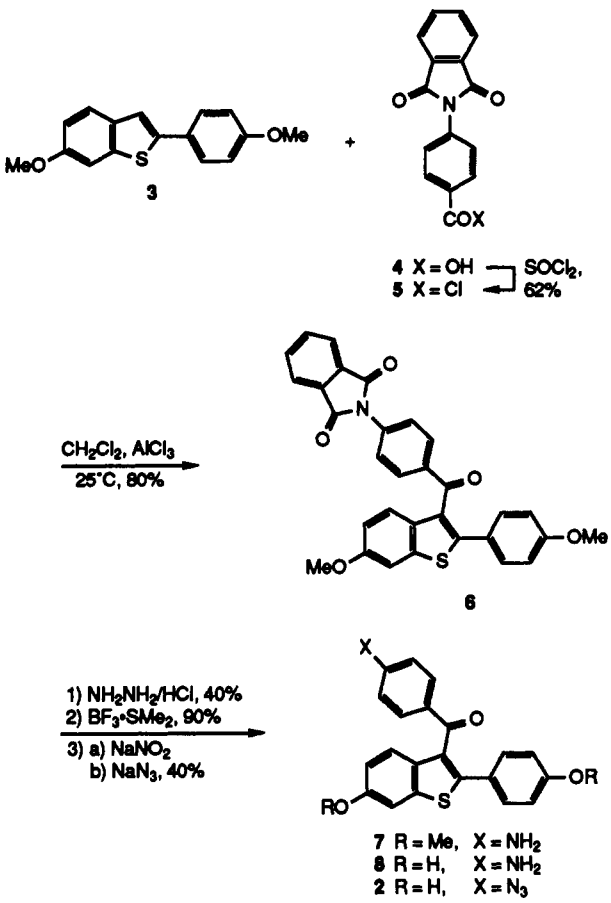
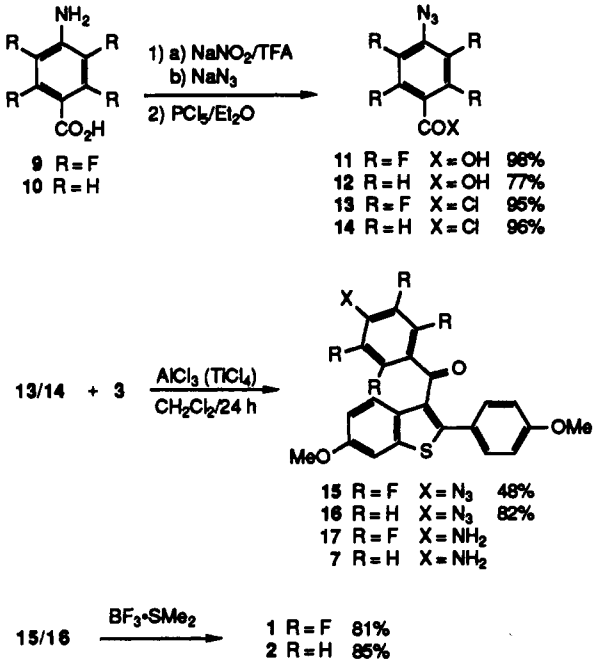
Scheme I. Initial Synthetic Pathway to Protio Aryl Azide 2



rivative 4 (Scheme I), known to tolerate Friedel–Crafts conditions.[13] Subsequent treatment with $SOCl_2$ gave the requisite amine-protected acid chloride 5 in moderate yield. Coupling of acid chloride 5 with C-3 of the benzo[*b*]-thiophene nucleus 3 was achieved in high yield (80%) using $AlCl_3$ (7.5 equiv). This type of Friedel–Crafts acylation has been previously demonstrated by Jones and co-workers (Eli Lilly and Co.) in their synthetic route to the antiestrogens LY117018 and LY156758.[11] Deprotection of the aryl amine functionality of the coupled ketone 6 was achieved by treatment with hydrazine, affording the amine 7. Subsequent cleavage of the methyl ether protecting groups with BF_3·SMe_2[14] provided the bis-hydroxy aryl amine 8. Finally, conversion to the aryl azide 2 was accomplished by diazotization of the amine 8, followed by displacement with NaN_3.

We were unable to protect the amine portion of the commercially available 4-amino-2,3,5,6-tetrafluorobenzoic acid (9) as a phthaloyl derivative, using phthalic anhydride or the more reactive *N*-carbethoxyphalimide,[15] or as a carbamate using adamantyl fluoroformate or isopropenyl chloroformate; in each case, only starting material 9 or byproducts were recovered. Apparently, the strong electron withdrawing effect of the four fluorine atoms greatly reduces the reactivity of amine 9. The plausibility of this explanation is supported by AMPAC[16] Molecular Orbital

Scheme II



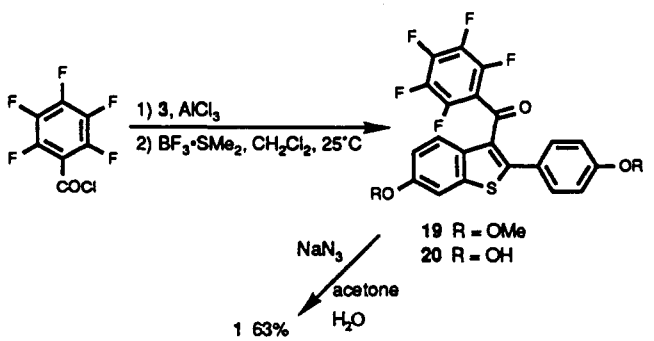
Calculations using the AM1[17] Hamiltonian: The E_{HOMO} of protio arylamine 10 = −9.0699 eV vs E_{HOMO} of tetrafluoroarylamine 9 = −9.6688 eV, corresponds to a difference in energy of 0.5989 eV (13.80 kcal/mol). The protio arylamine 10, with the higher lying HOMO, would be more reactive toward an electrophile (smaller HOMO–LUMO gap) than the tetrafluoroarylamine 9 with the lower lying HOMO.

Alternate Approaches to Protio Aryl Azide 2 and Tetrafluoro Aryl Azide 1. As an alternate approach, we investigated the feasibility of initially converting the tetrafluoroarylamine 9 to its corresponding azide, and then using this azide as a pseudo "protected amine" throughout the remaining synthesis. It is well known that treatment of aryl azides with Lewis acids results in the formation of anilines, diazo compounds and tars,[18] and to the best of our knowledge, there is no literature example which demonstrates successful Friedel–Crafts acylation chemistry in the presence of a free aryl azide functional group. Despite this lack of precedent, we have been successful in applying this approach to both the tetrafluoro and the protio systems.

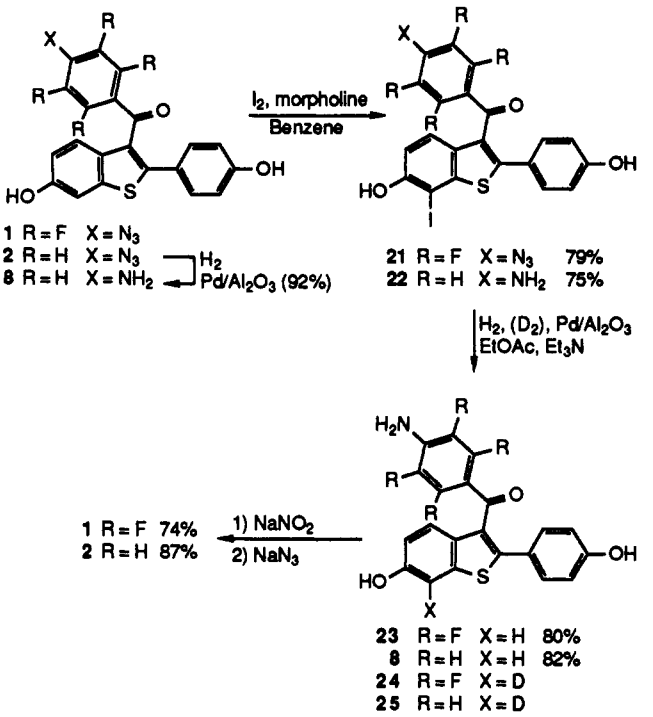
Diazotization of amines 9 and 10 with sodium nitrite, followed by displacement with NaN_3, afforded the aromatic azides 11[10c,19] and 12[20] in excellent yield (Scheme II). The choice of solvent is crucial for the success of this reaction: A combination of acetone and 1 M HCl worked well for the diazotization and azide displacement of 4-aminobenzoic acid 10, but was unsuccessful for the tetrafluoroarylamine 9, whereas trifluoroacetic acid (TFA)[21] worked well with both amines. The carboxylic acids 11 and 12 were converted to their corresponding acid chlorides 13[10] and 14.[22]

