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Synthesis of (±)-*threo*-3-[(Benzyloxycarbonyl)oxy]-2-fluorotetradecanoic Acid

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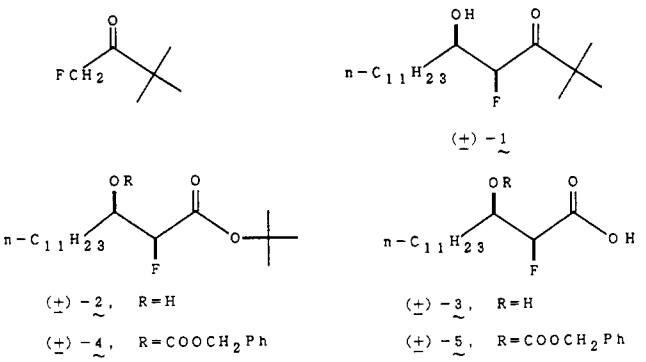
Endotoxic lipopolysaccharide (LPS) is a component of the outer membrane of Gram-negative bacteria, and most of its biological activity depends on its lipid A part.[1] Lipid A has two (*R*)-3-hydroxytetradecanoyl groups at the 2- and 3-positions of glucosamine, and also (*R*)-3-acyloxytetradecanoyl groups at the 2′- and 3′-positions of another glucosamine moiety (Figure 1). We are interested in the biological activity of lipid A analogues containing a fluorinated hydroxytetradecanoyl group at the 2-, 3-, 2′-, or 3′-position of two glucosamines. Therefore, we attempted to synthesize *threo*-3-[(benzyloxycarbonyl)oxy]-2-fluorotetradecanoic acid to obtain the fluorinated lipid A analogue.[2]

The synthesis of *threo*-2-fluoro-3-hydroxyalkanoic acids by the aldol reactions of the lithium enolate of ethyl fluoroacetate with various aldehydes has been reported by Welch et al.,[3] although the *threo*/*erythro* diastereoselectivity was moderate (ca. 1:3 to 1:1.2). It has also been reported that in aldol reactions of the lithium enolate of 1-fluoro-3,3-dimethyl-2-butanone with various aldehydes, a relatively high *threo* selectivity (ca. 16:1 to 49:1) was observed.[4] Therefore, we applied Welch's procedure to dodecanal. The result was excellent *threo* selectivity. Baeyer–Villiger reaction with various oxidizing agents of the resulting *threo*-2,2-dimethyl-4-fluoro-5-hydroxy-3-hexadecanone (1) gave the *tert*-butyl ester of (±)-*threo*-2-fluoro-3-hydroxytetradecanoic acid. The results are reported herein.

Treatment of the lithium enolate of 1-fluoro-3,3-dimethyl-2-butanone[4] with dodecanal[5] at −78 °C gave (±)-*threo*-2,2-dimethyl-4-fluoro-5-hydroxy-3-hexadecanone (1) in 78% yield as a crystalline solid (mp 35 °C) after chromatographic purification. In a gauche relationship, $J_{H4,H5}$ is predicted to be less than 5 Hz, in agreement with the observed value $J_{H4,H5}$ of 2.5 Hz.[4] The *erythro* isomer was not detected by ^1H and ^{13}C NMR analyses. Baeyer–Villiger oxidation of the ketone 1 with *m*-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid, or monoperoxyphthalic acid was carried out under various conditions.



However, the results were poor, due to formation of many byproducts. On the other hand, oxidation of 1 with 5 equiv of magnesium monoperphthalate hexahydrate in ethanol at 50 °C for 18 h gave (±)-*tert*-butyl *threo*-2-fluoro-3-hydroxytetradecanoate (2) in 57% yield accompanied by the starting ketone 1 (26%) after chromatographic separation. Treatment of 2 with trifluoroacetic acid yielded compound 3 quantitatively. In addition, compound 2 easily gave the benzyloxycarbonyl-protected compound 4 in the usual way, because the carboxylic acid was protected as its *tert*-butyl ester. Then, treatment of 4 with trifluoroacetic acid produced the corresponding acid 5 as a crystalline solid (mp 78 °C).

Thus the O-protected *threo*-2-fluoro-3-hydroxytetradecanoic acid was obtained in four steps from 1-fluoro-3,3-dimethyl-2-butanone.

Experimental Section

Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 60 and 67.8 MHz, respectively, using tetramethylsilane as an internal standard. Column chromatography was carried out on columns packed with Merck silica gel 60 (230–400 mesh ASTM) using slightly increased pressure (1.2 atm) for elution.

