Germanium and Silicon Linking Strategies for Traceless Solid-Phase Synthesis

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Here we describe the development and application of germanium and silicon linkage strategies for the solid-phase synthesis of aromatic compounds, as demonstrated for 1,4-benzodiazepine derivatives. The metal−aryl bond that attaches the benzodiazepine to the polymeric support may be cleaved by electrophilic reagents such as H^+ and Br_2 to provide the corresponding substituted derivatives. A number of compounds have been prepared in good overall yield for the eight- or nine-step process. This approach can also be applied to the solid-phase synthesis of libraries of other classes of aromatic compounds.

Introduction

The synthesis and screening of small-molecule libraries is a powerful method for the discovery of new molecules with a particular desired property.[2] A library of organic compounds can be made in solution or on a solid support; both approaches offer distinct advantages. When a library is made in solution, the development of chemistry is sometimes more straightforward than that on a solid support. Purity of the final product can be improved by the use of support-bound reagents,[3] and extractions can be used to remove charged impurities.[4] However, most of the chemical combinatorial libraries reported to date have been constructed using solid-phase methods. Reactions performed on a solid support can be driven to completion by the use of excess reagents, and purifications between reaction steps are simplified because noncovalently bound material may simply be rinsed away. For this reason, the multistep solution synthesis of a library of architecturally complex compounds is more difficult than that on a solid phase. A key aspect of any solid-phase synthesis strategy is the linkage element, which acts as a tether to the polymeric support material. Ideally, the linker should be stable to all reactions used in a synthesis sequence and should be cleaved quantitatively under conditions that do not degrade the desired target molecule.

Linking methods may be roughly grouped into three categories. The first strategy is to link through functionality already present in the desired target molecule, such as in solid-phase peptide and oligonucleotide synthesis. The second approach is a cleavage where the linking functional group is incorporated into the final molecule.[5] Additional diversity may be introduced at this site of linker attachment.[6] In many cases the previous two methods may not be applicable to a desired compound class or may limit the chemistry that can be performed. The third strategy, which is often necessary, is the introduction of an auxiliary functional group (such as a phenol, alcohol, amide, or carboxylate) as a handle for linker attachment. After cleavage from the solid support at the end of a synthesis sequence, the linking functional group can have a negligible, positive, or negative effect on the biological or chemical activity of the target molecule, depending on where it is situated and on the specific receptor/ligand interaction.

An alternative to the above approaches is linkage through a functional group that can be excised efficiently and quantitatively when desired, leaving behind no trace or "memory" of the solid-phase synthesis. For aromatic compounds, we felt that linkage by a bond between a Group IV metal and the aromatic ring would fulfill these requirements.[7] Periodic trends in the reactivity of Group IV metals are well documented.[8] Silylaromatic compounds are used to block reactivity at specific sites within an aromatic ring,[9,10] and arylsilanes can be removed by an acid or basic fluoride ion. The effect of aromatic substitution[11] and silicon substituents[12] on reaction rate has been studied extensively. Silicon-directed *ipso* substitution of arylsilanes is frequently used for the high-yielding, regiospecific introduction of electrophilic functional groups.[13] Germanium is used less frequently in organic synthesis, although an extensive compilation of organogermanium chemistry is available.[14] One notable use of germanium chemistry is Moerlein's synthesis of aryltrimethylgermanium substrates for the clean, high-yielding preparation of regiospecifically radiolabeled halo-

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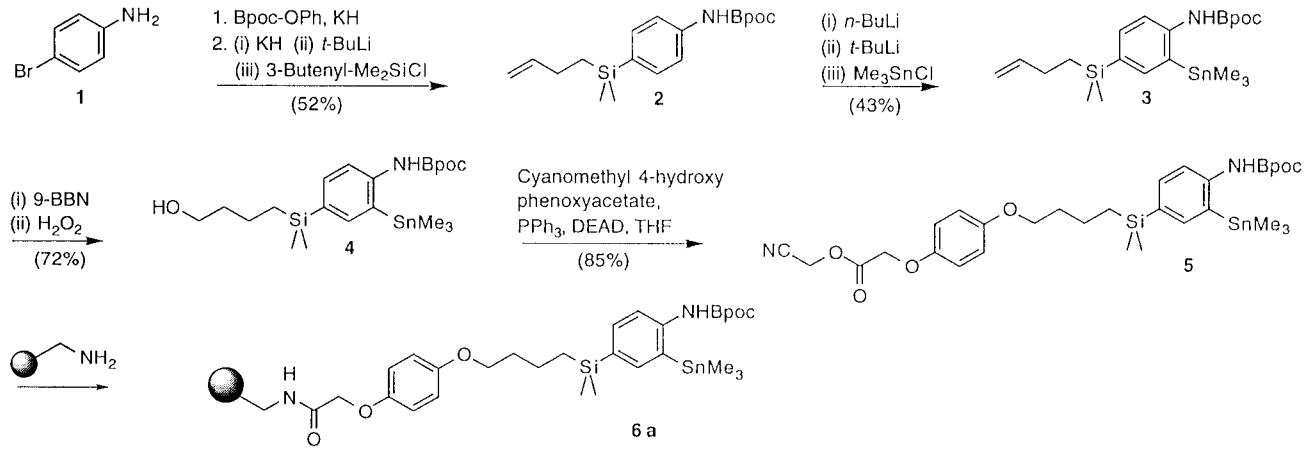
Scheme 1



aromatic compounds.[15] Electrophilic demetalations with iodine, bromine, and chlorine were found to proceed in high yield; for this system trimethylsilicon was judged to be too unreactive and trialkyltin was felt to be not stable enough.

We have previously developed a method for the solid-phase synthesis of chemically diverse 1,4-benzodiazepine derivatives.[16] The benzodiazepine derivatives are synthesized from a support-bound, protected (aminoaryl)-stannane and three variable components: acid chlorides, Fmoc amino acids, and alkylating agents. The synthesis sequence includes transition metal catalyzed bond formation, an acylation, and acidic and basic reaction conditions. We felt that the solid-phase synthesis of this class of pharmaceutically important molecules would be an ideal test of a metal-based linker, and we have published a preliminary communication on the application of a silyl linkage approach.[17] Since our initial communication of a silyl linker, two reports of silicon linking strategies for the synthesis of biaryl compounds have appeared.[18,19] Here, we expand on our previous report and document our investigations of alternate metal linkage approaches and different electrophile-mediated cleavages.

Results and Discussion

Silyl-Linked Benzodiazepines. The synthesis of an appropriately functionalized silicon-containing (aminoaryl)stannane is shown in Scheme 1. Synthesis began with protection of 4-bromoaniline (**1**) using the ((2-(4-biphenyl)isopropyl)oxy)carbonyl (Bpoc) group.[20] The reduced basicity of the aniline (compared to an aliphatic amine), and the thermal instability of the Bpoc reagent, required the use of potassium hydride to generate the anilide anion, which then added rapidly to biphenylisopropyl phenyl carbonate. Two equivalents of KH was used since the product is more acidic than the starting material. Carbamate deprotonation with potassium hydride, lithium−halogen exchange with *tert*-butyllithium,[21] and quenching with 3-butenylchlorodimethylsilane[22] gave the arylsilane **2** in high yield. The trimethyltin group was introduced using the directed ortho metalation reaction followed by addition of trimethyltin chloride to give **3**.[23] While we were not satisfied with the yield obtained in this reaction, variation of reaction stoichiometry, solvent, and lithium reagent failed to improve the amount of product obtained. In part, the low yield was due to alkene lithiation and subsequent alkene stannylation. Hydroboration of arylstannane **3** with 9-BBN and an oxidative workup with basic peroxide[24] provided the primary alcohol **4**. Mitsunobu reaction[25] of this alcohol with the cyanomethyl ester of (4-hydroxyphenoxy)acetic acid afforded the preactivated ester derivative **5** in good yield. Use of the cyanomethyl ester eliminates a saponification step from the synthesis sequence and also minimizes exposure of the acid-sensitive arylstannane to the free phenoxyacetic acid and to the acidic coupling additives that are often used for amide bond formation. Finally, (aminomethyl)polystyrene resin is acylated with **5** using DMAP and *i*-Pr_2EtN.[26]

The solid-phase synthesis route to benzodiazepine derivatives is shown in Scheme 2. (For clarity, we omitted the spacer in this scheme.) Stille coupling reactions of stannane **6a** with both aromatic and aliphatic acid chlorides are performed using the ligandless catalyst $Pd_2dba_3{\cdot}CHCl_3$ to give **7a**. The Bpoc protecting group is removed by brief treatment with 3% trifluoroacetic acid in CH_2Cl_2 to give 2-aminoaryl ketones **8a**. This compound is acylated with an α-*N*-Fmoc-amino acid fluoride,[27] and the protecting group is removed with 20% piperidine in DMF to give **9a**. This intermediate is cyclized with mild acidic catalysis at 65 °C to afford support-bound benzodiazepine derivative **10a**. Deprotonation and alkylation give the fully functionalized derivative **11a**.

