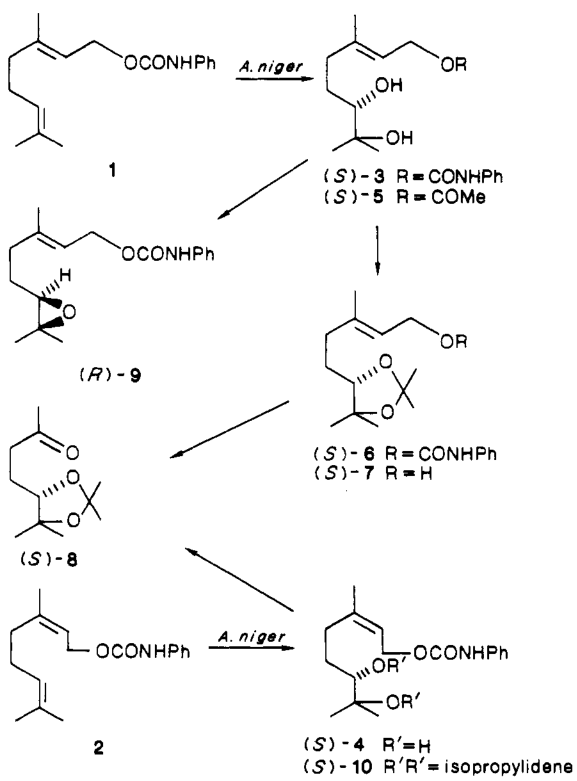
Scheme I



Bromosuccinimide (1.8 g) was added in small portions. The reaction was monitored by TLC analysis (silica gel, ether). At the end of the addition, 5 N NaOH (2 mL) and THF were added to keep the homogeneity of the medium. When all the bromohydrin was consumed, 20% H_2SO_4 (3 mL) was carefully added. At the end of the reaction, water was added and the medium was extracted with ether. The organic phase was washed with water and dried ($MgSO_4$). Recrystallization of the crude product from benzene gave the racemic diol **3** (2 g, 65%): mp 77–80 °C. Derivatization of the racemic diol with (1*S*)-(−)-camphanic acid chloride was performed exactly as previously described. The oily diastereoisomeric mixture had $[\alpha]^{20}_D$ −2.3° (*c* 1.7, MeOH).

(6*R*,2*E*)-6,7-Epoxy-3,7-dimethyl-2-octen-1-yl Phenylcarbamate (9). Diol **3** (300 mg, 1 mmol) and *p*-toluenesulfonyl chloride (200 mg, 1.05 mmol) were dissolved in dry benzene (20 mL). NaH (80% in oil, 100 mg, 3.3 mmol) was added in small portions. At the end of the reaction (monitored by TLC), water was carefully added and the organic layer was washed with water, dried ($MgSO_4$), and evaporated. Purification of the crude product by flash chromatography led to the colorless oily epoxide **9** (245 mg, 85%): $[\alpha]^{20}_D$ 0.5° (*c* 1.2, MeOH); IR (film) 3420 (NH), 1720 (C=O), 1590, 1500, 1430, 1360, 1300 cm^{-1}; ^1H NMR (80 MHz) 1.16, 1.18 (2 s, 2 × 3 H), 1.74 (s, 3 H, CH_3 vinylic), 1.5–2.3 (m, 2 H, allylic), 2.5 (t, *J* = 6 Hz, 1 H, C(6)-H), 4.46 (d, *J* = 7 Hz, 2 H, C(1)-H), 5.3 (t, *J* = 7 Hz, 1 H, C(2)-H), 6.8–7.5 (m, 6 H, aromatic and NH).

(6*R*,2*E*)-6,7-Dihydroxy-3,7-dimethyl-2-octen-1-yl Phenylcarbamate. This compound was obtained from **9** (200 mg) according to a literature procedure.[6b] The diol (170 mg, 85% after flash chromatography) had mp 90–91 °C (from benzene) and $[\alpha]^{20}_D$ 25.2° (*c* 0.87, EtOH). Derivatization of this (*R*)-diol with (1*S*)-(−)-camphanic acid chloride was performed as described previously on a 100-mg portion. The oily product has the same IR and ^1H NMR spectra as its diastereoisomer except for $[\alpha]^{20}_D$ −4.7° (*c* 1.2, MeOH). HPLC analysis indicated a 95% enantiomeric excess.