(±)-*threo*-2,2-Dimethyl-4-fluoro-5-hydroxy-3-hexadecanone (1). To a solution of hexamethyldisilazane (106.4 g, 0.66 mol) in THF (440 mL) was added a solution of butyllithium (1.6 M in hexane, 412 mL) at 0–10 °C under nitrogen with magnetic stirring. To the resulting solution was added a solution of 1-fluoro-3,3-dimethyl-2-butanone (74.4 g, 0.63 mol) in THF (300 mL) at −78 °C with stirring. After 5 min, dodecanal (115.8 g, 0.63 mol) was added with stirring at −78 °C. After 20 min of stirring the reaction mixture was quenched with a solution of acetic acid (40 g) in THF (200 mL), concentrated in vacuo, and diluted with EtOAc (2.5 L). The solution was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to give an oily residue that was chromatographed on a silica gel (1.2 kg) column. Elution with cyclohexane–EtOAc (19:1) gave 148 g of 1 (78% yield) as a crystalline solid: mp 34–35 °C (needles from hexane); ^1H NMR (60 MHz) ($CDCl_3$) δ 0.8–1.0 (3 H, m), 1.2–2.0 (29 H, m), 2.17 (1 H, d, J = 7 Hz, OH), 4.96 (1 H, dd, J = 2.5 Hz, $J_{H,F}$ = 48 Hz, C_4-H), 4.0 (1 H, m, $J_{H,F}$ = 24 Hz, C_5-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.6, 25.7 (2 C), 29.3, 29.5, 29.57 (2 C), 29.63 (2 C), 31.9, 32.57, 32.6, 44.3, 71.7 (d, $J_{C,F}$ = 21.5 Hz, C-5), 95.7 (d, $J_{C,F}$ = 189.7 Hz, C-4), 212.5 (d, $J_{F,C}$ = 19.6 Hz, C-3); IR ν_{max} (Nujol) 3500, 1703 cm^{-1}; MS m/z 303 (M^+ + 1). Anal. Calcd for $C_{18}H_{35}O_2F$: C, 71.48; H, 11.66; F, 6.28. Found: C, 71.08; H, 11.96; F, 6.20.

(±)-*tert*-Butyl *threo*-2-Fluoro-3-hydroxytetradecanoate (2). A mixture of 1 (112.8 g) and magnesium monoperphthalate hexahydrate (923 g, 5 equiv) in ethanol (2.3 L) was stirred at 50 °C for 18 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (6 L), washed with brine, and filtered. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give an oily mixture, which was chromatographed on a silica gel (5.4 kg) column. Elution with cyclohexane–EtOAc (19:1) gave 67.6 g of 2 (57% yield) and 29.6 g of 1 (26%): ^1H NMR ($CDCl_3$) δ 0.85–1.05 (3 H, m), 1.1–1.8 (29 H, m), 2.2 (1 H, broad, OH), 3.94 (1 H, m, $J_{H,F}$ = 25 Hz, C_3-H), 4.67 (1 H, dd, J = 3 Hz, $J_{H,F}$ = 49

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(2) The protection of the 3-hydroxy group of 3 is necessary for further conversion to the lipid A analogues.

(3) (a) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186. (b) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720.

(4) Welch, J. T.; Seper, K. W. *Tetrahedron Lett.* **1984**, *25*, 5247.

(5) When we use a solidified reagent stored for a long time, the yield becomes less than 10%.

(6) Compound 5 showed 41.4% inhibition of aldose reductase at 4 μg/mL in dimethyl sulfoxide.

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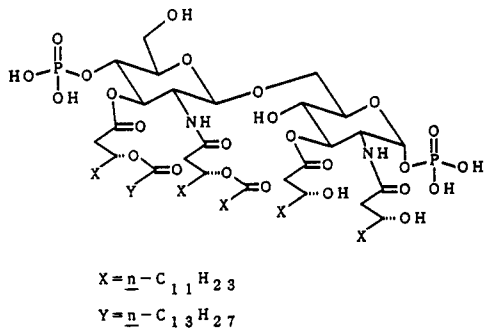

Figure 1. Structure of lipid A of *E. coli.*

Hz, C_2-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.5, 28.1 (2 C), 29.3 (2 C), 29.5, 29.57, 29.63 (2 C), 31.9, 32.8, 32.9, 71.9 (d, $J_{C,F}$ = 21.5 Hz, C-3), 83.1, 90.7 (d, $J_{C,F}$ = 187.8 Hz, C-2), 167.4 (d, $J_{F,C}$ = 23.5 Hz, C-1); IR ν_{max} (film) 3550, 1747 cm^{-1}; MS *m/z* 319 (M^+ + 1). Anal. Calcd for $C_{18}H_{35}O_3F$: C, 67.88; H, 11.08; F, 5.97. Found: C, 67.56; H, 10.73; F, 5.70.

