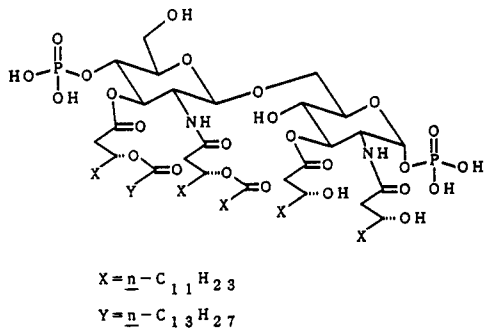

Figure 1. Structure of lipid A of *E. coli.*

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.

Acknowledgment. We thank Dr. Hiroyoshi Horikoshi for measurement of aldose reductase inhibition.

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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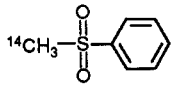
Received February 16, 1989

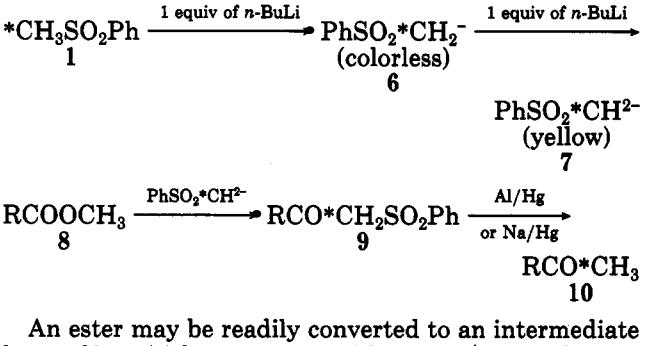
Isotopically labeled derivatives of biologically active substances are necessary in the study of pharmacokinetics, metabolism, and biosynthetic pathways. Introduction of a single carbon-14 atom into a molecule will provide a specific activity of 62.4 mCi/mmol, which is usually sufficient for these investigations. 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.



1

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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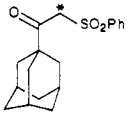
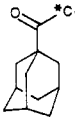
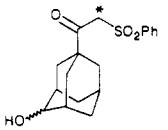
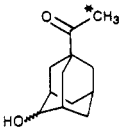
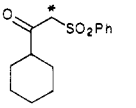
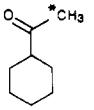
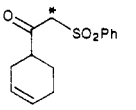
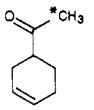
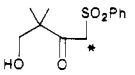
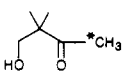
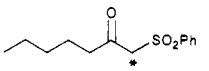
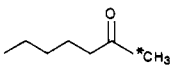
(3) Kondo, K.; Tumemoto, D. *Tetrahedron Lett.* **1975**, 1397.

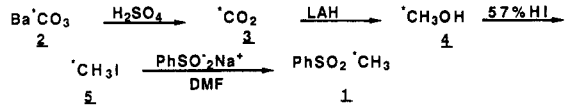
0022-3263/89/1954-3755$01.50/0

Table I

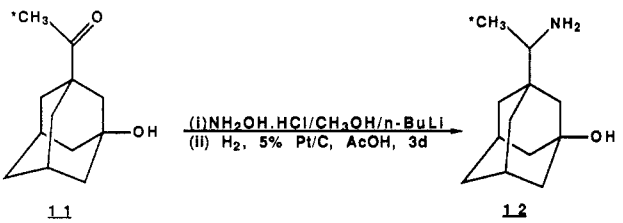
entry	keto sulfones	products	yields, %	method[a]
1			70	A
2[b]			95	A
3			89	B
4			90	B
5[b]			85	A
6			98	B

[a] Method A: Al/Hg, THF–H_2O (10:1), 65–75 °C, 2 h. Method B: Na/Hg, Na_2HPO_4, dry CH_3OH, room temperature, 1 h. [b] See ref 4.

