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Modification of the Swern Oxidation: Use of Stoichiometric Amounts of an Easily Separable, Recyclable, and Odorless Sulfoxide That Can Be Polymer-Bound

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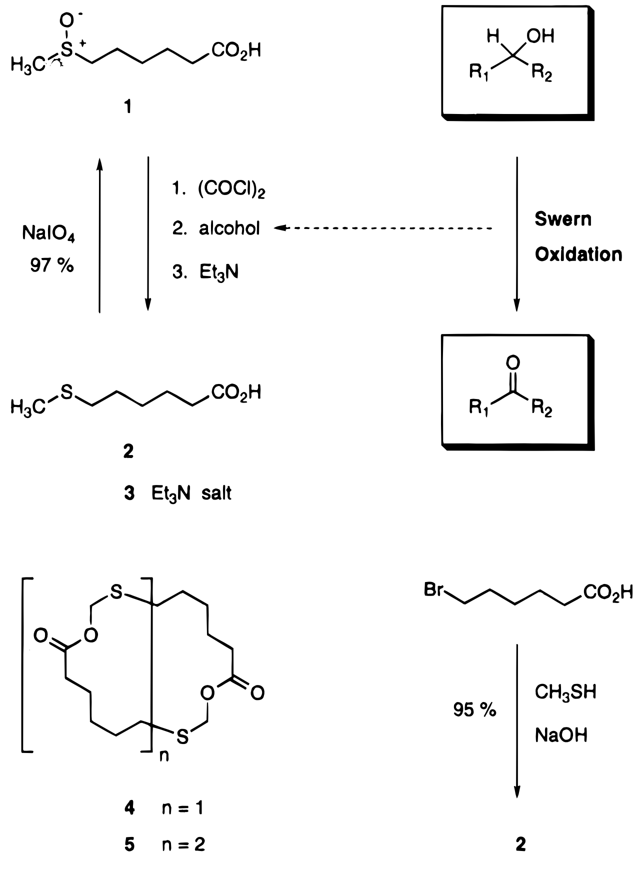
Readily available 6-(methylsulfinyl)hexanoic acid (**1**) is employed as a substitute for DMSO in Swern oxidation reactions using oxalyl chloride to smoothly convert primary or secondary alcohols to corresponding aldehydes or ketones in high yield. The resulting 6-(methylthio)hexanoic acid (**2**) is easily separable by aqueous extraction or by filtration through silica gel and can be reoxidized to **1** with sodium metaperiodate in 97% yield. Low temperature (−60 °C) ^{13}C NMR spectrometry is used to examine the intermediates of this Swern process. The results indicate that any residual unoxidized alcohol is generated during Pummerer elimination of the alkoxysulfonium intermediate and can be minimized by extended exposure to triethylamine at −40 °C. Reaction of the potassium salt of **1** with cross-linked chloromethyl polystyrene affords a polymer-bound reagent **12** that quantitatively oxidizes borneol to camphor when used in two-fold excess.

Oxidations of primary or secondary alcohols to aldehydes or ketones using activated dimethyl sulfoxide (DMSO) are among the most widely used reactions in organic synthesis.[1] The Swern procedure[1,2] employing DMSO and oxalyl chloride is especially effective, but the process typically uses excess reagent and produces the unpleasant-smelling volatile (bp 37 °C) byproduct, dimethyl sulfide. We now report that the readily available sulfoxide, 6-(methylsulfinyl)hexanoic acid (**1**), is a successful substitute for DMSO in Swern oxidation reactions (Scheme 1). This modification generates the nonvolatile sulfide **2**, which is easily separable from the reaction mixture by extraction or filtration through silica gel and can be smoothly recycled by aqueous periodate oxidation. We also describe the optimization of the oxidation process based on its mechanistic features and the attachment of **1** to commercial chloromethyl polystyrene beads (Merrifield resin) to form a polymer-bound reagent.