(±)-*threo*-2-Fluoro-3-hydroxytetradecanoic Acid (3). A solution of **2** (1.0 g) in CH_2Cl_2 (30 mL) and CF_3COOH (10 mL) was stirred for 3 h at room temperature. The reaction mixture was concentrated in vacuo. The obtained residue was washed with hexane to give 710 mg (86% yield) of **3** as a solid: mp 82–83 °C (from hexane); ^{1}H NMR (CD_3OD) δ 0.8–1.1 (3 H, m), 1.1–1.8 (20 H, m), 3.92 (1 H, m, $J_{H,F}$ = 26 Hz, C_3-H), 4.80 (1 H, dd, *J* = 3 Hz, $J_{H,F}$ = 48 Hz, C_2-H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 14.1, 22.8, 25.8, 29.5, 29.6, 29.7, 29.7, 29.8, 32.1, 32.7, 32.7, 71.5 (d, $J_{C,F}$ = 19.6 Hz, C-3), 90.9 (d, $J_{C,F}$ = 187.8 Hz, C-2), 171.0 (d, $J_{C,F}$ = 25.4 Hz, C-1); IR ν_{max} (Nujol) 3280, 3000–2400 (broad), 1736 cm^{-1}; MS *m/z* 263 (M^+ + 1). Anal. Calcd for $C_{14}H_{27}O_3F$: C, 64.09; H, 10.37; F, 7.24. Found: C, 64.14; H, 10.40; F, 7.39.

(±)-*tert*-Butyl *threo*-3-[(Benzyloxycarbonyl)oxy]-2-fluorotetradecanoate (4). To a solution of **2** (29.1 g, 91 mmol) and DMAP (22.3 g, 183 mmol) in CH_2Cl_2 (450 mL) was added a solution of ClCOOBn (23.3 g, 137 mmol) at 0 °C with stirring under nitrogen. After 1 h, the reaction mixture was concentrated in vacuo and diluted with EtOAc. The solution was washed with dilute HCl, water, and brine, dried over $MgSO_4$, and concentrated to give an oily residue, which was chromatographed on a silica gel (500 g) column. Elution with cyclohexane–EtOAc (9:1) gave 41.5 g of crude **4**, which was employed for the next reaction without further purification. A small portion of crude **4** was rechromatographed for an analytical sample: ^{1}H NMR ($CDCl_3$) δ 0.80–1.05 (3 H, m), 1.1–1.9 (32 H, m) 4.79 (1 H, dd, *J* = 3 Hz, $J_{H,F}$ = 47 Hz, C_2-H), 5.0–5.2 (3 H, m), 7.35 (5 H, s); ^{13}C NMR (CDCl) δ 14.1, 22.7, 25.0, 27.8 (2 C), 28.0, 29.2, 29.3, 29.5, 29.6 (2 C), 29.8, 29.9, 31.9, 69.9, 76.5 (d, C-3), 83.4, 88.2 (d, $J_{C,F}$ = 193.7 Hz, C-2), 128.3, 128.3 (2 C), 128.6 (2 C), 135.1, 154.6, 165.8 (d, $J_{C,F}$ = 25.4 Hz, C-1). Anal. Calcd for $C_{26}H_{41}O_5F$: C, 69.00; H, 9.13; F, 4.20. Found: C, 69.24; H, 9.02; F, 4.03.

