of various oxidation levels and carried these through to the aldehyde **10** via epoxidation/hydrolysis/$NaIO_4$-cleavage or via ozonolysis.

Although this approach avoided polymerization of the enone moiety, it was abandoned as a possible source of **1** in view of its many steps and of our successful and facile functionalization of lactone **3**.

In conclusion, we feel that the two approaches presented above are, in principle, adaptable to the preparation of not only other methylenomycins but also of various prostanoid compounds. The unsubstituted periphery of sarkomycin can be functionalized in either of the precursors **2** or **6** (see Scheme I) since carbons 2 and 3 of sarkomycin occupy different functional positions in **2** and **6** (see the symbolic representation of these in Scheme I). Thus a greater choice of precursory functionalities becomes available for the construction of compounds such as **1** in the context of a single method of general synthetic design.

Experimental Section

Melting and boiling points are uncorrected. ^1H NMR spectra were determined at 90 MHz (Varian EM-390), 200 MHz (JEOL-FX 200), and 300 MHz (Nicolet 300 spectrometer). ^{13}C NMR spectra were recorded at 20 MHz (Varian CFT-20), 15 MHz (JEOL-FX60Q), and 50 MHz (JEOL-FX 200 spectrometers). Chemical shifts are reported in parts per million relative to internal tetramethylsilane or chloroform-*d*. Infrared spectra were obtained on Perkin-Elmer 257, Pye-Unicam 3-300, and Beckman IR 20A-X spectrophotometers. Mass spectra were recorded on a DuPont 20-491 instrument, Varian MAT-112 instruments (low resolution), or on a double-focusing DuPont 21-110C instrument (high resolution and exact mass data).

Gas chromatography was performed on a Varian 3700 instrument (F.I.D., 5% OV-101 on Chromosorb, 50 cm, 30 mL/min N_2).

All solvents were distilled from usual drying agents (Et_2O/$LiAlH_4$; THF, benzene, toluene, DME/K, and benzophenone). All nonhydrolytic reactions were performed under an inert atmosphere and in previously flame-dried glassware.

Chromatography was performed with J.T. Baker Alumina, Macherey Nagle Co, with Silica gel 60 or silica PF 254 by EM reagents (TLC). Flash chromatography utilized Kieselgel 60 (230–400 mesh) by EM reagents.

Purity of all compounds was ascertained by GC, TLC, and carbon 13 and high-field proton spectra with emphasis on the latter.

3a,5,6,6a-Tetrahydro-3*H*-cyclopenta[*c*]furan-1,4-dione (5a) and Its Regioisomer (5b). Lactone **3**[4] (87 mg, 0.0007 mol) in 1.5 mL of dry THF was cooled to 0 °C under argon and treated dropwise with 0.4 mL of a 0.92 M solution (1.6 equiv) of a borane–THF complex. The cooling bath was removed after the addition (2 min), and the mixture was stirred at room temperature for 2 h, whereupon excess BH_3 was decomposed by the addition of 0.04 mL of H_2O. The reaction mixture was cooled in ice, 0.12 mL of 3 M NaOH solution was added followed by 0.1 mL of 30% H_2O_2, and the entire mixture was then heated at 50 °C for 1 h. The reaction mixture was cooled, acidified with 0.2 mL of 3 M HCl, and stirred at room temperature for $^1/_2$ h, when it was partitioned between brine and ethyl ether and extracted. The organic layers were combined, dried, and evaporated to give an oil, which was chromatographed (1 g of silica, hexane:Et_2O (1:1)) to give 40 mg (40%) of a mixture of alcohols **4**: IR (neat) 3400, 1780 cm^{-1}; mass spectrum (Chem. Ionization mode), *m/e* (relative intensity)) 143 ($M^+ + 1$) (B), 124 (15), 85 (60), 81 (70), 71 (B).

