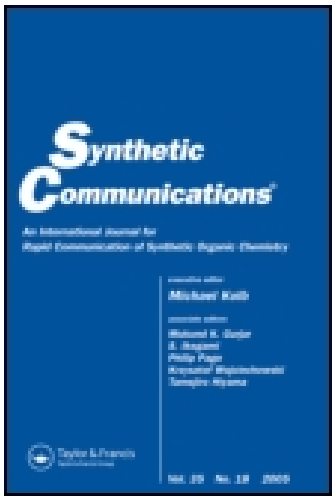

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

CONVENIENT SYNTHETIC METHODS FOR THE PREPARATION OF N-FLUOROALKYLHYDROXAMIC ACIDS

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Published online: 23 Aug 2006.

To cite this article: Nirmal Koshti, Gantla Vidyasagar Reddy, Hollie Jacobs & Aravamudan Gopalan (2002) CONVENIENT SYNTHETIC METHODS FOR THE PREPARATION OF N-FLUOROALKYLHYDROXAMIC ACIDS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:24, 3779-3790, DOI: 10.1081/SCC-120015396

To link to this article: http://dx.doi.org/10.1081/SCC-120015396

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SYNTHETIC COMMUNICATIONS
Vol. 32, No. 24, pp. 3779–3790, 2002

CONVENIENT SYNTHETIC METHODS FOR THE PREPARATION OF *N*-FLUOROALKYLHYDROXAMIC ACIDS

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ABSTRACT

Polyhydroxamate chelators containing fluoro substituents are of interest as potential extractants for actinides in separations involving supercritical carbon dioxide. In this context, we have developed three new reagents **1**, **2**, and **3**, that allow the efficient incorporation of an *N*-fluoroalkyl hydroxamate moiety onto a variety of substrates using acylation, alkylation, and Michael addition strategies.

Key Words: Hydroxamic acids; Fluorinated chelators; Supercritical carbon dioxide; Extractants

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DOI: 10.1081/SCC-120015396
0039-7911 (Print); 1532-2432 (Online)

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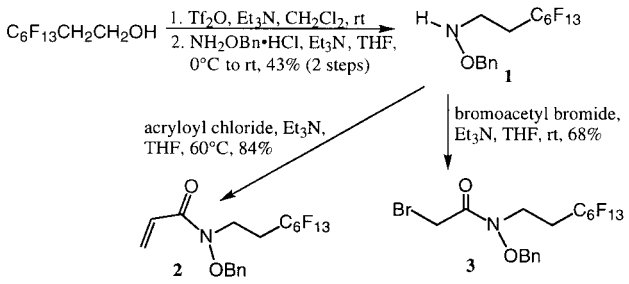
An attractive strategy in the area of remediation of toxic and radioactive metal ions involves the use of supercritical fluid extraction (SFE) for achieving selective separations.[1] Using SFE, it is possible to chelate and then extract target metal ions from solid radioactive wastes into supercritical carbon dioxide.[2] This technology avoids the use of hazardous organic solvents but a limiting factor is often the solubility of the chelator in supercritical carbon dioxide. The addition of fluorine in the chelating structure has been shown to greatly improve its solubility in supercritical carbon dioxide. Many of the chelators investigated so far have been fluorinated and unfluorinated derivatives of dithiocarbamates, β-diketones, and organophosphorous reagents. Such extractants have limited use for the extraction of hard metal ions such as Fe(III) or An(IV) ions.

Hydroxamic acids are well known to bind hard metal ions like Fe(III) or An(IV).[3] As part of our ongoing program on the synthesis of hydroxamic acids,[4] we have been interested in the synthesis of *N*-fluoroalkylhydroxamic acid ligands with the aim of developing chelating systems that have applications for the extraction of actinides into supercritical carbon dioxide. To our surprise, methodology to access *N*-fluoroalkylhydroxamates has not been documented in the literature. Some reports on the synthesis of hydroxamic acids with fluorinated acyl groups have been reported.[5–8] In this paper, we report the synthesis of three new reagents **1**, **2**, and **3** and their application to prepare a variety of *N*-fluoroalkylhydroxamic acids, a new class of extractants.

