Efficient Synthesis of β,γ-Dehydrovaline

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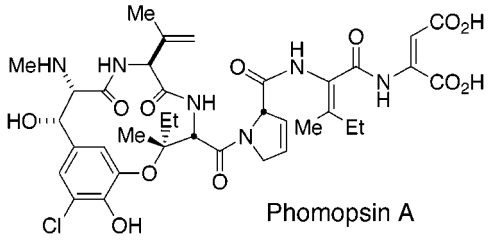
Received June 4, 1999

Unnatural amino acids continue to be the targets of much synthetic interest.[1] In particular, β,γ-unsaturated amino acids have been the subject of many synthetic studies because of their interesting biological activity and due to the inherent challenges that are associated with developing efficient synthetic routes to these sensitive compounds. Vinylglycine, the parent compound of this family, has been isolated from mushrooms[2] and is postulated to be an intermediate in the enzymatic conversion of homoserine to threonine[3] and α-ketobutyrate.[4] Several β,γ-unsaturated amino acids have been shown to be irreversible inhibitors of pyridoxal phosphate-dependent enzymes and have found use as herbicides and fungicides.[5] In addition, β,γ-unsaturated amino acids are of interest because of their unique conformational properties. The majority of the synthetic efforts toward β,γ-unsaturated amino acids have been directed specifically toward vinylglycine, with few reports describing routes to β,γ-dehydrovaline or other β,γ-unsaturated amino acids. Our laboratory studies antimitotic natural products that bind to microtubules, and we are presently pursuing the total synthesis of phomopsin A (Chart 1). These studies have resulted in new methods to prepare hindered alkyl aryl ethers and α,β-unsaturated amino acids.[6] As part of our effort, we required an efficient route to β,γ-dehydrovaline or an appropriately functionalized precursor that could be incorporated into the macrocycle and unveiled at the appropriate time.

Many of the reported syntheses of vinylglycine involve oxidative degradation of suitably modified, optically pure α-amino acids (e.g., L-methionine, L-glutamic acid, and L-homoserine);[7] however, these methods are not applicable to the synthesis of β,γ-dehydrovaline. More general strategies to prepare β,γ-unsaturated amino acids have been reported,[8] including olefination of serine

Chart 1



Phomopsin A

derivatives,[9a,b] reduction of alkynyl glycine derivatives,[9c] and Heck coupling approaches.[9d] However, none of these methods readily lend themselves to the synthesis of β,γ-dehydrovaline.

Two asymmetric syntheses of β,γ-dehydrovaline have been reported to date. The approach utilized by Baldwin et al. entails deconjugation of an α,β-dehydrovaline derivative followed by enzymatic resolution to separate the racemic mixture of enantiomers.[10] We initially chose to pursue the second approach reported by Schollkopf, which involves the formation of the bis-lactim ether from glycine and D-valine followed by hydroxyalkylation with acetone and subsequent dehydration.[11] In practice, this approach provides a mixture of both α,β-dehydrovaline and β,γ-dehydrovaline. Despite optimization, we achieved as our best result a 3:2 ratio of the two products with the desired unconjugated isomer as the minor component.

A more general method to synthesize the desired amino acid was necessary. Of the numerous methods to synthesize derivatives of α-amino acids, the methodology developed by Evans and co-workers is particularly attractive because of its proven utility in numerous applications.[12] The most straightforward approach would involve adding the chiral auxiliary to 3-methyl-3-butenoic acid and performing an asymmetric electrophilic amination. However, this transformation is known to generate a mixture of α- and γ-amination products.[13] We were also aware of the propensity for β,γ-unsaturated alkenes to migrate into conjugation, so we chose to develop a strategy in which an alkene precursor would be incorporated into the macrocycle precursor and transformed into the desired alkene later in the synthesis.