A mixture of alcohols **4** (51 mg, 0.000 35 mol) was dissolved in 1 mL of acetone and cooled to 0 °C. Standard Jones reagent was added dropwise until the solution remained reddish brown. Stirring was continued for additional 30 min, 2-propanol was added to quench excess reagent, and the solution was filtered through a plug of silica to remove inorgnaic materials. Evaporation yielded 46.8 mg (93%) of ketones **5**, shown by GC (50 cm OV-101, on Chromosorb W, FID., 150 °C → 200 °C (5° min^{-1}), 30 mL/min of N_2) to consist of 70% **5a** and 30% **5b**. Careful chromatography (silica, hexane → Et_2O, gradient elution) afforded 22 mg (44%) of **5a**[2b] and 8 mg (16%) of **5b**.

5a: IR ($CHCl_3$) 1770, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2–2.6 (m, 4 H), 3.1 (m, 1 H), 3.4 (m, 1 H) 4.5 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (t), 36.6 (t), 41.5 (d), 47.7 (d), 68.8 (t), 178.4 (s), 217.0 (s).

5b: IR ($CHCl_3$) 1735, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (d, 1 H, J = 7 Hz), 2.8 (m, 3 H), 3.3 (m, 2 H), 4.2 (dd, J = 6, 1 Hz), 4.56 (dd, J = 7, 4 Hz).

Sarkomycin (1). A. From Cyclosarkomycin 5a.[2b] Keto lactone **5a** (22 mg, 0.000 15 mol) was stirred in a mixture of acetone and 3 M HCl (1.5 mL, 1:1) at room temperature for 8 h. The reaction mixture was extracted with $CHCl_3$ (5 × 1 mL). The chloroform extract was concentrated to ~2 mL and extracted with cold 5% $NaHCO_3$ (3 × 0.5 mL). Acidification of the aqueous layer (3 N HCl) and extraction with $CHCl_3$ (5 × 1 mL) gave, after drying and evaporation, 4 mg (25%) of **1**: IR ($CHCl_3$) 3500–2900, 1730–1700, 1640, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (m, 2 H), 2.3 (m, 2 H), 2.6 (m, 1 H), 5.69 (s, 1 H), 6.23 (s, 1 H). The unreacted **5a** was recovered from the neutral extract.

B. From Olefin 7. Exocyclic olefin **7**[5a,6] (200 mg, 0.0014 mol) was dissolved in 5 mL of CH_2Cl_2 and cooled to −78 °C. To this solution was added 0.1 mL (1.5 equiv) of a saturated solution of ozone in CH_2Cl_3.[10] The reaction was stirred for 30 min, degassed with nitrogen, and poured into 10 mL of Me_2S (or 5 mL of HOAc containing 1 g of Zn dust). The resulting mixture was stirred for 20 min at 0 °C, evaporated, dissolved in acetone, and titrated with standard Jones reagent. Workup of this mixture as in the case of **5** gave oil, which was treated with ethereal diazomethane. From the resulting complex mixture, 25 mg (11%) of the methyl ester of sarkomycin was isolated by preparative TLC (CH_2Cl_2). Its NMR spectrum and R_f-value (0.7) were identical with those of an authentic sample: ^1H NMR ($CDCl_3$) δ 2.1–2.6 (m, 5 H), 3.75 (s, 3 H), 5.6 (d, 1 H, J = 4 Hz), 6.2 (d, 1 H, J = 4 Hz). No attempt was made to optimize the yields of the above sequence. The low yield of the ester is in part due to the pyrazoline formaiton at the site of the enone moiety. The yield would probably be greatly improved by utilizing the more selective ozonization procedure[11] and by purifying sarkomycin by base extraction rather than by the conversion to its methyl ester.

Acknowledgment. We are indebted to the National Science Foundation (Grant CHE-8102944) for the financial support of this work. We also thank Prof. Robert Boeckman and Dr. Paul Naegely of Wayne State University for providing us with a sample and NMR and IR spectra of sarkomycin methyl ester.

Registry No. (±)-**1**, 72581-31-8; (±)-**3** (R = H), 84899-17-2; **4** 4-OH, 86900-33-6; **4** 5-OH, 86853-72-7; (±)-**5a**, 86853-73-8; (±)-**5b**, 86853-74-9; (±)-**7**, 86900-34-7; (±)-**9**, 86853-75-0.