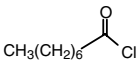
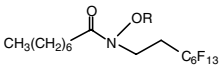
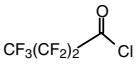
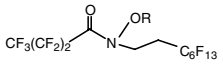
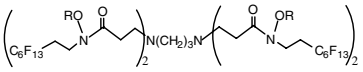
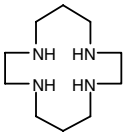
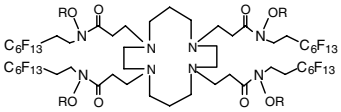
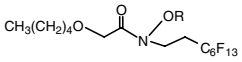
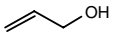
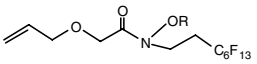
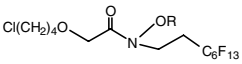
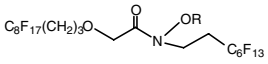
For this project, it was important to develop both electrophilic and nucleophilic reagents that allow the incorporation of *N*-fluoroalkylhydroxamic acids onto a variety of platforms (alcohols, amines and carboxylic acids). Treatment of commercially available 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanol with trifluoromethanesulfonic anhydride and triethylamine in dichloromethane afforded the corresponding triflate which was reacted with benzyloxyamine to furnish *N*-fluoroalkyl benzyloxyamine **1** in 43% overall yield after chromatographic purification (Sch. 1). Numerous attempts to react benzyloxyamine with the corresponding mesylates or iodides in the presence of various bases in different solvent systems gave only very low yields of the desired product. Treatment of amine **1** with acryloyl chloride and triethylamine in THF at 60°C gave the Michael acceptor **2** in excellent yields. The electrophilic α-bromohydroxamic acid **3**, was conveniently prepared by reaction of **1** with bromoacetyl bromide in THF in the presence of triethylamine.

We have prepared a variety of *N*-fluoroalkylhydroxamic acids by use of reagents **1–3** in good yields (Table 1). The hydroxylamine **1** was coupled with a number of acid chlorides in THF in the presence of triethylamine at room temperature to afford *O*-benzylhydroxamic acids in good yields



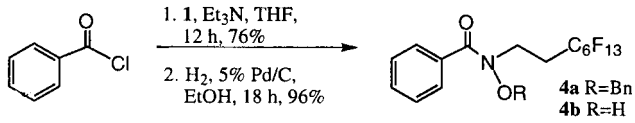
Scheme 1.

Table 1. Preparation of *N*-Fluoroalkyl Hydroxamic Acids

Starting Material	Reagent	Product	Yield (%)
	**1**		**7a** *R*=Bn, 82 **7b** *R*=H, 99
	**1**		**8a** *R*=Bn, 88 **8b** *R*=H, 99
$NH_2(CH_2)_3NH_2$	**2**		**9a** *R*=Bn, 79 **9b** *R*=H, 86
	**2**		**10a** *R*=Bn, 66 **10b** *R*=H, 85
$CH_3(CH_2)_4OH$	**3**		**11a** *R*=Bn, 87 **11b** *R*=H, 93
	**3**		**12a** *R*=Bn, 98
$Cl(CH_2)_4OH$	**3**		**13a** *R*=Bn, 44 **13b** *R*=H, 91
$C_8F_{17}(CH_2)_3OH$	**3**[a]		**14a** *R*=Bn, 53 **14b** *R*=H, 87

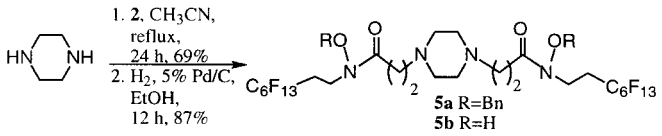
[a]rxn conditions: 2 eq. fluoroalcohol in ether.

