155.5–157 °C; NMR ($CDCl_3$) δ 1.83 (s, 3, CH_3), 2.06 (s, 3, CH_3), 2.25 (s, 3, CH_3), 2.36 (s, 3, CH_3); IR (Nujol) 3410 (m, NH), 1755 (s, C=O), 1725 (s, C=O), 1630 (s, C=O) cm^{-1}; UV max (CH_3OH) 212 nm (ε 1.48×10^4), 234 (9.31×10^3), 287 (3.29×10^4), and inflection at 312 nm (1.15×10^4); mass spectrum, *m/e* 477 (molecular ion).

Anal. Calcd for $C_{21}H_{23}N_3O_8S$: C, 52.82; H, 4.85; N, 8.8. Found: C, 52.56; H, 4.75; N, 8.2.

Hydrolysis of **12** with 10% HCl at 100 °C gave **13**.

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Registry No.—**1**, 68225-78-5; **2**, 68225-79-6; **3**, 68225-80-9; **4**, 68225-81-0; **5a**, 68225-82-1; **5b**, 68225-83-2; **7b**, 68225-84-3; **10**, 68225-85-4; **11**, 68225-86-5; **12**, 68225-87-6; **15**, 68225-88-7; ribose, 50-69-1; anthranilonitrile, 1885-29-6; 1-chloro-2,3,4-tri-*O*-acetylribopyranose, 57236-99-4; 1-chloro-2,3,5-tri-*O*-acetyl-D-ribofuranose, 40554-98-1; phenyl isocyanate, 103-71-9; methyl isothiocyanate, 556-61-6.

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Novel Synthesis of 2-Selenienylalanine

Paula M. Jacobs[1] and Michael A. Davis*

Department of Medicinal Chemistry and Pharmacology, Northeastern University College of Pharmacy and Allied Health Professions, Boston, Massachusetts 02115 and Department of Radiology, Joint Program in Nuclear Medicine, Harvard Medical School, Boston, Massachusetts 02115

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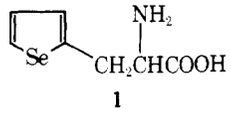
A novel synthesis of 2-selenienylalanine [2-amino-3-(selenophen-2′-yl)propanoic acid] was designed to permit the insertion of selenium late in the synthetic pathway so that a subsequent synthesis using selenium-75 would maximize the radiochemical yield while minimizing radiation exposure of the chemist. The coupling of *N*-acetylpropargylglycine ethyl ester with trimethylsilylacetylene in the presence of Hay's catalyst gave ethyl *N*-acetyl-2-amino-7-(trimethylsilyl)-4,6-heptadiynoate in 57% yield. This product was reacted with sodium hydrogen selenide which was prepared from selenium metal and sodium borohydride, and 2-selenienylalanine was generated in 33% yield.

As part of a current project investigating new radiopharmaceuticals for organ imaging, we desired to prepare 2-selenienylalanine [2-amino-3-(selenophen-2′-yl)propanoic acid], **1**, by a synthetic pathway which would allow insertion



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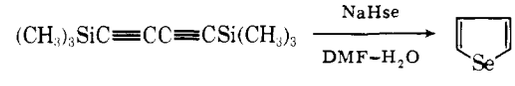
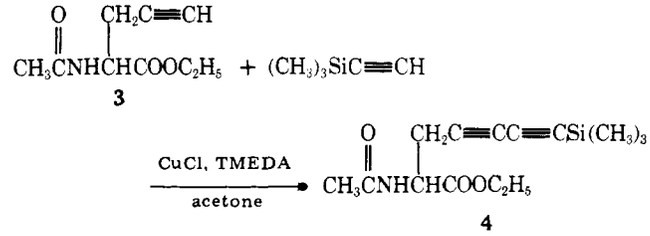
of radioactive selenium as late in the synthesis as possible. Thus, the radiochemical yield could be maximized while minimizing radiation exposure of the chemist. We expect that this compound will localize in the pancreas as do other aromatic amino acids.[2] The γ radiation of selenium-75 would then permit external visualization of the organ with a γ-scintillation camera, and a pathological lesion would be detected as a negative or "cold area" within the organ. This amino acid can be synthesized by the well-established method used to make thienylalanine,[3] beginning with selenophene, but the selenium must then be incorporated at the first step of a multistep synthesis.

