

Synthesis and Properties of ω -Aminooxyalkyliminodiacetic Acids, Bifunctional Chelating Agents for Carbonyl Labeling

Reiko YODA* and Yoshikazu MATSUSHIMA

Kyoritsu College of Pharmacy, Shibakoen 1-5-30, Minato-ku, Tokyo 105, Japan.

Received April 12, 1994; accepted May 19, 1994

3-Aminooxypropyliminodiacetic acid, 4-aminooxybutyliminodiacetic acid and 5-aminooxypentyliminodiacetic acid and their oxime derivatives with several carbonyl compounds were synthesized and characterized. The ω -aminooxyalkyliminodiacetic acids act as bifunctional chelating agents for metal-labeling of a carbonyl group.

Keywords ω -aminooxypropyliminodiacetic acid; bifunctional chelating agent; carbonyl labeling

In the previous paper,¹⁾ we reported the synthesis, properties and oxime formation of 2-aminooxyethyliminodiacetic acid (**1a**). Iminodiacetic acid and hydroxylamino groups are linked by an ethyl group in the molecule and the compound acts as a bifunctional chelating agent¹⁻⁵⁾ (BCA) for metal-labeling of a carbonyl group. As BCA's with a longer linking moiety would be advantageous for preparation of immunomaterials and radiopharmaceuticals, we undertook the synthesis of analogous compounds with an elongated methylene chain, *i.e.*, ω -aminooxyalkyliminodiacetic acids.

3-Aminooxypropyliminodiacetic acid (**1b**), 4-aminooxybutyliminodiacetic acid (**1c**) and 5-aminooxypentyliminodiacetic acid (**1d**) were synthesized. Their oxime derivatives with several carbonyl compounds were also prepared. The oxime derivatives were more readily formed using the propyl (**1b**) and butyl (**1c**) compounds than the ethyl analog (**1a**). Biodistribution of radioactive metal chelates of the oximes is under investigation. The radioactive chelates may also be useful in radioimmunoassay. The manganese(II) chelates of the oxime of a steroid were studied as described below. The Mn(II) chelates may be applicable as imaging agents in magnetic resonance imaging (MRI)-related techniques.⁶⁾

Results and Discussion

Three methods were reported for the synthesis of 2-aminooxyethyliminodiacetic acid (**1a**).¹⁾ Two of the methods used Mannich's reaction of 2-bromoethylamine with formaldehyde and sodium cyanide. However, analogous Mannich's reaction of ω -bromoalkylamines gave the desired products only in low yields, probably due to

side reactions forming cyclic products.

3-Aminooxypropyliminodiacetic acid (**1b**), 4-aminooxybutyliminodiacetic acid (**1c**) and 5-aminooxypentyliminodiacetic acid (**1d**) were successfully synthesized by the route outlined in Chart 1. The method corresponds to method C of the previous paper.¹⁾ The physical and analytical data for **1b—d** and for the compounds in the synthetic route (**2b—d**, **3b—d**), which have not been described so far, are given in the experimental section. The hydrolysis of **3b—d** to give **1b—d** was performed in aqueous KOH and HCl.⁷⁾

Compounds analogous to **1a—d** with $n=6, 8$ and 10 were not obtained by the method in amounts sufficient to allow full characterization. Attempts to hydrolyze analogs of **3** to give the desired products were unsuccessful.

Compounds **1a—d** formed oxime derivatives with various carbonyl compounds. Oximes of benzaldehyde, vanillin, pyridoxal, progesterone and testosterone with **1a** were described in the previous paper.¹⁾ Those with **1b—d** were prepared analogously. 3-Monooximes (**4a—d**) of 17- α -hydroxyprogesterone were prepared from 1:1 reaction mixtures with **1a—d** and 3,20-dioximes (**5a—d**) from reaction mixtures containing excess amounts of **1a—d**. Physical and analytical data of the oximes of 17- α -hydroxyprogesterone characterized are described in the experimental section. The monooxime and dioxime with **1d** (**4d**, **5d**) were mixed with MnCl₂ in methanol and refluxed and the products were separated. FAB-MS spectra showed the formation of Mn(II) chelates Mn-**4d** and Mn-**5d** as peaks at m/z 600 ($M^+ + 1$) and 869 ($M^+ + 1$), respectively.