(Eq. (1), Table 1) after chromatographic purification. Subsequent hydrogenolysis of the *O*-benzylhydroxamic acids using a catalytic amount of 5% Pd/C in ethanol gave the desired hydroxamic acids in excellent yields.



(1)

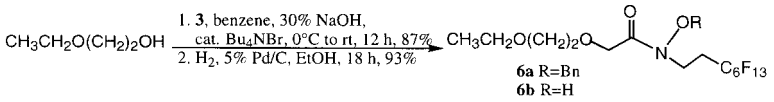
The *N*-fluoroalkylhydroxamic acid moiety can be readily introduced into a variety of commercially available amine platforms by use of reagent **2**. The reagent **2**, reacted cleanly with a number of amines (1.1 eq. of reagent **2** per amine equivalent) in refluxing acetonitrile to give the benzyl protected Michael adducts in good yields (Eq. (2), Table 1) after purification. As before, hydrogenolysis of the benzyl protected products using a catalytic amount of 5% Pd/C in ethanol gave the desired hydroxamic acids in excellent yields. Compound **5b** (Eq. (2)) is a fluorinated analog of the well known siderophore rhodotorulic acid.[9] Also, it is noteworthy that this methodology works very well for the preparation of tetra-*N*-fluoroalkylhydroxamic acids such as the cyclam derivative **10b**.



(2)

The electrophilic α-bromohydroxamic acid **3** has been reacted with a number of simple and bifunctional alcohols to give the benzyl protected hydroxamic acids in good yields after purification (Eq. (3), Table 1). Among the reaction conditions examined, biphasic conditions using sodium hydroxide and *t*-butylammonium bromide or bisulfate as the phase transfer catalyst was found best for this alkylation.[10] In the case of inexpensive alcohols, it was preferable to use a large excess of the alcohol in this alkylation to obtain a high yield of the desired product. Some hydrolysis of the reagent **3** was observed in its coupling to the less nucleophilic fluoroalcohol (preparation of **14a**). Hydrogenolysis of the benzyl protected products using a catalytic amount of 5% Pd/C in ethanol gave the desired hydroxamic acids in excellent yields. It should also be possible to react the α-bromohydroxamic acid **3** with amines, phenols, thiols and even

carbon nucleophiles to provide access to a wide range of *N*-fluoroalkylhydroxamic acids further enhancing its synthetic utility.



(3)

In summary, we have prepared three new reagents **1**, **2**, and **3** and utilized them for the synthesis of a diverse array of *N*-fluoroalkylhydroxamic acid ligands in good yields. All of the *N*-fluoroalkylhydroxamic acids prepared in this study exhibit good solubility in methanol, an important additive used in supercritical carbon dioxide extractions. Further applications of these reagents for the synthesis of other fluorinated polyhydroxamic acids including some polymers is under investigation.

EXPERIMENTAL

General

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Series 1720X Spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian XL 200 MHz operating at 200 MHz and 50 MHz, respectively, in $CDCl_3$ using TMS as an internal standard unless otherwise noted. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Column chromatography was performed on silica gel 60 (70–230 mesh) obtained from EM Science. All solvents for chromatography were HPLC grade and were obtained from either Fisher Scientific Co. or VWR Scientific Co. THF was freshly distilled from sodium/benzophenone. Reagents obtained from Aldrich Chemical Co., were used without purification unless otherwise noted.

O-Benzyl-*N*-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)-hydroxylamine (1)