Acknowledgment. We thank Dr. R. Azerad (CNRS, Paris) for very interesting discussions concerning the nomenclature used for asymmetric synthesis. Dr. G. Dauphin (Faculté des Sciences de Clermont Ferrand) is greatly acknowledged for having obtained the 400-MHz ^1H NMR spectrum of compound **3**.

Synthesis of Monotritiomethyl Iodide from Thioethers. Hydrogenolysis in the Presence of Thioethers

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Monotritiomethyl iodide with high specific activity is a valuable reagent for the incorporation of a tritiated methyl group and has attracted much attention in recent years.[1] The reagent can be used for specific tritium labeling of amines, alcohols, and thiols and for C-methylation of peptidic amino acid residues.[2,3] This reagent was previously prepared from bis(chloromethyl) ether at nearly theoretical specific activity.[4] However, this technique has received limited applications because the precursor is known to be a powerful carcinogen and the resulting tritiated ether is highly volatile (bp −24.8 °C) and difficult to control under the reaction conditions.

We recently reported a new procedure for the synthesis of monotritiomethyl iodide by the preparation of chloromethyl esters, followed by tritiodehalogenation with carrier free tritium gas and subsequent cleavage of the $[^3H_1]$ester by lithium iodide.[5] Due to the time necessary for C–Cl bond hydrogenolysis in these esters (normally 12 h), we observed significant isotopic dilution, and the theoretical specific activity was not attainable. Also, in most cases, only 75–80% of the precursor's specific activity could be preserved in the N-methylated products. To overcome these deficiencies, we have continued our investigations and now report a procedure that effectively proceeds with rapid tritium incorporation and essentially no isotope dilution.

Monotritiomethyl iodide can now be prepared from monotritiomethyl phenyl sulfide (**2**) as the precursor. When chloromethyl phenyl sulfide (**1**) was exposed to deuterium gas in the presence of Pd/C, we observed that hydrogenolysis of the C–Cl bond in this compound occurred within 3 h at room temperature and gave a single product in 95% yield. The product was identified as monodeuteriomethyl phenyl sulfide (GC and deuterium NMR evidence). This result was surprising because sulfides have long been known to poison the catalyst through direct linkage of the hetero atom to the catalyst.[6] Hydrogenolysis of the precursor with carrier-free tritium gas and 10% Pd/C gave the desired product in 95% yield and with a specific activity of 20 Ci/mmol. The reaction was much faster (less than 1 h) with 30% Pd/C as the catalyst (Scheme I). In this case, at 1 atm of carrier-free tritium gas, the rapid uptake of tritium was complete after 1 h and the monotritio thioether was obtained with a specific activity of 28.5 Ci/mmol (theoretical value, 29 Ci/mmol). The ^3H NMR spectrium of this compound showed a singlet

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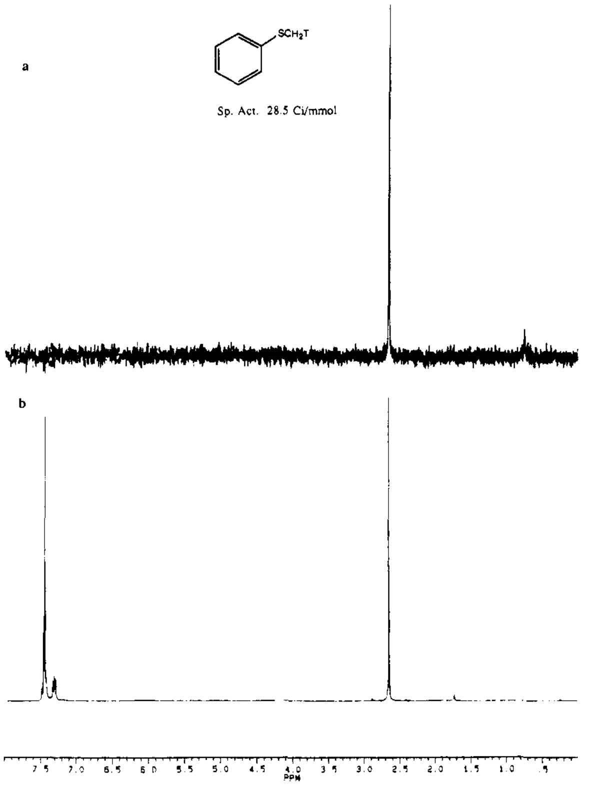
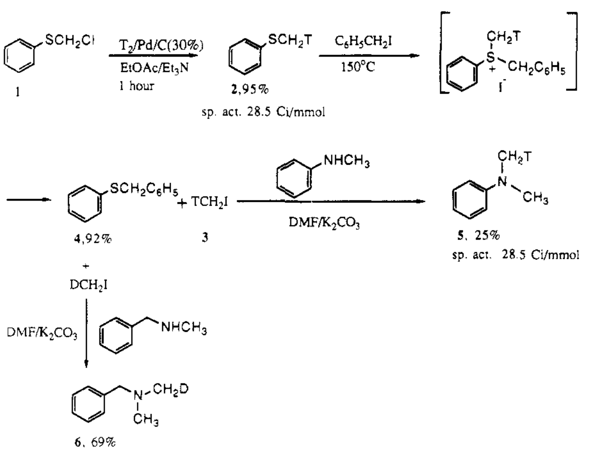


