2-oxazolidinone, 95891-61-5; 3-methyl-2-oxazolidinone, 19836-78-3; 3-acetyl-2-oxazolidinone, 1432-43-5; 3-phenyl-2-oxazolidinone, 703-56-0; 4-methyl-2,3-morpholinedione, 7624-61-5; 4-butyl-6-methyl-2,3-morpholinedione, 100994-73-8; 1-(*N*-*n*-butylamino)-propane-2,3-diol, 60278-95-7; *n*-butylamine, 109-73-9; glycidol, 556-52-5; 1-(*N*-phenylamino)propane-2,3-diol, 5840-15-3; aniline, 62-53-3; 3-butyl-5-(hydroxymethyl)-2-oxazolidinone, 100994-74-9; 1-phenylethanediol, 93-56-1; 4-phenyl-1,3-dioxalan-2-one, 4427-92-3; 3-phenyl-5-(hydroxymethyl)-2-oxazolidinone, 29218-21-1; 4-[*N*-(phenyl)methylamino]-1,3-dioxolan-2-one, 100994-75-0.

Organoselenium Chemistry. Alkylation of Acid, Ester, Amide, and Ketone Enolates with Bromomethyl Benzyl Selenide and Sulfide: Preparation of Selenocysteine Derivatives

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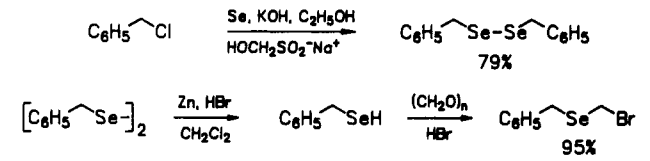
Bromomethyl benzyl selenide has been prepared and used for the alkylation of several carboxylic acid and amide dianions and certain ketones and ester enolates. Clean reaction could not be achieved for ketones and esters whose alkylation products were subject to selenolate elimination. The selenide reacted 18 times more slowly than bromomethyl benzyl sulfide, which alkylated ketones in fair yield even in some cases where the selenide failed. The bromomethyl benzyl sulfide alkylation products gave α-methylene ketones upon oxidation to sulfoxide and thermolysis. Several protected amino acid enolates (valine, alanine, and glycine) were alkylated with bromomethyl benzyl selenide. The product from glycine, **5b**, was converted to the protected dehydroalanine **11** by oxidation and to the protected selenocystine **10** by using bromine cleavage of the benzyl selenide. Halogen reagents (Br_2, SO_2Cl_2) were shown to very efficiently and generally convert benzyl selenides to selenenyl halides, which were converted to diselenides or selenides by reduction or alkylation.

We have long been interested in selenium as a "disposable" element in the construction of complex organic molecules and also as an inherent and crucial atom in important biomolecules. During our work on selenenic acids related to the active site of the seleno-enzyme glutathione peroxidase,[1c,2] we required a series of selenocysteine analogues, and α-alkylation of protected amino acids with a halomethyl selenide seemed the most effective route to them. Although the utilization of halomethyl sulfides as alkylating reagents has a long history,[1d,3] the related selenides had been only infrequently used,[4] and appeared to be much less satisfactory.[1d]

Scheme I



We have now developed an efficient synthesis of bromomethyl benzyl selenide and have found it to be a versatile reagent for the alkylation of several classes of enolates. The choice of a benzyl group was dictated by the requirement that the selenium be subsequently deprotected in the presence of other functional groups. From earlier studies on the chemistry of the halomethyl sulfides[1d] we had also observed that the benzyl sulfides were considerably more reactive than the phenyl analogues, and this proved true for the selenides as well. We here report the application of bromomethyl benzyl selenide and sulfide for the convenient preparation of a protected selenocystine and a series of related molecules and for the preparation of several α-methylene carbonyl compounds. This work also features a highly efficient oxidative removal of the benzyl protecting group from selenium.

Results and Discussion

Our preparation of bromomethyl benzyl selenide followed literature precedent (Scheme I).[4,5] Reduction of dibenzyl diselenide with zinc gave the selenol, which was converted directly to the bromide in 95% overall yield by treatment with paraformaldehyde. The selenide formed could not be effectively purified by distillation or other means, but was suitable for use (>95% pure) if pure di-

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(2) Tappel, A. L. *Cur. Top. Cell. Regul.* **1984**, *24*, 87. Sunde, R. A. *J. Am. Oil Chem. Soc.* **1984**, *61*, 1891. Stadtman, T. C. *Ann. Rev. Biochem.* **1980**, *49*, 93.

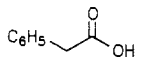
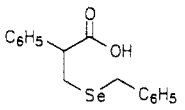
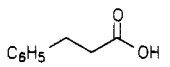
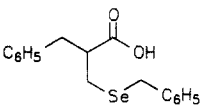
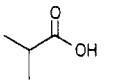
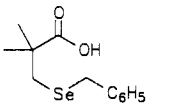
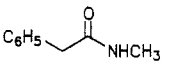
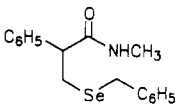
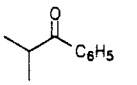
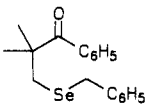
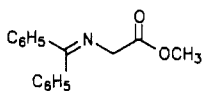
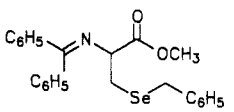
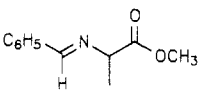
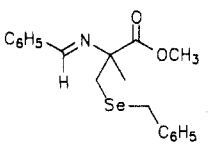
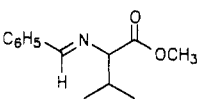
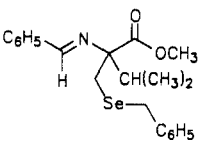
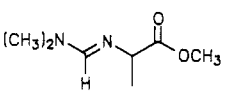
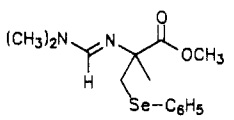
(3) (a) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 993, 995, 2179. Fleming, I.; Iqbal, *Tetrahedron Lett.* **1983**, *24*, 2913. Hosomi, A.; Sakata, Y. Sakurai, H. *Chem. Lett.* **1983**, *24*, 405. Ager, D. J. *Tetrahedron Lett.* **1983**, *24* 491. Lee, T. V.; Okonkwo, J. O. *Tetrahedron Lett.* **1983**, *24*, 323. (b) Upson, D. A.; Hruby, V. J. *J. Org. Chem.* **1976**, *41*, 1353. (c) Bey, P.; Vevert, J. P. *Tetrahedron Lett.* **1977**, 1455. (d) Ronald, R. C. *Tetrahedron Lett.* **1973**, 3831. Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2648. Grieco, P. A.; Wang, C. L. J.; Burke, S. D. *J. Chem. Soc., Chem. Commun.* **1975**, 537. Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752.

(4) (a) Williams, L. R.; Ravve, A. *J. Am. Chem. Soc.* **1948**, *70*, 1244, 3524. (b) Comasseto, J. V.; Ferreira, J. T. B.; Val Fontanillas, J. A. *J. Organomet. Chem.* **1984**, *277*, 261. Ferreira, J. T. B.; Comasseto, J. V.; Braga, A. L. *Synth. Commun.* **1982**, *12*, 595. (c) Ferraz, H. M. C.; Petragnani, N. *Can. J. Chem.* **1985**, *63*, 3216.

(5) Hollowood, J.; Jansen, A. B. A.; Southgate, P. J. *J. Med. Chem.* **1967**, *10*, 863. Böhme, H.; Fischer, H.; Frank, R. *Liebigs Ann. Chem.* **1949**, *563*, 54.

0022-3263/86/1951-2981$01.50/0

Table I. Alkylation of Enolates with Bromomethyl Benzyl Selenide

Entry	Starting Material	Product	Yield (%)
1			81
2			73
3			70
4			84
5			83[a]
6			67[a, b]
7			90[c]
8			96[c]
9			63[d]

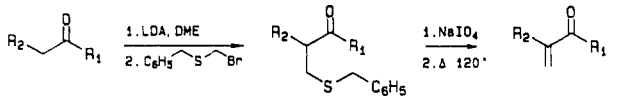
[a] Lithium hexamethyldisilazide instead of LDA was used for the deprotonation. [b] This alkylation was carried out in the presence of NaI. [c] These yields were determined by NMR integrations. The compounds were carried on to the more easily purified acetamides **3a** and **3b**. [d] Bromomethyl phenyl selenide was used for this entry.