(±)-*threo*-3-[(Benzyloxycarbonyl)oxy]-2-fluorotetradecanoic Acid (5). The crude **4** (41.3 g) obtained above was dissolved in CH_2Cl_2 (300 mL), and then CF_3COOH (100 mL) was added at 0–15 °C. The solution was stirred for 3 h at room temperature, concentrated in vacuo, and dried by a pump to give crude crystals, which were washed with hexane to give a pure **5** (29.5 g, 81.4% yield from **2**): mp 77.5–78 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 0.8–1.0 (3 H, m), 1.1–2.0 (20 H, m), 4.98 (1 H, dd, *J* = 3 Hz, $J_{F,H}$ = 48 Hz, C_2-H), 4.8–5.4 (1 H, m, C_3-H), 5.12 (2 H, s), 7.33 (5 H, s), 8.66 (1 H, b s, COOH); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.0, 29.3, 29.4, 29.5, 29.6, 29.8 (2 C), 29.8, 31.9, 70.1, 76.2 (d, $J_{C,F}$ = 23.5 Hz, C-3), 87.7 (d, $J_{C,F}$ = 193.7 Hz, C-2), 128.2 (3 C), 128.6 (2 C), 135.0, 154.6, 171.8 (d, $J_{F,C}$ = 25.4 Hz, C-1); IR ν_{max} (Nujol) 3200, 1752, 1727 cm^{-1}; MS *m/z* 396 (M^+); high-resolution mass spectrum calcd for $C_{22}H_{33}O_5F$ *m/z* 396.23122, found, M, 396.23192. Anal. Calcd for $C_{22}H_{33}O_5F$: C, 66.64; H, 8.39; F, 4.79. Found: C, 66.95; H, 8.48; F, 4.82.

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Registry No. **1**, 120927-30-2; **2**, 120927-31-3; **3**, 120927-32-4; **4**, 120927-33-5; **5**, 120927-34-6; $FCH_2COC(CH_3)_3$, 4538-80-1; $H_3C(CH_2)_{10}CHO$, 112-54-9.

[^{14}C]Methyl Phenyl Sulfone: A Novel Reagent for General and Facile Carbon-14 Labeling

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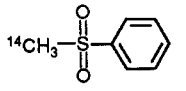
Isotopically labeled derivatives of biologically active substances are necessary in the study of pharmacokinetics, metabolism, and biosynthetic pathways. Introduction of a single carbon-14 atom into a molecule will provide a specific activity of 62.4 mCi/mmol, which is usually sufficient for these investigations. Procedures[1] for the introduction of a single carbon-14 are well established but generally require an organometallic reagent such as methylmagnesium iodide or dimethylcadmium. These reagents have the obvious disadvantages that they must be freshly prepared prior to each use in several steps from barium [^{14}C]carbonate. There still exists a need for a one-carbon reagent that is stable and versatile, can be easily prepared in sizable quantity, and can be conveniently weighed out when used.

One such reagent, [^{14}C]methyl phenyl sulfone, **1**, exhibits all these properties. It is a white crystalline solid that is stable to atmospheric moisture and oxygen and is easily prepared in over 70% yield starting from barium [^{14}C]-carbonate as shown in Scheme I.



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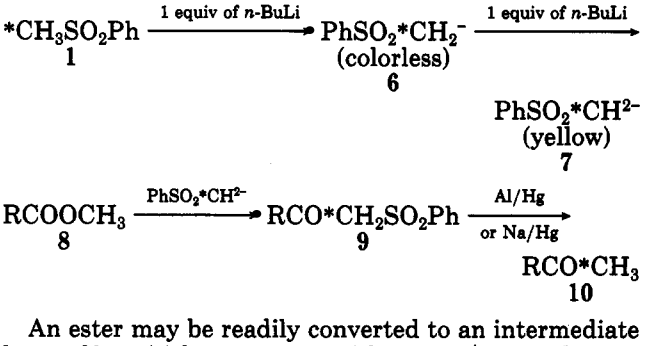
One-carbon substrates such as carbon dioxide, methanol, and methyl iodide have all been used in labeled form as carbon-14 carriers. While they can be prepared for small- to large-scale reactions, storage is a problem for each of them. Although there is a stable and storable single carbon nucleophile, [^{14}C]cyanide, it is difficult to prepare and purify and has limited applications. Using the reaction conditions described (vide infra), the unstable [^{14}C]methyl iodide can be incorporated into the very stable [^{14}C]methyl phenyl sulfone. The dianion **7**[2] of labeled methyl phenyl sulfone may be generated simply by the addition of 2 equiv of *n*-butyllithium in anhydrous tetrahydrofuran (THF). Additional reagents employed by earlier workers[3] such as hexamethylphosphoric triamide or tetramethylethylenediamine are not necessary.



An ester may be readily converted to an intermediate keto sulfone (**9**) by treatment with 1 equiv[4] of the dianion

(1) (a) Murray, A., III; Williams, D. L. *Organic Synthesis with Isotopes, Part I*; Interscience: New York, 1958. (b) Muccino, R. R. *Organic Syntheses with Carbon-14*; Wiley-Interscience: New York, 1983.

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