Working with a masked alkene would provide maximum flexibility, which is valuable in the context of a multistep synthesis. Phenylselenide functional groups are labile toward oxidative conditions but are generally stable toward a variety of other conditions, and this robust character makes them particularly attractive for use in the synthesis of complex molecules.[14] Elimination of the

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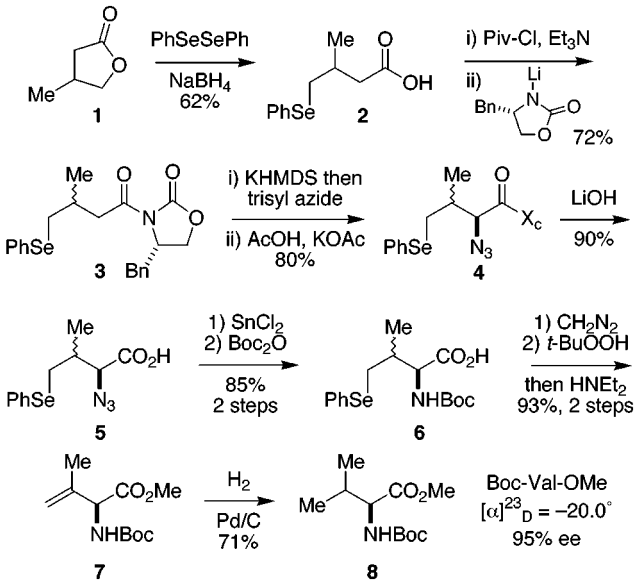
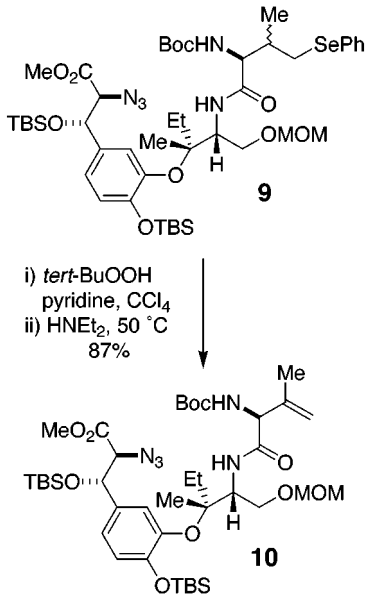
10.1021/jo990916s CCC: $18.00
Published on Web 09/09/1999

Scheme 1



Scheme 2



selenoxide functional group is a mild and useful method to prepare alkenes with good control of regioselectivity.[15] Berkowitz and co-workers have used this strategy to synthesize racemic α-vinylamino acids, suggesting that this strategy would be effective in our case as well.[16]

Lactone **1** was synthesized from citraconic anhydride as reported (Scheme 1).[17] Nucleophilic opening of lactone **1** was best accomplished by first reducing diphenyldiselenide with sodium borohydride in a solution of degassed DMF. Lactone **1** was then added as a solution in degassed DMF, and the resulting reaction was heated to 120 °C for 4 h. Subsequent isolation provided the desired carboxylic acid (**2**) in moderate yield. Berkowitz and co-workers noted that using sodium trimethoxyborohydride as the reducing agent gave superior results as it avoided the competing reduction of the lactone.[16] In our hands, use of sodium trimethoxyborohydride resulted in very slow reduction of diphenyldiselenide and inferior yields of the desired product as compared with sodium borohydride.

Condensation of the chiral auxiliary was accomplished following the procedure of Evans to provide oxazolidinone **3**.[13] As Evans and co-workers have noted, the azide transfer is a capricious reaction that is very sensitive to experimental conditions.[12b] In accord with their observations, this transformation was most successful when quenched with acetic acid at −78 °C after 3 min, followed by addition of potassium acetate and allowing the reaction to slowly warm from −78 °C to room temperature overnight. This protocol provided the desired α-azido carboxylic acid derivative **4** with >95% diastereoselectivity.

Hydrolytic removal of the auxiliary proceeded quickly and efficiently to provide carboxylic acid **5**. Subsequent reduction of the azide was unsuccessful using either catalytic hydrogenation or Staudinger reduction conditions.[18] Reduction of the azide using tin dichloride in *p*-dioxane and water was ultimately successful. The nascent amine was protected in situ as the *tert*-butyl carbamate during the alkaline workup.[19] This procedure produced the desired Boc-protected amino acid **6**, which was subsequently used to prepare the macrocycle precursor **9** shown in Scheme 2.[22]

We began to investigate reaction conditions to perform the desired selenoxide elimination.[15] A variety of oxidants have been used to oxidize the selenide to the selenoxide including hydrogen peroxide, *tert*-butyl hydroperoxide, ozone, *m*-CPBA, and sodium periodate.[20] As a model system, we converted Boc-protected amino acid **6** into the methyl ester followed by treatment with hydrogen peroxide and pyridine in CCl_4. Oxidation of the selenide to the selenoxide proceeded cleanly within 2 h, but the subsequent elimination to the alkene required heating the reaction to 40 °C for 12 h to provide the desired β,γ-unsaturated amino acid in 75% yield.