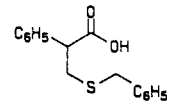
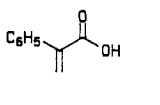
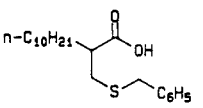
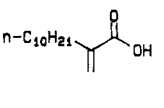
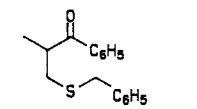
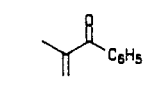
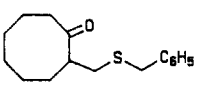
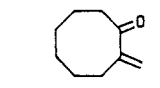
selenide starting material was used or if the intermediate selenol was distilled. The selenide was stable for extended periods when stored in the freezer.

The reaction of bromomethyl benzyl selenide with enolates derived from ketones and carboxylic acids, amides, and esters gave in a number of cases good yields of alkylation products. The results are shown in Table I. Several generalizations can be made about the alkylation. In all cases tried, the dianions of carboxylic acids and amides were efficiently converted to β-benzylseleno acids and amides. Ketone and ester derived enolates gave good yields if the center being alkylated was tertiary (i.e., in which the product lacked acidic α-hydrogens), but results were generally poor with less substituted systems.[4c] Attempts to alkylate cyclooctanone and propiophenone, for example, were unsuccessful.

Several bromo- and iodomethyl sulfides have been reported to alkylate ketones, lactones, and esters with varying degrees of success, occasionally even when the alkylation centers were not tertiary.[3] Our results on the alkylation of several enolates with bromomethyl benzyl sulfide are presented in Table II. The enolates of cyclooctanone and propiophenone, which could not be alkylated with the selenide in reasonable yields, were successfully alkylated with the sulfide, although side reactions appeared to be occurring here also (note the low yield in the alkylation of cyclooctanone). The alkylation products were subsequently converted to α-methylene carbonyl compounds by oxidation to sulfoxides followed by thermolysis.[6]

Table II. Preparation of α-Methylene Carbonyl Compounds



Entry	Sulfide	Yield	Olefin	Yield (%)
1		80		84
2		61[a]		73
3		60[b]		86
4		51[b]		62

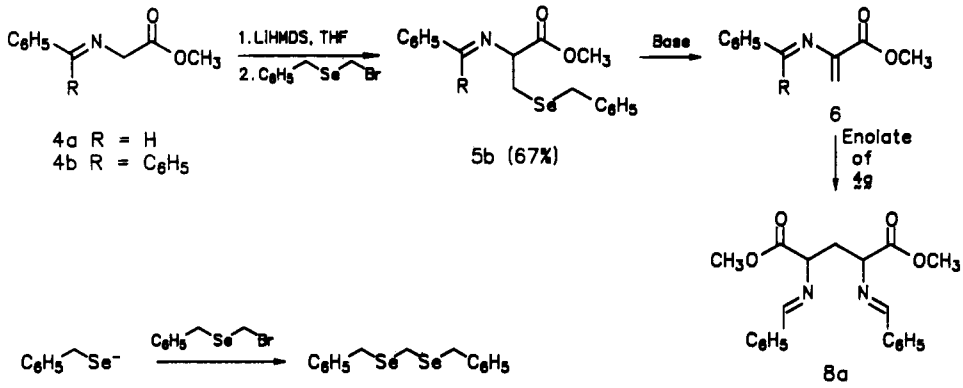
[a] Alkylation was done in THF rather than in DME. [b] LiI was added during the alkylation.

The selenide is a poorer alkylating agent than the sulfide for two reasons. First, the product selenides are probably more susceptible to base-induced elimination than are the sulfides, because the benzylseleno moiety is a better leaving group than is the benzylthio group. It is this base-induced elimination, we believe, which prevents the clean formation and the survival of β-benzylseleno ketones and esters containing acidic α-hydrogens. Second, the sulfide is simply a faster reactant; in a direct competition experiment, we found that bromomethyl benzyl sulfide reacted 18 times faster than the selenium analogue with isobutyric acid dianion. Thus, not only are the sulfides more stable but they are also subject to cross-enolization for a much shorter period of time. The clean alkylation of dianions by bromomethyl benzyl selenide, even when α-hydrogens are contained in the alkylation products (Table I, entries 1, 2, 4), presumably reflects the enhanced nucleophilicity of the dianions and the reduced acidity of the alkylation products, so that the rate of alkylation becomes much faster than the rate of selenolate elimination.

Since halomethyl sulfides have been reported to successfully alkylate silyl enol ethers under Lewis acid conditions,[3a] we have also attempted to use bromomethyl benzyl selenide to alkylate the ketene acetal 1-methoxy-1-(trimethylsiloxy)-2-methyl-1-propene. Preliminary experiments have not afforded the alkylation product in greater than 40% yield; however, conditions have not been optimized, and it is likely that under suitable conditions this reaction might be synthetically useful. Successful selenoalkylations using selenoketals as electrophiles, for

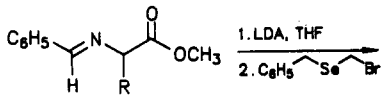
(6) Trost, B. M.; Salzman, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1977**, *98*, 4887. Trost, B. M.; Salzmann, T. N. *Ibid.* **1973**, *95*, 6840.

Scheme II

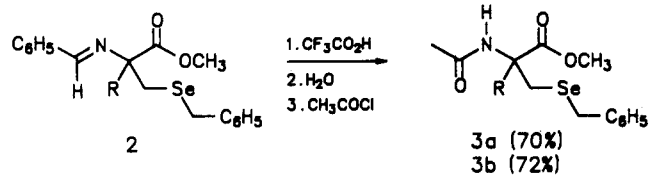


example, have been reported.[7]

Alkylation of Amino Acids. Both cysteine[3b] and selenocysteine[4] have been prepared by the alkylation of phthalimido or acetamido malonic esters with benzyl chloromethyl selenide or sulfide followed by decarboxylation. The benzal imine of alanine has also been alkylated with iodomethyl methyl sulfide.[3c] In our early exploratory experiments we found that bromomethyl phenyl selenide alkylated the *N,N*-dimethylformamide of alanine methyl ester[8a] in 63% yield (Table I, entry 9).[1e] We have now carried out alkylations of alanine and valine with bromomethyl benzyl selenide in high yield (Table I, entries 7,8) using the methyl ester of the benzal imines[8b] **1** because of their ease of preparation and deprotection. The imine



1a R = CH_3
1b R = $(CH_3)_2CH$

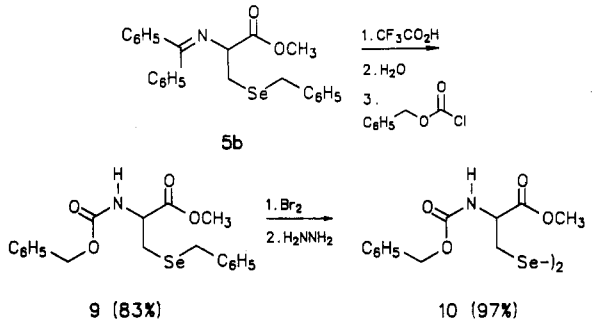


esters **2a,b** were not stable to purification, so they were carried on to the readily purified acetyl derivatives **3a,b** in overall yields of 70% and 72%, respectively.

Attempts to alkylate the glycine derivative **4a** (Scheme II), however, led to complex product mixtures, which included dehydroalanine **6a**, bis(benzylseleno)methane (**7**), and the dimerization product **8a**. Unsuccessful alkylations were also carried out by using the formamidine[8a] and stabase[8c] (tetramethyldisilazacyclopentane adduct) protected glycines. These results are in accord with the previously mentioned inability of the bromomethyl selenide to yield clean β-seleno ketones or esters which contain acidic α-hydrogens. The alkylation failed, we think, because of the reactions shown in Scheme II. Deprotonation of **5a** occurred rapidly relative to alkylation of **4a** to produce the elimination product **6a**. The benzyl selenolate thus produced reacted with bromomethyl selenide to form **7**, while the α,β-unsaturated ester **6a** that was produced was subject to Michael reaction with unreacted **4a** to give **8a**.

The problem was circumvented by use of the benzophenone imine enolate **4b** (R = Ph).[9] For this system, in contrast to the others tried,[8] good yields of alkylation products were obtained (Table I, entry 6). Presumably deprotonation of the product **5b** was suppressed because the resulting enolate would have been subject to severe allylic strain ($A_{1,3}$) and thus **5b** was relatively stable. Even so, minor amounts of the Michael product **8b** were produced when the bromomethyl selenide was used. This byproduct was eliminated by in situ conversion of the bromomethyl selenide to the more reactive iodomethyl selenide.