Since the reaction of 1,4-bis(trimethylsilyl)butadiyne with sodium hydrogen selenide generated from selenium metal gives selenophene **2**,[4] it was felt that the analogous reaction



2

of a suitably substituted butadiyne should give a substituted selenophene. Accordingly, the diyne **4** was prepared, as shown in the following scheme, from the known *N*-acetylpropargylglycine ethyl ester, **3**.[5] The coupling of **3** with trimethylsilylacetylene in the presence of Hay's catalyst[6,7] gave **4** in 55%



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* Address correspondence to this author at Harvard Medical School.

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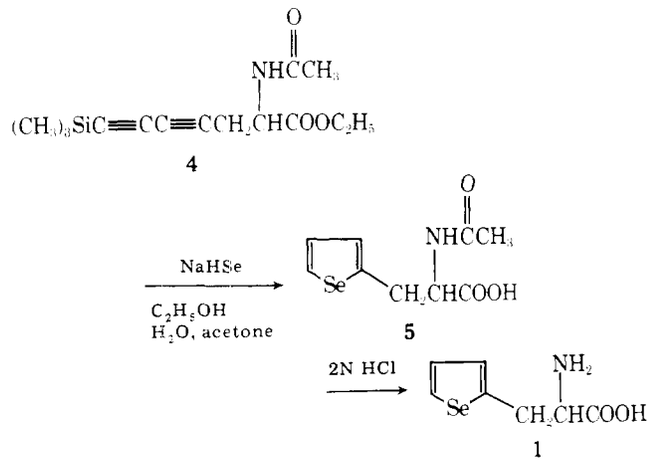
yield. Attempts to couple *N*-acetylpropargylglycine or free propargyl glycine with trimethylsilylacetylene under similar conditions led to quantitative recovery of the amino acid component.

Compound **4** is stable at room temperature for several months without decomposition, but it is probably better stored at −20 °C under nitrogen. It appears to be resistant to shock, but care should always be exercised with poly-ynes.



Treatment of **4** with an equimolar quantity of sodium hydrogen selenide generated in situ[8] gave *N*-acetyl-2-selenienylalanine (**5**) (the ester was hydrolyzed in the basic reaction mixture), which was hydrolyzed with aqueous hydrochloric acid to the free amino acid, **1**. Because propargylglycine has been resolved,[5] this pathway can also be used to prepare D- and L-2-selenienylalanine.

The synthesis of [^{75}Se]-2-selenienylalanine and its biological distribution will be reported elsewhere.

Experimental Section

CAUTIONS: All poly-ynes are potentially explosive. Selenium compounds are highly toxic.

Ethyl *N*-Acetyl-2-amino-7-(trimethylsilyl)-4,6-heptadiynoate (*N*-Acetyl-DL-(trimethylsilyl)butadiynylalanine Ethyl Ester) (4). (Trimethylsilyl)acetylene (1.54 g, 15.6 mmol) and DL-*N*-acetylpropargylglycine (**3**)[5] (1.0 g, 5.46 mmol) were mixed together in 25 mL of acetone in a flask equipped with an efficient condenser and a capillary air inlet. To this solution was added 5 mL of Hay's catalyst[6,7] (CuCl and tetramethylethylenediamine in acetone) prepared by the process of Eastmond et al.[7] The green solution was stirred vigorously overnight while a thin stream of air was passed into it. The reaction mixture was poured onto ice and 2 N sulfuric acid and extracted twice with ethyl acetate. The ethyl acetate was washed with water, dried over potassium carbonate, and evaporated to give 2.85 g of crude product mixture. This mixture was dissolved in a minimum amount of chloroform and chromatographed on silica gel 60 (E. Merck column, size B prepacked). The column was eluted first with hexane then with hexane–ethyl acetate (1:1, v/v), followed by hexane–ethyl acetate (1:3, v/v). The byproduct bis(trimethylsilyl)butadiyne was obtained first, 1 g (5.0 mmol), mp 108–109 °C (lit.[9] mp 106 °C), followed by the protected amino acid, 0.85 g (57%), as a light oil. It was crystallized from ether–hexane in a freezer: mp 47–49 °C; NMR ($CDCl_3$) δ 6.5 (d, 1 H, NH), 4.7 (m, 1 H, α-H), 4.25 (quartet, 2 H, J = 7, CH_2CH_3), 2.85 (d, 2 H, J = 5, β-CH_2), 2.1 (s, 3 H, CH_3C=O), 1.3 (t, 3 H, J = 7, CH_2CH_3); IR ($CDCl_3$) 3400, 2950, 2250 (d), 2120, 1740, 1670, 1500, 1380, 1340 cm^{-1}; MS *m/e* 279.1 (M), 280.1 (M + 1, 21.6% of M, Calcd 21.1), 264 ($M^+ - CH_3$), 220 ($M^+ - CH_3CONH_2$), 206 ($M^+ - CO_2C_2H_5$ and $M^+ - Me_4Si$).