Sulfoxide **1** is easily available by condensation of inexpensive[3] 6-bromohexanoic acid with methanethiol to give 6-(methylthio)hexanoic acid (**2**)[4] in high yield (ca 95%), followed by subsequent $NaIO_4$ oxidation,[5] which avoids any significant over-oxidation to the corresponding sulfone. Although methanethiol is toxic and has an even more obnoxious stench[6] than dimethyl sulfide, preparation of one large batch of **2**, which is odorless, can suffice for many subsequent Swern procedures because both **1** and **2** are polar and water soluble under basic conditions and can be readily recovered for reuse.

Scheme 1



In order to test the efficacy of **1** as a substitute for DMSO, a number of alcohols were oxidized by this reagent and oxalyl chloride with subsequent triethylamine treatment (Table 1). It is interesting to note that the carboxyl group does not interfere in the reaction despite the potential to form acid chloride or react with the activated sulfonium intermediate (see below). In a typical small scale procedure, a dichloromethane solution of **1** in slight excess (1.2 equiv) is treated at −50 to −60 °C with oxalyl chloride (1.1 equiv) followed by a solution of the alcohol (1.0 equiv), and finally, excess triethylamine (5 equiv). For optimal yield, it is important that

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[⊗] Abstract published in *Advance ACS Abstracts*, October 1, 1996.

(1) For reviews see: (a) Tidwell, T. T. *Synthesis* **1990**, 857−870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572. (c) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(2) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660. (c) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148−4150.

(3) In 100 g quantities, 6-bromohexanoic acid is typically five times more expensive than dimethyl sulfoxide.

(4) Clements, A. P.; White, R. H.; Ferry, J. G. *Arch. Microbiol.* **1993**, *159*, 296−300.

(5) (a) Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282−284. (b) Johnson, C. R.; Keiser, J. E. *Organic Syntheses*; Wiley: New York, 1973; Coll. Vol. 5, pp 791−793.

(6) Methanethiol has a bp 5.95 °C at 760 mm and the lethal concentration in air for rats is 10,000 ppm: *Merck Index*, 11th ed.; Merck: Rahway, NJ, 1983; No. 5867, p 5862.

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Table 1. Oxidation of Alcohols with Modified Swern Procedure Using 1

alcohol	product composition (%) R_2CO	R_2CHOH	isolated R_2CO yield (%)	lit. yield (%)[a]
endo-borneol	95	5	90	98
3,5-dimethoxybenzyl alcohol	96	1	94	–
n-dodecanol	96	4	92	99
cinnamyl alcohol	97	3	93	98
benzoin	97	3	94	95
phenethyl alcohol	44	33	31[b]	23

[a] See ref 1c. [b] Recovered alcohol 28%.

the solution then be kept at −40 °C for 2 h before warming to room temperature. Workup involves filtration through a silica gel column with further elution by ethyl acetate (5 column volumes). The sulfide byproduct is retained on the column as its triethylammonium salt **3**. The parent acid **2** can then be recovered by washing the silica gel with 5 column volumes of 1% acetic acid in ethyl acetate. For larger scale reactions, the carboxylic acid functionality in the reagent allows a convenient separation of products from **2** by acid−base extraction. The results are comparable with those of the original Swern reaction, except that this new procedure often leaves a small amount of unreacted alcohol (1−4%). Use of a two fold excess of oxidizing reagents gives no improvement and results in contamination by polymeric Pummerer rearrangement products. In a control experiment (same procedure without alcohol), two Pummerer products **4** and **5** (Scheme 1) were isolated in yields of 13% and 7%, respectively.