(12) The protected enones **8** were prepared from **7** in nearly quantitative yields by stirring **7** in CH_3CN saturated with CH_3SH and containing 10 mol % of diisopropylamine followed by evaporation of solvent (**8a**) or by stirring **7** with 1 equiv of thiophenol in CH_3CN at room temperature (**8c**). Oxidation of either **8a** or **8c** with 2 equiv of *m*-CPBA led to **8b** and **8d**, respectively. The use of 3 equiv of *m*-CPBA gave good yields of the corresponding epoxides. Ozonolysis of either **8a** or **8c** or $NaIO_4$ cleavage of the diols obtained by acid hydrolysis of the epoxides gave aldehydes **10a** or **10b**, respectively (^1H NMR ($CDCl_3$) 9.1 (d, 1 H, J = 6 Hz).

Chiral Ether Glycerides from a Marine Sponge

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Received October 4, 1982

Though sponges provide the most primitive example of a marine invertebrate, they have exhibited much fascinating natural products chemistry to date.[1] Many expo-

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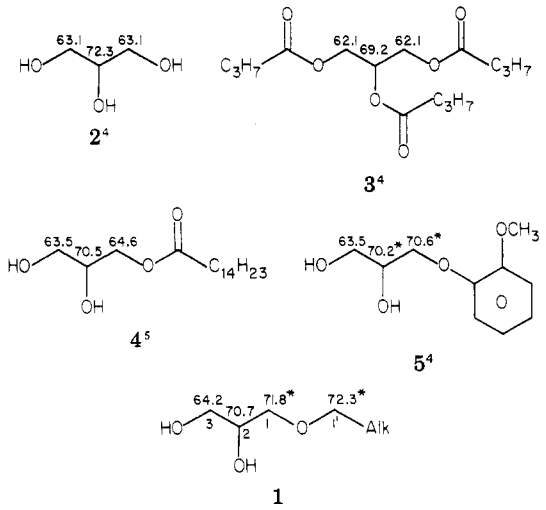
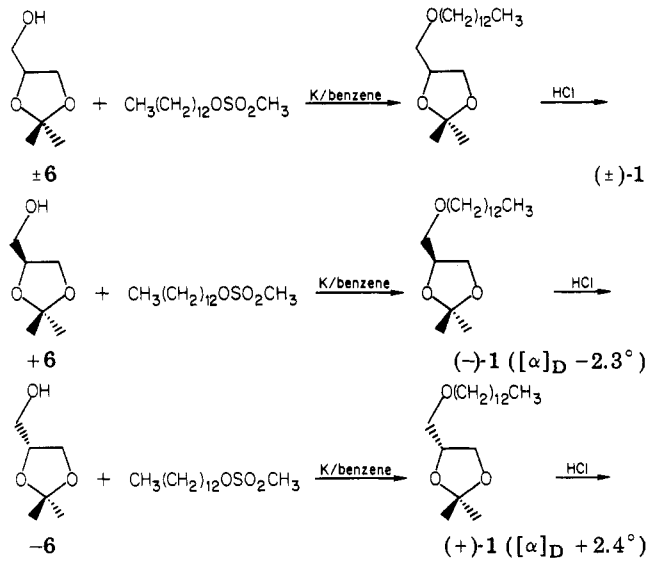
Chart I[a]



[a] Numbers with * can be switched.

Scheme I



sed, brightly colored sponges, which abound in coral reefs,[2] represent an easy target for prey and are regarded by some as having chemical defense capabilities.[3] Several conspicuous blood-red sponges attracted our attention during a survey of Demosponges from coral reefs in the Kingdom of Tonga (June 1981). Our chemical study of one undescribed specimen of the family Plocamiidae has revealed an interesting glyceride, (*S*)-(+)-1-tridecoxy-2,3-propanediol ((+)-**1**), which displays toxicity to goldfish. Reported below are the results of fish toxicity studies and the details of the NMR and synthetic experiments used to establish its structure.