(13) Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1981.
(14) Williard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731.
(15) Nefkens, H. G. L.; Tesser, G. I.; Nivard, R. J. F. *Recueil* **1960**, *79*, 688.
(16) The coefficients were obtained from optimized AM1 wave functions, utilizing the AMPAC [version 1.00] series of programs obtained from QCPE (Bloomington, IN), running on a VAX 11/780 computer.
(17) Dewar, M. J. S.; Zoebisch, E. G.; Healey, E. F.; Steward, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(18) Smith, P. A. S. *Derivatives of Hydrazine and other Hydronitrogens Having N–N Bonds*; The Benjamin/Cummings Publishing Co.: London, 1983; p 276.
(19) Compound 11 has been prepared by M. S. Platz, but is unpublished. Personal communication M. S. Platz, 1989.
(20) Compound 12 has been previously prepared, see: (a) Shields, C. J.; Falvey, D. E.; Schuster, G. B.; Buchardt, O.; Nielsen, P. E. *J. Org. Chem.* **1988**, *53*, 3501. (b) Greiss, P. *Z. Chem.* **1867**, 164.
(21) Kanakarajan, K.; Haider, K.; Czarnik, A. W. *Synthesis* **1988**, 566.

Scheme III



Scheme IV



Optimal experimental conditions for coupling of the azidoaroyl chlorides to benzo[*b*]thiophene **3** vary somewhat between the tetrafluorobenzoyl chloride **13** and the protio counterpart **14**. Both systems successfully coupled with 3.0 or more equivalents of $AlCl_3$, but isolated yields were low and a greater excess of $AlCl_3$ resulted in a reduction of the coupled azides **15** and **16** to the free amines **17** and **7**. The weaker Lewis acid $TiCl_4$ may be used in large excess without causing reduction and was the reagent of choice in the coupling to form the protio analogue **16**. However, even with a large excess of $TiCl_4$ (10 equiv), coupling of the tetrafluoro acid chloride **13** was sluggish and incomplete, and while the tetrafluoro analogue **15** can be obtained in 60–75% yield, it is very difficult to separate from remaining starting material **3** by either chromatography or recrystallization. The mixture may be separated after deprotection of the bis-methyl ethers with BF_3·SMe_2, as the diols separate readily by chromatography. Alternatively, coupling with $TiCl_4$ (3.4 equiv) followed by the addition of $AlCl_3$ (1.5 equiv) after 1.5 h resulted in complete conversion to the tetrafluoroaryl azide **15**, although the isolated yield was lower (48%). The synthesis of azides **1** and **2** was completed by removal of the bis-methyl ether protecting groups with BF_3·SMe_2.

An alternate preparation of tetrafluoroaryl azide **1** was achieved by direct displacement of NaN_3 on a pentafluoroaryl precursor **20** (Scheme III). Such direct nucleophilic displacement on activated polyfluoro aromatic systems is known,[23] and has been demonstrated on some simple systems with NaN_3.[10] Pentafluoro system **19** was prepared by direct coupling of **3** with commercially available pentafluorobenzoyl chloride under Lewis acid ($AlCl_3$) conditions (Scheme III). At best, we achieved a moderate yield of a 70:30 mixture of **19** and **3**, which again was difficult to separate. Cleavage of the methyl ether protecting groups with BF_3·SMe_2 afforded bisphenol **20** which could be purified readily and was obtained in 29% overall yield (37% based on consumed **3**) for the two step process. Treatment of **20** with NaN_3[10] afforded tetrafluoroaryl azide **1**.

Synthetic Adaptations To Accommodate Isotope Incorporation. In order to prepare azides **1** and **2** in tritium-labeled form, we have modified our synthetic route to accommodate a palladium-catalyzed tritium gas hydrogenolysis of an iodine-substituted precursor[24] at a late stage in the synthetic route, an approach we have taken in the labeling of other reactive estrogen analogues.[25] We present in this report only the synthetic aspects of this work leading up to and including deuterium incorporation as a model for the tritium labeling. The actual radiolabeling with tritium and further biological results will be presented elsewhere.[26]

Our case presents two problems, first, incorporation of iodine onto an aromatic position of **1** or **2** in the presence of an aryl azide, and second, development of conditions to re-form the aryl azide as a final step, since the palladium-catalyzed exchange will result in concomitant reduction of the aryl azides to the corresponding arylamines.

Iodination of tetrafluoroaryl azide **1** (Scheme IV) was accomplished using iodine–morpholine complex.[27] The iodinated tetrafluoroaryl azide **21** was substituted with iodine specifically at C-7, as determined by complete disappearance of the C-7 hydrogen atom in the ^1H NMR spectrum, and removal of the meta coupling component of the hydrogen atom at C-5.

Attempts to iodinate the protio aryl azide **2** with a wide variety of iodinating agents and experimental conditions were all unsuccessful. However, when the protio arylamine **8** (prepared in high yield by hydrogenation of protio aryl azide **2** over a palladium on alumina catalyst) was treated with the iodine–morpholine complex, the C-7 iodinated arylamine **22** was produced cleanly.

It is interesting to note that the iodine favors exclusively the C-7 position of the benzo[*b*]thiophene systems **1** and **8**, as opposed to the sterically less hindered C-5 location. While both positions are doubly activated by the –OH and –S– substituents (C-5 ortho –OH and para –S–; C-7 ortho –OH and ortho –S–), it is possible that the sulfur aids in the transfer of the iodine. Iodine may attach first to the sulfur, placing it in a position for intramolecular transfer

(22) Compound **14** has been previously prepared; for representative examples, see: (a) Nielsen, P. E.; Buchardt, O. *Photochem. Photobiol.* **1982**, *35*, 317. (b) Merrill, S. H.; Unruh, C. C. *J. Appl. Polymer Sci.* **1963**, *7*, 273.

(23) Birchall, J. M.; Haszeldine, R. N.; Jones, M. E. *J. Chem. Soc. C* **1971**, 1343.

(24) Evans, E. A. *Tritium and its Compounds*; John Wiley and Sons: New York, 1974; pp 318–415.

(25) (a) Katzenellenbogen, J. A.; Carlson, K. E.; Heiman, D. F.; Robertson, D. W.; Wei, L. L.; Katzenellenbogen, B. S. *J. Biol. Chem.* **1983**, *258*, 3487. (b) Elliston, J. F.; Zablocki, J. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Endocrinology* **1987**, *121*, 667. (c) Simpson, D. M.; Elliston, J. F.; Katzenellenbogen, J. A. *J. Steroid Biochem.* **1987**, *28*, 233.

(26) Pinney, K. G.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A.; *Biochemistry*, in press.

(27) Southwick, P. L.; Kirchner, J. R. *J. Org. Chem.* **1962**, *27*, 3305.

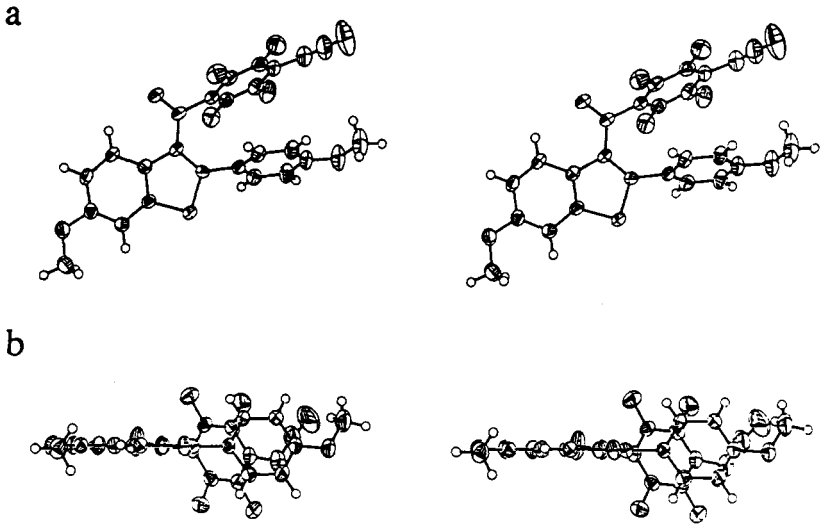
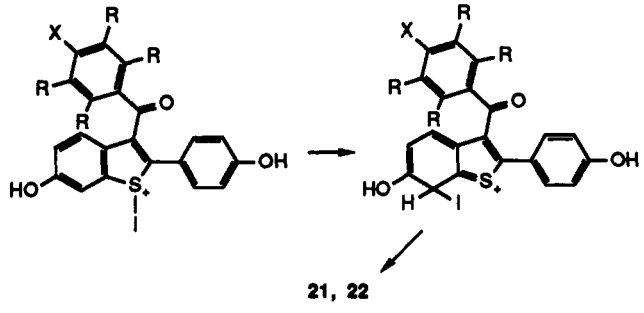


Figure 1. Stereoscopic thermal ellipsoid representations: (a) azide **15** plotted parallel to the best-plane normal; (b) azide **15** plotted perpendicular to the best-plane normal.

directly to the C-7 carbon. Alternatively, a second iodide ion may attack the iodosulfonium species at C-7 by an S_N2'-like process.[28] In addition, AM1[17] calculations on



the MM2 derived structure[29] of amine **18** show a significantly higher HOMO coefficient for C-7 (0.4240) as opposed to C-5 (0.0788), indicating that this is the preferred site for electrophilic attack of iodine.[16] A similar calculation on the X-ray crystallographic structure of azide **15** (see below) again shows a higher HOMO coefficient for C-7 (0.3809) versus C-5 (0.1170).