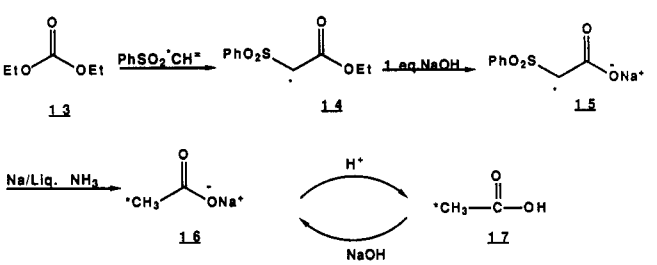
Scheme I



Scheme II



Scheme III



(7). The reaction is rapid and is complete in 15 min at 0 °C, and the keto sulfones (Table I) were obtained in almost quantitative yield. The sulfonyl group is removed cleanly by standard procedures: Al/Hg,[5a] THF–H_2O (10:1), 75 °C, 2 h or Na/Hg,[5b] Na_2HPO_4, dry CH_3OH, 25 °C, to provide a variety of labeled ketones in 70–90% yield.[6] These methyl-^{14}C ketones have been used as such or can be further elaborated into more complex structures in which the labeled carbon is secured within the carbon skeleton. We have prepared the rimantadine metabolite **12** from ketone **11** as shown in Scheme II.

A second use (Scheme III) of labeled methyl phenyl sulfone has been the preparation of ^{14}C-labeled acetic acid in a more convenient manner than established procedures. Condensation of the dianion **7** with diethyl carbonate provided labeled ethyl (phenylsulfonyl)acetate **14**. After saponification with 1 equiv of aqueous sodium hydroxide, the salt **15** was then treated with sodium in liquid ammonia[7] to afford sodium [2-^{14}C]acetate. The acetic acid is liberated by acidification and purified by codistillation with water in the conventional manner. Highly purified sodium [2-^{14}C]acetate may then be prepared by titration with aqueous sodium hydroxide and evaporation of water.

Since keto sulfones can be alkylated[2a] with a wide variety of alkyl halides and have also been converted into olefins and acetylenes,[8] the potential of [^{14}C]methyl phenyl sulfone is great. Further applications of this new method for the preparation of labeled compounds are currently under study.

Preparation of [^{14}C]Methyl Phenyl Sulfone. Barium [^{14}C]carbonate (600 mg, 3.0 mmol, 175.8 mCi), specific activity of 58.6 mCi/mmol, was placed in a carbon dioxide generator and treated in the usual manner with sulfuric acid. The liberated carbon-14 dioxide was vacuum transferred into a thick-walled round-bottom flask with a built-in reflux condenser containing 7.06 mL of freshly prepared 0.85 M lithium aluminum hydride in tetrahydrofuran (THF) solution. The resulting mixture was degassed twice and was allowed to stir at 0 °C for 0.5 h and at 25 °C for 1.5 h. The THF was removed, and the residue was dried under high vacuum for 2 h. A 1-L round-bottom flask was connected to the flask containing the dried residue by means of a Claisen adapter containing

(4) An extra equivalent of the dianion was used in entries 2 and 5 to quench the free hydroxy group; after workup, the excess methyl phenyl sulfone was recovered by chromatography.

(5) (a) Corey, E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 1345. (b) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(6) All yields are based on the absolute mass balance of chromatographically homogeneous material with greater than 95% purity as judged by radiographic scanner.

(7) Kurth, M. J.; O'Brien, M. J. *J. Org. Chem.* **1985**, *50*, 3846.

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a rubber septum and a stopcock. The system was reevacuated, isolated, and cooled to 0 °C. Then, 5.0 mL of 57% hydriodic acid (freshly distilled from red phosphorus) was carefully added portionwise. After degassing the system, the reaction mixture was refluxed for 3 h, and the resulting [^{14}C]methyl iodide was then isolated by vacuum transfer (twice) through a drying tower ($MgSO_4$ + KOH) in the usual manner.

A 25-mL round-bottom flask was charged with 656 mg (4 mmol) of sodium benzenesulfinate in 5 mL of dry dimethylformamide. The mixture was degassed twice, and the methyl iodide prepared above was vacuum transferred into this flask. The reaction flask was closed and allowed to stir for 4 days. The reaction mixture was then poured into 25 mL of water and extracted with 3 × 25 mL of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated, first at 70 mm and then under high vacuum, to give a brown solid, which was purified by flash chromatography[9] (230–400 mesh silica gel, 1 in. wide × 8 in. long column, 1 ethyl acetate/2 hexane) to give 328 mg (121.6 mCi) of [^{14}C]methyl phenyl sulfone (specific activity = 58.6 mCi/mmol).[10]

Acknowledgment. We are grateful to Drs. D. L. Coffen and A. A. Liebman for their support and encouragement during the course of this work.