The major side product arose from the electrophilic addition of benzeneselenenic acid, produced during the course of the reaction, to the nascent alkene in the desired product. Butyl vinyl ether was added to the reaction in order to trap the benzeneselenenic acid that is formed, but this tactic did not improve the yield.[21] We chose to postpone further optimization studies until the fully functionalized macrocycle precursor was available.

Subjecting the fully functionalized macrocycle precursor **9**[22] to the same conditions (hydrogen peroxide, pyri-

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(18) Hydrogenation conditions: PtO_2/H_2, $Pd(OH)_2/H_2$, 10%Pd/C/H_2, and Raney Ni/H_2. Staudinger conditions: Ph_3P/H_2O and Me_3P/H_2O.

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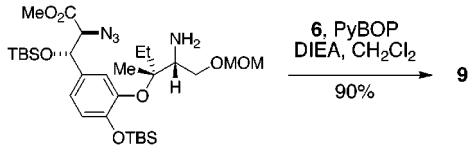
(21) We did isolate α-phenylselenylacetaldehyde, showing that butyl vinyl ether did react with benzeneselenenic acid.

(22) Compound **9** was prepared as follows:



dine, CCl_4) gave rise to a disappointing 25% isolated yield of the desired alkene product **10** (Scheme 2). To optimize this transformation, we used anhydrous *tert*-butyl hydroperoxide as the oxidant, and we added a variety of compounds to trap benzeneselenenic acid including 2-octene, 1-methyl-1-cyclohexene, diethylamine, and triethylamine. These studies provided dramatically improved yields of **10**, with the combination of *tert*-butyl hydroperoxide and diethylamine proving to be most efficient. Oxidation of **9** with *tert*-butyl hydroperoxide requires 8 equiv of oxidant in practice and is significantly slower relative to hydrogen peroxide. Nevertheless, *tert*-butyl hydroperoxide does accomplish the clean oxidation of the selenide to the selenoxide at which point addition of diethylamine, dilution with CCl_4, and heating to 50 °C for 10 h provides the desired α,β-unsaturated alkene **10** in 87% isolated yield (Scheme 2).

Oxidation of the methyl ester of compound **6** using *tert*-butyl hydroperoxide proved to be efficient as well, providing Boc-isodehydrovaline methyl ester **7** in 93% isolated yield (Scheme 1). The enantiomeric purity of the synthetic material was assessed by hydrogenation of **7** to **8** followed by comparison to authentic Boc-valine methyl ester.[23] Optical rotation measurements indicate that the synthetic material was produced in 95% enantiomeric excess.

The phenylselenide functional group is an excellent synthon for a carbon−carbon double bond, and this report demonstrates its utility in the context of complex natural product synthesis. Unnatural amino acids that contain unsaturation possess unique conformational and reactivity properties, and methods that improve access to these compounds will likely lead to new functional molecules. The variety of conditions that are tolerated by the phenylselenide indicate that amino acids that contain this functional group will also be amenable to solid-phase synthetic techniques.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ using the solvent resonance as an internal standard (7.26 ppm for ^1H and 77.0 for ^{13}C). Mass spectral data were obtained at the Scripps Research Institute Mass Spectrometry Facility. THF was distilled over sodium metal under an atmosphere of argon. All glassware was evacuated, flame-dried, and flushed with argon prior to use. Commercially available compounds were used without further purification. Chromatography was performed using 230−400 mesh silica gel and HPLC-grade solvents. TLC plates were stained with either ceric ammonium molybdate, potassium permanganate or ninhydrin solutions.