Hydrogenation of the iodine-substituted tetrafluoroaryl azide **21** over Pd/alumina proceeded rapidly in EtOAc (trace of Et_3N to scavenge HI), resulting in both iodine hydrogenolysis and reduction of the aryl azide (Scheme IV). After isolation and purification, tetrafluoroarylamine **23** was obtained in high yield. The iodinated protio precursor **22** was hydrogenated under similar conditions to afford protio arylamine **8**. In this case, the reaction was slower, going to completion in 4 h, and requiring a larger amount of the Pd/alumina catalyst.

Tetrafluoroarylamine **23** was diazotized with 1 equiv of $NaNO_2$ in TFA at 0 °C. Addition of excess NaN_3 (10 equiv) gave a satisfactory yield of tetrafluoroaryl azide **1** (Scheme IV). Similarly, the protio arylamine **8** could be converted to azide **2** in high yield with acetone/HCl as solvent.

As a model for the incorporation of tritium into azides **1** and **2**, we evaluated the efficiency of deuterium incorporation with iodo precursors **21** and **22** (Scheme IV). These reactions were carried out on a microscale quantitative hydrogenation apparatus,[30] fabricated in the glass shop at the University of Illinois, and the percent of isotope incorporation in carefully purified samples of the products **24** and **25** was determined by direct probe field ionization (FI) mass spectrometry (isotope ratio). Deuteriotetrafluoroarylamine **24** was found to incorporate 2.42% d_3, 15.27% d_2, 48.26% d_1, and 34.04% d_0. Deuterio protio arylamine **25** was found to incorporate 3.14% d_3, 15.57% d_2, 39.87 d_1, 41.42% d_0. The smaller amount of di- and trideuteration may be due to deuterium on the nitrogen of the arylamine moiety (despite our efforts to remove labile deuterium by several cycles of dissolution in ethanol followed by evaporation) or to palladium-catalyzed deuterium exchange on the aromatic rings.[31] The undeuterated material could result from isotope exchange of catalyst-bound tritium and solvent.

Table I. UV Spectral Data of Substituted Benzo[*b*]thiophenes

compound	λ_{max}, nm (ϵ)
tetrafluoroaryl azide **15**[a]	204 (28 980), 226 (28 980), 270 (22 980), 309 (sh) (10 350), 372 (sh) (3825)
protio aryl azide **16**[a]	204 (43 240), 226 (28 790), 302 (32 460) 385 (sh) (2090)
6-methoxy-2-(4-methoxyphenyl)benzo[*b*]-thiophene (**3**)[a,b]	236 (22 000), 262 (11 750), 273 (11 600), 310 (sh) (29 000), 317 (30 000)
4-methoxy-*trans*-stilbene[c,d,e]	306 (29 000), 310 (27 500)
4-methoxy-*cis*-stilbene[c,d]	280 (10 600)

[a] EtOH. [b] Reference 11. [c] 95% EtOH. [d] Reference 32. [e] Reference 33.

UV Spectra. The UV spectra of azides **15** and **16** (Table I) reflect the general degree to which these compounds retain the planar, *trans*-stilbene chromophore.

Molecular Structure of Tetrafluoroaryl Azide 15. Two orientations of the X-ray crystallographic structure

(28) We are grateful to a referee for suggesting this alternative bimolecular mechanism.

(29) MM2 geometries were obtained using MacroModel [version 2.5]. Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. 1989, MacroModel V2.5, Department of Chemistry, Columbia University, New York, NY 10027.

(30) Bindal, R. D. *Chem. Ind.* **1987**, 241.

(31) A referee has pointed out that the high level of dideuteration we see in the reduction of the aryl iodides suggests that tritium labeling of these compounds by direct exchange over a palladium catalyst may be possible. This method of labeling is well precedented, although the specific activities obtained are generally lower than by direct reduction.

(32) Shari, T.; Gazit, A.; Livshitz, T.; Biran, S. *J. Med. Chem.* **1985**, *28*, 1504.

(33) Anstead, G. M.; Katzenellenbogen, J. A. *J. Phys. Chem.* **1988**, *92*, 6249.

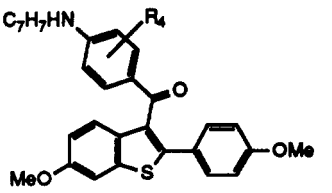
of tetrafluoroaryl azide **15** are presented in Figure 1. Azide **15** demonstrates no intermolecular contacts less than the sum of the van der Waals radii, thus the observed structure may be at or near the local energy minimum.[34]

The most prominent feature of the molecular structure of azide **15** is the stacking between the pendant *p*-methoxyphenyl ring and the tetrafluoro-substituted aryl ring. The distance between the centroids of each of the two π-stacked rings is 3.51 Å. This number lies outside the typical van der Waals contact distance of 3.4 Å between aromatic rings.[35] In addition, the stacked rings are perpendicularly oriented with respect to the benzo[*b*]-thiophene system. The stacking interaction observed between the electron-rich *p*-methoxyaryl ring and the electron-deficient *p*-azidotetrafluorobenzoyl system may be due to intramolecular charge transfer.[36]

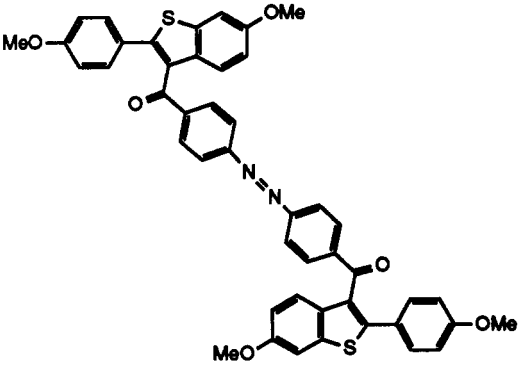
Photolysis of 15 and 16 in Toluene. A preliminary investigation of the photolysis behavior of azides **15** and **16** (5.00×10^{-2} M) in toluene at 30 °C was carried out. The samples were degassed by three freeze–thaw cycles prior to photolysis; the photolysis was carried out with a Hanovia mercury arc lamp equipped with a saturated aqueous $CuSO_4$ filter (effective wavelength >315 nm).[37] The photoproducts were purified by preparative thin-layer chromatography (TLC) and characterized by mass spectroscopy.

As expected from previous photochemical studies,[8-10] we obtained significant yields of toluene insertion products **26** from the photolysis of the tetrafluoroaryl azide **15**, as well as some reduction product **17** (32% and 36%, respectively, after 10 h of photolysis). In the photolysis of the protio aryl azide **2**, we were surprised to find in addition to aniline **7** (11% after 10 h of photolysis) and azo product **28**, a significant yield of toluene insertion products **27**. We estimate that the yield of the insertion process is at least 10%, although more careful quantitation was precluded by the limited amounts available for photolysis and the difficulties in separating the insertion product **27** from the coupled azo species **28**.

The extensive photochemical work that has been done on phenyl azide by both Schuster and co-workers[38] as well as Platz and co-workers[39] and others, unequivocally demonstrates the propensity of phenyl azide to undergo ring expansion to the complete exclusion of C–H insertion chemistry. It is possible that the electron-withdrawing capability of the carbonyl group in the protio azide **16** renders the resultant nitrene formed upon photolysis more capable of undergoing C–H insertion chemistry. However, it is known that both methyl 4-azidobenzoate[9] and 4-(dimethylamido)phenyl azide[20a,40] undergo ring expansion as opposed to C–H insertion, despite the presence of electron-withdrawing groups in the para position. It is conceivable that insertion product **27** is formed not via a nitrene, but rather through an alternative free-radical mechanism involving benzyl radical as an intermediate.[41]



26 R = F
27 R = H



28

A benzyl radical could add to the azide and, following loss of nitrogen and hydrogen atom abstraction, result in formation of insertion product **27**. This hydrogen atom abstraction from the benzylic position of toluene would result in propagation of the reaction. This mechanism is supported by a decrease in yield of the insertion product **27** observed when the photolysis was carried out in the presence of Bu_3SnH, an efficient free-radical scavenger (data not given).