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(10) A typical procedure as follows: A flame-dried two-neck round-bottom flask equipped with a stirring bar and a rubber septum under nitrogen atmosphere was charged with 156 mg (1 mmol, specific activity = 6 mCi/mmol) of [^{14}C]methyl phenyl sulfone in 5 mL of dry THF. The reaction flask was cooled to 0 °C, and 0.80 mL (2.0 mmol) of *n*-butyllithium in hexane was added to yield a fine yellow precipitate of the dianion. After mixture was stirred for 10 min at 0 °C, 156 mg (1.1 mmol) of methyl cyclohexanecarboxylate (Aldrich) in 2 mL of dry THF was added in one portion. The reaction mixture was allowed to stir at 0 °C for 0.5 h and at room temperature for 0.5 h before 3 mL of 1 N hydrochloric acid was added. After the addition of 25 mL of brine, the aqueous residue was extracted with 3 × 50 mL of ether, and the combined organic extracts were washed with 25 mL of brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, concentrated, and dried under high vacuum to give 246 mg of the intermediate keto sulfones, which was carried forward without any purification. The crude keto sulfone (246 mg) was dissolved in 8 mL of dry methanol in a 25-mL round-bottom flask containing 565 mg of disodium hydrogen phosphate. Sodium amalgam (5%, 2.8 g) was added until TLC (25% ethyl acetate in hexane) indicated the disappearance of starting material (1 h). The reaction mixture was diluted with 50 mL of deionized water and extracted with 3 × 50 mL of ether. The combined organic extracts was washed with 25 mL of brine and dried over anhydrous magnesium sulfate to give 125 mg of crude ketone. The product was purified by column chromatography on 12 g of silica gel (70–230 mesh), eluting with 15% ethyl acetate in hexane to give, after removal of solvents from the appropriate fractions, 112 mg (88.9% overall yield from methyl phenyl sulfone, specific activity = 6 mCi/mmol) of the desired labeled ketone in 97% purity was determined by radiochromatographic scanner.

An Electrophile-Assisted Nonsolvent Synthesis of Alkyl Macroisocyclic Ethers: An Improved Nonsolvent Williamson Synthesis of Medium-Sized Alkyl Carbocyclic Ethers

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Received November 1, 1988

Carbon–oxygen single bond linkages are among some of the oldest and most widely used transformations in organic chemistry. The Williamson synthesis, discovered in 1850, is still one of the best methods for preparing a wide range of symmetrical and unsymmetrical ethers.[1-4] We have developed an efficient synthesis specifically for medium-sized carbocyclic ethers which utilizes alkyl halides as both the solvent and reaction electrophile. This new approach provides an excellent route to ethers that previously could not be obtained in good yield and purity.[5,6]

The well-known fragrance and surfactant potential of medium-sized carbocyclic ethers prompted us to seek a rapid, economical, high-yield synthesis for these materials.[1] We felt that an alkyl halide displacement by an alkoxide ion would provide the best route to these ethers.[1,7,8] We elected to avoid methods that required sulfate esters due to the powerful odor influence of trace amounts of sulfur-containing species.[9-11] Preparative methods such as alkyloxymercuration of alkenes or the reaction of alcohols with diazoalkanes were unattractive due to the potential presence of toxic trace contaminants and the increased reaction times required, resulting in only low yields of product.[12-18]

The five- and six-member carbocyclic alcohols have found wide use and interest in Organic chemistry. Many Williamson type ether syntheses, using these ring sizes, have been reported in the literature.[19-22] A nonsolvent ether synthesis for small ring systems was recently reported by Loupy et al.[23] In this work very reactive aromatic components were used for most of the reactions, and many of the reported products have alternatively been prepared in solvent systems with no apparent difficulties.[4,13-16,21,24] The small ring carbocyclic ethers were not of interest in our study, and many attempts to adapt literature preparations for use with the medium-sized carbocyclic ethers proceeded with only marginal success.[1,24-27] When the medium-sized carbocyclic alkoxides were reacted with primary branched or unbranched alkyl halides in solvents such as 1,2-dimethoxyethane (glyme), 2-methoxyethyl ether (diglyme), tetrahydrofuran, di-*n*-butyl ether, or toluene, elimination rather than substitution predomi-

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