Figure 1. NMR spectra of methyl phenyl sulfide (2) in $CDCl_3$: (a) ^3H spectrum; (b) ^1H spectrum.

Scheme I



at 2.7 ppm for the CH_2T attached to sulfur (Figure 1). In all cases, after the reaction was complete, the catalyst was filtered off and the filtrate containing the tritiated sulfide was analyzed by radio-HPLC. The chromatograms showed tritiated thioanisole (2, t_R 4.6 min), isolated in 95% yield, as the only radioactive product.

For the generation of [$^3H_1$]methyl iodide, the monotritiomethyl phenyl sulfide (28.5 Ci/mmol) was mixed with excess benzyl iodide and heated for 48 h at 140 °C. The liberated monotritiomethyl iodide (3) was passed into *N*-methylaniline in DMF in the presence of anhydrous potassium carbonate and the product, [$^3H_1$]-*N*,*N*-dimethylaniline (5), was isolated. Analysis by radio-HPLC showed a specific activity of 28.5 Ci/mmol. The ^3H NMR spectrum of the product showed a singlet at 3.0 ppm for the CH_2T attached to the nitrogen (Figure 2). These results demonstrated that 100% of the precursor's specific activity can be preserved in the N-methylated product and that the faster the tritiodehalogenation, the less isotopic dilution occurred. Our preliminary work in a different investigation strongly suggests that adsorbed hydrogen on the catalyst as well as OH groups on the glassware are the major sources of dilution. When [$^2H_1$]methyl iodide was generated by the same procedure using D_2 gas and then the methyl iodide was captured using *N*-methylbenzylamine under the same conditions, a much better yield (69%) of the N-methylated product, [$^2H_1$]-*N*,*N*-dimethylbenzylamine (6), was obtained.

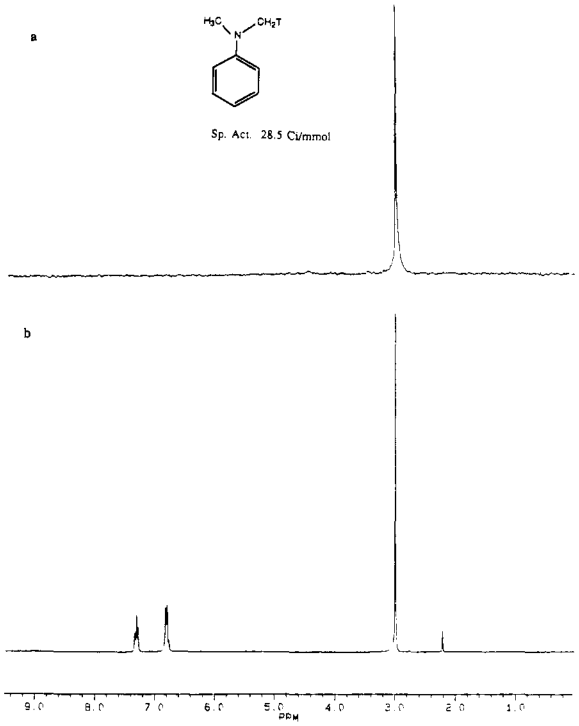


Figure 2. NMR spectra of *N*,*N*-dimethylaniline (5) in $CDCl_3$: (a) ^3H spectrum; (b) ^1H spectrum.