Estrogen Receptor (ER) Studies with Azides 1 and 2. The relative binding affinity (RBA) of aryl azides **1** and **2** for the estrogen receptor (ER) was determined at 4 °C by a competitive radiometric binding assay using [^{3}H]estradiol as tracer.[2b] The values are reported relative to estradiol which is assigned a value of 100%. Protio aryl azide **2** demonstrates high RBA (66%) for the ER, while tetrafluoroaryl azide **1** has a somewhat lower RBA (10%).

A preliminary study designed to investigate the photochemical behavior of azides **1** and **2** in the binding site of the ER was carried out. The photoinactivation efficiency was determined by photolyzing a receptor–cytosol preparation which had been previously incubated with azide **1** or **2**, respectively.[37] The receptor–ligand complexes were irradiated, and the time-course of loss of reversible binding capacity of the ER was assayed by an exchange process. Suitable controls were included to monitor the nonspecific component of photoinactivation as well as the stability of the ER under the photolysis conditions. Both azides **1** and **2** demonstrate favorable photoinactivation of the ER (**1** = 43%, **2** = 55% at 30 min). It is important to note that this assay is an indirect method by which photoreactivity and hence potential photocovalent attachment is determined.[42] There are other competing processes which may result in loss of the reversible binding capacity (such as photooxidation–reduction) but not photocovalent attachment. In order to unequivocally determine the extent of photocovalent attachment of azides **1** and **2** to the ER it is necessary to prepare **1** and **2** in high specific activity tritium-labeled form. The radiolabeling of azides **1** and **2** as well as further biochemical evaluation of their inter-

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action with the ER will be presented elsewhere.[26]

Conclusion

In this report, we have described the preparation of an aryl azide and its tetrafluoro analogue that are designed to be photoaffinity labeling agents for the estrogen receptor. Several alternative protection group strategies are explored in the synthesis, and we have developed as well, an iodination, hydrogenolysis, azide resynthesis sequence suitable for radiolabeling these compounds with tritium at a carrier-free level. In addition, we have determined that upon photolysis, both the tetrafluoro and protio aryl azides (15 and 16) are capable of demonstrating C–H insertion in the nonnucleophilic solvent toluene. The availability of these compounds and this radiolabeling sequence has enabled us to study these compounds as photoaffinity labeling reagents for the estrogen receptor and to compare their photocovalent attachment efficiency in a critical test of the effect of fluorine-substitution on photoaffinity labeling efficiency in a complex system. The results of the radiolabeling and photoaffinity labeling studies will be presented elsewhere.[26]

Experimental Section

General Methods. All melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F-254 precoated (0.2 mm) plastic- or glass-backed plates. Reversed-phase TLC utilized 0.20-mm octadecylsilane-bonded silica gel glass-backed plates with F-254 indicator (Merck). Visualization methods included ultraviolet light (short and/or long wave), phosphomolybdic acid, or iodine chamber. Flash chromatography was performed according to Still,[43] using Woelm 32–63-μm silcia gel.

Fluorine-19 nuclear chemical shifts are reported in ppm based on $CFCl_3$ (0 ppm) as an internal standard. Mass spectra were recorded at 70 eV. A Hewlett-Packard Ultra 1 capillary column (12 m × 0.2 mm × 0.33 μm film thickness) was used for analytical gas chromatography. A Varian SI-5 (0.4 × 30 cm) column with a solvent system consisting of 70% CH_2Cl_2 (5% isopropyl alcohol) and 30% hexane delivered at 1.0 mL/min was used for high-pressure liquid chromatography. All reactions involving aryl azides were carried out in the dark by carefully wrapping the reaction vessels with aluminum foil.

Unless otherwise indicated, the procedure for product isolation in all reactions was similar and entailed quenching with water, exhaustive extraction with an appropriate solvent, aqueous and brine washing, and drying over $MgSO_4$. The quenching media, extraction solvent, washing solutions, and drying agent are indicated after the phrase "product isolation".

***N*-Phthaloyl-4-aminobenzoic Acid (4).** 4-Aminobenzoic acid (0.938 g, 6.84 mmol) and sodium carbonate (0.732 g, 6.91 mmol) were dissolved in H_2O (15 mL) to which *N*-(ethyloxycarbonyl)-phthalimide (1.50 g, 6.84 mmol) was added in one portion. The solution was vigorously stirred for 15 min and then heated to 50 °C. Additional H_2O (10 mL) was added at 15 and 45 min to dilute the precipitate and enhance the stirring. After a total reaction time of 1 h, the mixture was cooled, diluted into H_2O, and acidified to pH = 1.0. The copious precipitate was collected by filtration, rinsed with H_2O and air-dried for 24 h, resulting in 4 (1.18 g, 4.41 mmol, 64%) as a white solid. Purification by trituration (EtOAc/hexane, 50/50) afforded 4 as a white powder (1.11 g, 41.4 mmol, 61%) with mp 284–287 °C (lit.[44] mp 289–291 °C): ^{1}H NMR (acetone-d_6) δ 8.18 (d, 2 H, J = 8.4 Hz, ArH ortho to CO_2H), 7.97–7.94 (m, 4 H, ArH on phthaloyl ring), 7.69 (d, 2 H, J = 8.6 Hz, ArH ortho to *N*-phthaloyl); IR (KBr) ν 3100–2850 (broad), 1704, 1598, 1506, 1415, 1373; MS m/z 267 (M^+, 100), 250 (11), 223 (43). Anal. Calcd for $C_{15}H_9O_4N$: C, 67.42; H, 3.39; N, 5.24. Found: C, 67.10; H, 3.26; N, 5.19.

***N*-Phthaloyl-4-aminobenzoyl Chloride (5).** Carboxylic acid 4 (3.0 g, 11.23 mmol) and $SOCl_2$ (32.6 g, 274 mmol, 20 mL) were heated to reflux under nitrogen. After 45 min, the reaction mixture was cooled to 0 °C and the solid was collected by filtration and thoroughly washed with cold hexane. Acid chloride 5 (2.00 g, 6.99 mmol, 62%, two crops) was thus obtained as a white solid with mp 260–263 °C (lit.[45] mp 272–274 °C); ^{1}H NMR (acetone-d_6) δ 8.30 (d, 2 H, J = 8.7 Hz, ArH ortho to COCl), 8.02–7.95 (m, 4 H, ArH on phthaloyl ring), 7.86 (d, 2 H, J = 8.7 Hz, ArH ortho to *N*-phthaloyl); MS m/z 285 (M^+, 6) 250 (100), 222 (27), 166 (9), 104 (15), 76 (20). Anal. Calcd for $C_{15}H_8O_3NCl$: C, 63.06; H, 2.82; N, 4.90; Cl, 12.41. Found: C, 62.87; H, 2.85; N, 4.92; Cl, 12.57.

3-[*N*-Phthaloyl-4-aminobenzoyl]-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (6). Benzo[*b*]thiophene 3[11] (0.0984 g, 0.364 mmol) and acid chloride 5 (0.156 g, 0.546 mmol) were combined in CH_2Cl_2 (15 mL) and stirred at 25 °C under a nitrogen atmosphere. $AlCl_3$ (0.364 g, 2.73 mmol) was slowly added in several portions over a 15-min period, and the mixture was stirred for 23 h. Product isolation (H_2O, CH_2Cl_2, EtOAc, brine, $MgSO_4$) and purification by flash chromatography (silica gel, 40 × 200 mm, 60/40 EtOAc/hexane) and trituration with hexane/EtOAc (4/1), afforded ketone 6 as a pale yellow solid (0.0959 g, 0.185 mmol, 51%). A second trituration (EtOAc/hexane, 9/1) gave 6 as a pale yellow solid (0.0383 g, 0.0737 mmol) with mp 216–219 °C: ^{1}H NMR ($CDCl_3$) δ 7.95 (dd, 2 H, J = 5.4, 3.1 Hz, ArH on phthalimide phenyl), 7.91 (d, 2 H, J = 8.6 Hz, ArH ortho to carbonyl), 7.80 (dd, 2 H, J = 5.4, 3.1 Hz, ArH on phthalimide phenyl), 7.62 (d, 1 H, J = 8.9 Hz, ArH on C-4), 7.45 (d, 2 H, J = 8.5 Hz, ArH ortho to phthalimide), 7.34 (d, 1 H, J = 2.3 Hz, ArH on C-7), 7.33 (d, 2 H, J = 8.5 Hz, Ar*H* meta to OCH_3 on pendant aryl ring), 7.00 (dd, 1 H, J = 8.9, 2.3 Hz, ArH on C-5), 6.77 (d, 2 H, J = 8.7 Hz, ArH ortho to OCH_3 on pendant aryl ring), 3.90 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3); MS m/z 519 (M^+, 100), 504 (15), 297 (14), 259 (13), 250 (16). Anal. Calcd for $C_{31}H_{21}O_5NS$: C, 71.66; H, 4.07; N, 2.70; S, 6.17. Found: C, 71.44; H, 4.10; N, 2.70; S, 6.04.