Deprotection and cleavage of the derivatives are shown in Scheme 3. Any amino acid side-chain protecting groups are removed by treatment of **11a** with trifluoroacetic acid/dimethyl sulfide/water. The silicon−aryl bond is stable to TFA (even at 60 °C) because of the extremely

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(16) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306.
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(20) Sieber, P.; Iselin, B. *Helv. Chim. Acta* **1968**, *51*, 622.
(21) KH is necessary because lithium−halogen exchange is faster than proton transfer. Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.
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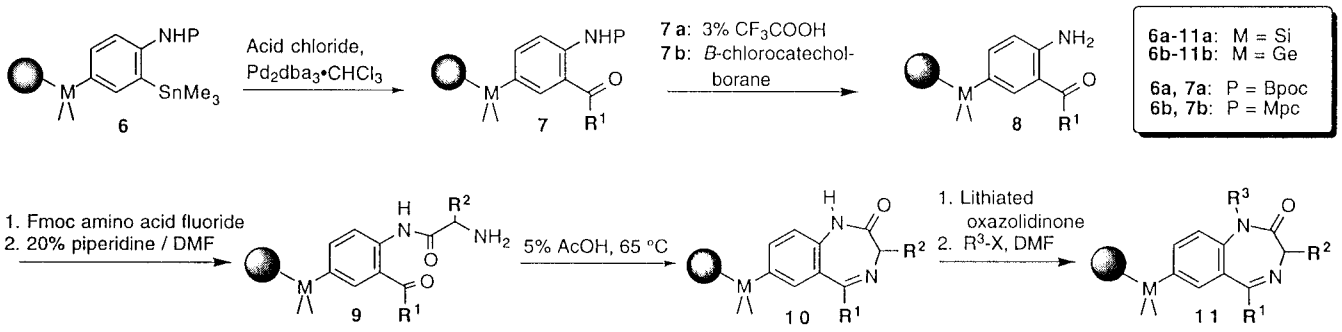
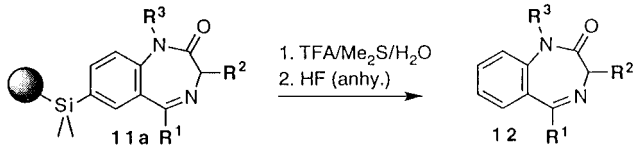
(25) Hughes, D. L. *Org. React. (N.Y.)* **1992**, *42*, 335.
(26) The active ester derived from (4-hydroxyphenyl)acetic acid acylates at least 10-fold more slowly under these conditions, perhaps due to reduced electrophilicity of the carbonyl carbon.
(27) Carpino, L. A.; Satat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651.

Scheme 2



Scheme 3



electron-poor nature of the protonated benzodiazepine. The aryl−silicon bond is then cleaved with anhydrous HF to give the product benzodiazepines **12**. When cleavage of **11a** with basic fluoride was attempted (DMF, CsF, 18-crown-6, 100 °C), no benzodiazepine product **12** was observed. The low reactivity under these conditions is not surprising because the benzodiazepine is no longer electron deficient when the imine is not protonated. Although basic fluoride-mediated cleavage of electron-poor arylsilanes proceeds cleanly,[18] other researchers have reported a lack of reactivity to fluoride for nonelectron deficient aromatic systems.[19]

Using this general route we have synthesized derivatives **12a**−**d**, shown in Figure 1. These compounds incorporate amide, phenol, ether, aromatic, and aliphatic functionality. The unpurified products appear more pure by TLC and NMR than the yields alone would suggest. One reason for this discrepancy is that the loading to give **6a** was not quantitative. After acylation of **5**, the unacylated aminomethyl groups were capped with Fmoc-alanine using hydroxybenzotriazole (HOBt) and diisopropylcarbodiimide. Fmoc quantitation then gives the percent of unreacted aminomethyl groups. If based upon the loading level of the protected (aminoaryl)stannane, the yields in Figure 1 would be higher by approximately 10%.

The initial silyl linker that we evaluated incorporated the three-carbon linker **13**, derived from allylchlorodimethylsilane and analogous to our successful system **11a**. However, upon HF treatment of some derivatives, this linker gives significant amounts of silicon-containing benzodiazepine products **14**, as determined by proton NMR and mass spectrometry (Figure 2). The alternative cleavage pathway is probably similar to the cyclopropane-forming decomposition of (3-chloropropyl)diethylmethylsilane.[28] We observed increased amounts of this side reaction when the substituent at R^1 is not strongly electron donating. As R^1 becomes less electron donating, more electron density is pulled from the silicon-appended aromatic ring. Since the rate-limiting step for the desired protodesilation reaction is *ipso* protonation of the aromatic ring, lower electron density in this ring will slow protodesilation. The observed trends are then explained if the rate of the undesired fragmentation is independent of substitution at R^1.

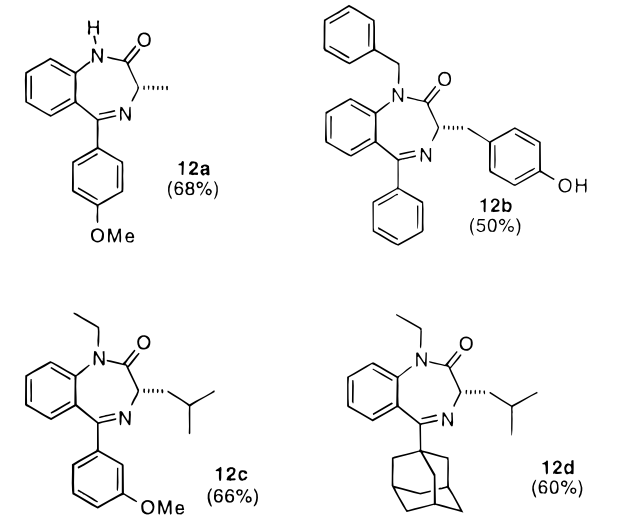


Figure 1. Benzodiazepine derivatives prepared using the silyl linker. The yields are based on the initial aminomethyl substitution level of the polystyrene resin and are determined by the mass balance of purified material. For compound **12b** an additional 11% of the debenzylated product was isolated.

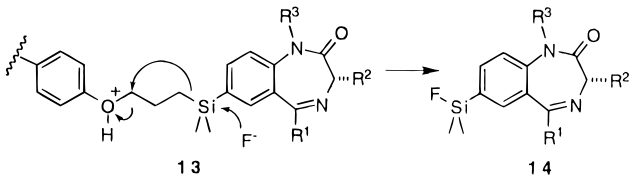


Figure 2. Possible mechanism for formation of silicon-containing benzodiazepines **14**.

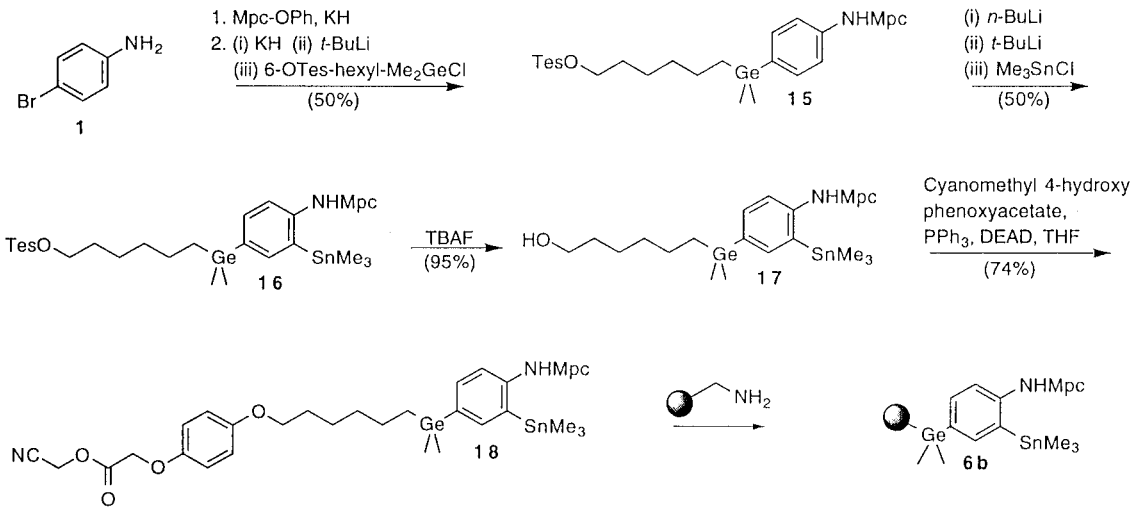
When we began these investigations, we had hoped that the products would be cleaved by the volatile reagent trifluoroacetic acid. Cleavage with HF will present problems with certain functional groups, such as the debenzylation seen for compound **12b**. However, the commonly used cleavage reagent trifluoroacetic acid should suffice for most classes of aromatic compounds.[29] Biaryl compounds synthesized using a silyl linker have been cleaved by TFA, fluoride ion, Br_2, and ICl.[18,19]

Modification of the alkyl substituents in an aryltrialkylsilane dramatically changes the rate of protodesilation, with smaller substituents accelerating the rate of cleavage. However, because we employ a dimethyl-substituted silicon-linker, substituent modifications to increase the lability of our system are not straightforward.[30] We were inspired to investigate an analogous

(28) Ponomarenko, V. A., et al. *Dokl. Akad. Nauk. SSSR* **1956**, *106*, 76. *Chem. Abstr.* **1956**, *50*, 13726e.

(29) The protodesilation of less electron-poor aromatic compounds is quite facile in TFA. Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253.

Scheme 4

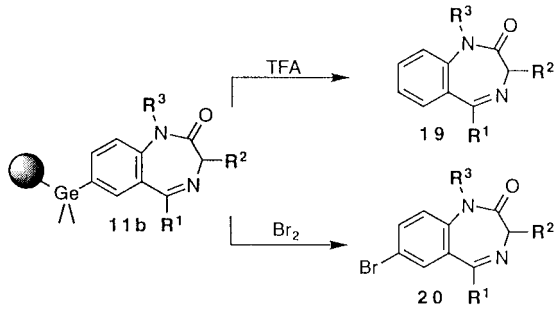


germanium linker by the periodic trends in the rate of protodemetalation.[8]

Germanium-Linked Benzodiazepines. To obtain a linking element that could be cleaved with trifluoroacetic acid, we decided to investigate a similar linker based on germanium. The synthesis of appropriately functionalized germanium-linked resin is shown in Scheme 4. Synthesis began with protection of 4-bromoaniline (**1**) as the 2-(4-methylphenyl)isopropyl carbamate (Mpc group). Deprotonation, lithium−halogen exchange, and then trapping of the aryl anion with chlorodimethyl(6-((triethylsilyl)oxy)hexyl)germane gave silyl ether **15**. The directed orthometalation reaction was used as before to introduce the trimethyltin group to give **16**. The silyl ether is removed cleanly with tetrabutylammonium fluoride (TBAF) to give alcohol **17**. Mitsunobu reaction with cyanomethyl (4-hydroxyphenoxy)acetate gives the preactivated ester **18**. (Aminomethyl)polystyrene resin is then directly acylated with **18** in N-methylpyrrolidinone (NMP) to give resin **6b**. The resin was again capped as for the silyl system, and Fmoc quantitation showed that 15% of the aminomethyl sites on the resin did not react with the cyanomethyl ester.