Experimental

General Procedures UV spectra were recorded on a Shimadzu UV-240 UV-visible recording spectrophotometer and IR spectra (KBr disks) on a JASCO FT/IR-5300. ¹H- and ¹³C-NMR spectra were taken on a JEOL JNM-GX270 spectrometer. Chemical shifts are expressed in ppm on the δ -scale from tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)-2,2,3,3-tetradeuteriopropionate (TSP-*d*₄) as an internal standard. TMS was used in DMSO-*d*₆ or CDCl₃, and TSP-*d*₄ in D₂O solutions. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. The coupling constants are expressed in hertz (Hz). Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. For TLC, precoated Silica gel 5724 plates (Merck) were used. Elemental analyses and MS and FAB-MS measurements were performed by the Faculty of Pharmaceutical Sciences, Showa University. Chemicals were obtained from commercial sources and were of reagent grade.

N-(3-Bromopropoxy)phthalimide (2b**)** 1,3-Dibromopropane (155 g, 0.768 mol) dissolved in 250 ml of dimethylformamide (DMF) and 50 g

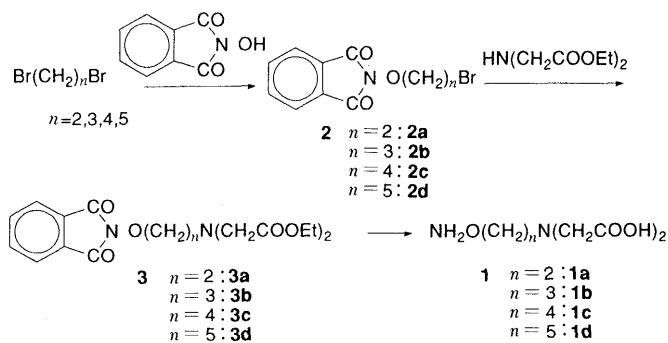


Chart 1. Synthesis of ω -Aminooxyalkyliminodiacetic Acids (**1**)

(0.307 mol) of *N*-hydroxyphthalimide were mixed vigorously and 43.5 g (0.43 mol) of triethylamine was added dropwise thereto. The mixture was stirred at room temperature for 30 min, heated gradually at 65 °C for 30 min, 70 °C for 1 h and 75 °C for 30 min, then cooled and filtered. The filtrate was evaporated *in vacuo* and 250 ml of water was added to the residue. The white precipitate was collected, washed with water and dissolved in CHCl_3 (250 ml). The CHCl_3 solution was washed twice with 65 ml of 1% NaOH and with 125 ml of water and dried over anhydrous Na_2SO_4 , and the solvent was evaporated *in vacuo*. The product was purified by silica gel chromatography with EtOAc:benzene = 1:4 and by recrystallization from 70% ethanol. Colorless needles. Yield, 57.29 g (65.7%). Compounds **2c** and **2d** were prepared analogously as colorless needles from 50 g of *N*-hydroxyphthalimide and an excess of 1,4-dibromobutane or 1,5-dibromopentane, in yields of 54.62 g (59.8%) and 48.87 g (51.1%), respectively.

2b: mp 77.1 °C (from 70% EtOH). IR (KBr): 1786, 1728 cm^{-1} (CO). UV $\lambda_{\text{max}}^{2\text{-ProH}}$ nm ($\epsilon/10^3$): 219 (34.0), 240 sh (8.8), 295 (1.4). MS m/z : 285, 283, (M^+), 204, 174, 164. Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{BrNO}_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.24; H, 3.51; N, 4.94. $^1\text{H-NMR}$ (in CDCl_3 , TMS) δ ppm: 2.31 (2H, m, CH_2), 3.71 (2H, t, $J=6.6$ Hz, CH_2Br), 4.37 (2H, t, $J=5.8$ Hz, OCH_2), 7.87–7.75 (4H, m, C_6H_4). $^{13}\text{C-NMR}$ (in CDCl_3 , TMS) δ ppm: 29.25 t (CH_2), 31.51 t (CH_2Br), 76.11 t (OCH_2), 123.63 d, 128.89 s, 134.61 d (C_6H_4), 163.58 s (CO–N–CO).