3-Methyl-4-(phenylseleno)butanoic Acid (2). Sodium borohydride (2.96 g, 77.8 mmol, 2.0 equiv) was added to a flame-dried two-neck 500-mL round-bottom flask equipped with a reflux condenser, stir bar, and septum. The flask was evacuated and purged with argon. Diphenyl diselenide (9.70 g, 31.1 mmol, 0.8 equiv) was added as a solution in 250 mL of DMF via cannula under argon and stirred at room temperature for 10 min. The DMF was rigorously degassed using the freeze−pump−thaw technique. The yellow diphenyldiselenide solution immediately cleared upon contact with $NaBH_4$. A solution of (±)-3-methyl-γ-butyrolactone **(1)**[17] (3.89 g, 38.9 mmol, 1.0 equiv) in 10 mL of degassed DMF was added via syringe. The resultant solution was heated to 120 °C for 4 h and then cooled to room temperature, diluted with 200 mL ether, and washed with 250 mL of 1 N aqueous HCl. The layers were separated, and the aqueous layer was extracted with ether twice. The organic layers were combined, dried over $MgSO_4$, and concentrated. Purification over silica gel (30% Et_2O in hexanes to 60% Et_2O in hexanes) provided 6.09 g (60% yield) of the desired product **2** as a pale yellow liquid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 7.30−7.25 (m, 3H), 3.02−2.92 (m, 2H), 2.68−2.62 (m, 1H), 2.34−2.26 (m, 2H), 1.13 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 132.6, 130.3, 129.1, 126.9, 40.6, 35.2, 30.8, 20.1; IR (neat) 3057, 2962, 1705. Anal. Calcd for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.49. Found: C, 51.37; H, 5.48.

3-(*R*,*S*)-4-(*S*)-4-Benzyl-3-[3-methyl-4-(phenylseleno)butanoyl]-1,3-oxazolidin-2-one (3). Following the general procedure of Evans et al.,[13] triethylamine (4.15 mL, 30.0 mmol, 1.3 equiv) and pivaloyl chloride (3.14 mL, 25.4 mmol, 1.1 equiv) were added to a flame-dried 250-mL round-bottom flask charged with 50 mL of THF under an argon atmosphere and cooled to −78 °C. A solution of **2** in 5 mL of THF was added dropwise and then warmed to 0 °C once addition was complete. After 1 h at 0 °C, the solution was recooled to −78 °C. In the meantime, (*S*)-4-benzyl-2-oxazolidinone (4.50 g, 25.4 mmol, 1.1 equiv) and triphenylmethane (6 mg) were added to a flame-dried 100-mL flask, placed under argon, dissolved in 50 mL of distilled THF, and cooled to −40 °C. *n*-Butyllithium (15.9 mL of 1.6 M solution in hexanes, 25.4 mmol, 1.1 equiv) was added dropwise, producing a bright orange color upon completion of the addition. This solution was cooled to −78 °C and added via cannula to the solution of the mixed anhydride that was formed in situ. The flask in which the lithiated oxazolidinone was generated was rinsed with 5 mL of THF and added via cannula to the mixed anhydride solution. The reaction was stirred at −78 °C for 30 min and then warmed to room temperature for 3 h, at which point it was diluted with 150 mL of CH_2Cl_2 and washed with 100 mL of pH 7-phosphate buffer. The aqueous layer was extracted with CH_2Cl_2 three times. The CH_2Cl_2 layers were combined, dried over $MgSO_4$, concentrated, and purified over silica gel (15% EtOAc in hexanes to 25% EtOAc in hexanes), which yielded 6.68 g (70% yield) of **3** as a white solid, which is a mixture of diastereomers: ^1H NMR (500 MHz, $CDCl_3$) δ 7.57−7.54 (m, 4H), 7.38−7.34 (m, 4H), 7.32−7.20 (m, 12H), 4.69−4.64 (m, 1H), 4.61−4.56 (m, 1H), 4.21−4.14 (m, 4H), 3.31−3.26 (m, 2H), 3.23−3.14 (m, 2H), 3.11−3.05 (m, 3H), 3.00−2.91 (m, 3H), 2.75−2.71 (m, 2H), 2.50−2.42 (m, 2H), 1.17 (d, J = 5.5−6.5 Hz, 3H), 1.16 (d, J = 5.5−6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.94, 171.90, 153.34, 153.29, 135.23, 132.72, 132.56, 129.37, 129.04, 128.94, 127.40, 127.32, 126.77, 126.72, 66.16, 66.09, 55.12, 55.08, 41.84, 41.56, 37.90, 35.47, 35.41, 30.35, 30.11, 20.30; IR (neat) 2961, 1780, 1698; HRMS calcd for $C_{21}H_{23}NO_3Se$ (M + Na) 440.0741, found (FAB, M + Na) 440.0756. Anal. Calcd for $C_{21}H_{23}NO_3Se$: C, 60.57; H, 5.57; N, 3.36. Found: C, 60.87; H, 5.82; N, 3.34.