Several types of transformations of the alkylated amino acids have been carried out. The conversion of **5b** into protected selenocystine **10** is shown below. The robust



benzophenone imine **5b** was hydrolized cleanly and rapidly by treating a dichloromethane solution with an equivalent of trifluoroacetic acid followed by water. The resulting amine was acylated with benzyl chloroformate to give **9** in 83% overall yield from **5b**. The benzyl group in **9** was oxidatively cleaved with 1 equiv of bromine to produce the selenenyl bromide which was reduced to diselenide **10** in situ by hydrazine in 97% overall yield.

As expected, we found that when **9** was oxidized its selenoxide eliminated readily,[1f,10] even at room temperature, to give the protected dehydroalanine **11** in 87% yield.[11]

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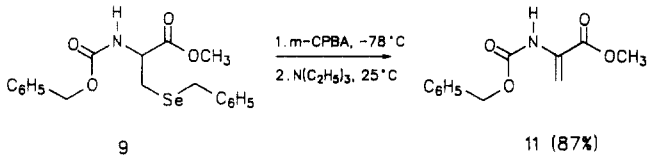
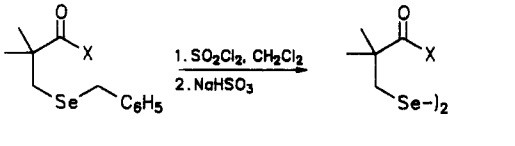
(11) A number of dehydro amino acids have been prepared by sulfoxide[12] and selenoxide[13] syn eliminations. The starting sulfides were, however, prepared by conjugate addition reactions.



9 11 (87%)

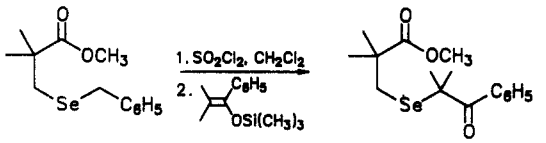
The instability of benzyl selenide dibromides and dichlorides (as well as those of sulfides) has long been known[14] but has not been much used in synthetic work for the deprotection of benzyl selenides. Such cleavages have typically been done under reducing metal conditions.[15] We have now found that the halogen cleavage is more easily controlled, is very efficient and convenient to carry out, and appears to be general. Although SO_2Cl_2, Cl_2, or Br_2 can be used, Br_2 appeared to be the most convenient and effective for sensitive compounds such as the amino acids; it is the fastest reagent, it is an easily measured liquid, and its use is usually accompanied by diagnostic color changes, both in the formation and in the reactions of selenenyl bromides.

In most of the benzyl selenide cleavages it was possible to cleanly form selenenyl bromides, which were usually reduced to diselenides in situ (e.g., **13**) but could also be trapped by silyl enol ethers to give, for example, **14**. In



12a X = OH
12b X = OCH_3
12c X = $NHCH_3$

13b (93%)
13c (82%)



12b 14 (80%)

all cases the yields were high. Thus the benzyl group itself can be viewed as a convenient protecting group for selenium, making both bromomethyl benzyl selenide and dibenzyl diselenide extremely versatile reagents with great potential for the synthesis of complex organoselenium systems.

Experimental Section

General Experimental. Nuclear magnetic resonance (NMR) spectra were obtained on either JEOL MH-100 (100 MHz), Bruker WP-200SY (200 MHz), Bruker WP-270 (270 MHz), or Bruker AM-500 (500 MHz) spectrometers, and all ^1H NMR spectra were referenced to Me_4Si as an internal standard (δ 0.0). Infrared spectra (IR) were obtained on a Beckman Acculab 7 spectrophotometer. Mass spectra (MS) were obtained on AEI-MS-902 or Kratos MS-80 spectrometers. Elemental analyses were performed by Galbraith Laboratories. Tetrahydrofuran (THF) and dimethoxyethane (DME) were freshly distilled from sodium benzophenone ketyl before use. Diisopropylamine and hexamethyldisilazane were distilled from solid KOH and stored over 4A molecular sieves. Hexamethylphosphoramide (HMPA) was distilled over CaH and stored over 4A molecular sieves. All reactions involving organometallics were carried out under an atmosphere of nitrogen in glassware dried at 110 °C for at least 3 h. Lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LHMDS), and all enolates were prepared in situ. Preparative thin layer chromatography (TLC) was carried out using Merck PF-254 (UV active) silica gel, and flash chromatography was carried out using Merck silica gel 60. Starting materials were commercially available except for compounds referenced in the text and in the subsequent experimental sections in which their use is discussed.

Dibenzyl Diselenide. Sodium hydroxymethanesulfinate (rongalite, 30.8 g, 200 mmol) was placed in a 2-L, round bottomed flask with a large stir bar, and 200 mL of H_2O and 500 mL of 95% EtOH were added to dissolve the sodium hydroxymethanesulfinate. KOH pellets (33.7 g, 600 mmol) were added. The solution was warmed to 65 °C, and gray selenium powder (31.6 g, 400 mmol) was added. The addition was done carefully, with vigorous stirring. The solution turned dark purple and was stirred at 65 °C for 6 h. Benzyl chloride (46.0 mL, 400 mmol) was added directly, causing the solution to turn yellow. Stirring was maintained for 11 h during which yellow crystals formed. The solution was diluted with 600 mL of brine and extracted with 3 × 400 mL portions of CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated by rotary evaporation. Recrystallization from hot ethanol gave 53.7 g (79%) of dibenzyl diselenide as beautiful yellow crystals, mp 90–93 °C (lit.[16] mp 92–94 °C): ^1H NMR ($CDCl_3$, 270 MHz) δ 3.82 (s, $^2J_{SeH}$ = 10.9 Hz, 2 H), 7.18–7.32 (m, 5 H).

Bromomethyl Benzyl Selenide. To a mechanically stirred mixture of 17.0 g (50.0 mmol) of dibenzyl diselenide, 125 mL of 48% HBr, and 70 mL of CH_2Cl_2 in a 500-mL, three-necked round-bottomed flask (equipped with a condenser) was added as rapidly as possible 18 g (0.28 mol) of Zn dust at 25 °C (foaming occurs). Zinc was added until the organic phase turned colorless, indicating complete consumption of the intensely yellow diselenide (the reduction generally took ~45 min). The excess zinc was removed by filtration, and the organic and aqueous layers were separated. The selenol solution was added dropwise, over a 4-h period, to a mechanically stirred mixture of 5.0 g (0.17 mol of CH_2O) of paraformaldehyde, 125 mL of 48% HBr, and 70 mL of CH_2Cl_2 in a 500-mL, three-necked round-bottomed flask at 45 °C under N_2. After the reaction mixture was cooled, the organic layer was separated, washed with 50-mL portions of 10% $NaHCO_3$ and brine, and dried (Na_2SO_4). Solvent removal gave 25.2 g (95%) of bromomethyl benzyl selenide, which was used without purification. It was thermally unstable, but could be stored for at least 6 months at −15 °C without decomposition: ^1H NMR ($CDCl_3$, 270 MHz) δ 4.00 (s, $^2J_{SeH}$ = 14.4 Hz, 2 H) 4.39 (s, $^2J_{SeH}$ = 15.2 Hz, 2 H) 7.2–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 15 MHz) δ 22.4, 28.3, 126.5, 127.9, 128.4, 136.7; IR (neat) 2860–3100, 1600, 1500, 1455, 1290, 1190–1030, 775, 695 cm^{-1}; MS, M^+ 265.9033 (calcd for C_8H_9SeBr, 265.9031). If the starting diselenide was not pure the selenol solution was concentrated and distilled, bp 48–50 °C (0.6 mmHg).

Bromomethyl Benzyl Sulfide. To a stirred solution of 7.5 g of paraformaldehyde in 50 mL of benzene was added 142 mL of 48% HBr over a 5-min period at 25 °C. After being stirred for 20 min, the reaction mixture was warmed to 40 °C and 24.8 g (23.5 mL, 0.2 mol) of benzyl mercaptan was added dropwise over a 20-min period. After the reaction mixture was stirred for 2 h at 50 °C, the benzene layer was separated, washed with 50 mL of water and 50 mL of saturated NaCl solution, and dried (Na_2SO_4). Solvent removal followed by distillation gave 31.2 g (72%) of sulfide: bp 65.5–67 °C (0.2 mm) (lit.[5a] bp 75–81 °C (0.2 mm)); ^1H NMR (CCl_4, 100 MHz) δ 3.80 (s, 2 H), 4.31 (s, 2 H), 7.25 (br s, 5 H).