The choice of tether length merits some discussion. Although a three-carbon spacer derived from the allylgermanyl chloride would be suitable for trifluoroacetic acid cleavage conditions, the synthesis of allyldimethylgermanium chloride is three steps from commercially available materials.[31] The four-carbon tether, derived from a homoallyl Grignard reagent, is difficult to form because of facile HBr elimination. We initially used a five-carbon spacer derived from 5-chloro-1-pentene, but the orthometalation reaction gave some products (as with the silyl system) that seemed to correspond to alkene stannylation. This prompted the investigation of a different alcohol masking group, one that could be removed using conditions that would not affect the germanium or tin but would be stable to distillation, Grignard reagents, and *tert*-butyllithium. The triethylsilyl ether was chosen because of its ease of cleavage, stability to carbon bases, and low molecular weight. The six-carbon linker, derived from 1-chloro-6-hexanol, was used because of cost considerations.

Scheme 5



The solid-phase route to germanium-linked benzodiazepines is shown in Scheme 2. The sequence is analogous to the silyl route except for the carbamate deprotecton of **7b** to give **8b**. While treatment of silyl-linked **7a** with 3% trifluoroacetic acid caused no detectable 2-aminobenzophenone cleavage from the resin, **7b** is less stable to acidic conditions. We initially protected the aniline as the Bpoc carbamate as with the silicon system but were unable to obtain less than 10−11% cleavage of the 2-aminobenzophenone using a variety of acids and reaction times. Substitution of the Mpc carbamate (which cleaves approximately 4× faster[32]) brought the amount of undesired cleavage to 4−5%.[33] Although this is only a small amount of material, we wanted to entirely eliminate any premature cleavage. We found that treatment of **7b** with the Lewis acid *B*-chlorocatecholborane and 0.5 equiv of *i*-Pr_2EtN cleaves the Mpc group rapidly[34] without any undesired 2-aminobenzophenone cleavage. It is important to maintain anhydrous conditions and to use pure reagent for this deprotection. Acylation of the aniline, Fmoc deprotection, cyclization,

(30) Myers has demonstrated an innovative approach for increasing the reactivity of silyl enol ethers by constraining the silicon as a silacyclobutane. When the silicon is predisposed to formation of a pentavalent intermediate, nucleophile-mediated silyl transfer reactions are accelerated. It is not clear if this approach would facilitate acid-catalyzed protodesilation reactions. Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922.

(31) Massol, M.; Cabadi, Y.; Satgé, J. *Bull. Soc. Chim. Fr.* **1971**, 3235. Attempts to prepare the allyl-substituted reagent by addition of allylmagnesium chloride to dimethylgermanium dichloride gave very poor selectivity for mono- vs diaddition of the Grignard reagent, even at −78 °C.

(32) Geiger, R.; König, W. In *The Peptides: Analysis, Synthesis, and Biology;* Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1981; Vol. 3, p 35.

(33) Complete carbamate deprotection can be obtained by treatment of **7b** with 0.2% of TFA in CH_2Cl_2 for 1 min or by 5% of dichloroacetic acid in CH_2Cl_2 for 5 min, as determined by cleavage of the germanium−aryl bond with bromine.

(34) Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

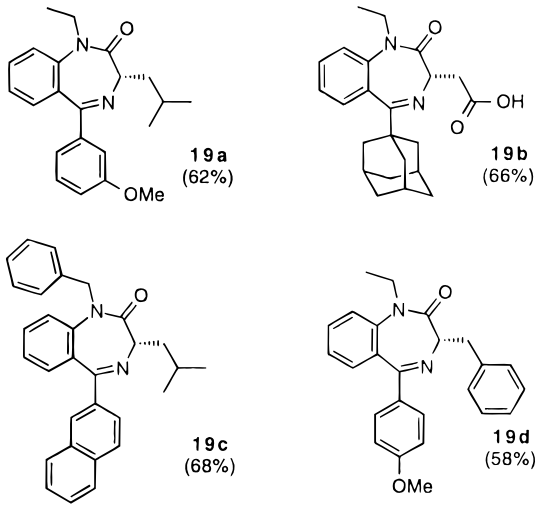


Figure 3. Figure 3. Germanium benzodiazepines prepared by proteolytic cleavage from resin. Yields are based on the mass balance of analytically pure material.

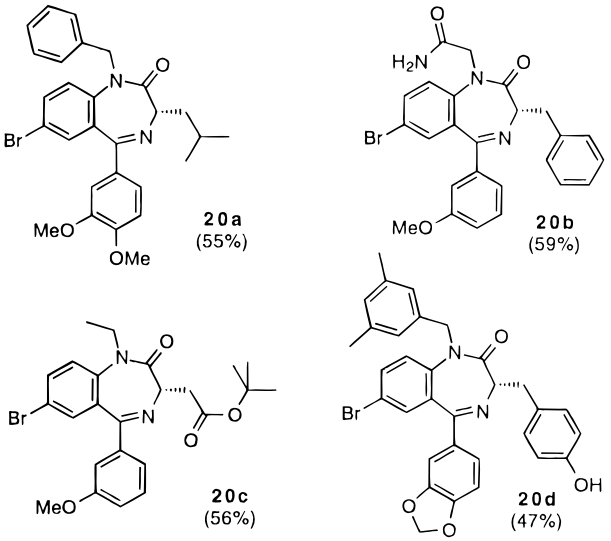


Figure 4. Figure 4. Germanium-linked benzodiazepines prepared by electrophilic cleavage with bromine. Yields are based on the mass balance of analytically pure material.

and alkylation were performed as for the silyl system. The two different cleavage options are shown in Scheme 5.

Derivatives **19a**−**d** were obtained by treatment of the fully functionalized benzodiazepine derivatives **11b** with neat trifluoroacetic acid at 60 °C (Scheme 5). As with the silicon system, side-chain protecting groups can be removed before the compound is cleaved from the resin, obviating the need for cation scavengers (such as water and dimethyl sulfide) in the final cleavage. No debenzylation (<2%) upon cleavage was seen for compound **19c** (Figure 3). This is in contrast to the significant amount of debenzylated product that was observed upon HF cleavage of the silyl-linked benzodiazepine **12b**.

We also investigated electrophilic cleavage of the germanium-linked benzodiazepines. Cleavage of silicon-linked biaryl compounds from resin by electrophiles such as Br_2 and ICl has recently been shown to proceed in good yield.[19] Shown in Figure 4 are several benzodiazepines prepared by electrophilic cleavage of the germanium−aryl bond with elemental bromine. The reaction is complete in 5 min, although some decomposition of the products (probably imine oxidation) is seen when the reaction is allowed to proceed for several hours. No overbromination was detected. Compound **20d** was synthesized with the phenol protected as the *tert*-butyl ether, and the protecting group was removed after the electrophilic cleavage from the resin. When the phenol of tyrosine-containing benzodiazepines is deprotected *before* electrophilic cleavage from the resin, most of the product reattaches to the resin as the germanyl ether. Optimization of this cleavage/reattachment could allow for further functionalization of alcohol-containing products at the linkage site by a variety of palladium-mediated methods.

Numerous functional groups are present in the derivatives we prepared by the germanium route, including amides, esters, acids, phenols, acetals, ethers, and halides. The tolerance of numerous functional groups, and the ease of electrophilic demetalation, makes the germanium route a significant improvement over the silyl method for traceless 1,4-benzodiazepine synthesis. Although dimethylgermanium dichloride is expensive (~$25/g), only small amounts would be needed for the synthesis of a thousand compounds on a 10 μmol scale per compound.

Conclusion

As demonstrated in this work, metal linking strategies are a viable approach for the solid-phase synthesis of aromatic compounds. The judicious selection of the metal or its appendant alkyl groups can give cleavage conditions for an aromatic structure that are straightforward to use and are compatible with a range of chemical functionality.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. The α-*N*-Fmoc-amino acid fluorides were prepared by the method of Carpino et al.[35] with slight modifications.[36] Tetrahydrofuran and diethyl ether were distilled under N_2 from sodium/benzophenone immediately prior to use. Organic layers were dried over Na_2SO_4 before concentration. Flash column chromatography was carried out using Merck 60 230-400 mesh silica gel according to the procedure described by Still.[37] Thin layer chromatography (TLC) analyses were performed with Merck 60 F_{254} 0.25 μm silica gel plates. Unless otherwise stated, TLC R_f values given were determined with the solvent used for column chromatography. IR spectra were recorded neat (for oils) and as films from $CHCl_3$ or CH_2Cl_2 (for crystalline compounds). ^{1}H NMR spectra were obtained with a UCB Bruker AM-400 or AM-500 FT spectrometer. Proton-decoupled ^{13}C spectra were obtained at 101 or 126 MHz with the same instruments. Chemical shifts are reported in ppm. *J* values are in hertz. High-resolution mass spectra were obtained at the University of California mass spectral laboratory using fast atom bombardment (FAB) with 3-nitrobenzyl alcohol as matrix solvent. Elemental analyses were performed by M-H-W Labs, Phoenix, AZ. Gel form (aminomethyl)-polystyrene resin was purchased from Bachem California (no. RMIS12, 100-200 mesh, cross-linked with 1% divinylbenzene). A Safe-Lab peptide flask (no. M2570, a glass cylinder with a frit and a three-way valve at the bottom) was often used with the resin. Solvents may be forced through by nitrogen pressure at the top, and reaction mixtures may be gently agitated by bubbling in nitrogen from below. A filtration

(35) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651. The fluorides are synthesized using 2.0 equiv of cyanuric fluoride and are purified by extraction.

(36) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Methods Enzymol.* **1996**, *267*, 486.

(37) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

cannula (Pharmacia, Inlet Tubing with Filter, catalog no. 19-4448-01; Filter Inserts, catalog no. 19-5086-01) was used for filtration from round bottom flasks.