Trifluoromethanesulfonic anhydride (1.01 g, 3.6 mmol) was added to a solution of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanol (1.09 g, 3.0 mmol) and triethylamine (0.36 g, 3.6 mmol) in dry dichloromethane (25 mL) at 0°C under N_2. The reaction mixture was stirred at 0°C for 2 h and then at r.t. for 12 h. The reaction mixture was again cooled to 0°C and

ice cold water (2 mL) was added slowly. The product was extracted into dichloromethane (20 mL) and then washed with 1 M HCl (10 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the triflate (1.21 g, 81%) which was used in the next step without purification. The crude triflate (1.21 g, 2.43 mmol) was added to a suspension of *O*-benzylhydroxylamine hydrochloride (0.48 g, 3.0 mmol) and triethylamine (0.61 g, 6.0 mmol) in dry THF (25 mL) under N_2. The mixture was stirred at 0°C for 2 h and then at r.t. for 12 h. The solvent was removed in vacuo and the residue was extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography to give **1** (0.49 g, 43%) as a colorless liquid. IR (neat) 3418, 2926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20–2.50 (m, 2H), 3.20 (t, 2H), 4.69 (s, 2H), 5.6 (s, 1H), 7.30–7.38 (br s, 5H); ^{13}C NMR ($CDCl_3$) δ 29.8 (t, $J_{C-F} =$ 18.0 Hz), 44.3, 76.8, 102–124 (m), 121.1, 128.0, 125.8, 137.6; Anal. calcd. for $C_{15}H_{12}F_{13}NO$: C, 38.37; H, 2.55; N, 2.98. Found: C, 38.37; H, 2.44; N, 3.00.

N-Benzyloxy-*N*-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)-acrylamide (2)

A solution of acryloyl chloride (0.348 g, 3.85 mmol) in dry THF (5 mL) was added to a solution of **1** (1.51 g, 3.21 mmol) and triethylamine (0.389 g, 3.21 mmol) in dry THF (15 mL) at 0°C under N_2. The mixture was then stirred at r.t. for 1 h and heated at 60°C for 12 h. The reaction mixture was cooled and the salt filtered off. After removal of the solvent, the residue was dissolved in dichloromethane (30 mL) and washed with saturated $NaHCO_3$ (10 mL), 1 N HCl (10 mL) and water (10 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed in vacuo. The crude product was purified by silica gel chromatography to give **2** (1.39 g, 83.5%) as a colorless liquid. IR (neat) 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30–2.58 (m, 2H), 3.93 (t, 2H), 4.87 (s, 2H), 5.77 (dd, 1H), 6.44 (dd, 1H), 6.71 (dd, 1H), 7.39 (br s, 5H); ^{13}C NMR ($CDCl_3$) δ 28.4 (t, $J_{C-F} = 20.0$ Hz), 39.2, 78.1, 102–124 (m), 123.0, 126.3, 129.4, 129.8, 130.4, 134.3, 167.8; Anal. calcd. for $C_{18}H_{14}F_{13}NO_2$: C, 41.30; H, 2.67; N, 2.67. Found: C, 41.43; H, 2.58; N, 2.69.

N-Benzyloxy-2-bromo-*N*-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)-acetamide (3)

A solution of bromoacetyl bromide (0.44 g, 2.2 mmol) in THF (5 mL) was added to a solution of **1** (0.94 g, 2.0 mmol) and triethylamine (0.22 g,

2.2 mmol) in THF (5 mL) at 0°C and then stirred at r.t. for 12 h. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (30 mL) and washed with saturated $NaHCO_3$ (10 mL), 2 N HCl (10 mL) and water (10 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude product was purified by silica gel chromatography to give **3** as a colorless liquid (0.81 g, 68%). IR (neat) 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26–2.58 (m, 2H), 3.89 (s, 2H), 3.91 (t, 2H), 4.94 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 25.8, 28.0 (t, $J_{C-F} = 22.0$ Hz), 39.3, 77.5, 102–124 (m), 129.3, 129.6, 129.9, 134.0, 169.2; Anal. calcd. for $C_{17}H_{13}BrF_{13}NO_2$: C, 34.57; H, 2.20; N, 2.37. Found: C, 34.80; H, 2.12; N, 2.35.