Bromomethyl Phenyl Selenide.[17] To a stirred mixture of 22.1 g (0.071 mol) of diphenyl diselenide,[1g] 380 mL of 48% HBr, and 240 mL of CH_2Cl_2 in a 1000 mL three-necked round-bottomed flask (equipped with a condenser) was slowly (foaming occurs)

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(16) Klayman, D. L.; Griffin, J. S. *J. Am. Chem. Soc.* **1973**, *95*, 197.
(17) Bromomethyl phenyl selenide has also been prepared by reaction of diazomethane with benzeneselenyl bromide (Petragnani, N.; Rodrigues, R.; Comasseto, J. V. *J. Organomet. Chem.* **1976**, *114*, 281) and by alkylation of benzeneselenolate with methylene bromide under phase-transfer catalysis conditions (Comasetto, J. V.; Ferreira, J. T. B.; Brandt, C. A.; Petragnani, N. *J. Chem. Res., Synop.* **1982**, 212.

added 24.0 g (0.367 mol) of zinc dust at 25 °C under nitrogen over a 30-min period. The colorless organic layer was separated, washed with 20 mL of 48% HBr, and added dropwise to a stirred mixture of 7.2 g (0.24 mol of CH_2O) of paraformaldehyde, 240 mL of 48% HBr, and 120 mL of CH_2Cl_2 in a 1000-mL three-necked round-bottomed flask (equipped with a 500-mL dropping funnel and condenser) at 50 °C under nitrogen over a 2-h period. After cooling the reaction mixture, the organic layer was separated, washed with 120 mL of 7% $NaHCO_3$ solution and 120 mL of saturated NaCl solution, and dried (Na_2SO_4). Solvent removal and distillation (bp 82–86 °C, 0.25 mmHg) gave 24.9 g (70%) of selenide: ^1H NMR (CCl_4, 100 MHz) δ 4.61 (s, 2 H), 7.24 (m, 3 H), 7.54 (m, 2 H); IR (neat) 3050, 1576, 1477, 1437, 1162, 1022, 774, 735, 690 cm^{-1}.

Phenyl bromomethyl selenide was characterized as the selenide dichloride, prepared by treatment of phenyl bromomethyl selenide with sulfuryl chloride in methylene chloride at 0 °C: ^1H NMR (CCl_4, 100 MHz) δ 5.45 (s, 3 H), 7.37 (m, 3 H), 7.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 15 MHz) δ 54.8, 129.5, 130.0, 132.1, 140.9.

Anal. Calcd for $C_7H_7BrCl_2Se$: C, 26.20; H, 2.20. Found: C, 26.23; H, 2.17.

3-(Benzylseleno)-2-phenylpropionic Acid (Table I, Entry 1). To a solution of LDA (prepared from 1.10 mL of 1.82 M *n*-BuLi, 2.00 mmol, and 0.311 mL of diisopropylamine, 2.2 mmol) in 5 mL of THF containing 0.750 mL of HMPA (4.0 mmol) at −78 °C was added via cannula 136 mg (1.00 mmol) of phenylacetic acid in 5 mL of THF. The solution was warmed to room temperature, stirred for 30 min, and cooled to −78 °C, and 0.166 mL (1.05 mmol) of bromomethyl benzyl selenide was added. The cold bath was immediately removed and the solution was stirred for 1 h at room temperature. The solution was diluted with 20 mL of 1:1 ether–pentane, washed with 10 mL of 3.3 M HCl, dried (Na_2SO_4), and concentrated. Preparative TLC (30% ether/2% MeOH/2% acetic acid/hexane, R_f 0.28) gave 258 mg (81%) of pure selenide: mp 82–84.8 °C (recrystallized from 1:1 ether–pentane); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.76 and 3.12 (AB of ABX, J_{AB} = 12.6 Hz, J_{AX} = 8.6 Hz, J_{BX} = 6.0 Hz, 2 H), 3.64 (X of ABX, 1 H, J_{AX} = 8.6, J_{BX} = 6.0 Hz, 1 H), 3.70 (s, 2 H), 7.25 (m, 5 H), 10.68 (br s, 1 H); IR ($CHCl_3$) 3600–2500, 1712, 1602 (w) cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_2Se$: C, 60.19; H, 5.05. Found: C, 60.19; H, 5.10.

3-(Benzylseleno)-2-benzylpropionic Acid (Table I, Entry 2). To a solution of LDA (prepared from 1.10 mL of 1.82 M *n*-BuLi, 2.00 mmol, and 0.31 mL of diisopropylamine, 2.2 mmol) in 5 mL of THF and 0.75 mL of HMPA at −78 °C was added via cannula 150 mg (1.0 mmol) of 3-phenylpropionic acid in 5 mL of THF. The solution was warmed to room temperature, stirred for 30 min, and cooled back to −78 °C, and 0.166 mL (1.05 mmol) of bromomethyl benzyl selenide was added. The cold bath was removed and the solution was stirred for 1 h at room temperature. It was then diluted with 10 mL of 1:1 ether–pentane, washed with 10 mL of 3.3 M HCl, dried (Na_2SO_4), and concentrated. Preparative TLC (30% ether/2% MeOH/2% acetic acid/hexane, R_f 0.26) gave 242 mg (73% yield) of pure selenide: ^1H NMR ($CDCl_3$, 500 MHz) δ 2.45–3.05 (m, 5 H), 3.69, 3.72 (AB, J_{AB} = 11 Hz, 2 H), 7.0–7.3 (m, 10 H), 10.25 (br s, 1 H); IR (CH_2Cl_2) 3500–2400, 1712 (str), 1610 (shp), 1500 (shp) cm^{-1}; MS, M^+ 334.0442 (calcd for $C_{17}H_{18}O_2Se$, 334.0467).

3-(Benzylseleno)-2,2-dimethylpropionic Acid (12a, Table I, Entry 3). To a solution of LDA (prepared from 38.5 mL of 1.61 M *n*-BuLi, 62.0 mmol, and 9.6 mL of diisopropylamine, 68 mmol) in 30 mL of THF at 0 °C was added 2.87 mL (31.0 mmol) of isobutyric acid in 50 mL of THF. The resulting solution was stirred for 1 h at room temperature and cooled to −78 °C, and 8.20 g (31.0 mmol) of bromomethyl benzyl selenide in 10 mL of THF was added via cannula. The solution was allowed to warm to room temperature and was stirred for 2 h. The product was diluted with 50 mL of 1:1 ether–pentane, quenched and washed with 50 mL of 3.3 M HCl, and then extracted in 50 mL of 10% NaOH (w/v). The basic aqueous solution was acidified to pH 1 and the product was extracted into 3 × 25 mL portions of CH_2Cl_2. These portions were combined, dried (Na_2SO_4), and concentrated in vacuo to remove not only solvent but also any unreacted isobutyric acid, giving 5.88 g (70% yield) of selenide as a light yellow oil. Preparative TLC (50% ether/hexane, R_f 0.40) gave an analytically pure sample: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.26 (s, 6 H), 2.73 (s, $^2J_{HSe}$ = 10.1 Hz, 2 H), 3.80 (s, $^2J_{SeH}$ = 12.4 Hz, 2 H), 7.2–7.3 (m, 5 H), 10.15 (br s, 1 H); IR ($CHCl_3$) 3300–2700 (br), 1705 (str), 1605 (w), 1495 (shp) cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_2Se$: C, 53.14; H, 5.95. Found: C, 53.30; H, 5.80.

***N*-Methyl-3-(benzylseleno)-2-phenylpropionamide (Table I, Entry 4).** To a solution of 149 mg (1.00 mmol) of *N*-methylphenylacetamide in 5 mL of THF at 0 °C was added 1.16 mL of 1.72 M *n*-BuLi (2.00 mmol). The first equivalent of the *n*-BuLi gave a precipitate, but upon addition of the second a homogeneous solution formed. This solution was stirred for 15 min at 0 °C and cooled to −78 °C, and 0.158 mL (1.00 mmol) of bromomethyl benzyl selenide was added. The resulting solution was allowed to warm to room temperature and stirred for 2 h. The solution was diluted with 15 mL of 1:1 ether–pentane, washed twice with brine, dried over Na_2SO_4, concentrated, and purified by preparative TLC (30% acetone/2% MeOH/hexane, R_f 0.40) to give 280 mg (84% yield) of selenide: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.66 (d, J = 5.0 Hz, 3 H), 2.72, 3.21, 3.29 (ABX, J_{AB} = 8.8 Hz, J_{AX} = 12.5 Hz, J_{BX} = 5.0 Hz, 3 H), 3.66 (s, $^2J_{SeH}$ = 13.5 Hz, 2 H), 5.25 (br, 1 H), 7.1–7.30 (m, 10 H); IR (neat) 3400–3250 (br, str), 3100–2900, 1670–1630, 1580–1560, 1500 (shp), 1460 (shp) cm^{-1}; MS, M^+ 333.0632 (calcd for $C_{17}H_{19}NOSe$, 333.0627).