Anal. Calcd for $C_{14}H_{21}NO_3Si$: C, 60.16; H, 7.58; N, 5.01. Found: C, 59.81; H, 7.46; N, 4.80.

2-Selenienylalanine (1). A sodium hydrogen selenide solution was prepared under nitrogen from 40 mg of selenium metal (0.5 mmol) and 40 mg of sodium borohydride (1.1 mmol) by the addition of 1 mL of 95% ethanol.[8] After the solution had cleared, 0.2 mL of acetone was added. This solution was transferred by syringe to a stoppered vial containing 73 mg of the ester **4** (0.26 mmol) and the mixture was allowed to stir overnight at room temperature under nitrogen. The reaction was exposed to air for 20 min while the stirring continued. Ethyl acetate and water were added, the mixture was filtered, and the ethyl acetate layer was discarded. The aqueous layer was acidified and extracted with ethyl acetate. The ethyl acetate layer was dried under vacuum to give 60 mg of a clear oil, *N*-acetyl-2-selenienylalanine (**5**): NMR ($CDCl_3$) δ 8.3 (s, 1 H, exchangeable), 7.8 (dd, 1 H, α-aromatic H), 7.0 (m, 2 H, β-aromatic H), 6.2 (broad s, 1 H, NH), 4.1 (m, 1 H, CH), 3.6 (d, 2 H, -CH_2-), 2.1 (s, 3 H, CH_3CO). The crude oil was hydrolyzed with 3 mL of 2 N hydrochloric acid at reflux for 2 h and then extracted with ethyl acetate and the aqueous layer was evaporated to dryness. It was dissolved in a minimum amount of water and purified by preparative thin-layer chromatography on 1000 μm Avicel plates in *n*-butyl alcohol–acetic acid–water (35:10:15, v/v/v) to give 19 mg (35%) of white solid. Larger amounts were purified on 2-mm thick silica gel plates (E. Merck) using the same solvent system. The ninhydrin color is blue-grey when allowed to develop in the cold: NMR (CF_3CO_2H) δ 8.04 (t, 1 H, 4 Hz), 7.3 (broad s, 3 H, NH_3^+), 7.2 (d, 2 H, 4 Hz), 4.63 (m, 1 H, α-H), 3.8 (d, 2 H, β-CH_2). Silica gel TLC showed only one compound in either of two solvent systems, chloroform–methanol–ammonia, 55:40:10, v/v/v (R_f 0.71), or *n*-butyl alcohol–acetic acid–water, 35:10:15, v/v/v (R_f 0.43).

Anal. Calcd for $C_6H_9NO_2Se$: C, 38.55; H, 4.16; N, 6.42. Found: C, 38.23; H, 4.32; N, 6.40.

The same amino acid was synthesized from 2-chloromethylselenophene[10] by reaction with sodium diethylacetamidomalonate, followed by hydrolysis with 2 N sodium hydroxide and with 6 N hydrochloric acid.[3] This product was identical to that obtained above in four chromatography systems.

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Registry No.—**1**, 68258-21-9; **3**, 23235-05-4; **4**, 68307-54-0; **5**, 68258-22-0; trimethylsilylacetylene, 1066-54-2; sodium hydrogen selenide, 12195-50-5.

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