Low temperature (−60 °C) ^{13}C NMR spectrometry provides information about the intermediates of this modified Swern oxidation (Scheme 2, Table 2). Reaction of **1** with oxalyl chloride at −60 °C rapidly generates the chlorosulfonium salt **6**, whose spectra exhibit an expected[2c] downfield shift for the carbons adjacent to sulfur: $\Delta\delta$ 10.72 ppm for C-7 and 13.44 ppm for C-6. The corresponding difference for the dimethyl chlorosulfonium intermediate derived from DMSO is $\Delta\delta$ 8.5 ppm.[2c] Although the carboxyl carbon also displays a considerable downfield displacement ($\Delta\delta$ 4.49 ppm), the cyclized form **8** can be excluded as a principal component, because oxalyl bromide gives a different intermediate (i.e. bromo analogue **7**) based on the chemical shifts for carbons adjacent to sulfur. Moreover, the carboxyl carbon resonance of **7** is shifted similarly to that in **6**. We tentatively attribute the change in carboxyl shift to disruption of a possible hydrogen bond between the sulfoxide and the acid moiety, based on its absence during conversion of the corresponding methyl ester **9**[7] to its chlorosulfonium analogue **10** with oxalyl chloride. Elegant studies by Tidwell and co-workers using competitive oxidation experiments indicate an equilibrium between the alkoxydimethylsulfonium intermediates and the chlorodimethylsulfonium species in the usual Swern oxidation (i.e. DMSO).[1a,b,8] An analogous mechanism could be verified for the reaction of **1** by addition of varying amounts of 2-propanol (0.5 to 2 equiv) to the chlorosulfonium intermediate **6** at −60 °C with ^{13}C NMR observation of the resulting mixtures of unreacted **6** as well as alkoxysulfonium product **11** (Figure 1). Low temperature addition of a solution of a different chlorosulfonium species **10** consumes the free alcohol and regenerates **6** to unambiguously confirm the existence of the equilibrium (Scheme 2).

Scheme 2

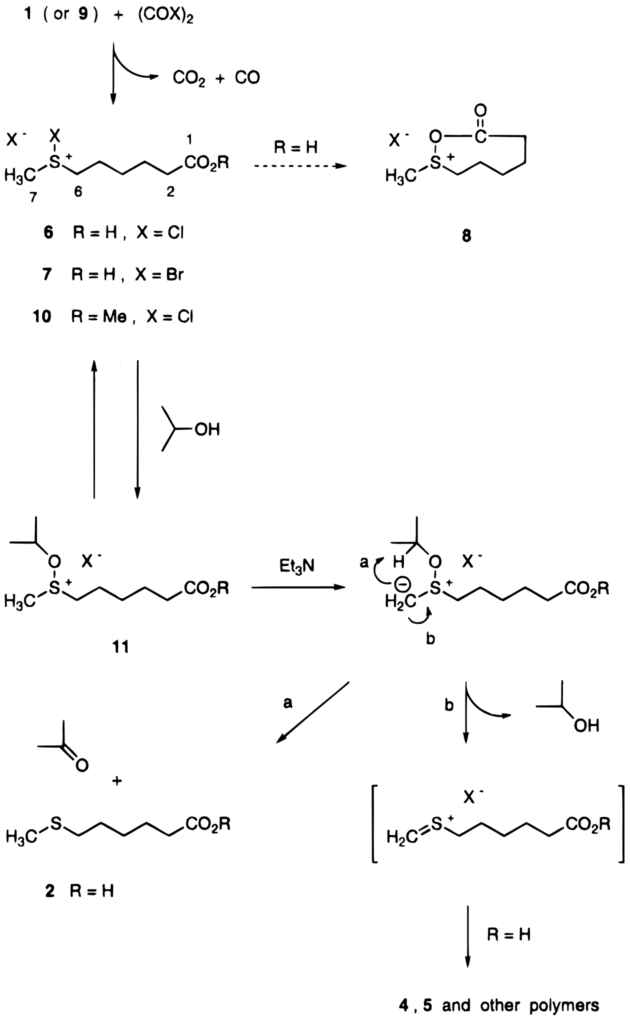

Table 2. ^{13}C NMR Data −60 °C (50 MHz, CD_2Cl_2)

compound[a]	chemical shift, δ C-7	C-6	C-2	C-1
1 R = H, X = O	36.92	52.32	33.22	176.31
6 R = H, X = Cl	47.64	65.76	33.25	180.80
7 R = H, X = Br	25.93	43.78	33.22	180.77
9 R = Me, X = O	38.05	51.54	33.11	173.81
10 R = Me, X = Cl	47.63	65.78	32.99	173.95

[a] For structures see Scheme 2. Compound **8** was not detected in any experiment.