Cyanomethyl (4-Hydroxyphenoxy)acetate. To (4-hydroxyphenoxy)acetic acid (1.68 g, 10.0 mmol) were added chloroacetonitrile (10 mL) and diisopropylethylamine (1.74 mL, 10.0 mmol). The reaction mixture was stirred overnight. The solvent was removed by rotary evaporation. Column chromatography (50:50 ethyl acetate/hexanes) gave 1.10 g (53%) of the desired product as a white solid: mp 90.5−92 °C. TLC: $R_f = 0.33$. IR: 1771, 1510 cm^{-1}. ^{1}H NMR: δ 4.68 (s, 2H), 4.92 (s, 2H), 6.71 (d, 2H, $J = 9.1$), 6.79 (d, 2H, $J = 9.1$). ^{13}C NMR: δ 48.4, 65.3, 114.4, 115.4, 115.6, 151.0, 151.8, 168.5. Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76, found C, 58.18; H, 4.54; N, 6.77.

***N*-Bpoc-4-bromoaniline.** To a Schlenk flask under nitrogen were added 2-(4-biphenylyl)isopropyl phenyl carbonate (14.95 g, 45.0 mmol), 4-bromoaniline (**1**) (8.60 g, 50.0 mmol), and tetrahydrofuran (200 mL). Potassium hydride (35%, 18.0 g, 150 mmol) was then slowly added. The reaction mixture was stirred for 15 min, then carefully quenched with water, and diluted with ethyl acetate (300 mL). The organic layer was washed with water (3 × 200 mL) and brine (200 mL), dried, and concentrated. Column chromatography (10:90 ethyl acetate/hexanes) gave 14.68 g (80%) of the desired product as white crystals: mp 152−153 °C. TLC: $R_f = 0.23$. IR: 1716, 1634 cm^{-1}. ^{1}H NMR: δ 1.89 (s, 6H), 6.74 (s, broad, 1H), 7.26 (d, 2H, $J = 9.2$), 7.33−7.39 (m, 3H), 7.45 (t, 2H, $J = 7.7$), 7.50 (d, 2H, $J = 8.4$), 7.57−7.62 (m, 4H). ^{13}C NMR: δ 28.8, 81.9, 115.5, 119.9, 124.7, 127.0, 127.1, 127.2, 128.6, 131.8, 137.1, 139.9, 140, 144.6, 151.7. Anal. Calcd for $C_{22}H_{20}NO_2Br$: C, 64.40; H, 4.91; N, 3.41, found C, 64.60; H, 5.00; N, 3.44.

***N*-Bpoc-4-(3-butenyldimethylsilyl)aniline (2).** To an oven-dried Schlenk flask under nitrogen were added *N*-Bpoc-4-bromoaniline (3.40 g, 8.29 mmol) and tetrahydrofuran (40 mL). Potassium hydride (35%, 1.20 g, 10.0 mmol) was then added slowly. The reaction mixture was cooled to −78 °C, and *tert*-butyllithium (1.7 M in pentane, 10.0 mL, 17.0 mmol) was added (the mixture turned red). After 10 min, 3-butenyldimethylchlorosilane (2.97 g, 20.0 mmol) was added in one portion. The reaction mixture was carefully quenched with water and diluted with ethyl acetate (100 mL). The organic layer was washed with water (3 × 100 mL), 1 M $NaHSO_4$ (2 × 100 mL), and brine (100 mL), dried, and concentrated. Column chromatography (5:95 ethyl acetate/hexanes) gave 2.39 g (65%) of the desired product as white crystals: mp 104−105 °C. TLC: $R_f = 0.16$. IR: 1708, 1588, 1517, 1141, 1102 cm^{-1}. ^{1}H NMR: δ 0.22 (s, 6H), 0.80 (m, 2H), 1.86 (s, 6H), 2.02 (m, 2H), 4.85 (dd, 1H, $J = 1.7$, 10.1), 4.95 (dd, 1H, $J = 1.7$, 17.1), 6.52 (tdd, 1H, $J = 6.2$, 10.1, 17.1), 6.63 (s, broad, 1H), 7.30−7.36 (m, 3H), 7.37−7.43 (m, 4H), 7.50 (d, 2H, $J = 8.3$), 7.57−7.62 (m, 4H). ^{13}C NMR: δ −3.0, 14.8, 27.8, 28.9, 81.6, 112.7, 117.7, 124.7, 127.0, 127.1, 127.1, 128.6, 133.2, 134.3, 138.7, 139.9, 140.7, 141.4, 144.8, 151.8. Anal. Calcd for $C_{28}H_{33}NO_2Si$: C, 75.80; H, 7.50; N, 3.16, found C, 75.66; H, 7.43; N, 3.15.

***N*-Bpoc-4-(3-butenyldimethylsilyl)-2-(trimethylstannyl)aniline (3).** Bpoc-protected aniline **2** (2.45 g, 5.52 mmol) and diethyl ether (12 mL) were added to an oven-dried Schlenk flask under nitrogen. The flask was cooled to −78 °C and stirred vigorously, and *n*-butyllithium (2.50 mL, 6.25 mmol) was added, followed by *tert*-butyllithium (4.00 mL, 6.80 mmol). The reaction mixture was allowed to warm to −10 °C (maintained by a salt bath); the mixture slowly turned red. After 2 h the mixture was cooled to −78 °C and trimethyltin chloride (10.0 mL, 1.0 M in hexane) was added; the solution rapidly turned a cloudy yellow color. After reaction mixture was warmed to room temperature, it was quenched with 50 mL of water, diluted with 50 mL of ethyl acetate, washed with water (3 × 50 mL) and brine (100 mL), dried, and concentrated. Column chromatography (5:95 ethyl acetate/hexanes) gave 1.43 g (43%) of the desired product as a clear oil. TLC: $R_f = 0.25$. IR: 1717, 1486, 1270 cm^{-1}. ^{1}H NMR: δ 0.27 (s, 6H), 0.41 (s, 9H), 0.85 (m, 2H), 1.90 (s, 6H), 2.09 (m, 2H), 4.90 (dd, 1H, $J = 1.7$, 7.4), 5.00 (dd, 1H, $J = 1.7$, 17.0), 5.89 (tdd, 1H, $J = 6.2$, 10.1, 17.0), 6.52 (s, broad, 1H), 7.35 (t, 1H, $J = 7.4$), 7.42−7.47 (m, 3H), 7.49−7.53 (m, 3H), 7.57−7.61 (m, 5H). ^{13}C NMR:[38] δ −8.6, −3.0, 14.8, 27.9, 28.8, 81.6, 112.8, 121.5 (b), 124.8, 127.0, 127.1, 127.1, 128.6, 134.6, 134.9, 139.9, 140.8, 141.4, 141.7, 143.8, 144.9, 152.7. Anal. Calcd for $C_{31}H_{41}NO_2SiSn$: C, 61.40; H, 6.81; N, 2.31, found C, 61.39; H, 7.00; N, 2.40.

***N*-Bpoc-4-(dimethyl(4-hydroxybutyl)silyl)-2-(trimethylstannyl)aniline (4).** Stannane **3** (1.23 g, 2.03 mmol) and 9-BBN (6 mL, 0.5 M in THF) were added to an oven-dried Schlenk flask under nitrogen. The reaction mixture was stirred until the starting material was completely consumed, as determined by TLC analysis. The flask was cooled to 0 °C, and 2.0 M aqueous KOH (5.00 mL, 10.0 mmol) was added, followed by 5.00 mL of 30% aqueous H_2O_2. After 1 min the mixture was taken up in 50 mL of ethyl acetate, washed with water (3 × 50 mL) and brine (50 mL), dried, and concentrated. Column chromatography (25:75 ethyl acetate/hexanes) gave 0.91 g (72%) of the desired compound as a clear oil. TLC: $R_f = 0.23$. IR: 3300 (b), 2927, 1712, 1487, 1245, 1140 cm^{-1}. ^{1}H NMR: δ 0.23 (s, 6H), 0.38 (s, 9H), 0.73 (m, 2H), 1.38 (m, 2H), 1.57 (m, 2H), 1.88 (s, 6H), 3.60 (m, 2H), 6.49 (s, broad, 1H), 7.33 (t, 1H, $J = 7.4$), 7.40−7.45 (m, 3H), 7.46−7.49 (m, 3H), 7.53−7.59 (m, 5H). ^{13}C NMR: δ −8.7, −3.1, 15.5, 20.0, 28.8, 36.5, 62.6, 81.5, 121.5 (b), 124.8, 127.0, 127.0, 127.1, 128.6, 134.8, 134.8, 139.8, 140.8, 141.6, 143.7, 144.9, 152.7. Anal. Calcd for $C_{31}H_{43}NO_3SiSn$: C, 59.63; H, 6.94; N, 2.24, found C, 59.62; H, 7.08; N, 2.25.

Cyanomethyl Ester 5. To an oven-dried Schlenk flask under nitrogen were added the cyanomethyl ester of (4-hydroxyphenoxy)acetic acid (269 mg, 1.30 mmol), primary alcohol **4** (740 mg, 1.18 mmol), triphenylphosphine (341 mg, 1.30 mmol), and tetrahydrofuran (7 mL). The flask was cooled to 0 °C. Diethyl azodicarboxylate (197 μL, 1.25 mmol) was added dropwise, and the ice bath was removed. After 1 h the reaction mixture was concentrated, and column chromatography (25:75 ethyl acetate/hexanes) gave 0.82 g (85%) of the desired product as a clear oil. TLC: $R_f = 0.27$. IR: 2932, 1780, 1718, 1507, 1242 cm^{-1}. ^{1}H NMR: δ 0.28 (s, 6H), 0.40 (s, 9H), 0.83 (m, 2H), 1.78 (m, 2H), 1.90 (s, 6H), 3.85 (t, 2H, $J = 6.7$), 6.53 (s, broad, 1H), 6.81 (d, 2H, $J = 9.2$), 6.84 (d, 2H, $J = 9.2$), 7.35 (t, 1H, $J = 7.3$), 7.42−7.47 (m, 3H), 7.48−7.53 (m, 3H), 7.56−7.62 (m, 3H). ^{13}C NMR: δ −8.6, −3.0, 15.5, 20.4, 28.8, 32.9, 48.6, 65.8, 68.1, 81.5, 113.7, 115.5, 115.9, 121.5 (b), 124.8, 127.0, 127.0, 127.1, 128.6, 134.7, 134.8, 139.8, 140.8, 141.6, 143.7, 144.9, 151.4, 152.7, 154.4, 167.8. Anal. Calcd for $C_{41}H_{50}N_2O_6SiSn$: C, 60.53; H, 6.19; N, 3.44, found C, 60.85; H, 6.41; N, 3.40.