Results and Discussion

Freshly collected sponge from Lotuma of the Vava'u Island group was extracted at room temperature with dichloromethane. The resultant crude oil was partitioned between hexanes–methanol, and the methanol fraction was investigated further. Pure (+)-**1**, $[\alpha]^{19.5}_D$ +2.0°, mp 57 °C was obtained via flash chromatography followed by HPLC. The molecular formula, $C_{16}H_{34}O_3$, was deduced by analysis of the mass spectrum, highest *m/e* 256 ($M^+ - H_2O$), and an integrated ^{13}C NMR spectrum. An unsymmetrical glyceride backbone, $-CH_2OCH_2CH(OH)CH_2OH$, was evident from ^{13}C NMR peaks at δ 64.2 (t), 70.7 (d), 72.3 (t), and 71.8 (t). Assignment of these resonances to specific carbons was accomplished by correlating the data of **1** with that for glyceride derivatives **2**–**5** shown in Chart I.[4,5] The glyceride group was also evident from ^1H NMR peaks at δ 3.21 (dt, *A* = 2), 3.26 (dd, *A* = 1), 3.30 (dd, A =1), 3.48 (dd, *A* = 1), 3.58 (dd, *A* = 1), 3.74 (m, *A* = 1). Spin decoupling at C_2-H (δ 3.74) caused the two adjacent diastereotopic methylene H's to collapse into separate AB patterns. An unbranched alkyl ether group was indicated by a lone ^{13}C methyl at δ 13.9 (q), but defining its exact length was not straightforward. A nuclear Overhauser suppressed ^{13}C NMR spectrum revealed five lines of one carbon each and one intense resonance at 29.0 ppm with an area of 7–8 C's. A similar intense ^1H NMR peak at δ 1.31 had an area of 18 ± 2 H's.[6] Comparison of the spectroscopic properties of **1** to racemic **1**,[7] synthesized as shown in Scheme I showed OR to be a $CH_3(CH_2)_{11}CH_2O$ unit. Repetition of this synthesis with (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol (**6**) gave (*S*)-(+)-1-tridecoxy-2,3-propanediol (**1**), whose $[\alpha]^{19.5}_D$ +2.4° matched that of natural product **1**. The remaining ^{13}C NMR peaks in **1** could be assigned (see Experimental Section) by comparison to the ^{13}C NMR of 1-tridecanol.[4]

Our isolation of (+)-**1** did not involve either saponification or enzymic hydrolysis of the extract. Alternatively, to the best of our knowledge, all of the marine alkyl ether glycerides reported to date[8] were obtained after the crude extracts were subjected to saponification or enzyme treatment.[9-12] For these cases it is not possible to decide whether the alkyl ether glycerides are genuine natural products or hydrolysis products of alkyl ether acetylglycerides.[9]

Shark liver oil represents the most common marine source of alkyl ether glycerides.[11] Compounds such as (*S*)-(+)-batyl alcohol (**1**, OR, R = *n*-$C_{18}H_{37}$)[13] or (*S*)-(+)-chimyl alcohol (**1**, OR, R = *n*-$C_{16}H_{33}$)[13] are seminal because of their abundance in these oils.[12] By contrast, alkyl ether glycerides are not commonly observed from marine invertebrates; though quite some time ago Bergman isolated

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(2) See, for example: George, D. J.; George, J. J. In "Marine Life—An Illustrated Encyclopedia of Invertebrates in the Sea"; Harrap: London, England, 1979, pp 11–18 and plates pp 1–9.

(3) Compare arguments in: (a) Bakus G. J. *Science (Washington D.C.)* **1981**, *211*, 498. (b) Walker, R. P.; Thompson, J. E.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4976. vs. those in: (c) Bergquist, P. R.; Bedford, J. J. *Marine Biol.* **1978**, *46*, 215. (d) Randall, J. E.; Hartman, W. D. *Ibid.* **1968**, *1*, 216.

(4) Catalog of ^{13}C NMR Spectra, Sadtler Research Labs, **1982**, Philadelphia, PA.

(5) Andersen, R. J.; Sum, F. W. *Tetrahedron Lett.* **1980**, *21*, 797.

(6) The $C_{12}H_{25}O$ possibility was tentatively rule out by comparing the ^{13}C NMR spectrum of $CH_3(CH_2)_nCH_2OH$ for *n* = 9–12 and noting that when *n* = 9 or 10, the CH_2 of $PrCH_2R$ does not overlap with the CH_2 envelope,[4] but does when *n* = 11–12.[4]

(7) Synthesis of (±)-**1** (mp 47.5 °C): Baumann, W. J. In "Ether Lipids"; Snyder, F., Ed.; Academic Press: New York, 1972; pp 56–7.