Representative Procedure for Coupling Reagent 1 with Acid Chlorides

Preparation of 4a: A solution of benzoyl chloride (0.10 g, 0.76 mmol) in dry THF (2 mL) was added to a solution of **1** (0.30 g, 0.63 mmol) and triethylamine (0.077 g, 0.76 mmol) in THF (2 mL) under N_2 at r.t. After stirring for 1 h at r.t., the reaction mixture was heated at 60°C for 12 h. The reaction mixture was cooled, the salt filtered off, and the solvent removed in vacuo. The remaining residue was dissolved in dichloromethane (20 mL) and washed with saturated $NaHCO_3$ solution (10 mL), 2 N HCl (10 mL) and water (10 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by silica gel chromatography to give **4a** (0.28 g, 76.4%) as a colorless liquid. IR (neat) 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35–2.65 (m, 2H), 3.92 (t, $J = 8.0$ Hz, 2H), 4.64 (s, 2H), 7.00–7.64 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 27.9 (t $J_{C-F} =$ 22.0 Hz), 39.3, 76.3, 102–124 (m), 127.5, 128.2, 128.6, 129.0, 130.4, 133.4, 169.9; Anal. calcd. for $C_{22}H_{16}F_{13}NO_2$: C, 46.07; H, 2.79; N, 2.44. Found: C, 45.99; H, 2.61; N, 2.49.

7a: Colorless oil (82%). IR (neat) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, $J = 7.0$ Hz, 3H), 1.15–1.40 (m, 8H), 1.50–1.70 (m, 2H), 2.20–2.55 (m, 4H), 3.85 (t, $J = 6.6$ Hz, 2H), 4.80 (s, 2H), 7.30–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.5, 24.2, 27.8 (t, $J_{C-F} = 21.6$ Hz), 29.0, 31.6, 32.3, 38.5, 76.9, 102–124 (m), 128.8, 129.2, 134.2, 175.9; Anal. calcd. for $C_{23}H_{26}F_{13}NO_2$: C, 46.39; H, 4.40; N, 2.35. Found: C, 46.72; H, 4.48; N, 2.42.

8a: Pale yellow oil (88%). IR (neat) 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25–2.60 (m, 2H), 3.80–4.00 (m, 2H), 4.90 (s, 2H), 7.30–7.50 (m, 5H).^{13}C NMR ($CDCl_3$) δ 24–28 (m), 38.7, 76.8, 102–126 (m), 127.0, 127.4, 127.9, 131.6, 157–159 (m); Anal. calcd. for $C_{19}H_{11}F_{20}NO_2$: C, 34.30; H, 1.67; N, 2.11. Found: C, 34.30; H, 1.56; N, 2.18.

Representative Procedure for Reaction of Reagent 2 with Amines

Preparation of 5a: A solution of **2** (0.5 g, 0.95 mmol) and piperazine (0.041 g, 0.47 mmol) in acetonitrile (5 mL) was stirred under N_2 at reflux for 24 h. The reaction mixture was cooled and the acetonitrile removed under reduced pressure. The crude product was purified by silica gel chromatography to give **5a** (0.366 g, 68.8%) as a pale yellow liquid. IR (neat) 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22–2.60 (m, 20H), 3.80 (t, $J = 7.6$ Hz, 4H), 4.78 (s, 4H), 7.31 (br s, 10H); ^{13}C NMR ($CDCl_3$) δ 28.3 (t, $J_{C-F} =$ 22.0 Hz), 30.6, 30.9, 53.3, 53.6, 77.3, 102–124 (m), 118.1, 129.2, 129.5, 134.6, 175.1; Anal. calcd. for $C_{40}H_{38}F_{26}N_4O_4$: C, 42.40; H, 3.35; N, 4.94. Found: C, 42.72; H, 3.70; N, 4.71.

9a: Pale yellow oil (79%). IR (neat) 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52–1.63 (m, 2H), 2.20–2.80 (m, 28H), 3.81 (t, $J = 8.0$ Hz, 8H), 4.82 (s, 8H), 7.36 (br s, 20H); ^{13}C NMR ($CDCl_3$) δ 25.2, 28.3 (t, $J_{C-F} = 21.0$ Hz), 30.5, 39.0, 48.9, 52.6, 77.5, 102–124 (m), 121.1, 129.2, 129.8, 134.7, 175.1; Anal. calcd. for $C_{75}H_{66}F_{52}N_6O_8$: C, 41.55; H, 3.04; N, 3.87. Found: C, 41.52; H, 3.01; N, 3.89.