2-(*S*)-3-(*R*,*S*)-4(*S*)-3-[2-Azido-3-methyl-4-(phenylseleno)-butanoyl]-4-benzyl-1,3-oxazolidin-2-one (4). A solution of KHMDS (34.2 mL of a 0.48 M solution in toluene, 16.4 mmol, 1.1 equiv) was added to a flame-dried 500-mL flask containing 50 mL of THF under argon and cooled to −78 °C. A solution of **3** (6.20 g, 14.9 mmol, 1.0 equiv) in 35 mL of THF cooled to −78 °C was added to the KHMDS solution via cannula, and the reaction was stirred at −78 °C for 40 min. A solution of trisyl azide (5.55 g, 17.9 mmol, 1.2 equiv) in 50 mL of THF that was precooled to −78 °C was added via cannula. This addition process took approximately 3 min. The reaction was allowed to stir for an additional 1 min, and then acetic acid (3.80 mL, 67.1 mmol, 4.5 equiv) was added via syringe. The reaction was allowed to warm slowly from −78 °C, and once it had reached −30 °C, potassium acetate (4.40 g, 44.7 mmol, 3 equiv) was added and the reaction was allowed to slowly warm to room temperature overnight. The reaction solution was filtered over Celite, rinsed with Et_2O, and washed with 0.1 N aqueous HCl. The layers were separated, and the aqueous layer was extracted with Et_2O three times. The organic layers were combined, dried over $MgSO_4$, concentrated, and purified over silica gel (4:1 hexanes/CH_2Cl_2 with 4% Et_2O to 4:1 hexanes/CH_2Cl_2 with 10% Et_2O) to yield 5.46 g of the desired product **4** as a yellow oil (80%), which is a mixture of diastereomers: ^1H NMR (500 MHz, $CDCl_3$) δ 7.53−7.49 (m, 4H), 7.37−7.19 (m, 16H), 5.28 (d, J = 6.0 Hz, 1H), 5.16 (d, J = 6.5 Hz, 1H), 4.59−4.53 (m, 2H), 4.21−4.08 (m, 4H), 3.32−3.27 (m, 2H), 3.22−3.19 (m, 1H), 3.13−3.09

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(m, 1H), 2.97−2.93 (m, 1H), 2.86−2.81 (m, 2H), 2.78−2.73 (m, 1H) 2.43−2.37 (m, 1H), 2.33−2.27 (m, 1H), 1.18 (d, J = 6.5 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.49, 169.20, 152.78, 152.57, 134.65, 133.12, 132.56, 130.09, 129.40, 129.38, 129.13, 129.10, 129.04, 127.55, 127.52, 127.21, 126.92, 66.55, 66.49, 64.75, 64.58, 55.53, 55.50, 37.54, 37.48, 36.84, 35.91, 32.36, 30.69, 17.38, 15.44; IR (neat) 2973, 2107, 1781, 1700; HRMS calcd for $C_{21}H_{22}N_4O_3Se$ (M + Na) 481.0755, found (FAB, M + Na) 481.0765. Anal. Calcd for $C_{21}H_{22}N_4O_3Se$: C, 55.15, H, 4.85, N, 12.25. Found: C, 55.26; H, 4.76; N, 12.26.