2-(4-Methylphenyl)isopropyl Phenyl Carbonate. Dichloromethane (200 mL), 2-(4-methylphenyl)isopropyl alcohol (30.0 g, 200 mmol), and pyridine (40.5 mL, 500 mmol) were combined in a round bottom flask. The reaction mixture was cooled to −78 °C, and phenyl chloroformate (26.4 mL, 210 mmol) was added in one portion. Large amounts of white solids immediately formed. The mixture was stirred for 3 h at room temperature and then quenched with water (200 mL). The organic layer was washed with 1 M $NaHSO_4$ (3 × 200 mL) and 1 M NaOH (3 × 200 mL), dried, and concentrated. The mixed carbonate was used without further purification.

***N*-Mpc-4-bromoaniline.** To a Schlenk flask under nitrogen were added 2-(4-methylphenyl)isopropyl phenyl carbonate (14.0 g, 50.0 mmol), 4-bromoaniline (**1**) (8.60 g, 50.0 mmol), and tetrahydrofuran (100 mL). The reaction mixture was cooled to 0 °C, and potassium hydride (35%, 13.2 g, 110 mmol) was added slowly. The reaction mixture was stirred for 30 min, then carefully quenched with water, and diluted with ethyl acetate (150 mL). The organic layer was washed with water (3 × 200 mL) and brine (200 mL), dried, and concentrated. Column chromatography (10:90 ethyl acetate/hexanes) gave 14.7 g (84%) of the desired product as white crystals: mp 151−152 °C. TLC (5:95 ethyl acetate/hexanes): $R_f = 0.10$. IR: 1701, 1526, 1230, 1145 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.84 (s, 6H), 2.35 (s, 3H), 6.71 (s, broad, 1H), 7.18 (d, 2H, $J = 8.1$), 7.24 (d, 2H, $J = 8.8$), 7.32 (d, 2H, $J = 8.1$), 7.36 (d, 2H, $J =$

(38) For compounds **3**−**5** and **16**−**18** one of the expected carbon peaks was not detected, even with very long acquisition times. This is presumably because two carbon atoms have nearly the same resonance frequency.

8.8). ^{13}C NMR (101 MHz): δ 21.0, 28.8, 82.0, 115.4, 119.9, 124.1, 129.0, 131.7, 136.7, 137.2, 142.6, 151.8. Anal. Calcd for $C_{17}H_{18}NO_2Br$: C, 58.63; H, 5.21; N, 4.02, found C, 58.70; H, 5.17; N, 4.06.

6-Chloro-1-((triethylsilyl)oxy)hexane. To a round bottom flask were added CH_2Cl_2 (150 mL), 6-chloro-1-hexanol (25.0 g, 183 mmol), imidazole (34.0 g, 500 mmol), and triethylsilyl chloride (28.63 g, 190 mmol). The reaction mixture was stirred for 10 min, then washed with water (3×), dried, and concentrated. Vacuum distillation (0.1 mmHg, 80−88 °C) gave 41.2 g (90%) of the desired product as a clear oil. IR: 1458, 1238, 1099 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.59 (q, 6H, J = 7.9), 0.95 (t, 9H, J = 7.9), 1.33−1.57 (m, 6H), 1.77 (quintet, 2H, J = 7.0), 3.52 (t, 2H, J = 6.7), 3.60 (t, 2H, J = 6.5). ^{13}C NMR (101 MHz): δ 4.4, 6.7, 25.1, 26.7, 32.6, 32.7, 44.9, 62.6. Anal. Calcd for $C_{12}H_{27}ClOSi$: C, 57.45; H, 10.85, found C, 57.29; H, 10.68.

Chlorodimethyl(6-((triethylsilyl)oxy)hexyl)germane.[39] To a flame-dried Schlenk flask under nitrogen were added 1-chloro-6-((triethylsilyl)oxy)hexane (18.1 g, 72.0 mmol), magnesium turnings (2.44 g, 100 mmol), and tetrahydrofuran (60 mL). A drop of 1,2-dibromoethane was added to initiate the reaction, and the reaction mixture was heated to reflux. Heating was continued for 1 h, and then the flask was cooled to 0 °C. In a separate flame-dried Schlenk flask THF (30 mL) and dichlorodimethylgermane (10.0 g, 57.6 mmol) were combined and cooled to −78 °C. The Grignard reagent was transferred to the germanium flask by cannula; gray magnesium salts precipitated out. The mixture was allowed to warm to ambient temperature and stirred for 1 h. The mixture was concentrated by rotary evaporation and then taken up in hexane (40 mL). The salts were removed by vacuum filtration, and the organic layer was reconcentrated. Vacuum distillation (0.1 mmHg, 110−130 °C) gave 14.2 g (70%) of the desired compound as a clear oil. ^{1}H NMR (400 MHz): δ 0.60 (q, 6H, J = 7.9), 0.68 (s, 6H), 0.96 (t, 9H, J = 7.9), 1.18 (m, 2H), 1.34−1.40 (m, 4H), 1.47−1.56 (m, 4H), 3.60 (t, 2H, J = 6.6). ^{13}C NMR (101 MHz): δ 3.3, 4.4, 6.8, 21.6, 23.9, 25.4, 32.3, 32.7, 62.8.

***N*-Mpc-4-(dimethyl(6-((triethylsilyl)oxy)hexyl)germanyl)aniline (15).** To an oven-dried Schlenk flask under nitrogen were added Mpc-protected 4-bromoaniline (11.7 g, 33.5 mmol) and tetrahydrofuran (120 mL). The flask was cooled to 0 °C, and KH (35%, 35 mmol, 4.2 g) was added dropwise. The flask was cooled to −78 °C and stirred vigorously, and *tert*-butyllithium (39.4 mmol) was added slowly by syringe. After 2 h chlorodimethyl(6-((triethylsilyl)oxy)hexyl)-germane (13.1 g, 37.0 mmol) was added dropwise. After the reaction mixture was warmed to ambient temperature, the reaction mixture was quenched with 50 mL of water, diluted with 100 mL of ethyl acetate, washed with water (3 × 100 mL) and brine (100 mL), dried, and concentrated. Column chromatography (eluting with 5:95 ethyl acetate/hexanes) gave 11.9 g (60%) of the desired product as a waxy solid: mp 43−44 °C. TLC: R_f = 0.21. IR: 1705, 1593, 1516, 1235, 1141 cm^{-1}. ^{1}H NMR: δ 0.32 (s, 6H), 0.60 (q, 6H, J = 8.0), 0.90 (m, 2H), 0.97 (t, 9H, J = 8.0), 1.26−1.43 (m, 6H), 1.48−1.54 (m, 2H), 1.83 (s, 6H), 2.34 (s, 3H), 3.58 (t, 2H, J = 6.8), 6.61 (s, broad, 1H), 7.16 (d, 2H, J = 8.0), 7.30−7.34 (m, 6H). ^{13}C NMR: δ −3.7, 4.4, 6.8, 16.0, 21.0, 25.0, 25.4, 28.9, 32.8, 33.0, 63.0, 81.6, 118.0, 124.2, 129.0, 133.8, 135.7, 136.6, 138.2, 142.9, 151.8. Anal. Calcd for $C_{31}H_{51}GeNO_3Si$: C, 63.50; H, 8.77; N, 2.39, found C, 63.69; H, 9.00; N, 2.52.

***N*-Mpc-4-(dimethyl(6-((triethylsilyl)oxy)hexyl)germanyl)-2-(trimethylstannyl)aniline (16).** To an oven-dried Schlenk flask under nitrogen were added Mpc-protected aniline **15** (0.88 g, 1.50 mmol) and diethyl ether (4.0 mL). The flask was cooled to −78 °C and stirred vigorously, and *n*-butyllithium (0.70 mL, 1.8 mmol) was added slowly by syringe. *tert*-Butyllithium (1.10 mL, 1.87 mmol) was then added slowly by syringe. The reaction mixture was allowed to warm to −10 °C (maintained by a salt bath); the mixture slowly turned the bright red color of the dianion. After 2 h the mixture was cooled to −78 °C and trimethyltin chloride (2.0 mL, 1.0 M in hexane) was added in one portion. The mixture rapidly turned a cloudy yellow color and was allowed to warm to room temperature. The reaction mixture was quenched with 25 mL of water, diluted with 50 mL of ethyl acetate, washed with water (3 × 50 mL) and brine (50 mL), dried, and concentrated. Column chromatography (5:95 ethyl acetate/hexanes) gave 0.56 g (50%) of the desired product as a clear oil. TLC: R_f = 0.30. ^{1}H NMR: δ 0.37 (s, 6H), 0.41 (s, 9H), 0.64 (q, 6H, J = 8.0), 0.95 (m, 2H), 1.00 (t, 9H, J = 8.0), 1.30−1.45 (m, 6H), 1.51−1.56 (m, 2H), 1.87 (s, 6H), 2.37 (s, 3H), 6.48 (s, broad, 1H), 7.18 (d, 2H, J = 8.0), 7.34 (d, 2H, J = 8.0), 7.40 (d, 1H, J = 8.0), 7.47 (s, 1H), 7.58 (d, 1H, J = 8.0). ^{13}C NMR: δ −8.7, −3.7, 4.4, 6.7, 16.0, 20.9, 24.9, 25.4, 28.8, 32.8, 33.0, 62.9, 51.6, 122.0 (b), 124.2, 128.9, 134.3, 136.5, 137.3, 141.0, 143.0, 143.2, 152.8. Anal. Calcd for $C_{34}H_{59}GeNOSiSn$: C, 54.51; H, 7.94; N, 1.81, found C, 54.67; H, 7.89; N, 1.86.