3-(Benzylseleno)-2,2-dimethyl-1-phenylpropanone (Table I, Entry 5). To a solution of LHMDS (prepared from 7.06 mL of 1.77 M *n*-BuLi, 12.5 mmol, and 2.95 mL of hexamethyldisilazane, 14 mmol) in 50 mL of THF and 5 mL of HMPA at 0 °C was added 1.80 mL (12.0 mmol) of isobutyrophenone. The cold bath was removed and the solution was stirred at room temperature for 10 min and cooled to −78 °C again, and 1.90 mL (12.0 mmol) of bromomethyl benzyl selenide was added. The resulting solution was warmed to room temperature and stirred for 3 h. The solution was then diluted with 50 mL of 1:1 ether–pentane, washed twice with 30-mL portions of brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (10% ether/1% MeOH/hexane, R_f 0.30) to yield 3.30 g (83% yield) of selenide as a viscous, colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.28 (s, 6 H), 2.78 (s, $^2J_{SeH}$ = 9.7 Hz, 2 H), 3.60 (s, $^2J_{SeH}$ = 13.0 Hz, 2 H), 7.05–7.25 (m, 5 H), 7.25–7.40 (m, 3 H), 7.52 (d, J = 8.4 Hz, 2 H); IR (neat) 3080–2850, 1690–1650 (str), 1595, 1490 cm^{-1}; MS, M^+ 332.0679 (calcd for $C_{18}H_{20}SeO$, 332.0674).

Methyl 3-(Benzylseleno)-2-[(diphenylmethyl)imino]-propionate (5b, Table I, Entry 6). To a solution of the glycine imine **4b**, which was prepared by the method of O'Donnell[9] in 30 mL of THF at −78 °C was added LHMDS (prepared from 5.20 mL of 2.11 M *n*-BuLi, 11.0 mmol, and 2.5 mL of hexamethyldisilazane, 12 mmol) in 30 mL of THF. The resulting enolate solution was immediately added to a solution prepared from 1.60 mL (10.1 mmol) of bromomethyl benzyl selenide and 3.0 g (20 mmol) of NaI in 30 mL of THF at −78 °C. The solution was warmed to room temperature, stirred for 2 h, diluted with 50 mL of 1:1 ether–pentane, washed with 3 × 25 mL portions of brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (12% ethyl acetate/hexane, R_f 0.25) to yield 2.92 g (67% yield) of clean **5b** as a viscous oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 2.93, 3.02 (AB of ABX, J_{AB} = 12.5 Hz, J_{AX} = 8.1 Hz, J_{BX} = 5.3 Hz, 2 H), 3.63, 3.68 (AB, J_{AB} = 12.0 Hz, 2 H), 3.71 (s, 3 H), 4.35 (X of ABX, J_{AX} = 8.1 Hz, J_{BX} = 5.3 Hz, 1 H), 7.1–7.7 (m, 15 H); IR (neat) 3070–2950, 1740 (str), 1625, 1450, 700 cm^{-1}; MS, M^+ 437.0878 (calcd for $C_{24}H_{23}NO_2Se$, 437.0888).

Methyl 3-(Benzylseleno)-2-(acetylamino)-2-methylpropionate (3a, Table I, Entry 7). To a solution of LDA (prepared from 5.21 mL of 2.11 M *n*-BuLi, 11.0 mmol, and 1.7 mL of diisopropylamine, 12 mmol) in 50 mL of THF at −78 °C was added 1.75 mL (10.0 mmol) of methyl 2-(benzylimino)-propionate (**1a**), which had been prepared by literature procedures[9b] in 93% overall yield from alanine. The bloody red enolate solution was stirred for 15 min at −78 °C and 1.66 mL (10.5 mmol) of bromomethyl benzyl selenide was added. The resulting solution was warmed to room temperature and stirred for 3 h, diluted with 50 mL of 1:1 ether–pentane, washed with 3 × 30 mL portions of brine, dried (Na_2SO_4), and concentrated to yield crude **2a**: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.58 (s, 3 H), 2.00, 2.14 (AB, J_{AB} = 12.7 Hz, 2 H), 2.75 (s, 3 H), 2.81 (s, $^2J_{SeH}$ = 11.0 Hz, 2 H), 7.15–7.35 (m, 5 H), 7.35–7.40 (m, 3 H), 7.78 (dd, 2 H, J = 7.1, 3.2 Hz), 8.27 (s, 1 H); IR (neat) 3100–2800, 1730 (str), 1700, 1640, 1600, 1580, 1495 cm^{-1}; MS, M^+ 375.0739 (calcd for $C_{19}H_{21}NO_2Se$, 375.0732).

Crude **2a** in 15 mL of CH_2Cl_2 was treated with 0.77 mL (10 mmol) of CF_3CO_2H followed by 800 mL of H_2O. The solution was stirred for 15 min, and the CH_2Cl_2 was stripped by rotary evaporation. The resulting oil was diluted in 50 mL of ether, washed with 30-mL portions of 10% $NaHCO_3$ (w/v) and brine, dried (Na_2SO_4), and concentrated to give the crude amino ester: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 3 H), 1.8 (br s, 2 H), 2.68, 3.01 (AB, J_{AB} = 13.0 Hz, $^2J_{SeH}$ = 11.3 Hz, 2 H), 2.81 (s, $^2J_{SeH}$ = 12.0 Hz, 2 H), 3.72 (s, 3 H), 7.15–7.30 (m, 5 H); IR (neat) 3500–3350, 3070–2900, 1750–1720 (str), 1630 (shp), 1490 (shp), 760, 700 cm^{-1}; MS, M^+ 287.0424 (calcd for $C_{12}H_{17}NO_2Se$, 287.0420).

The crude amino ester was diluted in 25 mL of CH_2Cl_2 and treated with 0.72 mL (10.0 mmol) of acetyl chloride and 0.81 mL (10.0 mmol) of pyridine. The resulting solution was stirred at 25 °C for 1 h, washed with 20-mL portions of 3.3 M HCl, 10% Na_2CO_3 (w/v), and brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (ether, R_f 0.34) to give 2.30 g (70% overall yield) of clean **3a**, which crystallized slowly upon standing: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.60 (s, 3 H), 1.96 (s, 3 H), 3.06, (d, J = 12.9 Hz, 1 H), 3.52 (d, J = 12.9 Hz, 1 H), 3.72 (s, 3 H), 3.75 (s, 2 H), 6.30 (br s, 1 H), 7.2–7.3 (m, 5 H); IR (CCl_4) 3300–3200, 3100–2950, 1745 (str), 710 (shp), 660 (shp) cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_3Se$: C, 51.22; H, 5.83. Found: C, 50.90, H, 5.90.

Methyl 3-(Benzylseleno)-2-(acetylamino)-2-isopropylpropionate (3b, Table I, Entry 8). To a solution of LDA (prepared from 0.67 mL of 1.72 M *n*-BuLi, 1.2 mmol, and 0.18 mL of diisopropylamine, 1.3 mmol) in 5 mL of THF at −78 °C was added 0.219 mL (1.00 mmol) of methyl 2-(benzylimino)-3-methylbutanoate **15b**, which had been prepared by the method of Stork.[8b] The enolate solution was stirred for 15 min at −78 °C, 0.166 mL (1.05 mmol) of bromomethyl benzyl selenide was added, and the resulting solution was warmed to room temperature and stirred for 3 h. It was then diluted with 10 mL of 1:1 ether–pentane, washed with three 5-mL portions of brine, dried (Na_2SO_4), and concentrated to yield crude **2b** as a viscous oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (d, J = 7.0 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 2.34 (septet, J = 7.0 Hz, 1 H), 2.81 (d, J = 12.5 Hz, 1 H), 3.23 (d, J = 12.5 Hz, 1 H), 3.61, 3.63 (AB, J_{AB} = 11.3 Hz, 2 H), 3.73 (s, 3 H), 7.10–7.45 (m, 8 H), 7.75–7.85 (m, 2 H), 8.43 (s, 1 H); IR (neat) 3050–2850, 1730 (str), 1640, 1600, 1490, 760, 690 cm^{-1}; MS, M^+ 403.1050 (calcd for $C_{21}H_{25}NO_2Se$, 403.1044).