2-(*S*)-3-(*R*,*S*)-2-Azido-3-methyl-4-(phenylseleno)butanoic Acid (5). To a solution of **4** (2.68 g, 5.86 mmol, 1.0 equiv) in 44 mL of THF at 0 °C was added a 1.0 M solution of LiOH (14.7 mL, 14.7 mmol, 2.5 equiv) in H_2O precooled to 0 °C. The reaction was stirred for 30 min at 0 °C and then diluted with 75 mL of CH_2Cl_2 and washed with 100 mL of brine. The aqueous layer was extracted with CH_2Cl_2 three times. The pH of the aqueous layer was adjusted from pH 14 to pH 2 using a pH 2.4 aqueous phosphate buffer and 1 N HCl, which caused a white precipitate to form. The aqueous layer was again extracted with CH_2Cl_2 four times and temporarily set aside. The initial three CH_2Cl_2 extracts were combined and washed with 1:1 0.1 N NaOH/brine twice. At this point, the CH_2Cl_2 layer was dried over $MgSO_4$, concentrated, and purified over silica gel (40% EtOAc in hexanes) to yield 905 mg (87% recovery) of (*S*)-4-benzyl-2-oxazolidinone. The NaOH/brine washings were acidified to pH 2, extracted with CH_2Cl_2 three times, combined with the above four CH_2Cl_2 extracts, dried over $MgSO_4$, concentrated, and purified over silica gel (2% MeOH in CH_2Cl_2 to 8%MeOH in CH_2Cl_2) to provide 1.57 g of the desired product **4** as a yellow oil (90%), which is a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.43 (m, 4H), 7.30−7.25 (m, 6H), 4.63 (d, J = 3.2 Hz, 1H), 4.10 (d, J = 5.6 Hz, 1H), 3.12−3.08 (m, 1H), 2.95−2.81 (m, 3H), 2.32−2.28 (m, 2H), 1.15 (d, J = 6.8 Hz, 3H) 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.69, 174.66, 133.15, 132.89, 129.62, 129.28, 129.20, 129.13, 127.45, 127.26, 66.15, 64.50, 36.32, 36.26, 32.02, 31.02, 16.89, 15.22; IR (neat) 2969, 2111, 1714; HRMS calcd for $C_{11}H_{13}N_3O_2Se$ (M + Na) 322.0071, found (FAB, M + Na) 322.0079.

2-(*S*)-3-(*R*,*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-methyl-4-(phenylseleno)butanoic Acid (6). Tin dichloride (1.9 g, 8.4 mmol, 2.5 equiv) was dissolved in a solution of 20 mL of dioxanes and 7 mL of H_2O in a 50-mL flask. The azide **5** (1.00 g, 3.36 mmol, 1.0 equiv) was added dropwise as a neat liquid, and the solution was stirred at 0 °C for 1 h before warming to room temperature and stirring for an additional 3.5 h. At this point, an additional 760 mg (1.0 equiv) of $SnCl_2$ was added and the reaction stirred an additional 2.5 h, at which time NaOH was added as a 2.0 M solution in H_2O (23.5 mL, 47.0 mmol, 14 equiv) followed by Boc anhydride (3.66 g, 16.8 mmol, 5 equiv) and stirred 1 h at room temperature. The solution was acidified to approximately pH 2.5 using pH −2.4 phosphate buffer and 1 N HCl and extracted with EtOAc five times. The organic layers were combined, dried over $MgSO_4$, concentrated, and purified over silica gel (1%MeOH in CH_2Cl_2, to 10%MeOH in CH_2Cl_2) to yield 1.11 g of the desired product as a yellow oil (89%), which is a mixture of diastereomers: ^{1}H NMR (400 MHz, CD_3OD) δ 7.52−7.48 (m, 4H), 7.27−7.22 (m, 6H), 4.52 (d, J = 3.6 Hz, 1H), 4.26 (d, J = 5.2 Hz, 1H), 3.09−3.05 (m, 1H), 2.96−2.91 (m, 1H), 2.82−2.76 (m, 2H), 2.30−2.20 (m, 1H), 2.20−2.10 (m, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.05 (d, J = 7.2 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.32, 174.89, 158.35, 158.08, 133.85, 133.65, 131.58, 130.18, 128.03, 127.93, 80.62, 80.58, 59.14, 57.84, 37.72, 37.41, 32.95, 32.09, 28.70, 16.86, 15.43; IR (neat) 3426, 1651; HRMS calcd for $C_{16}H_{23}NO_4Se$ (M + Na) 396.0690, found (FAB, M + Na) 396.0679.