Cleavage of the sulfide 2 with benzyl iodide is a facile and convenient process. Through the intermediacy of the sulfonium salt, methyl iodide is liberated and the new sulfide, benzyl phenyl sulfide (4), is formed.

Experimental Section

Tritium gas was purchased from Oak Ridge National Laboratory and contained 97.9% T_2, with the largest contaminant being DT (1.76%) Chloromethyl phenyl sulfide was purchased from Aldrich Chem. Co. and purified prior to use; EtOAc was distilled from P_2O_5 and Et_3N from BaO prior to use. Proton and triton NMR spectra were recorded on an IBM-AF-300 NMR spectrometer. HPLC analyses of the precursor and the N-methylated products were performed on a Waters Associates C-18 radial pak column with a mobile phase of $MeOH/H_2O/NH_4OH$ (50/50/1, 3 mL/min). Gas chromatographic analyses were performed on a Varian 3700 instrument using a carbowax 20M column. Tritiated samples were counted with a Packard 2002 liquid scintillation counter. Generation and reaction of monotritiomethyl iodide was performed in a manifold with two small vessels, isolated by Teflon-brand stopcocks. The generation section consisted of a microcondensor on top of the heated generation vessel and kept at 15 °C. After generation of the methyl iodide was complete, the stopcocks were opened and the methyl iodide was vacuum transferred to the reaction vessel.

Synthesis of Monotritiomethyl Phenyl Sulfide (2). (a) Chloromethyl phenyl sulfide (1, 30 μL, 0.26 mmol) and triethylamine (30 μL, 0.22 mmol) were dissolved in purified, dried ethyl acetate (2 mL), Pd/C (10%, 66 mg) was added, and the substrate was hydrogenolyzed under 1 atm of T_2 for 3 h. Rapid uptake of tritium gas was complete after 2 h, and the reaction was continued for an additional hour. The catalyst was filtered off and a portion of the filtrate was analyzed by radio-HPLC. The radiochromatogram showed a clean peak for [$^3H_1$]thioanisole: yield 28 μL (96%); specific activity 20 Ci/mmol; ^{3}H NMR (CDCl$_3$) δ 2.6 (s, T).

(b) Chloromethyl phenyl sulfide (1, 30 μL, 0.26 mmol) and triethylamine (30 μL, 0.22 mmol) were dissolved in ethyl acetate (2 mL), Pd/C (30%, 22 mg) was added, and the substrate was tritiated under 1 atm of T_2 for 1 h. Rapid uptake of tritium gas was complete after 40 min. The reaction was discontinued at this stage, the catalyst was filtered off, and a portion of the filtrate was analyzed by radio-HPLC. The radiochromatogram showed the corresponding peak for [$^3H_1$]thioanisole: yield 28 μL (96%); specific activity 28.5 Ci/mmol; ^{3}H NMR (CDCl$_3$) δ 2.6 (s, T).

Synthesis of Monotritiomethyl Iodide (3) from [$^3H_1$]-Thioanisole (2). (a) [$^3H_1$]Thioanisole (2, 28 μL, 0.25 mmol) in ethyl acetate (2 mL) was mixed with benzyl iodide (300 μL, 2.3 mmol) and placed in the generation flask of the apparatus described above. The system was kept at a pressure of $^1/_2$ atm. In the reaction flask were placed *N*-methylaniline (30 μL, 0.27 mmol), DMF (0.5 mL), and anhydrous potassium carbonate (150 mg). The generation flask was then heated at 140 °C for 48 h and the liberated tritiated methyl iodide passed over into the reaction flask where it reacted with the substrate. After this 48 h, the solvent containing the remaining methyl iodide was vacuum transferred into the reaction flask and the entire mixture was stirred overnight. Analysis by radio-HPLC and GC showed that the generation flask contained unreacted [$^3H_1$]thioanisole (2, 8%) and benzyl phenyl sulfide (4, 90%): mp 39 °C (lit.[7] mp 41-43 °C); ^{1}H NMR (CDCl$_3$) δ 4.1 (s, 2 H), 7.2-7.3 (m, 10 H). Similarly, the reaction flask was shown to contain [$^3H_1$]-*N*,*N*-dimethylaniline (5, 25%), specific activity 28.5 Ci/mmole.