3-(4-Aminobenzoyl)-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (7). Phthalimide 6 (1.00 g, 1.92 mmol) was added to a 1.0 M solution of hydrazine hydrate in absolute ethanol (2.0 mL). The mixture was further diluted with EtOH (6.0 mL) and heated at reflux for 1 h. A white salt precipitate (0.317 g, mp >300 °C) was removed by filtration, and the mother liquor was concentrated under reduced pressure to leave a pale green solid. This material was heated (50 °C) in 3 M HCl (15 mL) and EtOH (5.0 mL) for 15 min and then cooled (0 °C), and a solid precipitate formed with mp >300 °C. The mother liquor was again concentrated under reduced pressure to leave amine 7 as a pale orange oil which solidified under vacuum as a puffy orange solid (0.302 g, 0.775 mmol, 40%). A portion of the material was further purified by flash chromatography (silica gel, 40 × 200 mm, EtOAc/hexane, 70/30) and trituration with hexane/EtOAc (20/1) to obtain 7 as a pale yellow solid (0.0764 g, 0.196 mmol) with mp 142–145 °C: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2 H, J = 8.6 Hz, ArH meta to NH_2), 7.49 (d, 1 H, J = 8.9 Hz, ArH on C-4), 7.38 (d, 2 H, J = 8.7 Hz, ArH meta to OCH_3 on pendant aryl ring), 7.31 (d, 1 H, J = 2.3 Hz, ArH on C-7), 6.94 (dd, 1 H, J = 8.9, 2.3 Hz, ArH on C-5), 6.77 (d, 2 H, J = 8.7 Hz, ArH ortho to OCH_3 on pendant aryl ring), 6.48 (d, 2 H, J = 8.6 Hz, ArH ortho to NH_2), 3.87 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3); MS m/z 389 (M^+, 100), 374 (17), 372 (6), 297 (7), 195 (9), 120 (54), 92 (23), 65 (17); HRMS (EI) M^+ calcd for $C_{23}H_{19}O_3NS$ 389.1086, found 389.1095. Anal. Calcd for $C_{23}H_{19}O_3NS$: C, 70.93; H, 4.92; N, 3.60; S, 8.23. Found: C, 71.10; H, 5.01; N, 3.56; S, 8.05.

3-(4-Aminobenzoyl)-6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophene (8). Procedure A (Scheme I). Amine 7 (0.100 g, 0.257 mmol) was dissolved in CH_2Cl_2 (7.0 mL) to which a BF_3·SMe_2 solution (3.0 mL) was slowly added. The mixture was heated to reflux for 0.5 h, and the solvent was removed in vacuo to leave a red oil which was crystallized from EtOH to obtain an off-white solid (0.0687 g) which did not show any chromophore upon UV visualization of a TLC plate and was discarded. The mother liquor was concentrated under reduced pressure to obtain

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8 as a brown oil which was recrystallized from $CHCl_3$ to give a pale brown solid (0.0806 g, 0.223 mmol, 87%). See procedure B for further characterization.

Procedure B (Scheme IV). Protio aryl azide **2** (0.0820 g, 0.212 mmol) was dissolved in EtOAc (15 mL) and Et_3N (0.6 mL), and after 5 min, the catalyst Pd/alumina (0.005 g, palladium content 5%) was added. The flask containing the mixture was transferred to a hydrogenator and vigorously stirred at room temperature in the dark under an H_2 atmosphere (1.1 atm) for 3 h at which time the reaction was complete. The mixture was filtered through a pad of Celite, rinsed several times with EtOAc, and concentrated in vacuo to a yellow oil. Crystallization from Et_2O/EtOAc, 9/1, afforded amine **8** as pale yellow needles (0.0580 g, 0.161 mmol, 76%) with mp 77–80 °C: ^1H NMR (acetone-d_6) δ 8.62 (bs, 2 H, OH), 7.53 (d, 2 H, J = 8.6 Hz, ArH meta to NH_2), 7.35 (d, 1 H, J = 2.2 Hz, ArH on C-7), 7.32 (d, 1 H, J = 8.6 Hz, ArH on C-4), 7.30 (d, 2 H, J = 8.6 Hz, ArH meta to OH on pendant aryl ring), 6.89 (dd, 1 H, J = 8.7, 2.2 Hz, ArH on C-5), 6.75 (d, 2 H, J = 8.6 Hz, ArH ortho to OH on pendant aryl ring), 6.54 (d, 2 H, J = 8.7 Hz, ArH ortho to NH_2), 5.57 (bs, 2 H, NH_2); MS m/z 361 (M^+, 92), 344 (14), 269 (16), 120 (100), 92 (42), 65 (35); HRMS (EI) M^+ calcd for $C_{21}H_{15}O_3NS$ 361.0773, found 361.0782.

4-Azido-2,3,5,6-tetrafluorobenzoic Acid (11). Arylamine **9** (2.0 g, 9.57 mmol) dissolved in CF_3CO_2H (TFA) (50 mL) was diazotized in the dark at 0 °C by the addition of $NaNO_2$ (1.32 g, 19.1 mmol). After stirring for 0.5 h, NaN_3 (6.22 g, 95.7 mmol) was slowly added to the reaction mixture over a 5-min period followed immediately by the addition of Et_2O (40 mL). After 1 h, the reaction was quenched with H_2O, and the product was isolated (Et_2O extraction, brine wash, $MgSO_4$, filtration, concentration) as a tan solid. Purification by hexane trituration afforded the requisite aryl azide **11** (2.04 g, 8.68 mmol, 91%) as a pale yellow solid with mp 135–141 °C. A small sample was recrystallized (EtOAc, −30 °C) to afford off-white needles of **11** with mp 142–144 °C (lit.[10,19] mp 140–141 °C).

4-Azidobenzoic Acid (12). 4-Aminobenzoic acid **10** (4.0 g, 29.2 mmol) dissolved in TFA (60 mL) was diazotized in the dark at 0 °C with $NaNO_2$ (4.03 g, 58.3 mmol). After stirring for 0.5 h, NaN_3 (19.0 g, 292 mmol) was slowly added to the reaction mixture over a 5-min period. After an additional 15 min, Et_2O (40 mL) was added, and the entire mixture stirred for 1 h. Product isolation (H_2O, Et_2O, $MgSO_4$) and removal of excess TFA as an azeotrope with benzene gave **12** as a white powder (4.32 g, 26.5 mmol, 91%) with mp 179–180 °C (decomposition) (lit.[20] mp 185 °C).

4-Azido-2,3,5,6-tetrafluorobenzoyl Chloride (13). Carboxylic acid **11** (1.0 g, 4.25 mmol) was dissolved in Et_2O (15 mL) followed by the addition of PCl_5 (0.939 g, 4.51 mmol) in a glovebag under N_2. The mixture was agitated by hand for 10 min. The solvent was removed in vacuo to leave a yellow oil which was further dried for 1 h at 25 °C under vacuum. Acid chloride **13** was obtained as a yellow oil (1.09 g, 4.31 mmol, 100%) (lit.[10] bp 47–49 °C (0.01 mmHg)) and used without further purification.

4-Azidobenzoyl Chloride (14). 4-Azidobenzoic acid **12** (2.0 g, 12.3 mmol) was dissolved in Et_2O (25 mL) in a N_2 glovebag followed by the addition of PCl_5 (2.71 g, 13.0 mmol). The reaction mixture was agitated by hand for 20 min. The Et_2O was removed in vacuo to afford a yellow oil which crystallized under vacuum. The solid was triturated with hexane, at 0 °C and together with a second crop, gave **14** as a white solid (2.01 g, 11.1 mmol, 90%) with mp 55–57 °C (lit.[22b] mp 57–58 °C).