***N*-Mpc-4-(dimethyl(6-hydroxyhexyl)germanyl)-2-(trimethylstannyl)aniline (17).** Silyl ether **16** (3.90 g, 5.21 mmol) was treated with 8 mL of 1.0 M Bu_4NF in THF for 5 min. The reaction mixture was diluted with 50 mL of ethyl acetate, washed with water (3×) and brine, dried, and concentrated. Column chromatography (20:80 ethyl acetate/hexanes) gave 3.14 g (95%) of the desired compound as a clear oil. TLC (25:75 ethyl acetate/hexanes): R_f = 0.21. IR (film from CH_2Cl_2): 1705, 1504, 1236, 1140 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.37 (s, 6H), 0.41 (s, 9H), 0.95 (m, 2H), 1.30−1.36 (m, 4H), 1.40 (m, 2H), 1.46 (t, 1H, J = 5.3), 1.48−1.54 (m, 2H), 1.83 (s, 6H), 2.33 (s, 3H), 3.58 (dt, 2H, J = 5.3, 6.5), 6.45 (s, broad, 1H), 7.15 (d, 1H, J = 8.0), 7.31 (d, 2H, J = 8.0), 7.36 (d, 1H, J = 7.9), 7.44 (s, 1H), 7.52 (d, 1H, J = 7.9). ^{13}C NMR (101 MHz): δ −8.7, −3.7, 15.9, 20.9, 24.9, 25.2, 28.8, 32.6, 32.8, 62.9, 81.6, 122.1 (b), 124.2, 128.9, 134.3, 136.5, 137.3, 141.0, 143.0, 143.1, 152.9. Anal. Calcd. for $C_{28}H_{45}GeNO_3Sn$: C, 52.97; H, 7.14; N, 2.21, found C, 52.95; H, 6.90; N, 2.14.

Cyanomethyl Ester 18. To an oven-dried Schlenk flask under nitrogen were added the cyanomethyl ester of (4-hydroxyphenoxy)acetic acid (1.57 g, 7.60 mmol), primary alcohol **17** (4.40 g, 6.93 mmol), triphenylphosphine (2.00 g, 7.60 mmol), and tetrahydrofuran (30 mL). The flask was cooled to 0 °C. Diethyl azodicarboxylate (1.15 mL, 7.30 mmol) was added dropwise, and the ice bath was removed. After 1 h, the reaction mixture was concentrated. Column chromatography (50:50 CH_2Cl_2/hexanes) gave 4.22 g (74%) of the desired product as a clear oil. TLC (25:75 ethyl acetate/hexanes): R_f = 0.21. ^{1}H NMR: δ 0.31 (s, 6H), 0.36 (s, 9H), 0.88−0.93 (m, 2H), 1.25−1.29 (m, 2H), 1.34−1.43 (m, 4H), 1.68−1.74 (m, 2H), 1.81 (s, 6H), 2.31 (s, 3H), 3.87 (t, 2H, J = 6.6), 4.67 (s, 2H), 4.82 (s, 2H), 6.41 (s, broad, 1H), 6.81 (d, 2H, J = 9.0), 6.84 (d, 2H, J = 9.0), 7.13 (d, 2H, J = 8.0), 7.29 (d, 2H, J = 8.0), 7.34 (d, 1H, J = 8.0), 7.41 (s, 1H), 7.52 (d, 1H, J = 8.0). ^{13}C NMR: δ −8.7, −3.7, 15.9, 20.9, 24.9, 25.5, 28.8, 29.1, 32.9, 48.6, 65.8, 68.4, 81.6, 113.6, 115.4, 115.9, 122.0, 124.2, 128.9, 134.3, 136.5, 137.3, 141.0, 143.0, 143.2, 151.4, 152.8, 154.4, 167.8. Anal. Calcd for $C_{38}H_{52}GeN_2O_6Sn$: C, 55.38; H, 6.36; N, 3.40, found C, 55.26; H, 6.37; N, 3.19.

Coupling Cyanomethyl Ester 5 to the (Aminomethyl)-polystyrene Resin. (The procedure for ester **18** is identical.) To an oven-dried Schlenk flask under nitrogen were added the activated ester **5** (0.72 g, 0.88 mmol), 4-(dimethylamino)-pyridine (110 mg, 0.90 mmol), diisopropylethylamine (235 μL, 1.35 mmol), *N*-methylpyrrolidinone (8.0 mL), and (aminomethyl)polystyrene resin (1.20 g, 0.624 mmol). The reaction mixture was heated at 70 °C for 12 h, at which point the Ninhydrin test indicated that the reaction had gone to >85% completion. The resin was transferred to a peptide flask, rinsed with ethyl acetate (5×) and CH_2Cl_2 (5×), and then dried under vacuum. The resin **6a** was calculated to have a loading of 0.37 mmol/g, assuming the coupling reaction went to completion. The resin **6b** was calculated to have a loading of 0.46 mmol/g, assuming the coupling reaction went to completion. A description of the procedure used to determine the percent completion of the acylation is contained in the Supporting Information.

General Procedure for Stille Couplings on the Solid Support. The procedure for a typical experiment follows. To

(39) Our procedure is based on the synthesis for ω-alkenyldimethylchlorogermanes. Mochida, K.; Asami, K. *J. Organomet. Chem.* **1982**, *232*, 13.

an oven-dried Schlenk flask under nitrogen were added the resin **6** (0.100 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (30 mg, 0.030 mmol), K_2CO_3 (10 mg), THF (2.0 mL), and diisopropylethylamine (20 μL, 0.10 mmol). The resin was stirred for 3 min to ensure complete solvation, at which point the acid chloride (0.50 mmol) was added slowly. The reaction was allowed to proceed for 1 h, after which the mixture was transferred to a peptide flask and rinsed with CH_2Cl_2 (3×), DMSO saturated with KCN (1×), methanol (1×), water (1×), methanol (3×), and CH_2Cl_2 (3×). For silyl-linked derivatives **7a** the resin was treated with 97:3 CH_2Cl_2/trifluoroacetic acid for 5 min, then rinsed with CH_2Cl_2 (5×) and methanol (5×), and dried under nitrogen to provide support-bound 2-aminobenzophenone or 2-aminoacetophenone **8a**. For germanium-linked derivatives **7b** the resin was treated with 8 equiv of *B*-chlorocatecholborane and 4 equiv of *i*-Pr_2EtN in CH_2Cl_2 (2 min, 0.05 M in borane). The resin was rinsed with CH_2Cl_2 (5×), 10:1:1 CH_2Cl_2/methanol/piperidine (1×), and methanol (5×) and dried under nitrogen to give support-bound 2-aminobenzophenone or 2-aminoacetophenone **8b**.

General Procedure for 1,4-Benzodiazepine Synthesis. Support-bound 2-aminoaryl ketone **8** was added to a 24/40 single-neck 50 mL round bottom flask with stir bar, followed by CH_2Cl_2, 2,6-di-*tert*-butyl-4-methylpyridine (10 equiv), and Fmoc-protected-amino acid fluoride (10 equiv, final concentration 0.2 M). After the resulting slurry was stirred for 15−24 h at ambient temperature, the solution was removed by filtration cannula and the support-bound anilide was washed with CH_2Cl_2 (3×) and DMF (3×). A mixture of 20% piperidine in DMF (15 mL) was then added, and the slurry was stirred for 20−30 min at room temperature. The solvent was removed by filtration cannula, and the resin was rinsed with DMF (3×) and with CH_2Cl_2 (3×) to give **9**. At this point, 25 mL of 5% acetic acid in DMF was added to the resin and the slurry was stirred at 60 °C for 12 h to give **10**. The solvent was removed by filtration cannula, and the resin was rinsed with DMF (3×) and CH_2Cl_2 (5×). The reaction flask was sealed with a fresh rubber septum and was flushed with N_2 followed by cooling to 0 °C. Freshly distilled THF and 5-(phenylmethyl)-2-oxazolidinone (12 equiv, 0.2 M) were added to an oven-dried Schlenk flask. The flask was cooled to −78 °C, and *n*-butyllithium in hexanes (10 equiv) was added. After the mixture was stirred for 10 min, the solution was transferred by cannula to the resin. The mixture was stirred at 0 °C for 10 min, and then the appropriate alkylating agent was added by syringe (15 equiv) followed by addition of anhydrous DMF to give a final solvent ratio of approximately 70:30 THF/DMF. The slurry was allowed to warm to room temperature with stirring. After the slurry was stirred for 1 h, the solvent was removed by filtration cannula. The support was washed with THF (1×), 1:1 THF/water (2×), THF (2×), and CH_2Cl_2 (2×).

Benzodiazepine Protecting Group Cleavage. For derivatives incorporating side-chain protecting groups, the fully derivatized 1,4-benzodiazepine **11** on solid support was treated with 15 mL of 95:5:10 trifluoroacetic acid/water/dimethyl sulfide for 15−30 min. No cleavage of the support-bound benzodiazepine was seen. The cleavage solution was removed by filtration cannula, and the resin was rinsed with CH_2Cl_2 (5×) and methanol (5×) and dried under vacuum.

HF Cleavage for Silyl-Linked Benzodiazepines. The resin **11a** was transferred to a perfluorinated plastic reaction vessel for HF cleavage. (CAUTION!! Hydrogen fluoride gas is EXTREMELY toxic, and reactions with this gas should only be performed with the proper equipment and training. There are two excellent reviews[40] that address safety issues with respect to the handling and use of this reagent.) Anhydrous hydrogen fluoride gas (Matheson) was condensed in the reaction vessel and allowed to react (under some pressure since HF boils at 19.5 °C) for 12 h, at which point the hydrogen fluoride was removed with gentle nitrogen flow. The vapor was removed with two sequential KOH traps. The resin was rinsed with 20 mL of 1:4 methanol/CH_2Cl_2 (5 × 2 min). Concentration of the combined filtrates and column chromatography gave the purified derivatives **12a**−**d**. NMR spectra for **12a**−**d** were obtained using a mixture of 20% CD_3OD in $CDCl_3$ (v/v).