Crude **2b** in 5 mL of CH_2Cl_2 was treated with 0.077 mL (1.00 mmol) of CF_3CO_2H and then with 0.080 mL of H_2O. The solution was stirred for 15 min and washed with 3.3 M HCl. The organic phase was dried (Na_2SO_4) and concentrated to yield the crude amine hydrochloride: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.03 (d, J = 7 Hz, 3 H), 1.08 (d, J = 7 Hz, 3 H), 2.34 (septet, J = 7 Hz, 1 H), 3.01, 3.14 (AB, J_{AB} = 13.5 Hz, 2 H), 3.67 (s, 3 H), 3.81, 3.85 (AB, J_{AB} = 11.7 Hz, 2 H), 7.0–7.35 (m, 5 H), 9.55 (br, 3 H); IR (CCl_4) 3250–2600, 1750 cm^{-1}.

The crude amine hydrochloride in 5 mL of CH_2Cl_2 was treated with 0.087 mL (1.2 mmol) of acetyl chloride and 0.42 mL (3.0 mmol) of NEt_3 and was stirred at room temperature for 8 h. The solution was washed with 5-mL portions of 3.3 M HCl, 10% Na_2CO_3 (w/v), and brine, dried (Na_2SO_4), concentrated, and purified by preparative TLC (40% acetone/2% MeOH/hexane, R_f 0.40) to give 256 mg (72% overall yield) of **3b**, which crystallized upon standing at −15 °C: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 2.01 (s, 3 H), 2.66 (septet, J = 7.0 Hz, 1 H), 3.16 (d, J = 12.2 Hz, 1 H), 3.70 (s, 3 H), 3.72, 3.75 (AB, J_{AB} = 11.2 Hz, 2 H), 3.94 (d, J = 12.2 Hz, 1 H), 6.55 (br s, 1 H), 7.2–7.3 (m, 5 H); IR (CCl_4) 3400–3300, 3050–2900, 1735 (str), 1680–1650, 1500 cm^{-1}; MS, M^+ 357.0816 (calcd for $C_{16}H_{23}NO_3Se$, 357.0843).

Methyl 2-((Phenylseleno)methyl)-2-[((dimethylamino)methyl)imino]propionate (Table I, Entry 9). To a solution of LDA (prepared from 1.56 mL of 1.41 M *n*-BuLi, 2.2 mmol, and 0.34 mL of diisopropylamine) in 5 mL of THF at −78 °C was added 0.310 mL (2.00 mmol) of methyl *N*-[[(dimethylamino)methyl]-imino]alaninate, which was prepared by the method of Gschwend.[8a] The enolate solution was stirred for 15 min at −78 °C, 0.350 mL (2.00 mmol) of bromomethyl phenyl selenide was added, and the resulting solution was warmed to room temperature and stirred for 3 h. The solution was diluted with 10 ml of 1:1 ether/pentane, washed with 25-mL portions of 10% $NaHCO_3$ (w/v) and brine, dried over Na_2SO_4, concentrated, and purified by preparative TLC (ether, R_f 0.25) to give 412 mg (63% yield) of pure selenide as a thin yellow oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.49 (s, 3 H), 2.78 (s, 6 H), 3.32, 3.40 (AB, J_{AB} = 11.95 Hz, 2 H), 3.62 (s, 3 H), 7.2–7.5 (m, 6 H); IR 2978, 1739, 1650–1485, 901, 700 cm^{-1}; MS, M^+ 328.0691 (calcd for $C_{14}H_{20}N_2O_2Se$, 328.0685).

Methyl 3-(Benzylseleno)-2-(carbobenzoxyamino)-propionate (9). A solution containing 1.66 g (6.24 mmol) of **5b** in 15 mL of CH_2Cl_2 was treated with 0.48 mL (6.5 mmol) of CF_3CO_2H, stirred for 1 min, and then treated with 0.50 mL of H_2O. This solution was stirred for 15 min and washed with 10% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and treated with 0.94 mL (6.2 mmol) of benzyl chloroformate and 0.57 mL (7.0 mmol) of pyridine. The solution was stirred for 30 min, washed with 15 mL of 10% $NaHCO_3$ (w/v), concentrated by rotary evaporation, and heated to 100 °C at 0.01 mm to remove relatively volatile byproducts. Flash chromatography (50% ether/hexane, R_f 0.24) of the residue gave 2.11 g (83% yield) of pure **9** as a viscous oil, which crystallized within a week upon standing: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.92 (d, J = 5.0 Hz, 2 H), 3.73 (s, 3 H), 3.76 (s, 2 H), 4.66 (dt, J = 8.0, 5.0 Hz, 1 H), 5.11 (s, 2 H), 5.53 (d, J = 8.0 Hz, 1 H), 7.20–7.28 (m, 5 H), 7.30–7.38 (m, 5 H); IR (CCl_4) 3330, 3100–2900, 1750–1690 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_4Se$: C, 56.16; H, 5.21. Found: C, 56.15; H, 5.38.

Dimethyl 3,3'-Diselenobis[2-(carbobenzoxyamino)-propionate] (10). To 1.66 g (4.09 mmol) of the benzyl selenide **9** in 5 mL of CH_2Cl_2 was added 2.04 mL of 2.00 M Br_2/CCl_4 solution (4.09 mmol). The solution was stirred for 15 h and treated with 0.06 mL (2.0 mmol) of anhydrous hydrazine, which immediately turned the brown solution yellow. This mixture was stirred for 30 min, washed with 15-mL portions of 10% $NaHCO_3$ (w/v) and brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (67% ether/hexane, R_f 0.17) to yield 1.25 g (97% yield) of **10** as a viscous yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 3.25–3.50 (m, 2 H), 3.72 (br s, 3 H), 4.68 (br dt, J = 5.0, 7.6 Hz, 1 H), 5.12 (s, 2 H), 5.69 (d, J = 7.6 Hz, 1 H), 7.30–7.37 (m, 5 H); IR (CCl_4) 3350 (str), 3100–2900, 1760–1690 (str) cm^{-1}. Anal. Calcd $C_{24}H_{28}N_2O_8Se_2$: C, 45.73; H, 4.48. Found: C, 45.49; H, 4.58.

Methyl 2-(Carbobenzoxyamino)-2-propenoate (11). A solution containing 435 mg (1.07 mmol) of **9** in 10 mL of CH_2Cl_2 was cooled to −78 °C and treated with 240 mg (1.3 mmol) of MCPBA powder. After the solution was stirred at −78 °C for 5 min, 0.35 mL (2.5 mmol) of triethylamine was added, and the resulting solution was stirred at room temperature for 30 min. The solution turned deep yellow. The solution was washed with 25 mL of saturated $NaHCO_3$, dried over Na_2SO_4, concentrated, and purified by preparative TLC (50% ether/hexane, R_f 0.55) to give 217 mg (87% yield) of **11** as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 3.82 (s, 3 H), 5.16 (s, 2 H), 5.78 (s, 1 H), 6.24 (s, 1 H), 7.25–7.35 (m, 6 H); IR (neat) 3450–3350, 3100–2900, 1750–1710, 1650 cm^{-1}; MS, M^+ 235.0843 (calcd for $C_{12}H_{13}NO_4$, 235.0841).

Methyl 3-(Benzylseleno)-2,2-dimethylpropionate (12b). To a neat solution of the acid **12a** (1.897 g, 7.0 mmol) was added 1.35 mL of oxalyl chloride (15.5 mmol). The solution bubbled vigorously and turned brown. After 45 min of stirring solvent removal gave the acid chloride: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 6 H), 2.70 (s, $^2J_{SeH}$ = 10.0 Hz, 2 H)8 3.78 (s, $^2J_{SeH}$ = 12.5 Hz, 2 H), 7.15–7.25 (m, 5 H).

Addition of 40 mL of methanol to the acid chloride caused the brown solution to almost immediately turn yellow. The solution was stirred at room temperature for 1 h, diluted with 20 mL of CH_2Cl_2, washed with 20-mL portions of 3.3 M HCl, 10% NaOH (w/v), and brine, and dried over Na_2SO_4. Concentration and distillation (100–105 °C, 1.0 mmHg) gave 1.59 g (79% yield) of pure **12b** as a yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (s, 6 H), 2.73 (s, $^2J_{SeH}$ = 10.0 Hz, 2 H), 3.67 (s, 3 H), 3.78 (s, $^2J_{SeH}$ = 12.4 Hz, 2 H), 7.2–7.3 (m, 5 H); IR (neat) 3000–2950, 1725 (str), 1610, 1500 (shp), 762, 700 cm^{-1}; MS, M^+ 286.0471 (calcd for $C_{13}H_{18}O_2Se$, 286.0467).