As mentioned above, control of temperature and reaction time after addition of triethylamine is important for oxidation efficiency. In the original Swern process, the reaction mixture is allowed to stir for 5 min at −60 °C after triethylamine addition and is then warmed to room temperature. However, 7−9% unreacted alcohol remains when the same conditions are employed using **1**. It is necessary to maintain stirring at −40 °C for 2 h (or at −60 °C for 4 h) after triethylamine addition before warming to obtain optimum results. Since excess oxidizing reagent does not improve the efficiency, this temperature dependence suggests two competing pathways after the addition of base, namely proton transfer from the alkoxy moiety with elimination to give the desired

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[7] Methyl ester **7** is readily available by a number of routes including diazomethane esterification of **1**. It can also be used effectively in the Swern reaction.

[8] Marx, M.; Tidwell, T. T. *J. Org. Chem.* **1984**, *49*, 788−793.

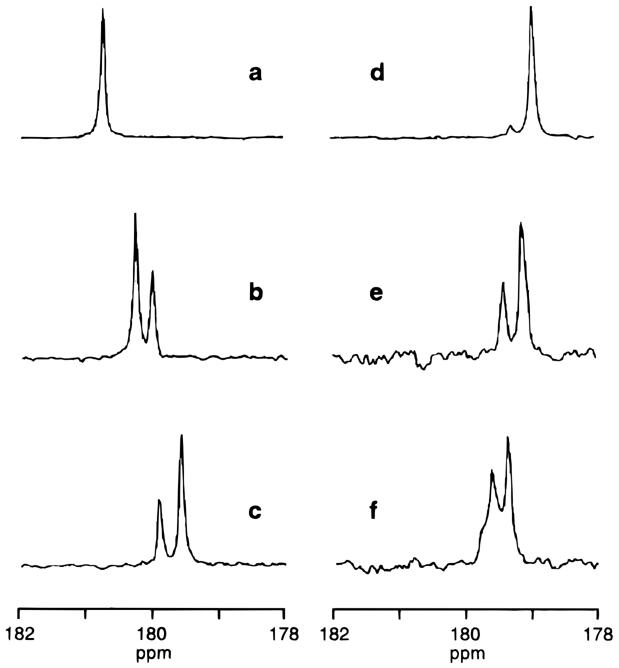
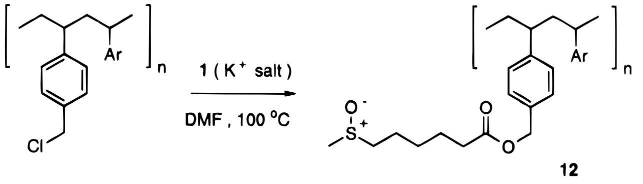


Figure 1. ^{13}C NMR (50 MHz, CD_2Cl_2, −60 °C) spectra of the carboxyl region for the reaction of **6** with 2-propanol. The upfield signal is for product **11** and the carbonyl carbon of **10** (δ 174 ppm) is not shown: (a) **6** only; (b) **6** + 0.5 equiv of 2-propanol; (c) **6** + 1.0 equiv of 2-propanol; (d) **6** + 2.0 equiv of 2-propanol; (e) **6** + 2.0 equiv of 2-propanol + 0.75 equiv of **10**; (f) **6** + 2.0 equiv of 2-propanol + 1.0 equiv of **10**.

Scheme 3



carbonyl compound and α,β-elimination to a methylenesulfonium cation enroute to Pummerer products. It is interesting to note that only polymeric Pummerer adducts (e.g. **4** and **5**) are isolated and direct intramolecular cyclization to generate a monomer is not detected.