10a: Pale yellow oil (66%). ^1H NMR ($CDCl_3$) δ 1.48–1.51 (m, 4H), 2.21–2.55 (m, 32H), 2.58–2.80 (m, 8H), 3.83 (t, $J = 8.0$ Hz, 8H), 4.83 (s, 8H), 7.35 (br s, 20H); ^{13}C NMR ($CDCl_3$) δ 24.2, 28.1 (t $J_{C-F} = 22.0$ Hz), 30.4, 38.8, 50.2, 51.2, 51.4, 77.2, 102–124 (m), 118.0, 129.0, 129.5, 134.4, 175.1; Anal. calcd. for $C_{82}H_{80}F_{52}N_8O_8$: C, 42.93; H, 3.49; N, 4.88. Found: C, 42.89; H, 3.38; N, 4.99.

Representative Procedure for Reaction of Reagent 3 with Alcohols

Preparation of 6a: To a solution of **2** (0.300 g, 0.50 mmol) and 2-ethoxyethanol (0.178 g, 1 mmol) in benzene (5 mL) at 10°C was added aqueous 30% NaOH solution (0.5 mL) and a catalytic amount of tetrabutylammonium bromide (0.010 g). The mixture was stirred vigorously at 10°C for 1 h and at r.t. for 12 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (5 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by silica gel chromatography (5–15% ethyl acetate/hexane) to give **6a** as a colorless oil (0.263 g, 87%). IR (neat) 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, $J = 7.0$ Hz, 3H), 2.31–2.51 (m, 2H), 3.50 (q, $J = 7.0$ Hz, 2H), 3.60–3.68 (m, 4H), 3.88 (t, $J = 7.8$ Hz, 2H), 4.25 (s, 2H), 4.83 (s, 2H), 7.33–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 27.6 (t, $J_{C-F} = 21.8$ Hz), 38.5, 66.5, 69.0, 69.8, 70.7, 76.9, 102–126 (m), 128.7, 129.3, 133.8, 172.4;

Anal. calcd. for $C_{21}H_{22}F_{13}NO_4$: C, 42.08; H, 3.70; N, 2.34. Found: C, 42.02; H, 3.70; N, 2.38.

11a: Colorless oil (89%). IR (neat) 1694 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (t, $J = 7.0$ Hz, 3H), 1.27–1.37 (m, 4H), 1.50–1.70 (m, 2H), 2.30–2.60 (m, 2H), 3.45 (t, $J = 6.6$ Hz, 2H), 3.88 (t, $J = 7.4$ Hz, 2H), 4.14 (s, 2H), 4.83 (s, 2H), 7.37–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.1, 21.7, 26.9 (t, $J_{C-F} = 21.6$ Hz), 27.3, 28.5, 39.0, 67.9, 71.2, 76.2, 102–122 (m), 128.1, 128.3, 133.2, 171.9.; Anal. calcd. for $C_{22}H_{24}F_{13}NO_3$: C, 44.23; H, 4.05; N, 2.34. Found: C, 44.49; H, 4.23; N, 2.37.

12a: Colorless oil (98%). IR (neat) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30–2.55 (m, 2H), 3.85–3.95 (m, 2H), 4.02–4.08 (m, 2H), 4.15 (s, 2H), 4.69 (s, 2H), 5.20–5.32 (m, 2H), 5.80–6.00 (m, 1H), 7.30–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.6 (t, $J_{C-F} = 21.8$ Hz), 38.5, 67.4, 72.2, 76.0, 102–124 (m), 128.7, 129.3, 133.8, 172.2; Anal. calcd. for $C_{23}H_{26}NO_2F_{13}$: C, 42.34; H, 3.20; N, 2.47. Found: C, 42.47; H, 3.32; N, 2.56.