***N*-Methyl-3-(benzylseleno)-2,2-dimethylpropionamide (12c).** To a solution containing 554 mg (2.0 mmol) of the acid **12a** in 2 mL of CH_2Cl_2 was added 0.38 mL (4.4 mmol) of oxalyl chloride. The solution was stirred for 20 min until effervescence ceased. The solution was subjected to rotary evaporation on a steam bath to remove residual oxalyl chloride, diluted in 10 mL

of CH_2Cl_2, cooled to 0 °C, and treated dropwise with 0.39 mL (5.0 mmol) of 40% aqueous methylamine. The solution was stirred for 1 h, washed with 10-mL portions of 3.3 M HCl, 10% $NaHCO_3$ (w/v), and brine, dried over Na_2SO_4, and concentrated to give 0.572 g (98%) of the desired amide **12c** as a deep orange oil. The product was quite pure and was used without further purification. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.23 (s, 6 H), 2.74 (s, $^2J_{SeH}$ = 12.7 Hz, 2 H), 7.2–7.3 (m, 5 H); IR (neat) 3340 (br), 3070–2850, 1650–1620 (str), 1550–1520 (str), 760, 695 cm^{-1}; MS, M^+ 285.0624 (calcd for $C_{13}H_{19}NOSe$, 285.0627).

Dimethyl 3,3'-Diselenobis[2,2-dimethylpropionate] (13b). Sulfuryl chloride (0.087 mL, 1.2 mmol) was added to neat benzyl selenide **12b** (0.230 mL, 1.0 mmol). The flask was swirled for 10 min until bubbling ended and the solution was subjected to 30 min of rotary evaporation to remove excess SO_2Cl_2. Saturated $NaHSO_3$ (8 mL) was added and the solution was stirred vigorously for 20 min at room temperature. The organic layer was extracted with 15 mL of CH_2Cl_2 and dried over Na_2SO_4. Concentration and preparative TLC (5% ether/hexane, R_f 0.12) gave 0.18 g (93% yield) of diselenide **13b** as a yellow oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.30 (s, 12 H), 3.30 (s, $^2J_{SeH}$ = 12.0 Hz, 4 H), 3.69 (s, 6 H); IR (neat) 2990–2960, 1730 (str), 1470–1430, 1190, 1165, 1130 cm^{-1}; MS, M^+ 389.9850 (calcd for $C_{12}H_{22}O_4Se_2$, 389.9842).

3,3'-Diselenobis(*N*-methyl-2,2-dimethylpropionamide) (13c). To a solution of benzyl selenide **12c** (516 mg, 1.82 mmol) in 10 mL of CH_2Cl_2 was added sulfuryl chloride (0.146 mL, 1.82 mmol). The solution was stirred for 40 min and then concentrated by rotary evaporation on a steam bath. The residue was diluted in 10 mL of CH_2Cl_2 and treated with hydrazine (0.15 mL, 4.6 mmol). An immediate exothermic reaction ensued. The solution was stirred for 45 min, and the organic phase was washed with 15-mL portions of 3.3 M HCl, 10% NaOH (w/v), and brine. After drying over Na_2SO_4 the organic solution was concentrated and then heated to 100 °C at 0.35 mmHg to give 288 mg (82%) of diselenide **13c** as the yellow residual oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (s, 6 H), 2.75 (d, J = 4.8 Hz, 3 H), 3.23 (s, $^2J_{SeH}$ = 11.2 Hz, 2 H), 5.93 (br, 1 H); IR (neat) 2980–2880, 1660–1610 (str), 1570–1539 (str) cm^{-1}; MS, M^+ 388.0168 (calcd for $C_{12}H_{24}N_2O_2Se_2$, 388.0162).

Methyl 3-((2-Benzoylpropyl)seleno)-2,2-dimethylpropionate (14). To a solution of neat benzyl selenide **12b** (0.700 mL, 2.94 mmol) was added 0.260 mL of SO_2Cl_2 (3.23 mmol). The flask was swirled for 10 min until bubbling ended and the solution was subjected to 30 min of rotary evaporation to remove excess SO_2Cl_2. After diluting the solution with 10 mL of CH_2Cl_2 the silyl enol ether 1-(trimethylsiloxy)-1-phenyl-2-methylpropene[1c] (1.41 ml, 5.88 mmol) was added, causing the brown solution to turn yellow. The solution was washed with 10-mL portions of 3.3 M HCl, 10% $NaHCO_3$ (w/v), and brine, dried over Na_2SO_4, concentrated, and distilled (100–105 °C, 0.35 mmHg) to give 0.80 g of **14** (80% yield from **12b**) as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 6 H), 1.63 (s, $^3J_{SeH}$ = 12.0 Hz, 6 H), 2.74 (s, $^2J_{SeH}$ = 5.5 Hz, 2 H), 3.50 (s, 3 H), 7.27–7.50 (m, 3 H), 7.99 (dd, J = 8.0, 1.6 Hz, 2 H); IR (neat) 2985–2965, 1730 (str), 1655 (str), 700 cm^{-1}; MS, M^+ 342.0733 (calcd for $C_{16}H_{22}O_3Se$, 342.0728).

Competition Experiment. Bromomethyl Benzyl Selenide vs. Bromomethyl Benzyl Sulfide. To a solution of LDA (prepared from 0.94 mL of 2.11 M *n*-BuLi, 2.00 mmol, and 0.31 mL of diisopropylamine, 2.2 mmol) in 5 mL of THF at 0 °C was added 0.0923 mL (1.00 mmol) of isobutyric acid. The resulting solution was stirred for 30 min at room temperature. The solution was then cooled to −78 °C, and a solution of 0.456 mL (3.0 mmol) of bromomethyl benzyl sulfide and 0.525 mL (90% pure, 3.0 mmol) bromomethyl benzyl selenide in 5 mL of THF was added via cannula. The solution was allowed to warm to room temperature and stirred for 2 h. The product was diluted with 15 mL of 1:1 ether–pentane, washed twice with 3.3 M HCl, and extracted in 4 × 10 mL portions of 10% NaOH. The basic aqueous solution was acidified to pH 1, and the product was extracted in 4 × 10 mL portions of CH_2Cl_2. The organic solution was dried (Na_2SO_4) and concentrated. ^1H NMR showed a 15:1 ratio of 3-(benzylthio)-2,2-dimethylpropionic acid to 3-(benzylseleno)-2,2-dimethylpropionic acid.

3-(Benzylthio)-2-phenylpropionic Acid (Table II, Entry 1). Into a 50-mL, two-necked round-bottomed flask equipped with a magnetic stirrer and septum was distilled 15 mL of DME under N_2. The flask was cooled to −50 °C, and 1.02 mL (7.2 mmol) of diisopropylamine was added, followed by 4.8 mL of 1.47 M *n*-BuLi (7.1 mmol) in hexane. A solution of 408 mg (3 mmol) of phenylacetic acid in 2 mL of DME was added, and the stirred solution was warmed to 25 °C for 30 min to ensure complete dianion formation. The reaction mixture was cooled to 0 °C and a solution of 651 mg (3 mmol) of bromomethylbenzyl sulfide in 1 mL of DME was added. After being stirred for 25 min, the reaction mixture was added to 10 mL of 10% HCl solution and 10 mL of ether. The aqueous layer was washed with 10 mL of ether, and the combined organic layers were dried ($MgSO_4$). Solvent was removed and 652 mg (80%) of sulfide was isolated by crystallization from pentane: mp 103–104 °C; ^1H NMR ($CDCl_3$, 100 MHz) δ 2.75, 3.12 (AB of ABX, J_{AB} = 13.5 Hz, J_{AX} = 9 Hz, J_{BX} = 7 Hz, 2 H), 3.68 (X of ABX, J_{AX} = 9, J_{BX} = 7 Hz, 1 H), 3.69 (s, 2 H), 7.3 (br s, 5 H), 11.12 (br s, 1 H); IR ($CHCl_3$) 3600–2400, 1715, 1601 (w), 1586 (w) cm^{-1}; MS, M^+ 272.0870 (calcd for $C_{16}H_{16}O_2S$, 272.0870).

2-Phenylacrylic Acid via Sulfoxide Elimination (Table II, Entry 1). A mixture of 272 mg (1 mmol) of 3-(benzylthio)-2-phenylpropionic acid and 428 mg (2 mmol) of $NaIO_4$ in 10 mL of 80% aqueous methanol was stirred at 25 °C under nitrogen for 2 h. After filtration and solvent removal, the crude reaction mixture was added to 10 mL of $CHCl_3$ and washed with 5 mL of 7% $NaHCO_3$ solution and 5 mL of saturated NaCl solution and dried ($MgSO_4$). Solvent removal gave 296 mg of crude sulfoxide.