3-(4-Azido-2,3,5,6-tetrafluorobenzoyl)-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (15). To a well-stirred solution of acid chloride **13** (1.62 g, 6.38 mmol) in CH_2Cl_2 (50 mL) at 25 °C under N_2 in the dark was added benzo[*b*]thiophene **3** (1.03 g, 3.81 mmol) in one portion. To this solution was slowly added $TiCl_4$ (2.42 g, 12.8 mmol) over a 10-min period. After 1 h of stirring, $AlCl_3$ (0.762 g, 5.72 mmol) was slowly added over a 5-min period, and after 7 h, additional $AlCl_3$ (0.254 g, 1.90 mmol) was added. The reaction mixture was quenched after an additional 13 h with cold H_2O (150 mL, 0 °C; exothermic!). Product isolation (CH_2Cl_2, H_2O, brine, $MgSO_4$) gave a dark brown oily solid which was recrystallized from EtOAc/hexane (30/70) and combined with a second and third crop obtained by flash chromatography (silica gel, 40 × 200 mm, 60/40 EtOAc/hexane) and recrystallization of the mother liquor, to give **15** as a pale yellow solid (0.894 g, 1.83 mmol, 48%) with mp 154–158 °C dec: ^1H NMR ($CDCl_3$) δ 8.44 (d, 1 H, J = 9.0 Hz, ArH at C-4), 7.30 (d, 1 H, J = 2.0 Hz, ArH at C-7), 7.24 (d, 2 H, J = 8.7 Hz, PhH ortho to OCH_3), 7.15 (dd, 1 H, J = 9.0, 2.1 Hz, ArH at C-5), 6.78 (d, 2 H, J = 8.6 Hz, PhH meta to OCH_3), 3.91 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3); IR (KBr) ν 3084, 2965, 2922, 2831, 2112, 1633, 1591, 1520, 1471, 1408, 1344; MS m/z 487 (M^+), 459, 424, 304, 297 (base peak), 254, 211, 139. Anal. Calcd for $C_{23}H_{13}F_4N_3O_3S$: C, 56.68; H, 2.69; F, 15.59; N, 8.62; S, 6.58. Found: C, 56.94; H, 2.79; F, 15.51; N, 8.36; S, 6.66.

3-(4-Azido-2,3,5,6-tetrafluorobenzoyl)-6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophene (1). BF_3·SMe_2 (5.0 mL) was added directly to a solution of bis-methyl ether **15** (0.751 g, 1.54 mmol) dissolved in CH_2Cl_2 (40 mL). The solution was stirred at 25 °C under N_2 in the dark for 13 h. Product isolation (H_2O, CH_2Cl_2, brine, $MgSO_4$), purification by flash chromatography (silica gel, 40 × 200 mm, 60/40 EtOAc/hexane), and trituration with cold hexane gave tetrafluoroaryl azide **1** as a pale yellow solid (0.567 g, 1.24 mmol, 80%) with mp 168–169 °C dec: ^1H NMR (acetone-d_6) δ 8.35 (d, 1 H, J = 8.9 Hz, ArH at C-4), 7.41 (d, 1 H, J = 2.2 Hz, ArH at C-7), 7.21 (d, 2 H, J = 8.4 Hz, PhH meta to OH), 7.13 (dd, 1 H, J = 8.8, 2.2 Hz, ArH at C-5), 6.79 (d, 2 H, J = 8.4 Hz, PhH ortho to OH); ^{19}F NMR (acetone-d_6)[46] −142.37 (AA'XX', 2 F, J_{AX} = 21.86 Hz, $J_{AA'}$ = 3.14 Hz, $J_{AX'}$ = −10.17 Hz, $J_{XX'}$ = 0 Hz), −152.50 (AA'XX', 2 F, J_{AX} = 21.86 Hz, $J_{AA'}$ = 3.14 Hz, $J_{AX'}$ = −10.17 Hz, $J_{XX'}$ = 0 Hz); IR (KBr) ν 3373 (broad) 2112. 1612, 1471, 1400; MS m/z 459 (M^+, 37), 433 (11), 403 (12), 269 (100), 213 (13), 197 (23). Anal. Calcd for $C_{21}H_9F_4N_3O_3S$: C, 54.91; H, 1.97; F, 16.54; N, 9.15; S, 6.98. Found: C, 54.67; H, 2.12; F, 16.39; N, 8.88; S, 7.20.

3-(4-Azidobenzoyl)-6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophene (16). To a well-stirred solution of benzo-[*b*]thiophene **3** (0.991 g, 3.67 mmol) and acid chloride **14** (0.932 g, 5.13 mmol) in CH_2Cl_2 (60 mL) at 20 °C in the dark under N_2 was added $TiCl_4$ (3.48 g, 18.3 mmol) over a 10-min period. The reaction was complete after 5.5 h. Product isolation (H_2O, CH_2Cl_2, brine, $MgSO_4$) and purification by flash chromatography (silica gel, 40 × 200 mm, 60/40 EtOAc/hexane) and recrystallization (EtOH/EtOAc/hexane, 3/1/6, second crop also recovered) afforded ketone **16** as a pale yellow finely divided solid (1.25 g, 3.01 mmol, 82%) with mp 102–105 °C dec: ^1H NMR ($CDCl_3$) δ 7.77 (d, 2 H, J = 8.6 Hz, ArH meta to N_3), 7.60 (d, 1 H, J = 8.9 Hz, ArH on C-4), 7.32 (d, 1 H, J = 2.9 Hz, ArH on C-7), 7.30 (d, 2 H, J = 9.0 Hz, ArH meta to OCH_3 on pendant aryl ring), 6.99 (dd, 1 H, J = 8.9, 2.3 Hz, ArH on C-5), 6.88 (d, 2 H, J = 8.6 Hz, ArH ortho to N_3), 6.75 (d, 2 H, J = 8.7 Hz, ArH ortho to OCH_3 on pendant aryl ring), 3.89 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3); IR (KBR) ν 2936, 2831, 2394, 2105, 1626, 1591, 1556, 1520; MS m/z 415 (M^+, 100), 387 (43), 297 (45), 211 (27), 139 (29). Anal. Calcd for $C_{23}H_{17}N_3O_3S$: C, 66.49; H, 4.12; N, 10.11; S, 7.72. Found: C, 66.32; H, 4.07; N, 9.80; S, 8.04.

3-(4-Azidobenzoyl)-6-hydroxy-2-(4-hydroxyphenyl)-benzo[*b*]thiophene (2). Bis-methyl ether **16** (0.400 g, 0.963 mmol) was dissolved in CH_2Cl_2 (35 mL) at 20 °C in the dark under N_2 atmosphere. To this stirred solution was added BF_3·SMe_2 complex (5 mL). After 6 h, product isolation (H_2O, CH_2Cl_2, EtOAc, $MgSO_4$) and purification by flash chromatography (silica gel, 40 × 200 mm, 60/40 EtOAc/hexane) followed by recrystallization from hexane, afforded protio aryl azide **2** as a pale yellow finely divided solid (0.196 g, 0.506 mmol, 53%) with mp 145–151 °C dec: ^1H NMR (acetone-d_6) δ 8.70 (bs, 2 H, OH), 7.77 (d, 2 H, J = 8.5 Hz, ArH ortho to carbonyl), 7.49 (d, 1 H, J = 8.8 Hz, ArH on C-4), 7.40 (d, 1 H, J = 2.2 Hz, ArH on C-7), 7.23 (d, 2 H, J = 8.5 Hz, ArH meta to OH on pendant aryl ring), 7.02 (d, 2 H, J = 8.5 Hz, ArH ortho to N_3), 6.96 (dd, 1 H, J = 8.8, 2.2 Hz, ArH on C-5), 6.73 (d, 2 H, J = 8.5 Hz, ArH ortho to OH on pendant aryl ring); IR (KBr) ν 3331 (broad), 3154 (broad), 2112, 1725, 1577; MS m/z 387 (M^+, 100), 361 (58), 331 (79), 269 (70), 242 (38), 213 (38), 197 (49), 120 (71); HRMS (EI) M^+ calcd for $C_{21}H_{13}N_3O_3S$ 387.0678, found 387.0675.