Reagent **1** can also be easily attached to a solid support by reaction with commercially available cross-linked chloromethylated polystyrene beads (Merrifield resin) to give **12** (Scheme 3). If exactly 1 equiv of this polymeric reagent is employed to oxidize *endo*-borneol, only 92% of the alcohol is converted to camphor and 8% remains unchanged. However, use of a two-fold excess of the polymeric reagent in the Swern process permits quantitative oxidation to camphor with no residual alcohol remaining. The subsequent removal of the insoluble resin involves simple filtration. Although use of an insoluble polymeric thioanisole with chlorine for oxidation of alcohols has been reported in 1975,[9] the yields were variable and reaction of benzyl alcohol gave benzaldehyde in only 53% with concomitant formation of benzyl chloride. The present reagent promises to maintain the efficiency of the classical Swern reaction and will enhance ease of product purification. Further studies on the use and recycling of modified sulfoxides as recyclable oxidation reagents applicable to combinatorial chemistry are in progress.

Experimental Procedures

General. Most common procedures and instrumentation have been previously described.[10] Cross-linked (divinyl benzene) chloromethylated polystyrene resin (4.15 mequiv/g, Bio-Beads S-X1) was obtained from Bio-Rad Laboratories (Mississauga, ON). Solvents were dried and distilled prior to use according to standard procedures.[11]

6-(Methylthio)hexanoic Acid (2).[4] A solution of 6-bromohexanoic acid (50.8 g, 0.261 mol) in 300 mL of methanol at 0 °C was carefully treated with liquid methanethiol (40 g, 0.83 mol), followed by 98 mL of 6 N sodium hydroxide. The mixture was then warmed to 20 °C and stirred overnight. Excess thiol was removed by bubbling argon into the solution (vent to bleach solution in hood), and methanol was evaporated *in vacuo*. The residue was acidified to pH 1 with HCl and then extracted five times with hexane. The dried extracts (Na_2SO_4) were concentrated to give 40.2 g (95%) of **2** as a colorless oil: IR ($CHCl_3$) 3037 (br m), 1708 (s) cm^{-1}; ^{1}H NMR (360 MHz, CD_2Cl_2) δ 11.85 (br, 1H), 2.48 (t, 2H, J = 7.3 Hz), 2.36 (t, 2H, J = 7.4 Hz), 2.06 (s, 3H), 1.62 (m, 4H), 1.44 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 180.54, 34.29, 34.27, 29.17, 28.52, 24.65, 15.53; MS (EI) calcd for $C_7H_{14}O_2S$ 162.0715, found 162.0714 (M^+). Anal. Calcd for $C_7H_{14}O_2S$: C, 51.82; H, 8.70; S, 19.76. Found: C, 51.66; H, 9.07; S, 19.51.

6-(Methylsulfinyl)hexanoic Acid (1). A solution of **2** (40.0 g, 0.247 mol) in methanol (500 mL) at 0 °C was treated with 0.50 M sodium metaperiodate (494 mL, 0.247 mol) overnight. It was concentrated to dryness below 10 °C, and the residue was extracted with CH_2Cl_2 (4 × equal volume). Combined extracts were dried (Na_2SO_4) and evaporated to give **1** (42.6 g, 97%) as an oil which solidified upon standing: mp 48−50 °C; IR ($CHCl_3$) 3200−2500 (br m), 1718 (s), 1002 (s) cm^{-1}; ^{1}H NMR (360 MHz, CD_2Cl_2) δ 10.76 (br, 1H), 2.65−2.88 (m, 2H), 2.59 (s, 3H), 2.28 (t, 2H, J = 7.3 Hz), 1.73 (m, 2H), 1.62 (m, 2H), 1.48 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 176.44, 53.91, 38.01, 33.99, 28.41, 24.65, 22.53; MS (EI) calcd for $C_7H_{14}O_3S$ 178.0664, found 178.0668 (M^+). Anal. Calcd for $C_7H_{14}O_3S$: C, 47.17; H, 7.92; S, 17.99. Found: C, 46.82; H, 8.00; S, 17.81.