2-(*S*)-3-(*R*,*S*)-Methyl 2-[(*tert*-Butoxycarbonyl)amino]-3-methyl-4-(phenylseleno)butanoate. A solution of **6** (1.02 g, 2.74 mmol, 1.0 equiv) in 20 mL of Et_2O was treated with CH_2N_2 generated by decomposing Diazald (1.17 g, 5.48 mmol, 2.0 equiv) in a solution of KOH (307 mg, 5.48 mmol, 2.0 equiv) in 450 mL of EtOH and 50 mL of Et_2O and bubbling the generated CH_2N_2 gas into the Et_2O solution using fire-polished glass tubing. When TLC showed complete consumption of the starting material (2 h), argon gas was bubbled through the Et_2O solution for 30 min, and then the ether was removed under reduced pressure and the resulting residue was purified over silica gel (20% Et_2O in hexanes to 30% Et_2O in hexanes), yielding 1.0 g of the desired methyl ester of **6** as a light yellow oil (95%), which is a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.48 (m, 4H), 7.29−7.25 (m, 6H), 5.10−5.05 (m, 2H), 4.69−4.67 (m, 1H), 4.44−4.41 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.01−2.96 (m,2H), 2.76−2.67 (m, 2H), 2.31−2.21 (m, 1H), 2.21−2.15 (m, 1H), 1.45 (s, 9H), 1.44 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.56, 172.15, 155.67, 155.39, 132.88, 132.75, 130.32, 130.12, 129.07, 127.06, 126.94, 80.03, 57.64, 56.59, 52.36, 52.17, 37.42, 36.93, 32.13, 31.15, 28.27, 16.60, 15.04; IR (neat) 3349, 2975, 1747, 1714; HRMS calcd for $C_{17}H_{25}NO_4Se$ (M + Na) 410.0846, found (FAB, M + Na) 410.0832. Anal. Calcd for $C_{17}H_{25}NO_4Se$: C, 52.85;, H, 6.52; N, 3.63. Found: C, 52.73; H, 6.49; N, 3.63.

2-(*S*)-Methyl 2-[(*tert*-Butoxycarbonyl)amino]-3-methyl-3-butenoate (7). To a solution of the methyl ester of **6** (30.0 mg, 0.078 mmol, 1.0 equiv) in 800 μL of distilled CCl_4 was added pyridine (13 μL, 0.16 mmol, 2.0 equiv, distilled over CaH_2) followed by *tert*-butyl hydroperoxide (47 μL of a 5 M solution in anhydrous decane, 0.23 mmol, 3.0 equiv). This solution was stirred at room temperature under an argon atmosphere for 3 h before an additional 78 μL of *tert*-butyl hydroperoxide (5 M in anhydrous decane, 0.39 mmol, 5.0 equiv) was added, and the reaction was allowed to stir for an additional 10 h at room temperature under argon. At this point, 1.6 mL of distilled CCl_4 was added followed by diethylamine (32 μL, 0.31 mmol, 4.0 equiv, distilled over CaH_2), and the solution was heated to 50 °C for 4 h. The reaction solution was cooled, solid sodium sulfite (98 mg, 0.78 mmol, 10 equiv) was added, and the mixture was stirred vigorously for 5 min and then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The organic layers were combined, dried over Na_2SO_4, concentrated, and purified over silica gel (5% Et_2O in hexanes to 15% Et_2O in hexanes) to yield 17 mg of the desired product **7** as a clear oil (93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (m, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 4.76 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 1.77 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ? 171.35, 154.86, 140.36, 114.86, 80.02, 58.93, 52.58, 28.29, 19.35; IR (neat) 3378, 2979, 1746, 1715; HRMS calcd for $C_{11}H_{19}NO_4$ (M + Na) 252.1212, found (FAB, M + Na) 252.1219.