6-Methoxy-2-(4-methoxyphenyl)-3-(2',3',4',5',6'-pentafluorobenzoyl)benzo[*b*]thiophene (19). Pentafluorobenzoyl

(46) The fluorine-19 NMR coupling constants were determined by computational simulation utilizing ITRCAL by Nicolet Technology Corporation running on a Nicolet 1180E computer.

chloride (1.00 g, 4.34 mmol) and benzo[*b*]thiophene **3** (0.586 g, 2.169 mmol) were combined in freshly distilled (from CaH_2) CH_2Cl_2 (80 mL) under a nitrogen atmosphere at 23 °C. $AlCl_3$ (2.17 g, 16.27 mmol) was slowly added (in three portions over a 5-min period), and the solution was stirred for 8 h. Product isolation (H_2O, EtOAc, brine, $MgSO_4$) and purification by flash chromatography (silica gel, 40 × 200 mm, 2/3 EtOAc/hexane) and trituration with hexane gave pentafluoro adduct **19** (0.660 g) as a pale yellow solid. ^1H NMR confirmed that the product actually was a mixture of **19** (70%) and **3** (30%), which proved very difficult to purify. A portion (0.36 g) of the product mixture was purified by three crystallizations (Et_2O/EtOH, 1/1; EtOAc, and EtOH/Et_2O, 3/1) to afford **19** (0.105 g, 0.226 mmol, 19% overall yield, 25% based on consumed starting material **3**) as pale yellow finely divided needles with mp 144–147 °C: ^1H NMR ($CDCl_3$) δ 8.47 (d, 1 H, J = 9.1 Hz, ArH on C-4), 7.30 (d, 1 H, J = 2.3 Hz, ArH on C-7), 7.24 (d, 2 H, J = 8.7 Hz, ArH meta to OCH_3 on pendant aryl ring), 7.16 (dd, 1 H, J = 9.1, 2.3 Hz, ArH on C-5), 6.77 (d, 2 H, J = 8.6 Hz, ArH ortho to OCH_3 on pendant aryl ring), 3.92 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3); IR (KBr) ν 3000, 2965, 2929, 2823, 1640, 1591, 1520, 1478, 1239; MS m/z 464 (M^+, 100), 449 (30), 297 (15), 195 (21). Anal. Calcd for $C_{23}H_{13}F_5O_3S$: C, 59.49; H, 2.82; F, 20.45; S, 6.90. Found: C, 59.55; H, 2.87; F, 20.32; S, 7.04.

The remaining portion of the product mixture (0.30 g) was subjected to methyl ether cleavage and purified chromatographically as the bisphenol **20** (see the following procedure).

6-Hydroxy-2-(4-hydroxyphenyl)-3-(2′,3′,4′,5′,6′-pentafluorobenzoyl)benzo[*b*]thiophene (20). A 0.300-g mixture containing 70% **19** (0.517 mmol) and 30% **3** (0.222 mmol) was dissolved in CH_2Cl_2 (60 mL) at 23 °C under a nitrogen atmosphere. BF_3·SMe_2 complex (6 mL) was added in one portion, and the mixture stirred for 28 h. Product isolation (H_2O, CH_2Cl_2, EtOAc, $MgSO_4$), purification by flash chromatography (silica gel, 40 × 200 mm, 7/3 hexane/EtOAc), and recrystallization (hexane/Et_2O:1/1) gave **20** as a pale yellow solid (0.123 g, 0.281 mmol, 54%) with mp 251–252 °C. This corresponds to a 29% overall yield (37% based on consumed starting material of **20** for the two-step sequence from benzo[*b*]thiophene **3**): ^1H NMR (acetone-d_6) δ 8.89 (bs, 2 H, OH), 8.36 (d, 1 H, J = 8.9 Hz, ArH on C-4), 7.42 (d, 1 H, J = 2.3 Hz, ArH on C-7), 7.21 (d, 2 H, J = 8.4 Hz, ArH meta to OH on pendant aryl ring), 7.13 (dd, 1 H, J = 8.9, 2.3 Hz, ArH on C-5), 6.78 (d, 2 H, J = 8.5 Hz, Ar*H* ortho to OH on pendant aryl ring); IR (KBr) ν 3366, 1591, 1499, 1457, 1429, 1358, 1218; MS m/z 436 (M^+, 100), 269 (51), 197 (19). Anal. Calcd for $C_{21}H_8F_5O_3S$: C, 57.80; H, 2.08; F, 21.77; S, 7.35. Found: C, 57.44; H, 2.07; F, 21.85; S, 7.64.

3-(4-Azido-2,3,5,6-tetrafluorobenzoyl)-6-hydroxy-2-(4-hydroxyphenyl)-7-iodobenzo[*b*]thiophene (21). Iodine (0.332 g, 1.31 mmol) was added to a solution of freshly distilled morpholine (0.326 g, 3.92 mmol, 0.326 mL) in benzene (40 mL) at 20 °C in the dark under an N_2 atmosphere (orange precipitate). After 25 min, tetrafluoroaryl azide **1** (0.200 g, 0.435 mmol) was added in one portion and the mixture was stirred for 9 h. Product isolation (5% HCl, EtOAc, 20% $Na_2S_2O_3$, H_2O, brine, $MgSO_4$), purification by flash chromatography (silica gel, 40 × 200 mm, EtOAc/hexane, 60/40), and recrystallization (EtOAc/hexane, 1/9), gave **21** as a pale yellow solid (0.150 g, 0.256 mmol, 59%). Further recrystallization ($CHCl_3$/hexane, 50/50) gave **21** as a finely divided pale yellow solid with mp 125–128 °C dec: ^1H NMR (acetone-d_6) δ 9.70 (bs, 1 H, OH), 9.00 (bs, 1 H, OH), 8.32 (d, 1 H, J = 8.8 Hz, ArH on C-4), 7.25 (d, 2 H, J = 8.4 Hz, ArH meta to *OH* on pendant aryl ring), 7.18 (d, 1 H, J = 8.8 Hz, ArH on C-5), 6.81 (d, 2 H, J = 8.4 Hz, ArH ortho to OH on pendant aryl ring); MS m/z 585 (M^+, 13), 559 (7), 395 (22), 254 (100); MS (FAB) m/z 586 (M + 1), 560, 515, 461, 309; HRMS (FAB) MH^+ calcd for $C_{21}H_9IF_4N_3O_3S$ 585.9346, found 585.9356.

3-(4-Aminobenzoyl)-2-(4-hydroxyphenyl)-6-hydroxy-7-iodobenzo[*b*]thiophene (22). Iodine (0.105 g, 0.415 mmol) and morpholine (0.104 g, 1.25 mmol) were mixed in benzene (14 mL) at 20 °C under nitrogen in the dark (orange precipitate). After 15 min, amine **8** (0.050 g, 0.138 mmol) was added in one portion. Product isolation (5% HCl, EtOAc, 20% $Na_2S_2O_3$, brine, $MgSO_4$) and purification by flash chromatography (silica gel, 40 × 200 mm, EtOAc/hexane, 60/40) afforded **22** (0.027 g, 0.055 mmol, 40%) as a pale yellow solid with mp 77–83 °C dec: ^1H NMR (acetone-d_6) δ 9.38 (bs, 1 H, OH), 8.62 (bs, 1 H, OH), 7.53 (d, 2 H, J = 8.5 Hz, ArH meta to NH_2), 7.34 (d, 2 H, J = 8.2 Hz, ArH meta to OH on pendant aryl ring), 7.33 (d, 1 H, J = 8.7 Hz, ArH on C-4), 6.96 (d, 1 H, J = 8.6 Hz, ArH on C-5), 6.77 (d, 2 H, J = 8.4 Hz, ArH ortho to OH on pendant aryl ring), 6.54 (d, 2 H, J = 8.6 Hz, ArH ortho to NH_2), 5.60 (bs, 2 H, NH_2); MS m/z 487 (M^+, 2), 361 (13), 254 (91), 242 (100), 127 (95); MS (FAB) m/z 488 (M + 1), 372, 309, 279, 251, 195; HRMS (EI) M^+ calcd for $C_{21}H_{14}IO_3NS$ 486.9739, found 486.9735.

3-(4-Amino-2,3,5,6-tetrafluorobenzoyl)-6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophene (23). Tetrafluoroaryl azide **1** (0.100 g, 0.218 mmol) was dissolved in EtOAc (16 mL) and Et_3N (0.8 mL) followed, after 5 min, by Pd/alumina (0.005 g, palladium content, 5%). The flask containing the mixture was transferred to a hydrogenator and vigorously stirred at 0 °C in the dark under an H_2 atmosphere (1.1 atm) for 2.5 h. The mixture was filtered through a pad of Celite and concentrated in vacuo to a brilliant yellow oil which solidified under vacuum and was purified by trituration with hexane to afford amine **23** as a pale yellow solid (0.0925 g, 0.213 mmol, 98%) with mp 265–267 °C: ^1H NMR (acetone-d_6) δ 8.76 (bs, 2 H, OH), 8.09 (d, 1 H, J = 8.8 Hz, ArH on C-4), 7.37 (d, 1 H, J = 2.2 Hz, ArH on C-7), 7.19 (d, 2 H, J = 8.5 Hz, ArH meta to OH on pendant aryl ring), 7.06 (dd, 1 H, J = 8.9, 2.2 Hz, ArH on C-5), 6.75 (d, 2 H, J = 8.5 Hz, ArH ortho to OH on pendant aryl ring), 5.80 (bs, 2 H, NH_2); MS m/z 433 (M^+, 100), 385 (11), 269 (64). Anal. Calcd for $C_{21}H_{11}F_4NO_3S$: C, 58.20; H, 2.56; F, 17.53; N, 3.23; S, 7.40. Found: C, 57.11; H, 2.98; F, 17.33; N, 3.10; S, 7.04.