Benzodiazepine 12a. This compound was synthesized from 0.240 g (0.089 mmol) of resin **6a**, 3-methoxybenzoyl chloride, racemic leucine acid fluoride, and ethyl iodide. Column chromatography (20:80 ethyl acetate/hexanes) gave 20.5 mg (66%) of the desired compound as beige crystals: mp 105−106 °C. TLC (50:50 ethyl acetate/hexanes): $R_f = 0.53$. IR: 1676, 1562 cm^{-1}. ^1H NMR: δ 0.69 (d, 3H, $J = 6.5$), 0.85 (d, 3H, $J = 6.5$), 0.97 (t, 3H, $J = 7.1$), 1.74−1.88 (m, 2H), 2.06−2.15 (m, 1H), 3.47 (dd, 1H, $J = 5.2, 8.7$), 3.63 (qd, 1H, $J = 7.1, 14.0$), 3.70 (s, 3H), 4.18 (qd, 1H, $J = 7.1, 14.0$), 6.88 (dd, 1H, $J = 1.7, 8.2$), 6.93 (d, 1H, $J = 7.9$), 6.99 (t, 1H, $J = 1.7$), 7.11 (t, 1H, $J = 7.5$), 7.15−7.20 (m, 2H), 7.33 (d, 1H, $J = 8.2$), 7.44 (t, 1H, $J = 7.8$). ^{13}C NMR: δ 13.0, 21.7, 22.9, 24.5, 39.5, 55.0, 61.5, 114.6, 115.8, 121.9, 122.0, 124.3, 129.0, 130.0, 131.4, 139.8, 141.8, 159.2, 168.7, 169.5. HRMS: calcd for $C_{22}H_{27}N_2O_2$: 351.2073, found 351.2075.

Benzodiazepine 12b. This compound was synthesized from 0.240 g (0.089 mmol) of resin **6a**, 1-adamantanecarbonyl chloride, racemic leucine acid fluoride, and ethyl iodide. Column chromatography (20:80 ethyl acetate/hexanes) gave 20.1 mg (60%) of the desired compound as white crystals: mp 87−88 °C. TLC: $R_f = 0.45$. IR: 2903, 1678, 1608, 1446 cm^{-1}. ^1H NMR: δ 0.58 (d, 3H, $J = 6.5$), 0.74 (d, 3H, $J = 6.5$), 0.89 (t, 3H, $J = 7.1$), 1.52−1.60 (m, 6H), 1.61−1.90 (m, 12H), 3.25 (dd, 1H, $J = 5.2, 8.6$), 3.45 (qd, 1H, $J = 7.1, 14.0$), 4.18 (qd, 1H, $J = 7.1, 14.0$), 7.07 (dt, 1H, $J = 1.1, 7.8$), 7.18 (dd, 1H, $J = 1.1, 7.8$), 7.30 (dt, 1H, $J = 1.5, 7.8$), 7.46 (dd, 1H, $J = 1.5, 7.8$). ^{13}C NMR: δ 12.9, 21.6, 22.8, 24.4, 28.4, 36.3, 39.2, 41.2, 41.3, 41.7, 60.6, 122.1, 123.6, 126.8, 129.6, 130.9, 140.3, 171.5, 175.7. HRMS: calcd for $C_{25}H_{35}N_2O$ 379.2749, found 379.2757.

Benzodiazepine 12c. This compound was synthesized from 0.240 g (0.089 mmol) of resin **6a**, benzoyl chloride, L-tyrosine (O-*t*-Bu) acid fluoride, and benzyl bromide. Column chromatography (50:50 ethyl acetate/hexanes) gave 19.4 mg (50%) of the desired compound as ivory crystals: mp 120−120.5 °C. TLC: $R_f = 0.41$. IR: 1672, 1602, 1515, 1448 cm^{-1}. ^1H NMR: δ 3.36 (dd, 1H, $J = 7.6, 14.0$), 3.46 (dd, 1H, $J = 6.2, 14$), 3.72 (dd, 1H, $J = 6.2, 7.6$), 4.68 (d, 1H, $J = 15.3$), 5.52 (d, 1H, $J = 15.3$), 6.63 (d, 2H, $J = 8.5$), 6.86 (d, 2H, $J = 6.5$), 6.95−7.02 (m, 5H), 7.06 (d, 2H, $J = 8.5$), 7.13 (dd, 2H, $J = 1.4, 8.5$), 7.21 (t, 2H, $J = 7.7$), 7.30−7.39 (m, 3H). ^{13}C NMR: δ 36.5, 50.0, 65.2, 114.8, 122.3, 124.4, 127.0, 127.1, 127.9, 128.3, 129.4, 129.7, 130.1, 130.2, 130.5, 130.5, 131.3, 136.3, 138.1, 141.1, 154.9, 169.4, 169.5. HRMS: calcd for $C_{29}H_{25}N_2O_2$ 433.1916, found 433.1916. An additional 3.5 mg (11%) of the debenzylated product was obtained: $R_f = 0.24$.

Benzodiazepine 12d. This compound was synthesized from 0.200 g (0.074 mmol) of resin **6a**, 4-methoxybenzoyl chloride, and L-alanine acid fluoride. Column chromatography (50:50 ethyl acetate/hexanes) gave 14.0 mg (68%) of the desired compound as white crystals: mp 247−248.5 °C dec. TLC: $R_f = 0.36$. IR: 1669, 1597, 1564 cm^{-1}. ^1H NMR: δ 1.54 (d, 3H, $J = 6.5$), 3.56 (q, 1H, $J = 6.5$), 3.70 (s, 3H), 6.76 (d, 2H, $J = 8.7$), 6.99−7.08 (m, 2H), 7.19 (dd, 1H, $J = 1.5, 8.0$), 7.30 (d, 2H, $J = 8.7$), 7.38 (dt, 1H, $J = 1.5, 7.7$). ^{13}C NMR: δ 16.1, 55.0, 58.1, 113.3, 120.7, 123.0, 127.6, 131.1, 131.1, 131.4, 131.5, 138.4, 161.3, 169.2, 172.7. HRMS: calcd for $C_{17}H_{17}N_2O_2$ 281.1290, found 281.1282.

TFA Cleavage for Germanium-Linked Benzodiazepines. To the dried resin **11b** was added 15 mL of anhydrous trifluoroacetic acid. The resin was heated at 60 °C for 24 h. The cleavage solution was removed by filtration cannula, and the resin was rinsed with CH_2Cl_2 (3×) and methanol (3×). Concentration of the combined filtrates and column chromatography gave the final products **19a**−**d**.

Benzodiazepine 19a. This compound was made from 3-methoxybenzoyl chloride, L-leucine acid fluoride, and ethyl iodide. Cleavage of 118 mg (0.0567 mmol) of resin and then column chromatography gave 13.4 mg (62%) of the desired product as ivory crystals: mp 60−62 °C. TLC: $R_f = 0.28$. IR: 1675, 1599, 1448 cm^{-1}. ^1H NMR (400 MHz): δ 0.82 (d, 3H, $J = 6.3$), 0.99 (d, 3H, $J = 6.5$), 1.10 (t, 3H, $J = 7.1$), 1.90−2.01 (m, 2H), 2.28−2.36 (m, 1H), 3.59 (dd, 1H, $J = 4.8, 9.0$), 3.75 (dq, 1H, $J = 14.0, 7.1$), 3.83 (s, 3H), 4.31 (dq, 1H, $J = 14.0,$

(40) (a) Sakakibara, S. In *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*; Weinstar, B., Ed.; New York: 1971; p 51. (b) Lenard, J. *Chem. Rev.* **1969**, *69*, 625.

7.1), 6.99 (ddd, 1H, J = 0.9, 2.6, 8.2), 7.09 (dt, 1H, J = 7.7, 1.2), 7.17−7.22 (m, 2H), 7.30 (d, 1H, J = 7.9), 7.33 (dd, 1H, J = 1.5, 7.8), 7.41 (d, 1H, J = 8.3), 7.55 (ddd, 1H, J = 1.7, 7.2, 8.3). ^{13}C NMR (101 MHz): δ 13.4, 22.0, 23.4, 24.7, 40.0, 42.5, 55.2, 61.7, 114.7, 115.7, 122.0, 122.1, 124.0, 129.1, 130.0, 130.5, 131.1, 140.4, 142.2, 159.4, 167.8, 169.5. Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99, found C, 75.60; H, 7.23; N, 7.72.

Benzodiazepine 19b. This compound was made from 1-adamantanecarbonyl chloride, L-aspartate (O-*t*-Bu) acid fluoride, and ethyl iodide. Cleavage of 160 mg (0.0736 mmol) of resin and then column chromatography (50:50:1 ethyl acetate/hexanes/acetic acid) gave 18.6 mg (66%) of the desired product as white crystals: mp 86−90 °C. TLC: R_f = 0.20. IR (film from chloroform): 2904, 1710, 1674, 1448 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.87 (t, 3H, J = 7.1), 1.69 (d, 3H, J = 12.2), 1.75 (d, 3H, J = 12.2), 1.86 (d, 3H, J = 12.2), 1.98 (d, 3H, J = 12.2), 2.07 (s, 3H), 2.82 (dd, 1H, J = 5.7, 16.1), 2.98 (dd, 1H, J = 3.3, 16.1), 3.62 (dq, 1H, J = 14.0, 7.1), 3.82 (dd, 1H, J = 3.3, 5.7), 4.39 (dq, 1H, J = 14.0, 7.1), 7.28 (dd, 1H, J = 7.1, 7.9), 7.37 (d, 1H, J = 7.9), 7.52 (dt, 1H, J = 1.4, 7.1), 7.69 (dd, 1H, J = 1.4, 7.9). ^{13}C NMR (101 MHz): δ 13.2, 28.3, 34.8, 36.2, 41.1, 41.6, 42.6, 58.8, 122.7, 124.3, 127.3, 129.8, 130.9, 140.4, 167.6, 172.6, 178.9. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36, found C, 72.64; H, 7.33; N, 7.08.