2c: mp 67.4 °C (from 70% EtOH). IR (KBr): 1786, 1728 cm^{-1} (CO). UV $\lambda_{\text{max}}^{2\text{-ProH}}$ nm ($\epsilon/10^3$): 220 (32.9), 240 sh (9.6), 295 (1.9). FAB-MS m/z : 300, 298 (M^+), 218. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{BrNO}_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.18; H, 4.04; N, 4.69. $^1\text{H-NMR}$ (in CDCl_3 , TMS) δ ppm: 1.95 (2H, m, CH_2), 2.17 (2H, m, CH_2), 3.55 (2H, t, $J=6.4$ Hz, CH_2Br), 4.25 (2H, t, $J=6.1$ Hz, OCH_2), 7.86–7.74 (4H, m, C_6H_4). $^{13}\text{C-NMR}$ (in CDCl_3 , TMS) δ ppm: 26.79 t (CH_2), 28.84 t (CH_2), 33.27 t (CH_2Br), 77.33 t (OCH_2), 123.54 d, 128.97 s, 134.53 d (C_6H_4), 163.61 s (CO–N–CO).

2d: mp 69.3 °C (from petroleum ether). IR (KBr): 1781, 1730 cm^{-1} (CO). UV $\lambda_{\text{max}}^{2\text{-ProH}}$ nm ($\epsilon/10^3$): 221 (31.3), 242 sh (7.5), 297 (1.3). MS m/z : 314, 312 (M^+), 232. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{BrNO}_3$: C, 50.02; H, 4.52; N, 4.49. Found: C, 50.24; H, 4.69; N, 4.43. $^1\text{H-NMR}$ (in CDCl_3 , TMS) δ ppm: 2.01–1.60 (6H, m, $\text{CH}_2 \times 3$), 3.45 (2H, t, $J=6.6$ Hz, CH_2Br), 4.22 (2H, t, $J=6.3$ Hz, OCH_2), 7.86–7.74 (4H, m, C_6H_4). $^{13}\text{C-NMR}$ (in CDCl_3 , TMS) δ ppm: 24.34 t (CH_2), 27.33 t (CH_2), 32.35 t (CH_2), 33.46 t (CH_2Br), 78.08 t (OCH_2), 123.49 d, 128.91 s, 134.50 d (C_6H_4), 163.61 s (CO–N–CO).

Diethyl 3-*N*-Phthalimidoxypopyliminodiacetate (3b) A 70-ml volume of absolute xylene solution of **2b** (15 g, 0.053 mol) and diethyl iminodiacetate (22.06 g, 0.117 mol) was refluxed for 15 h. After removal of the resulting red gum by decantation, the xylene layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by silica gel chromatography and LH-20 pharmacaria chromatography with EtOAc:benzene = 1:4. Pale yellow oil. Yield, 15.35 g (73.8%). Compounds **3c** and **3d** were prepared analogously from **2c** (15 g) and **2d** (15 g), in yields of 11.39 g (55.7%) and 13.84 g (68.5%), respectively.

3b: Oil, UV $\lambda_{\text{max}}^{2\text{-ProH}}$ nm ($\epsilon/10^3$): 220 (10.9), 243 sh (2.7), 295 (0.5). MS m/z : 392 (M^+), 346 ($\text{M}^+ - \text{EtOH}$), 320 ($\text{M}^+ - \text{CH}_2\text{CH}_2\text{COO}$), 319.202 ($\text{CH}_2\text{N}(\text{CH}_2\text{COOEt})_2^+$). $^1\text{H-NMR}$ (in CDCl_3 , TMS) δ ppm: 1.27 (6H, t, $J=7.1$ Hz, CH_2CH_3), 1.99 (2H, m, CH_2), 3.01 (2H, t, $J=6.9$ Hz, CH_2N), 3.59 (4H, s, CH_2), 4.16 (m, 4H, CH_2CH_3), 4.33 (2H, t, $J=6.4$ Hz, OCH_2), 7.85–7.74 (4H, m, C_6H_4). $^{13}\text{C-NMR}$ (in CDCl_3 , TMS) δ ppm: 14.25 q (CH_2CH_3), 27.06 t (CH_2), 50.83 t (CH_2N), 55.26 t (NCH_2COO), 60.46 t ($\text{COOCH}_2\text{CH}_3$), 76.38 t (OCH_2), 123.46 d, 129.02 s, 134.45 d (C_6H_4), 163.61 s (CO), 171.38 s ($\text{COOCH}_2\text{CH}_3$).