Conversion of Tetrafluoroarylamine 23 to Azide 1. Amine **23** (0.0091 g, 0.0210 mmol) was dissolved in TFA (0.3 mL) at 0 °C in the dark. $NaNO_2$ (0.0015 g, 0.0210 mmol, as 0.1 mL of a stock solution (0.015 g $NaNO_2$/1.0 mL TFA)) was added to the reaction mixture, which immediately turned nearly black in color. After stirring for 30 min in the dark, NaN_3 (0.0137 g, 0.210 mmol) was added, and the mixture was stirred for 70 min. Et_2O (1.0 mL) was subsequently added, and the mixture was stirred for an additional 30 min. Product isolation (H_2O, Et_2O, $MgSO_4$) and removal of excess TFA as a benzene azeotrope afforded azide **1** (0.0094 g, 0.0204 mmol, 97%).

Conversion of Protio Arylamine 8 to Azide 2. Amine **8** (0.0100 g, 0.0277 mmol) was dissolved in 5% HCl (0.25 mL) and acetone (0.25 mL) at 0 °C in the dark. $NaNO_2$ (0.00190 g, 0.0277 mmol, as 0.1 mL of a standard solution (0.0190 g $NaNO_2$/1.0 mL H_2O)) was added to the reaction mixture, causing a color change to dark red. After 30 min of stirring, NaN_3 (0.0180 g, 0.277 mmol) was added in H_2O (0.3 mL) causing an immediate color change to a pale yellow. After 30 min of stirring, product isolation (H_2O, Et_2O, brine, $MgSO_4$) gave azide **2** as a pale yellow oil (quantitative).

General Procedure for Photolysis of Aryl Azides in Toluene. The azides (ca. 0.05 mmol) were dissolved in toluene (1.00 mL, freshly distilled from CaH_2), and the samples were degassed by three freeze–thaw cycles before being flame-sealed under vacuum. The photolysis was carried out with a 450-W medium-pressure Hanovia mercury vapor arc lamp equipped with a saturated $CuSO_4$ filter (effective wavelength >315 nm).[37] The photolysis was stopped after either 5 or 10 h, and the photoproducts were purified by preparative TLC (EtOAc/hexane, 50/50) and characterized by mass spectroscopy. The products are reported in order of decreasing R_f.

Photolysis (10 h) of Tetrafluoroaryl Azide 15. Azide **15** (0.0248 g, 0.0509 mmol) was photolyzed in toluene (1.00 mL) for 10 h: recovered azide **15** (0%); insertion product **26** (0.0091 g, 0.0165 mmol, 32%), MS (EI) m/z 551 (M^+, 84), 297 (35), 91 (100); MS (FAB) m/z 552 (M + 1); HRMS (EI) M^+ calcd for $C_{30}H_{21}F_4NO_3S$ 551.1178, found 551.1187; aniline **17** (0.0084 g, 0.0182 mmol, 36%), MS (EI) m/z 461 (M^+, 100), 446 (22), 297 (23); HRMS (EI) M^+ calcd for $C_{23}H_{15}F_4NO_3S$ 461.0709, found 461.0718.

Photolysis (10 h) of Protio Aryl Azide 16. Azide **16** (0.0253 g, 0.0609 mmol) was photolyzed in toluene (1.00 mL) for 10 h: recovered azide **16** (0.0055 g, 0.0132 mmol, 22%); insertion product **27** and azo adduct **28** were contained in the same band on the preparative TLC plate (0.0047 g); for compound **27**, MS (EI) m/z 479 (M^+, 100), 389 (17), 210 (25), 91 (75); MS (FAB) m/z 480 (M + 1); HRMS (EI) M^+ calcd for $C_{30}H_{25}NO_3S$ 479.1555, found 479.1547; for azo compound **28**, MS (EI) m/z 774 (M^+, 8); MS (FAB) m/z 775 (M + 1); aniline **7** (0.0038 g, 0.0098 mmol, 20%),

Table II. Crystal Data for Tetrafluoroaryl Azide 15

formula	$C_{23}H_{23}F_4N_3O_3S$
crystal system	$P\bar{1}$
space group	centric
a, Å	7.808 (2)
b, Å	9.611 (2)
c, Å	14.940 (3)
α, deg	104.925 (6)
β, deg	91.860 (6)
γ, deg	102.797 (5)
V, Å^3	1051.6 (8)
Z	2
density calcd, g/cm^3	1.539 g/cm^3
crystallizing solvent	ethyl acetate
crystal habit	prismatic (yellow)
crystal dimensions, mm	0.2 × 0.2 × 0.3
μ, cm^{-1}	2.11
transmission factor range	not applied
extinction	not applied
2θ limit, deg (octants)	46 ($+h\pm k\pm l$)
intensities (unique, R_i)	3285 (2397, 0.038)
intensities > $2.58\sigma(I)$	1690
R	0.046
R_w[for $w = 1/\sigma^2(F_o) + pF\sigma^2$]	0.053 (p = 0.010)
max density in ΔF map, e/Å^3	0.19

MS (EI) m/z 389 (M$^+$, 100), 374 (18), 297 (8), 195 (10), 120 (55), 92 (22); HRMS (EI) M$^+$ calcd for $C_{23}H_{19}NO_3S$ 389.1086, found 389.1095.

X-ray Crystallography. Crystals of **15** were obtained from ethyl acetate at room temperature. Diffraction data were measured at room temperature using a Syntex $P2_1$ diffractometer equipped with monochromated Mo radiation [λ (Kα) = 0.71073 Å]. Final cell dimensions were obtained by a least-squares fit to the automatically centered settings for at least 15 reflections. Three reference reflections monitored during the experiment showed no significant variation. Intensity data were corrected for Lorentz-polarization effects. Crystal data are listed in Table II. The average values of the normalized structure factors for **15** suggested a centric space group; this was confirmed by successful refinement.

The structure was solved by direct methods (SHELXS-86);[47] correct positions for all non-hydrogen atoms were deduced from an E map. Difference Fourier electron density maps gave positions for the hydrogen atoms; due to paucity of data, hydrogens were included as fixed contributors in idealized positions. In the final least-squares refinement cycle, anisotropic thermal coefficients were varied for non-hydrogen atoms and a common isotropic thermal parameter was varied for the hydrogens. The final difference Fourier map had no significant features. Atomic scattering factors, mass attenuation coefficients, and anomalous dispersion corrections were taken from ref 48.

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Supplementary Material Available: Atomic numbering scheme for **15**, tables of atomic coordinates, thermal parameters, bond distances, and bond angles, and ^{1}H NMR spectra for compounds **8**, **2**, **21**, **22** (11 pages). Ordering information is given on any current masthead page.

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trans-3,4-Diaminopiperidines. Azacyclohexane Congeners of κ Agonist U-50488

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A variety of *trans*-3,4-diaminopiperidines were synthesized regio- and stereoselectively from 1-(carbobenzyloxy)-1,2,3,6-tetrahydropyridine. These compounds are structurally related to the selective κ agonist U-50488. The two key reactions which determine the stereo- and regiochemistry of the final products involve the S_N2 ring opening of an epoxide and an aziridinium species. Reaction of secondary amines with epoxide **3** led to ca. 1.5:1 mixtures of amino alcohols **4** and **5**, while S_N2 attack by methylamine on aziridinium intermediate **6** occurs diastereoselectively at C-4 to give diamines **7**. Depending upon the isolation procedure, trimethylsilyl iodide cleavage of the carbobenzyloxy group in compounds **8** and **9** provides either *N*-benzyl compounds **12** and **13** or the unsubstituted piperidines **10** and **11**.

The replacement of carbon by a heteroatom in a drug template is a common strategy in medicinal chemistry. In our continuing efforts to elucidate the SAR of the unique κ opiate agonist U-50488,[1] we desired a variety of 4-aza analogs. If any of these compounds retained the desired analgesic activity and selectivity, they could provide access to a number of bis-ligands by attachment of an appropriate

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