2-(*S*)-Methyl 2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutanoate. (8) A heterogeneous mixture of **7** (14 mg, 0.061 mmol) and 2 mg of 10% Pd/C in 1.0 mL of EtOAc was stirred under a balloon of H_2 for 3 h at room temperature. The solution was filtered over Celite to remove the catalyst, rinsed with Et_2O, and concentrated to yield 10 mg (71%) of the desired amino acid **8** as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (d, J = 8.0 Hz, 1H), 4.22 (dd, J = 9.0, 4.5 Hz, 1H), 3.73 (s, 3H), 2.12 (m, 1H), 1.44 (s, 9h), 0.95 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H); $[\alpha]^{23}_D$ −20.0° (*c* 1.0, CH_3OH) (lit.[23] $[\alpha]^{21}_D$ −21.2° (*c* 1.1, CH_3OH)).

Methyl 2-(*S*)-Azido-3-(3-[2-(*S*)-((2-(*S*)-[(*tert*-butoxycarbonyl)amino]-3-methyl-3-butenoyl)amino]-1-(*R*)-ethyl-3-(methoxymethoxy)-1-methylpropoxy]-4-[[*tert*-butyl(dimethyl)-silyl]oxy]phenyl)-3-(*S*)-[[*tert*-butyl(dimethyl)silyl]oxy]propanoate. (10) To a solution of **9** (152 mg, 0.153 mmol, 1.0 equiv) in 1.5 mL of distilled CCl_4 was added pyridine (25.0 μL, 0.306 mmol, 2.0 equiv, freshly distilled over CaH_2) followed by *tert*-butyl hydroperoxide (92 μL of a 5 M solution in anhydrous decane, 0.46 mmol, 3.0 equiv) and the mixture stirred at room temperature under an argon atmosphere. After 3 h, an additional 154 μL of *tert*-butyl hydroperoxide (5 M solution in anhydrous decane, 0.77 mmol, 5.0 equiv) was added and the mixture stirred an additional 10 h at room temperature under argon. At this time, 3.0 mL of distilled CCl_4 was added followed by diethylamine (79 μL, 0.77 mmol, 5 equiv, freshly distilled over CaH_2) and the mixutre heated to 50 °C for 10 h. The reaction solution was cooled, solid Na_2SO_4 (193 mg, 1.53 mmol, 10 equiv) was added, and the mixture was stirred vigorously for 5 min. The reaction solution was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The organic layers were combined, dried over Na_2SO_4, concentrated, and purified over silica gel (30% Et_2O in hexanes to 35% Et_2O in hexanes) to yield 106 mg of the desired product 10 as a clear oil (83%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96−6.94 (m, 2H), 6.84

(d, $J = 6.0$ Hz, 1H), 6.27 (d, $J = 9.5$ Hz, 1H), 5.80 (d, $J = 4.5$ Hz, 1H), 5.20 (s, 1H), 5.05 (s, 1H), 4.83 (d, $J = 8.0$ Hz, 1H), 4.67−4.64 (m, 1H), 4.65 (d, $J = 6.5$ Hz, 1H), 4.58 (d, $J = 6.5$ Hz, 1H), 4.45−4.39 (m, 1H), 3.97−3.94 (m, 1H), 3.94 (d, $J = 7.5$ Hz, 1H), 3.77 (s, 3H), 3.77−3.74 (m, 1H),3.35 (s, 3H), 1.87−1.81 (m, 1H), 1.71 (s, 3H), 1.69−1.63 (m, 1H), 1.44 (s, 9H), 1.24 (s, 3H), 0.96 (s, 9H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.83 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.02 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.75, 155.83, 150.53, 145.71, 143.39, 133.54, 125.16, 123.46, 121.69, 116.73, 97.04, 86.41, 80.27, 75.69, 69.15, 67.49, 61.49, 56.01, 54.40, 53.16, 42.98, 31.73, 29.07, 26.70, 26.23, 21.56, 19.36, 18.65, 9.92, −3.03, −3.92, −4.69; IR (neat) 3330, 2932, 2112, 1755, 1719, 1682; HRMS calcd for $C_{40}H_{71}N_5O_{10}Si_2$ (M + Cs) 970.3794, found (FAB, M + Cs) 970.3768.

Acknowledgment. Support has been provided by the NIH (CA-77317), the Beckman Foundation, and Pharmacia & Upjohn. For predoctoral fellowships, T.F.W. acknowledges the NSF and the ACS Division of Organic Chemistry (sponsored by Hoechst Marion Roussel).

JO990916S