3c: Oil, UV $\lambda_{\text{max}}^{2\text{-ProH}}$ nm ($\epsilon/10^3$): 226 (11.7), 240 sh (6.7), 295 (1.2). FAB-MS m/z : 407 ($\text{M}^+ + 1$), 333 ($\text{M}^+ - \text{EtCOO}$), 202 ($\text{CH}_2\text{N}(\text{CH}_2\text{COOEt})_2^+$). $^1\text{H-NMR}$ (in CDCl_3 , TMS) δ ppm: 1.32–1.25 (6H, m, CH_2CH_3), 1.75 (2H, m, CH_2), 1.84 (2H, m, CH_2), 2.81 (2H, CH_2N), 3.58–3.55 (4H, m, CH_2COO), 4.26–4.14 (m, 6H, OCH_2 , CH_2CH_3), 7.85–7.75 (4H, m, C_6H_4). $^{13}\text{C-NMR}$ (in CDCl_3 , TMS) δ ppm: 14.27 q (CH_2CH_3), 23.93 t (CH_2), 25.77 t (CH_2), 53.75 t (CH_2N), 55.04 t (NCH_2COO), 60.44 t ($\text{COOCH}_2\text{CH}_3$), 78.22 t (OCH_2), 123.46 d, 129.02 s, 134.47 d (C_6H_4), 163.61 s (CO–N–CO), 171.30 s ($\text{COOCH}_2\text{CH}_3$).

3d: Oil, UV $\lambda_{\text{max}}^{2\text{-ProH}}$ nm ($\epsilon/10^3$): 221 (17.0), 242 sh (4.6), 298 (0.6). MS m/z : 420 (M^+), 374 ($\text{M}^+ - \text{EtOH}$), 348 ($\text{M}^+ - \text{CH}_2\text{CH}_2\text{COO}$), 347 ($\text{M}^+ - \text{EtCOO}$). $^1\text{H-NMR}$ (in CDCl_3 , TMS) δ ppm: 1.27 (6H, t, CH_2CH_3), 1.56 (4H, $\text{CH}_2 \times 2$), 1.81 (2H, CH_2), 2.75 (2H, CH_2N), 3.55 (4H, s, CH_2COO), 4.23–4.13 (m, 6H, OCH_2 , CH_2CH_3), 7.86–7.74

(4H, m, C_6H_4). $^{13}\text{C-NMR}$ (in CDCl_3 , TMS) δ ppm: 14.27 q (CH_2CH_3), 23.18 t (CH_2), 27.57 t (CH_2), 28.01 t (CH_2), 54.15 t (CH_2N), 55.12 t (NCH_2COO), 60.41 t ($\text{COOCH}_2\text{CH}_3$), 78.38 t (OCH_2), 123.46 d, 129.05 s, 134.42 d (C_6H_4), 163.61 s (CO–N–CO), 171.30 s ($\text{COOCH}_2\text{CH}_3$).

3-Aminooxypropyliminodiacetic Acid (1b) **3b** (2 g) was dissolved in 10 ml of 6M KOH and the solution was refluxed for 1 h. After cooling, the mixture was adjusted to pH 1.8 by addition of 60% HClO_4 , and a white precipitate was collected. To the precipitate, 30 ml of water and 5 ml of concentrated HCl were added and the suspension was heated at 130 °C for 50 min. After further addition of 10 ml of concentrated HCl, heating was continued for 0.5 h. The mixture was cooled in a refrigerator overnight and filtered, and the filtrate was evaporated to dryness. The residue was dissolved in a small amount of cold water and insoluble materials were removed by filtration. The solution was adjusted to pH 4.0 by addition of 33% NaOH and evaporated *in vacuo*. The crude product was purified by chromatography on a column of Dowex 50W $\times$ 8 cation exchange resin (H form, 100–200 mesh). After eluting with water, 0.5N and 1N HCl, the HCl salt of **1b** was obtained from the 3N HCl eluate as white hygroscopic crystals.