13a: Colorless oil, (44%). IR (neat) 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75–1.92 (m, 2H), 2.27–2.58 (m, 2H), 3.46 (t, $J = 5.7$ Hz, 2H), 3.56 (t, $J = 6.3$ Hz, 2H), 3.84–3.91 (m, 2H), 4.11 (s, 2H), 4.80 (s, 2H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.8, 27.7 (t, $J_{C-F} = 21.7$ Hz), 29.1, 38.6, 44.6, 68.5, 70.7, 106–122 (m), 128.7, 129.3, 133.8, 172.3; Anal. calcd. for $C_{21}H_{21}ClF_{13}NO_3$: C, 40.83; H, 3.43; N, 2.27. Found: C, 41.14; H, 3.74; N, 2.6.

14a: Colorless oil, (53%). IR (neat) 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63–1.92 (m, 4H), 2.07–2.58 (m, 4H), 3.51 (t, $J = 7.0$ Hz, 2H), 3.90 (t, $J = 8.0$ Hz, 2H), 4.11 (s, 2H), 4.82 (s, 2H), 7.40 (m, 5H).; ^{13}C NMR ($CDCl_3$) δ 20.7, 27.8 (t, $J_{C-F} = 22.0$ Hz), 27.9 (t, $J_{C-F} = 21.7$ Hz), 38.7, 68.5, 70.1,106–122 (m), 128.8, 129.1, 129.4,133.8, 172.2.

Representative Procedure for Hydrogenolysis of *O*-Benzyl Protecting Group

Preparation of 4b: Palladium on carbon (5%, 50 mg) was added to **4a** (0.36 g, 0.62 mmol) in absolute ethanol (20 mL) and stirred under H_2 at r.t. for 18 h. The catalyst was removed by centrifugation and filtration followed by removal of the solvent in vacuo to give **4b** (0.29 g, 96%) as a white solid: m.p. 63–64°C; IR (KBr) 3176, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45–2.75 (m, 2H), 3.98 (t, 2H), 7.26–7.53 (m, 5H), 8.87–9.13 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0 (t, $J_{C-F} = 22.0$ Hz), 42.8, 102–124 (m), 127.3, 128.2, 130.8, 131.7, 173.7; Anal. calcd. for $C_{15}H_{10}F_{13}NO_2$: C, 37.26; H, 2.0; N, 2.89. Found: C, 37.23; H, 1.98; N, 2.90.

5b: Pale yellow solid (86%). M.p. 139–140°C; ^1H NMR ($CDCl_3$) δ 2.20–2.90 (m, 20H), 3.97 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 28.3

(t, $J_{C-F} = 22.0$ Hz), 32.6, 40.1, 53.1, 56.5, 102–124 (m), 171.6; Anal. calcd. for $C_{26}H_{26}F_{26}N_4O_4 \cdot H_2O$: C, 32.18; H, 2.91; N, 5.77. Found: C, 32.19; H, 2.79; N, 5.71.

6b: Colorless solid (93%). M.p. 33–34°C; ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H), 2.30–2.65 (m, 2H), 3.45–3.75 (m, 6H), 3.85–4.00 (m, 2H), 4.32 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.7, 27.8 (t, $J_{C-F} = 21.8$ Hz), 40.4, 66.7, 69.4, 69.8, 70.3, 104–124 (m), 170.9; Anal. calcd. for $C_{14}H_{16}F_{13}NO_4$: C, 33.02; H, 3.17; N, 2.75. Found: C, 32.78; H, 3.09; N, 2.79.

7b: Pale yellow solid (99%). M.p. 56–58°C; IR (KBr) 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–0.95 (m, 3H), 1.20–1.45 (m, 8H), 1.55–1.75 (m, 2H), 2.25–2.70 (m, 4H), 3.85 (t, $J = 6.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.4, 24.6, 28.0, 28.8, 29.1, 31.6 (overlapped with triplet), 40.9, 102–124 (m), 175.6; Anal. calcd. for $C_{16}H_{20}F_{13}NO_2$: C, 38.03; H, 3.99; N, 2.77. Found: C, 37.89; H, 3.90; N, 2.80.