General Procedure for the Modified Swern Oxidation. A solution of **1** (1.07 g, 6 mmol) in dichloromethane (15 mL) was cooled to −50 to −60 °C, and oxalyl chloride (5.5 mL, 1M solution in CH_2Cl_2, 5.5 mmol) was added dropwise, followed after 15 min by a solution of the alcohol (5 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 30 min, triethylamine (25 mmol) was added, and the solution was kept at −40 °C for 2 h before warming to room temperature. Workup involves filtration through a silica gel column with further elution by ethyl acetate (5 column volumes). Simple evaporation of the filtrate affords the product, which was analyzed by ^{1}H NMR spectrometry using a long relaxation delay (12 s) to determine the alcohol/carbonyl product composition. A portion (200 mg) of the product was then further purified by flash chromatography (20 g of SiO_2, 30% Et_2O in hexane) to determine the isolated yields. All the carbonyl products after the Swern oxidation were characterized by comparing chromatographic and/or spectral properties (^{1}H NMR, IR, MS) with the authentic samples or literature.

The parent acid **2** can then be recovered by washing the silica gel with 5 column volumes of 1% acetic acid in ethyl acetate and then evaporating *in vacuo*. The residue was diluted with water and extracted five times with hexane. The extract was dried (Na_2SO_4) and concentrated to give **2**. The sulfide recovered this way was essentially pure, and the yield of recovery was normally >95%. For larger scale reactions, the carboxylic acid functionality in the reagent allows a convenient separation of products from **2** by acid−base extrac-

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(9) Crosby, G. A.; Weinshenker, N. M.; Uh, H.-S. *J. Am. Chem. Soc.* **1975**, *97*, 2232−2235.

(10) Witter, D. J.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 2613−2623.

(11) *Purification of Laboratory Chemicals*, 3rd ed.; Perrin, D. D., Armarego, W. L. F., Eds.; Pergamon: New York, 1988.

tion. Any excess sulfoxide reagent **1** is not recovered by this procedure since it is water soluble.

Pummerer Products 4 and 5. The general procedure for the modified Swern oxidation was followed except no alcohol was added. Dimer **4** and trimer **5** were isolated by SiO_2 flash chromatography. For **4** (13%): IR ($CHCl_3$) 1739 (s), 1157 (m) cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 5.16 (s, 4H), 2.68 (t, 4H, J = 7.4 Hz), 2.33 (t, 4H, J = 7.3 Hz), 1.67 (m, 8H), 1.45 (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 173.06, 67.30, 34.75, 32.76, 29.98, 27.98, 25.02; MS (EI) calcd for $C_{14}H_{24}O_4S_2$ 320.1116, found 320.1128 (M^+); (CI, NH_3) 338 (MNH_4^+) 321 (MH^+).

For trimer **5** (7%): IR ($CHCl_3$) 1737 (s), 1127 (m) cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 5.15 (s, 6H), 2.67 (t, 6H, J = 7.4 Hz), 2.33 (t, 6H, J = 7.3 Hz), 1.66 (m, 12H), 1.45 (m, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 173.24, 67.17, 34.55, 32.79, 30.14, 28.33, 24.75; MS (EI) calcd for $C_{21}H_{36}O_6S_3$ 480.1674, found 480.1668 (M^+); (CI, NH_3) 498 (MNH_4^+), 481 (MH^+).

Methyl 6-(Methylsulfinyl)hexanoate (9). To a solution of **1** (1.00 g, 5.61 mmol) in CH_2Cl_2 (40 mL) cooled in an ice bath was added dropwise a CH_2N_2/Et_2O solution until a pale yellow color was obtained. The mixture was stirred at room temperature for 30 min, and a few drops of formic acid were added to destroy the excess CH_2N_2. Evaporation of solvent under reduced pressure gave 1.07 g (99%) of **9** as a pale yellow oil. IR ($CHCl_3$) 1735 (s), 1033 (m) cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 3.61 (s, 3H), 2.63 (m, 2H), 2.48 (s, 3H), 2.30 (t, 2H, J = 7.4 Hz), 1.72 (m, 2H), 1.64 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 173.93, 54.78, 51.61, 38.99, 33.91, 28.54, 24.79, 22.58; MS (EI) calcd for $C_8H_{16}O_3S$ 192.0820, found 192.0820 (M^+). Anal. Calcd for $C_8H_{16}O_3S$: C, 49.97; H, 8.39; S, 16.67. Found: C, 50.10; H, 8.55; S, 16.50.