(8) A report describing the isolation of a sponge ether glyceride (with OR = even number of carbons) appeared after our manuscript was submitted: Cardellina, J. H.; Graden, C. J.; Greer, B. J.; Kern, J. R. *Lipids* **1983**, *18*, 107.

(9) Bergelson, L. D. *Prog. Chem. Lipids Other Fats* **1970**, *10*, 244.

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(11) (a) Hashimoto, Y. In "Marine Toxins and Other Bioactive Marine Metabolites"; Japan Scientific Societies Press: Tokyo, 1979; pp 127–138. (b) Mahadevan, V. *Prog. Chem. Lipids Other Fats* **1978** *15*, 255.

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(+)-batyl alcohol from a gorgonian.[14] Our observation of 1 from a marine sponge is noteworthy because alkyl ether glycerides with an OR having an odd number of carbons are rare.[8] Of further significance is that 1 along with all other chiral 1-ether glycerides known to date is of *S* configuration. Rather interesting biological activity seems to be associated with *S* ether glycerides. For example, it was recently reported that (*S*)-1-(1,3,5,7,9-dodecapentenoxy)-2,3-propanediol, a natural product from human feces,[15] displays potent mutagenic activity. Glyceride (+)-1 showed toxicity to goldfish, death in 70 min at 290 μg/mL, while (−)-1 showed no toxicity at this concentration, and (±)-1 displayed toxicity, death in 80 min at 360 μg/mL.

Experimental Section

Our general analytical, chemical, and chromatographic methods have been described previously.[16] Mass spectral data were obtained by direct inlet with an impact voltage of 20 eV and temperature programed at 100 °C for 1 min followed by a 3°/min ramp to 200 °C. Rotations were measured on an Autopol III Automatic polarimeter with a 1.0-dm cell (0.8 mL) at Stanford University. (±)-2,2-Dimethyl-1,3-dioxolane-4-methanol (**6**) was synthesized[17] and purified by distillation (bp 80–81 °C, 11 mm); commercially available compounds (Aldrich Chemical Co.) were used without further purification and included (+)-**6**, (−)-**6**, 1-tridecanol, and methanesulfonyl chloride. Bioassays were done by using the Bakus assay procedure.[3a]

(*S*)-(+)-1-Tridecoxy-2,3-propanediol (1). A red sponge (168 g, dry weight, collection No. DM-I-2) was collected from Lotuma of the Tonga Vava'u Island group. This sponge is in an undescribed genus, though it may belong to the family Plocamiidae, and it is probably closest to the genus *Tumata*.[18] Immediate extraction, with CH_2Cl_2 at room temperature, of the freshly collected sponge yielded 3.43 g of crude oil. A ^1H NMR spectrum (benzene-d_6) was obtained on the crude oil, and peaks characteristic of 1 were visible. The crude oil was partitioned between wet methanol–hexanes (1:1) to yield 1.10 g of methanol solubles; 1.0 g of this oil was flash chromatographed with a solvent gradient of ether–hexanes (1:1), followed by ether and methanol. Polar fractions 13 and 14 (0.0434 g) showing one TLC spot (R_f 0.25; ethyl acetate–hexanes (1:1)) were further purified by HPLC. Though only one HPLC peak was observed, 18 fractions were collected. Fractions 8–9 gave slightly impure 1 (10.8 mg), while fractions 10–14 yielded pure 1 (8 mg): mp 57 °C; $[\alpha]^{19.5}_D$ +2° (*c* 0.02 M, $CHCl_3$); ^1H NMR (benzene-d_6, 360 MHz) δ 3.74 (m, H_2), 3.58 (dd, J = 10.8, 4.7 Hz, H_{1a}), 3.48 (dd, J = 10.8, 5.4 Hz, H_{1b}), 3.30 (dd, J = 10.8, 5 Hz, H_{3a}), 3.26 (dd, J = 10.8, 5 Hz, H_{3b}), 3.21 (dt, J = 5.5, 5.5, 2 Hz, $H_{1'}$), 2.8 (br s, OH), 2.3 (br s, OH), 1.48 (m, $H_{2'}$), 1.31 (br s, A = 18 ± 2), 1.28 (m, $H_{3'}$), 0.92 (t, J = 5.5, $Me_{13'}$) [Spin-decoupling at δ 3.74 eliminated J = 4.7 at δ 3.58, J = 5.4 at δ 3.48, J = 5 at δ 3.30 and J = 5 at δ 3.26; spin-decoupling at δ 3.21 collapsed the multiplet at δ 1.48 to a triplet; spin-decoupling at δ 1.48 collapsed the multiplet at δ 3.21 to a broad singlet and simplified a shoulder of the δ 1.31 peak]; ^{13}C NMR (benzene-d_6, 25 MHz) δ 72.3 (t, J_R = 77.0, $C_{1'}$), 71.8 (t, J_R = 77.0, C_1), 70.7 (d, J_R = 85.5, C_2), 64.2 (t, J_R = 77.0, C_3), 31.9 (t, $C_{11'}$), 29.0 (t, A = 7–8, $C_{2'}$, C_4–$C_{10'}$), 26.0 (t, J_R = 47.0, $C_{3'}$), 22.6 (t, $C_{12'}$), 13.9 (q, $C_{13'}$) (multiplet data for entries without J_R is based upon INEPT experimental results); MS, *m/e* 256 ($M^+ - H_2O$), 225, 224 ($M^+ - H_2O$, CH_3OH).