1b: HCl FAB-MS (m/z , $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_5$ requires 206.20): 207 ($\text{M}^+ + 1$), 131, 115, 93. $^1\text{H-NMR}$ (in D_2O , TSP- d_4) δ ppm: 2.24 (2H, m, CH_2), 3.57 (2H, t, CH_2N), 4.23 (2H, t, OCH_2), 4.31 (4H, s, CH_2COO). $^{13}\text{C-NMR}$ (in D_2O , TSP- d_4) δ ppm: 24.96 t (CH_2), 56.28 t (CH_2N), 57.39 t (CH_2 , COOH), 74.49 t (OCH_2), 170.52 s (CH_2COOH).

1c: HCl FAB-MS (m/z , $\text{C}_8\text{H}_{16}\text{N}_2\text{O}_5$ requires 220.23): 221 ($\text{M}^+ + 1$), 154, 136. $^1\text{H-NMR}$ (in D_2O , TSP- d_4) δ ppm: 1.88–1.78 (4H, m, $\text{CH}_2 \times 2$), 3.46 (2H, t, CH_2N), 4.16 (2H, t, OCH_2), 4.31 (4H, s, CH_2COO). $^{13}\text{C-NMR}$ (in D_2O , TSP- d_4) δ ppm: 22.69 t (CH_2), 26.63 t (CH_2), 57.55 t (CH_2COOH), 59.17 t (CH_2N), 77.27 t (OCH_2), 170.68 s (CH_2COOH).

1d: FAB-MS (m/z , $\text{C}_9\text{H}_{18}\text{N}_2\text{O}_5$ requires 234.25): 236 ($\text{M}^+ + 2\text{H}$), 160, 147, 116. $^1\text{H-NMR}$ (in D_2O , TSP- d_4) δ ppm: 1.9–1.4 (6H, m, $\text{CH}_2 \times 3$), 3.3 (2H, m, CH_2N), 3.8 (4H, s, CH_2COO), 4.0 (2H, t, OCH_2). $^{13}\text{C-NMR}$ (in D_2O , TSP- d_4) δ ppm: 24.80 t, 26.33 t, 29.27 t ($\text{CH}_2 \times 3$), 58.87 t (CH_2N), 60.09 t (CH_2COOH), 78.06 t (OCH_2), 173.38 s (CH_2COOH).

Oxime of 1 A methanol solution of a carbonyl compound and one of **1a–d** was refluxed for 0.5–1 h. After cooling, the resultant precipitate was collected by filtration, washed with water and purified by crystallization from an appropriate solvent. The following oximes were prepared and characterized: 3-monooxime of 17- α -hydroxyprogesterone with **1a** (**4a**), **1b** (**4b**) and **1d** (**4d**), 3,20-dioxime of 17- α -hydroxyprogesterone with **1a** (**5a**), **1b** (**5b**), **1c** (**5c**) and **1d** (**5d**), pyridoxal-oxime of **1b** (**6b**), testosterone-oxime of **1b** (**7b**) and **1c** (**7c**), epiandrosterone-oxime of **1a** (**8a**), estrone-oxime of **1a** (**9a**).

4a: M.W., 504.62; mp 213.5 °C (from MeOH). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 250 nm ($\epsilon=20200$). FAB-MS m/z : 505 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_7 \cdot \text{H}_2\text{O}$: C, 62.05; H, 8.10; N, 5.36. Found: C, 61.88; H, 8.04; N, 5.28.

5a: M.W., 678.78; mp 203 °C (ppt. MeOH–DMSO– H_2O). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 250 nm. FAB-MS m/z : 679 ($\text{M}^+ + 1$).

4b: M.W., 518.65; mp 164 °C (from MeOH). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 248 nm ($\epsilon=19300$). FAB-MS m/z : 519 ($\text{M}^+ + 1$).