Low Temperature ^{13}C NMR Analysis. Spectra were acquired on a Bruker AM200 spectrometer with a 20 mm probe at −60 °C. CD_2Cl_2 was dried by distillation from CaH_2 before use. The reaction was done on 1 mmol scale in a 12 mm NMR tube cooled to −60 °C. After attachment of the apparatus to a pressure-equalizing argon line, the reagents were added *via* a syringe. Chlorosulfonium intermediate **10** was added *via* a cannula which was cooled with dry ice. After each addition the NMR tube was kept at −60 °C for 15 min with occasional shaking before the spectral analysis. The ^{13}C NMR chemical shifts (δ) for the intermediates are as follows: **1**, 176.31, 52.32, 36.92, 33.22, 27.50, 23.84, 22.13; **6**, 180.80, 65.76, 47.64, 33.25, 26.84, 24.00, 23,48; **7**, 180.77, 43.78, 33.22, 27.19, 25.93, 25.60, 23.35; **9**, 173.81, 53.47, 51.54, 38.05, 33.11, 27.66, 24.02, 22.18; **10**, 173.95, 65.78, 51.69, 47.63, 32.99, 26.92, 23.99, 23.79; **11**, 178.94, 83.64, 49.69, 34.78, 33.10, 26.83, 23.49, 22.33, 21.98.

Polymer-Bound Reagent 12. Sulfoxide **1** (2.95 g, 16.6 mmol) and KOH (0.93 g, 16.6 mmol) were dissolved in H_2O (20 mL). The solution was concentrated and dried under vacuum for 2 days. The resulting potassium salt was mixed with DMF (50 mL) and *p*-chloromethylated polystyrene resin (2.00 g, 8.30 mmol, Bio-Beads S-X-1, Bio-Rad, 4.15 mequiv/g). The mixture was heated at 100 °C for 20 h with a gentle stirring. After cooling, the resin was filtered, washed (MeOH, THF, CH_2Cl_2 (3 × each)), and dried at 60 °C *in vacuo* for 40 h. A total of 2.96 g (93%) of white resin was obtained: IR (microscope) 3025 (m), 2929 (s), 1736 (s), 1173 (m), 1029 (m) cm^{-1}; ^{13}C NMR (75 MHz, CD_2Cl_2) δ 173.33, 128.51, 66.34, 54.83, 40.87, 39.12, 34.23, 28.67, 24.91, 22.70. Anal. Calcd based on 100% conversion: C, 71.12; H, 8.07; S, 8.33. Found: C, 70.33; H, 7.64; S, 8.33.

Polymer-Supported Swern Oxidation. Polymer-supported sulfoxide **12** (1.00 g, 2.60 mmol, based on elemental analysis) was swollen in CH_2Cl_2 (20 mL) at room temperature for 15 min and then cooled to ca −50 °C. Oxalyl chloride (1 equiv) in CH_2Cl_2 (5 mL) was added dropwise. After 1 h at that temperature, *endo*-borneol (201 mg, 1.30 mmol, 0.5 equiv) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred for 3 h before the addition of triethylamine (3 equiv). The mixture was allowed to slowly warm to room temperature and stirred overnight. The resin was removed by filtration and washed with CH_2Cl_2. The filtrate was condensed to 50 mL and then diluted with Et_2O (50 mL) and washed three times with H_2O. The ethereal phases were dried (Na_2SO_4) and concentrated under reduced pressure. The product was analyzed by ^1H NMR spectrometry, which showed complete oxidation with no trace of borneol. A total of 188 mg (95%) of camphor was obtained, with the loss being due to its volatility during evaporation. In a separate experiment, 1 equiv of *endo*-borneol was used for the reaction with 1 equiv of polymer-supported sulfoxide: 92% of the alcohol was oxidized to give camphor with 8% left unchanged.

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Supporting Information Available: Copies of ^1H NMR spectra of **4** and **5** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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