Three synthetic samples of 1 were prepared via literature methods[17,19] from 1-tridecanol and (±)-**6** to yield (±)-1 (mp 48 °C (petroleum ether)), (−)-**6** to yield (+)-1 (mp 54 °C $[\alpha]^{19.5}_D$ +2.4° (*c* 0.06 M, $CHCl_3$)) and (+)-**6** to yield (−)-1 (mp 54 °C, $[\alpha]^{19.5}_D$ −2.3° (*c* 0.05 M, $CHCl_3$)).

Acknowledgment. Support for this research was under a grant from the California Sea Grant Program, Department of Commerce, and a Sea Grant Traineeship for B. L.M. We thank the University of California Research Expeditions Program for support of our field work. We are also grateful to Jim Loo for his technical assistance with some of the spectroscopic work at UCSC and Joe Hanke (UCSC) and Steve Naylor (UCSC) for their stimulating comments. The 360-MHz NMR spectra were obtained at the Stanford Magnetic Resonance Laboratory supported by the National Science Foundation (Grant No. GR23633) and the National Institutes of Health (Grant No. RR00711).

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Onium Ions. 27.[1a] Oxidation of Sulfoxides to Sulfones with Nitronium Salts

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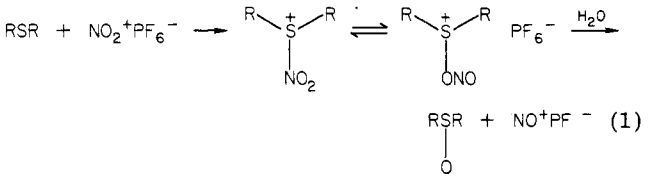
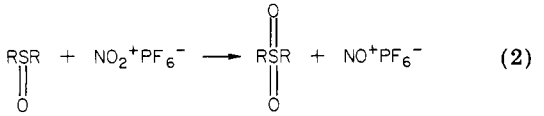
Received March 8, 1983

Recently we reported[3] a detailed study of the ambident reactivity of nitronium ion with heteroorganic (S, Se, P, As, and Sb) compounds. Sulfides, for example, reacted readily at −78 °C with nitronium hexaflourophosphate (tetrafluoroborate), affording, upon basic workup, sulfoxides (**4**) as the major products (eq 1) Even when an



(1)

excess of nitronium salt was used, the reaction did not lead to any observable amounts of sulfones. This selective oxidation of sulfides to sulfoxides led to the conclusion that the intermediate-formed *S*-nitrito onium ions prevented further oxidation by NO_2^+ and gave upon workup sulfoxides. In continuation of our work, we now investigated the reaction of sulfoxides with nitronium salts[1b] and found that sulfoxides (alkyl or aryl) on treatment with NO_2^+ are oxidized to sulfones in good to excellent yield (eq 2).



(2)

Interestingly, in the case of aromatic sulfoxides, there is no ring nitration observed.[4] This approach allows an easy

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