5b: M.W., 706.83; mp 180 °C (from MeOH). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 249 nm ($\epsilon=23000$). FAB-MS m/z : 707 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{35}\text{H}_{54}\text{N}_4\text{O}_{11} \cdot \text{H}_2\text{O}$: C, 58.00; H, 7.79; N, 7.73. Found: C, 58.44; H, 7.93; N, 7.74.

5c: M.W., 734.89; mp 173–176 °C (from MeOH). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 250 nm; FAB-MS m/z : 735 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{37}\text{H}_{58}\text{N}_4\text{O}_{11} \cdot \text{H}_2\text{O}$: C, 59.03; H, 8.03; N, 7.44. Found: C, 58.35; H, 7.91; N, 7.44.

4d: M.W., 546.71; mp 163–169 °C. FAB-MS m/z : 547 ($\text{M}^+ + 1$).

5d: M.W., 762.94; mp 165–170 °C (from MeOH– H_2O). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 252 nm ($\epsilon=22500$). FAB-MS m/z : 763 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{39}\text{H}_{62}\text{N}_4\text{O}_{11} \cdot \text{H}_2\text{O}$: C, 59.98; H, 8.26; N, 7.17. Found: C, 59.31; H, 8.09; N, 7.04.

6b: M.W., 355.35; mp 126–130 °C (from MeOH–ether). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 214 nm ($\epsilon=14000$), 266 (10100), 325 (4700). FAB-MS: m/z : 356 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_7 \cdot \text{H}_2\text{O}$: C, 48.25; H, 6.21; N, 11.25. Found: C, 47.26; H, 6.22; N, 10.76.

7b: M.W., 476.61; mp 155–158 °C (ppt. MeOH–ether). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 250 nm ($\epsilon=16600$). FAB-MS m/z : 477 ($\text{M}^+ + 1$).

7c: M.W., 490.64; mp 174–175 °C (from MeOH–DMSO). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 250 nm ($\epsilon=22100$). FAB-MS m/z : 491 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{27}\text{H}_{42}\text{N}_2\text{O}_6 \cdot \text{H}_2\text{O}$: C, 63.76; H, 8.72; N, 5.51. Found: C, 63.76; H, 9.01; N, 5.43.

8a: M.W., 464.60; mp 210.3 °C (from MeOH–ether). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 214 nm ($\epsilon=14100$); FAB-MS m/z : 465 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{25}\text{H}_{40}\text{N}_2\text{O}_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 64.59; H, 8.89; N,

5.94.

9a: M.W., 444.53; mp 260 °C. (from MeOH–DMSO). FAB-MS m/z : 445 ($M^+ + 1$), negative m/z : 443 ($M^+ - 1$). HR-MS m/z : 445.2354 ($M^+ + 1$, Calcd for $C_{24}H_{33}N_2O_6$: 445.2339). *Anal.* Calcd for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.53; H, 7.40; N, 6.17.

Acknowledgment This work was supported by a grant from the Science Research Promotion Fund of the Japan Private School Promotion Foundation. We thank the members of Faculty of Pharmaceutical Sciences, Showa University for elemental analyses and MS and FAB-MS measurements. We also thank Nippon Denshi Co. for FAB-MS measurement. Technical assistance by Masumi Mikkaichi, Motoko

Yoshimura, Michiko Sekiguchi and Moyuru Tanbata is gratefully acknowledged.

References and Notes

- 1) R. Yoda, Y. Matsushima, *Chem. Pharm. Bull.*, **42**, 686 (1994).
- 2) C. H. Chang, C. F. Meares, D. A. Goodwin, *Appl. Nucl. Radiochem.*, **1982**, 103.
- 3) C. F. Meares, D. A. Goodwin, *J. Protein Chem.*, **3**, 215 (1984).
- 4) K. Kina, *Bunseki*, **1991**, 704.
- 5) M. Studer, C. F. Meares, *Bioconjugate Chem.*, **3**, 420 (1992).
- 6) R. B. Lauffer, *Chem. Rev.*, **87**, 901 (1987).
- 7) T. Yokoyama, M. Kanosato, T. Kimura, T. M. Suzuki, *Chem. Lett.*, **1990**, 693.