Benzodiazepine 19c. This compound was made from 2-naphthoyl chloride, L-leucine acid fluoride, and benzyl bromide. Cleavage of 128 mg (0.0589 mmol) of resin and then column chromatography (25:75 ethyl acetate/hexanes) gave 17.4 mg (68%) of the desired product as white crystals: mp 60−62 °C. TLC: R_f = 0.39. IR: 1682, 1603, 1449 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.88 (d, 3H, J = 6.3), 1.06 (d, 3H, J = 6.3), 2.02−2.14 (m, 2H), 2.39−2.46 (m, 1H), 3.80 (dd, 1H, J = 4.9, 8.9), 4.77 (d, 1H, J = 15.3), 5.76 (d, 1H, J = 15.3), 7.02−7.17 (m, 6H), 7.25 (d, 1H, J = 8.2), 7.46−7.58 (m, 5H), 7.67 (dd, 1H, J = 1.5, 8.5), 7.74 (d, 1H, J = 7.8), 7.83 (d, 1H, J = 8.5), 7.87 (d, 1H, J = 7.9). ^{13}C NMR (101 MHz): δ 22.1, 23.4, 24.7, 40.2, 50.0, 61.8, 122.5, 124.4, 126.2, 126.3, 127.0, 127.1, 127.5, 127.6, 127.8, 128.4, 128.6, 129.9, 130.1, 131.1, 131.2, 132.5, 134.1, 136.2, 136.9, 141.8, 168.5, 170.1. Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 83.30; H, 6.52; N, 6.48, found C, 83.29; H, 6.72; N, 6.25.

Benzodiazepine 19d. This compound was made from 4-methoxybenzoyl chloride, L-phenylalanine acid fluoride, and ethyl iodide. Cleavage of 176 mg (0.0828 mmol) of resin and then column chromatography (25:75 ethyl acetate/hexanes) gave 18.4 mg (58%) of the desired product as pale yellow crystals: mp 174−176 °C. TLC: R_f = 0.21. IR: 1673, 1600, 1510, 1251 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.10 (t, 3H, J = 7.1), 3.57−3.61 (m, 2H), 3.70−3.78 (m, 2H), 4.33 (dq, 1H, J = 14.0, 7.0), 6.90 (d, 2H, J = 8.9), 7.14−7.21 (m, 2H), 7.25−7.30 (m, 3H), 7.34−7.40 (m, 3H), 7.49−7.54 (m, 3H). ^{13}C NMR (101 MHz): δ 13.4, 38.0, 42.6, 55.4, 65.0, 113.6, 122.2, 124.1, 126.0, 128.1, 129.9, 130.3, 130.7, 131.0, 131.1, 131.7, 139.7, 142.2, 161.4, 167.4, 169.3. Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29, found C, 77.93; H, 6.40; N, 6.97.

Bromine Cleavage for Germanium-Linked Benzodiazepines. To the dried resin were added 15 mL of CH_2Cl_2 and 4 equiv of Br_2. The mixture was stirred for 5 min, then the cleavage solution was removed by filtration cannula, and the resin was rinsed with CH_2Cl_2 (3×) and methanol (3×). The procedure was repeated once to ensure that all material had been cleaved from the support. Concentration of the combined filtrates and column chromatography gave the final products **20a**−**d**.

Benzodiazepine 20a. This compound was made from 3,4-dimethoxybenzoyl chloride, L-leucine acid fluoride, and benzyl bromide. Cleavage of 146 mg (0.0671 mmol) of resin and then column chromatography (25:75 ethyl acetate/hexanes) gave 19.1 mg (55%) of the desired product as pale yellow crystals: mp 73−74 °C. TLC: R_f = 0.18. IR: 1683, 1269 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.87 (d, 3H, J = 6.6), 1.02 (d, 3H, J = 6.6), 1.94 (m, 1H), 2.07 (ddd, 1H, J = 5.3, 8.0, 13.7), 2.33 (ddd, 1H, J = 5.9, 8.7, 13.7), 3.68 (dd, 1H, J = 5.3, 8.7), 3.85 (s, 3H), 3.93 (s, 3H), 4.69 (d, 1H, J = 15.4), 5.70 (d, 1H, J = 15.4), 6.75 (dd, 1H, J = 1.9, 8.4), 6.80 (d, 1H, J = 8.4), 6.97−7.01 (m, 2H), 7.07−7.16 (m, 4H), 7.30 (d, 1H, J = 8.8), 7.37 (d, 1H, J = 2.3), 7.56 (dd, 1H, J = 2.3, 8.8). ^{13}C NMR (101 MHz): δ 22.2, 23.3, 24.8, 40.1, 49.7, 55.7, 55.9, 61.5, 110.2, 111.6, 117.2, 123.3, 124.0, 127.2, 127.4, 128.5, 130.9, 132.4, 132.6, 133.9, 136.5, 140.8, 148.6, 151.1, 166.4, 169.9. Anal. Calcd for $C_{28}H_{29}N_2O_3$-Br: C, 64.49; H, 5.61; N, 5.37, found C, 64.24; H, 5.73; N, 5.17.

Benzodiazepine 20b. This compound was made from 3-methoxybenzoyl chloride, L-phenylalanine acid fluoride, and iodoacetamide. Cleavage of 155 mg (0.0725 mmol) of resin and then column chromatography (100% ethyl acetate) gave 21.2 mg (59%) of the desired product as white crystals: mp 110−112 °C. TLC: R_f = 0.39. IR (film from chloroform): 1698, 1682, 1479, 1325 cm^{-1}. ^{1}H NMR (400 MHz): δ 3.51 (dd, 1H, J = 5.3, 13.9), 3.60 (dd, 1H, J = 8.6, 13.9), 3.83 (s, 3H), 3.86 (dd, 1H, J = 5.3, 8.6), 4.27 (d, 1H, J = 15.8), 4.58 (d, 1H, J = 15.8), 5.76 (s, broad, 1H), 6.28 (s, broad, 1H), 7.01 (dd, 2H, J = 2.0, 8.0), 7.14 (t, 1H, J = 2.0), 7.21 (t, 1H, J = 7.2), 7.26−7.31 (m, 3H), 7.34 (d, 2H, J = 7.0), 7.38 (d, 1H, J = 2.3), 7.47 (d, 1H, J = 8.8), 7.64 (dd, 1H, J = 2.3, 8.8). ^{13}C NMR (101 MHz): δ 37.6, 51.8, 55.2, 64.6, 114.3, 116.8, 117.8, 122.3, 124.0, 126.2, 128.1, 129.3, 129.8, 130.9, 132.6, 134.8, 138.6, 139.3, 141.4, 159.5, 167.4, 170.0, 170.3. HRMS: calcd for $C_{25}H_{23}N_3O_3$-Br 492.0910, found 492.0923.

Benzodiazepine 20c. This compound was made from 3-methoxybenzoyl chloride, L-aspartate (O-*t*-Bu) acid fluoride, and ethyl iodide. Cleavage of 176 mg (0.0828 mmol) of resin and then column chromatography (25:75 ethyl acetate/hexanes) gave 22.7 mg (56%) of the desired product as white crystals: mp 49−51 °C. TLC: R_f = 0.22. IR: 1720, 1673, 1156 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.10 (t, 3H, J = 7.1), 1.46 (s, 9H), 3.13 (dd, 1H, J = 6.7, 17.0), 3.35 (dd, 1H, J = 7.3, 17.0), 3.71 (dq, 1H, J = 14.0, 7.0), 3.84 (s, 3H), 4.06 (dd, 1H, J = 6.7, 7.3), 4.30 (dq, 1H, J = 14.0, 7.0), 7.00−7.05 (m, 2H), 7.17 (m, 1H), 7.29−7.34 (m, 2H), 7.45 (d, 1H, J = 2.3), 7.65 (dd, 1H, J = 2.3, 8.8). ^{13}C NMR (101 MHz): δ 13.4, 28.1, 37.8, 42.7, 55.3, 60.7, 80.6, 114.4, 116.6, 117.3, 122.2, 123.9, 129.4, 132.1, 132.6, 134.4, 139.5, 141.2, 159.7, 167.1, 168.4, 171.3. Anal. Calcd for $C_{24}H_{27}N_2O_4Br$: C, 59.14; H, 5.58; N, 5.75, found C, 58.81; H, 5.61; N, 5.57.

Benzodiazepine 20d. This compound was made from piperonyloyl chloride, L-tyrosine (O-*t*-Bu) acid fluoride, and 3,5-dimethylbenzyl bromide. Cleavage of 129 mg (0.0568 mmol) of resin and then column chromatography (35:65 ethyl acetate/hexanes): gave 16.0 mg of the desired product (47%) as pale yellow crystals: mp 110−112 °C. TLC (50:50 ethyl acetate/hexanes) R_f = 0.35. IR: 3400 (b), 1673, 1443, 1261, 1238 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.07 (s, 6H), 3.50 (dd, 1H, J = 7.7, 13.9), 3.59 (dd, 1H, J = 6.1, 13.9), 3.76 (dd, 1H, J = 6.1, 7.7), 4.59 (d, 1H, J = 15.5), 4.76 (s, broad, 1H), 5.63 (d, 1H, J = 15.5), 6.02 (d, 1H, J = 1.3), 6.03 (d, 1H, J = 1.3), 6.54 (s, 2H), 6.74−6.78 (m, 5H), 6.98 (s, 1H), 7.21−7.25 (m, 3H), 7.31 (d, 1H, J = 2,4), 7.51 (dd, 1H, J = 2.4, 8.8). ^{13}C NMR (101 MHz): δ 20.9, 37.0, 49.6, 65.3, 101.4, 107.8, 109.3, 115.0, 117.2, 124.0, 124.7, 124.9, 129.0, 130.9, 131.2, 132.2, 132.3, 132.4, 133.9, 136.1, 138.1, 140.7, 148.0, 149.6, 153.9, 166.5, 169.4. Anal. Calcd for $C_{31}H_{27}BrN_2O_4 \cdot H_2O$: C, 63.90; H, 4.86; N, 4.66, found C, 63.54; H, 5.22; N, 4.34.

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Supporting Information Available: Procedures for the determination of resin amine substitution level and yields of cyanomethyl ester acylations to give **6** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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