8b: Pale yellow solid (99%). M.p. 42–44°C; IR (KBr) 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40–2.80 (br s, 2H), 4.00–4.25 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 26–30 (m), 42.8, 102–108 (m), 157–160 (m); Anal. calcd. for $C_{12}H_5F_{20}NO_2$: C, 25.06; H, 0.88; N, 2.44. Found: C, 24.84; H, 0.87; N, 2.84.

9b: Colorless oil (86%). IR ($CDCl_3$) 1631, 3196 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52–1.64 (m, 2H), 2.30–2.95 (m, 28H), 3.92 (t, $J = 8.0$ Hz, 8H); ^{13}C NMR ($CDCl_3$) δ 22.3, 28.1 (t, $J_{C-F} = 22.0$ Hz), 29.8, 40.5, 50.0, 51.1, 102–124 (m), 173.2; Anal. calcd. for $C_{47}H_{42}F_{52}N_6O_8$: C, 31.22; H, 2.32; N, 4.65. Found: C, 30.98; H, 2.16; N, 4.72.

10b: Pale yellow solid (84%). M.p. 54–56°C; IR ($CDCl_3$) 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53–1.7 (m, 4H), 2.3–2.99 (m, 40H), 3.81–4.02 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 23.1, 28.2 (t, $J_{C-F} = 22.0$ Hz), 29.8, 40.9, 49.4, 50.0, 102–124 (m), 172.8; Anal. calcd. for $C_{54}H_{56}F_{52}N_8O_8$: C, 33.54; H, 2.89; N, 5.79. Found: C, 33.16; H, 2.74; N, 6.09.

11b: Pink colored solid (95%). M.p. 57–59°C; IR (KBr) 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, $J = 7.0$ Hz, 3H), 1.22–1.34 (m, 4H), 1.50–1.75 (m, 2H), 2.30–2.70 (m, 2H), 3.50 (t, $J = 6.6$ Hz, 2H), 3.90–4.40 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.3, 27.9, 28.9, 40.4, 41.5, 68.6, 72.0, 102–124 (m), 171.2; Anal. calcd. for $C_{15}H_{18}F_{13}NO_3$: C, 35.52; H, 3.58; N, 2.76. Found: C, 35.07; H, 3.33; N, 2.78.

13b: Colorless solid (91%). M.p. 69.5–71°C; IR (KBr) 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70–1.92 (m, 4H), 2.32–2.65 (m, 2H), 3.50–3.60 (m, 4H), 3.88–4.00 (m, 2H), 4.35 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 26.7, 27.8 (t, $J_{C-F} = 22.0$ Hz), 29.1, 40.6, 68.2, 70.9, 102–124 (m), 171.4; Anal. calcd. for $C_{14}H_{15}F_{13}ClNO_3$: C, 31.87; H, 2.87; N, 2.65. Found: C, 32.26; H, 2.91; N, 2.63.

14b: Pale yellow solid (87%). M.p. 41–43°C; IR (KBr) 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83–2.02 (m, 2H), 2.05–2.56 (m, 4H), 3.55–3.73

(m, 4H), 3.98 (s, 2H); ^{13}C NMR ($CDCl_3$ with 2 drops CD_3OD) δ 20.4, 28.1 (m), 30.4 (m), 31.1, 67.7, 69.7, 102–126 (m), 170.0; Anal. calcd. for $C_{21}H_{13}F_{30}NO_3$: C, 28.11; H, 1.46; N, 1.56. Found: C, 27.96; H, 1.48; N, 1.82.

ACKNOWLEDGMENTS

We thank WERC, New Mexico for their support of our program in the actinide remediation area. This work was also supported in part by a grant from the National Institutes of Health under PHS Grant No. SO6 GM08136-27.

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Received in the USA December 7, 2001