A solution of 144 mg (0.5 mmol) of sulfoxide prepared above in 3 mL of toluene was refluxed for 1.5 h. After solvent removal, preparative TLC (50% ether–pentane) gave 62 mg (84%) of 2-phenylacrylic acid: mp 97–100 °C (recrystallized from ether–pentane, lit.[18] mp 106 °C); ^1H NMR ($CDCl_3$, 100 MHz) δ 6.01 (d, J = 1.1 Hz, 1 H), 6.54 (d, J = 1.1 Hz, 1 H), 7.1–7.5 (m, 5 H), 11.44 (br s, 1 H); IR ($CHCl_3$) 3600–2400, 1695, 1612 cm^{-1}.

2-((Benzylthio)methyl)dodecanoic Acid (Table II, Entry 2). Following the alkylation procedure outlined for Table II, entry 1 (THF, alkylation at 25 °C for 1 h), 0.6 g (3 mmol) of dodecanoic acid gave 0.61 g (61%) of product after preparative TLC; mp 48–49.2 °C (recrystallized from pentane); ^1H NMR (CCl_4, 100 MHz) δ 0.7–1.1 (m, 3 H), 1.1–1.7 (m, 18 H), 2.26–2.68 (m, 3 H), 3.64 (br s, 2 H), 7.22 (m, 5 H), 11.80 (br s, 1 H); IR ($CHCl_3$) 3600–2400, 1710, 1600 (w) cm^{-1}; MS, M^+ 336.2127 (calcd for $C_{20}H_{32}O_2S$, 336.2121).

2-Methylenedodecanoic Acid (Table II, Entry 2). Following the oxidation (4 h) and elimination (2 h) procedures outlined for Table II, entry 1, 134 mg (0.4 mmol) of 2-((benzylthio)methyl)-dodecanoic acid gave 69 mg (97% pure, ca. 73% yield) of product after preparative TLC (50% ether–pentane): mp 34–35 °C (recrystallized from pentane, lit.[19] mp 33–34 °C); ^1H NMR ($CDCl_3$, 100 MHz) δ 0.7–1.1 (m, 3 H), 1.1–1.7 (m, 16 H), 2.1–2.5 (m, 2 H), 5.62 (m, 1 H), 61.28 (m, 1 H), 10.4 (br s, 1 H); IR ($CHCl_3$) 3600–2400, 1694, 1627 cm^{-1}.

3-(Benzylthio)-2-methyl-1-phenyl-2-propanone (Table II, Entry 3). The alkylation procedure outlined for Table II, entry 1 was followed using 402 mg of LiI (added to the reaction flask before LDA formation), 3.6 mmol of LDA, and 402 mg (3 mmol) of propiophenone. The enolate was quenched at −78 °C with $PhCH_2SCH_2Br$ and was warmed to 25 °C for 1 h. Workup, followed by preparative TLC, gave 487 mg (60%) of sulfide, mp 39.4–41.6 °C (recrystallized from ether–pentane); ^1H NMR (CCl_4, 100 MHz) δ 1.13 (d, $J \simeq$ 7 Hz, 3 H), 2.44 and 2.85 (AB of ABX, J_{AB} = 13.5 Hz, J_{AX} = 5.6 Hz, J_{BX} = 7 Hz, 2 H), 3.47 (X of ABX, J_{AX} = 5.6, J_{BX} = 7 Hz, 1 H), 3.63 (s, 2 H), 7.1–7.6 (m, 8 H), 7.83 (m, 2 H); IR 1689, 1588, 1580 cm^{-1}; MS, M^+, 270.1079 (calcd for $C_{18}H_{18}OS$, 270.1077).

2-Methyl-1-phenyl-2-propen-1-one (Table II, Entry 3). Following the oxidation (2 h) and elimination (6 h) procedures outlined for Table II, entry 1, 135 mg (0.5 mmol) of 3-(benzylthio)-2-methyl-1-phenyl-1-propanone gave 55 mg (75% yield) of 2-methyl-1-phenyl-2-propen-1-one[20] after preparative TLC: ^1H NMR (CCl_4, 100 MHz) δ 2.02 (m, 3 H), 5.52 (m, 1 H), 5.78 (m,

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1 H), 7.17–7.80 (m, 5 H); IR (CCl_4) 1661, 1628 (w), 1600, 1580 (w) cm^{-1}.

2-((Benzylthio)methyl)cyclooctanone (Table II, Entry 4). Following the alkylation procedure outlined for Table II, entry 3, 379 mg of cyclooctanone gave 403 mg (51%) of sulfide after preparative TLC: ^1H NMR (CCl_4, 100 MHz) δ 1.1–2.1 (m, 10 H), 2.1–2.8 (m, 5 H), 3.59 (br s, 2 H), 7.22 (br s, 5 H); IR 1703, 1600 (w) cm^{-1}; MS, M^+, 262.1393 (calcd for $C_{16}H_{22}OS$, 262.1370).

2-Methylenecyclooctanone. Following the oxidation (4.5 h) and elimination (3.5 h) procedures outlined for Table II, entry 1, 262 mg (1 mmol) of 2-((benzylthio)methyl)cyclooctanone gave 85 mg (62%) of 2-methylenecyclooctanone[21] after preparative TLC: ^1H NMR (CCl_4, 100 MHz) δ 1.4–1.9 (m, 8 H), 2.4–2.7 (m, 4 H), 5.12 (m, 1 H), 5.76 (d, J = 2.5 Hz, 1 H); IR 1701, 1605 (w) cm^{-1}.

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Nitrogen Bridgehead Compounds. 63.[1] Ring–Chain Tautomerism of [(α-Azaarylamino)methylene]malononitriles

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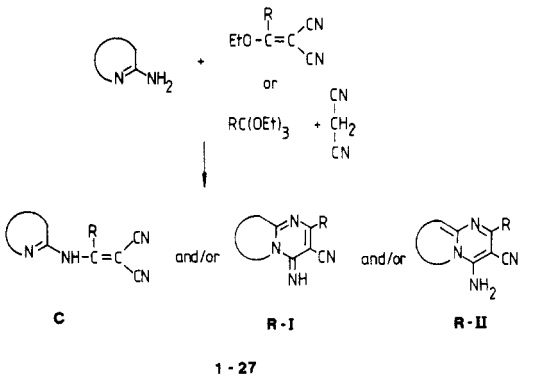
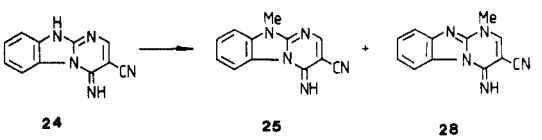
Twenty-one α-amino aza heterocycles were reacted with (ethoxymethylene)malononitrile. UV and ^1H and ^{13}C NMR studies indicated that in solution the structures of the condensation products can be described as chain and ring tautomers. Investigations were also made of the solvent and temperature dependence of the position of equilibrium of the ring and chain tautomer forms and the effect of protonation on the ring–chain tautomerism of the 2-aminopyridine derivative. The proportion of the ring form is increased by the presence of a substituent in position 2 of the pyridopyrimidine skeleton type ring tautomer and also by electron-donating substituents in position 7 or 8, while electron-accepting groups increase the content of the chain tautomer. A substituent in position 6 sterically favors the chain form, while substituent in position 9 influences the equilibrium between the ring and chain tautomer forms through its electronic and steric properties and its hydrogen bond forming ability. The 1-aminoisoquinoline derivative is present in ring form in both $CDCl_3$ and Me_2SO-d_6. The derivatives of 2-aminoquinoline, 3-aminoisoquinoline, 2-aminopyrimidine, and 2-aminopyrazine predominantly exist as chain tautomers. The derivatives of π-excess five-membered heterocycles—of 2-aminothiazole, 3-aminopyrazole, 2-aminobenzthiazole, and 2-aminobenzimidazoles—favor the ring form. In the case of 3-aminopyrazole, the chain and ring forms could be separated.

(Ethoxymethylene)malononitrile is a versatile reagent for the preparation of heterocyclic ring systems.[2] Its reaction with aromatic α-amino aza heterocycles affords antiallergic[3] and bactericidal[4] agents and also intermediates for the preparation of antiallergenics,[5,6] bronchodilators,[6] and vasodialtors.[5] The structures of these products have been reported to be chain form **C**[3-13] or ring forms **R**-I[14] or **R**-II[15] (see Scheme I). For the sake of clarity the numbering used for certain open-chain heterocycles follows from the ring-closed form (e.g., **1R**-I → **1C**). Although investigated by UV and ^1H and ^{13}C NMR,[6,11,14,16] these forms have often proved to be incorrectly assigned.

Scheme I



Scheme II



We have recently focused our interest on the factors that determine the structures of these products. Our studies included 2-aminopyridine and its methyl, ethoxycarbonyl,

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