(b) [$^2H_1$]Thioanisole (28 μL, 0.25 mmol) was synthesized by the same procedure and used as the precursor. [$^2H_1$]Methyl iodide was generated and reacted with *N*-methylbenzylamine (40 μL, 0.31 mmol) in DMF (0.5 mL) and anhydrous potassium bicarbonate (150 mg). Gas chromatographic analysis of the reaction flask showed a single peak corresponding to [$^2H_1$]-*N*,*N*-dimethylbenzylamine (6, 69%): ^{1}H NMR (CDCl$_3$) δ 2.3 (s, 5 H), 3.5 (s, 2 H), 7.4 (m, 5 H); ^{2}H NMR (CHCl$_3$) δ 2.3 (s, 1 D).

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Novel Synthesis of 4-[Alkyl(aryl)sulfonyl]benzaldehydes: Alkyl(aryl)sulfinate Anion as a Nucleophile in Aromatic Substitutions

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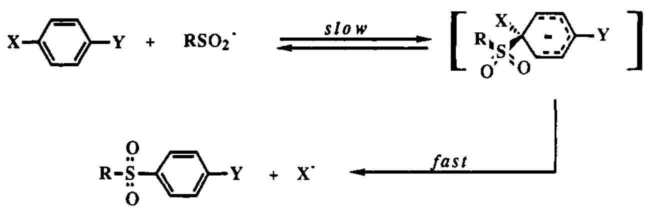
4-[Alkyl(aryl)sulfonyl]benzaldehydes are intermediates in the preparation of fluorescent brighteners,[1] liquid crystals,[2] antiobesity and hypoglycemic drugs,[3] β-lactam antibiotics,[4] antiinflammatory and antiarthritic materials,[5] and other bioactive materials.[6-8] The preparation of 4-(methylsulfonyl)benzaldehyde was accomplished previously by either of two routes: (a) dibromination of 4-tolyl methyl sulfone and hydrolysis with dilute sulfuric acid[9] and (b) oxidation of 4-(methylthio)benzaldehyde dimethyl acetal with *m*-chloroperbenzoic acid in CH$_2$Cl$_2$.[10] 4-(Phenylsulfonyl)benzaldehyde was prepared by the reduction of 4-(phenylsulfonyl)benzoyl chloride,[11] while 4-(phenylsulfonyl)acetophenone was prepared by the oxidation of the corresponding sulfide.[12] 4-(Phenylsulfonyl)benzophenone was prepared by the reaction of 4-(chlorosulfonyl)benzoyl chloride with benzene.[13] The displacement of a nitro group of substituted nitrobenzenes by different nucleophiles was described by Korenblum et al.[14] In that paper they described the reaction of sodium benzenesulfinate with 4-nitrobenzonitrile and with *p*-dinitrobenzene in hexamethylphosphoramide (HMPA) to give 4-(phenylsulfonyl)benzonitrile and 4-(phenylsulfonyl)nitrobenzene, respectively. However, we did not find any evidence in the literature for a reaction of sulfinate anions with benzaldehyde derivatives.

We explored the possibility of preparing this type of molecule in one step by sulfinate anion replacement of an activated halide in an aromatic nucleophilic substitution (S$_N$Ar mechanism)[15] with DMSO as the solvent. (A wide variety of sulfinic acids can be prepared by the reduction of the corresponding sulfonyl chlorides.[16])



Therefore, we have examined the reaction of 4-fluorobenzaldehyde (X = F, Y = CHO) with sodium methanesulfinate (R = CH$_3$) in dry DMSO. It was found that at 100 °C the reaction is clean, and we isolated 4-(methylsulfonyl)benzaldehyde in 85% yield. The reaction of 4-fluorobenzaldehyde with sodium benzenesulfinate (R = Ph) was carried out at 100 °C, and 4-(phenylsulfonyl)benzaldehyde was isolated in 72% yield.

Since fluoroorganic materials are more expensive than the corresponding chloro derivatives, we reacted 4-chlorobenzaldehyde (X = Cl, Y = CHO) with sodium benzenesulfinate (R = Ph) at 130 °C and isolated 4-(phenylsulfonyl)benzaldehyde in 70% yield.[17] Repeating

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