1.22-1.38 (m, 2 H, CH_2), 1.47 (d, J = 5.1 Hz, CH_3), 1.55-1.63 (m, 4 H, CH_2CH_2), 2.48 (d, J = 16.0 Hz, AB system, 1 H, CH_AC=O), 2.66 (d, J = 16.0 Hz, AB system, 1 H, CH_BC=O), 5.52 (q, J = 5.0 Hz, 1 H, OCHO); ^{13}C NMR δ 13.71, 20.52, 22.84, 25.45, 27.18, 29.83, 41.13, 70.64, 95.10, 172.53.

(3*S*)-3-Methyl-3-hydroxypentanoic Acid (8a) (General Procedure A). Dioxanone **5c** (423 mg, 2.1 mmol) was dissolved in THF (4 mL) and hydrochloric acid (6 mL, 1 N) and stirred at 20 °C over 45 min. The reaction mixture was extracted with ether (3 × 40 mL), dried, and evaporated. The residue was purified by flash chromatography (eluant hexane/ether, 1:2) to give the acid **8a** (166.4 mg, 60%) as an oil: $[\alpha]_D$ -0.94° (c 2.26); IR ($CHCl_3$) 3700-2400 (br), 3660 (w), 3500 (m), 2980 (s), 2940 (m), 2880 (m), 2630 (w), 1700 (s), 1460 (m), 1405 (m), 1380 (m), 1210 (s), 1140 (m), 940 (m), 880 cm^{-1} (m); ^{1}H NMR δ 0.94 (t, J = 7.5 Hz, CH_3), 1.28 (s, CH_3), 1.60 (q, J = 7.5 Hz, CH_2), 2.51 (d, J = 15.7 Hz, A part of the AB system, CH_AC=O), 2.60 (d, J = 15.7 Hz, B part of the AB system, CH_BC=O), 6.2-7.2* (br, OH, COOH); ^{13}C NMR δ 8.30, 25.98, 34.51, 44.20, 71.86, 177.38; MS, m/z 117 (5), 103 (25), 99 (7), 85 (42), 73 (33), 72 (6), 61 (6), 60 (5), 57 (25), 55 (13), 45 (8), 43 (100), 42 (8), 41 (7), 39 (6), 29 (12), 27 (8). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.08; H, 9.39.

(3*R*)-3-Methyl-3-hydroxypentanoic Acid (*ent*-8a). Via general procedure A, 407.7 mg (2.03 mmol) of dioxanone **5i** gave the acid ***ent*-8a** (268.3 mg, 86%) as an oil, $[\alpha]_D$ +107° (c 2.25).

(3*R*)-3-Phenyl-3-hydroxybutanoic Acid (8b). Via general procedure A, 200 mg (1.18 mmol) of dioxanone **5g** gave after 48 h of reaction time the acid **8b** (136.6 mg, 65%) as a solid: mp 83.4-83.7 °C (lit.[14] mp 83-84 °C), $[\alpha]_D$ -10.22° (c 1.34, EtOH) (lit.[14] $[\alpha]_D$ +9.07° (c 3.76, EtOH), for the S isomer (92% ee)).

(*S*)-Mevalolactone. Dioxanone **5h** (125 mg, 0.59 mmol) was dissolved in methanol (10 mL) and treated with ozone at -78 °C until the colour of the reaction mixture became blue. Sodium borohydride (22.3 mg, 0.59 mmol) was added, and the suspension was stirred over 2 h at 0 °C. After evaporation of the solvent, the residue was dissolved in sodium hydroxide[1] (1 mL, 1 N) and stirred at 0 °C for 13 h. The solution was acidified (HCl, 5 N), extracted with chloroform (3 × 20 mL), dried, and evaporated. The residue was purified by flash chromatography (eluant ethyl acetate) to give (*S*)-mevalolactone (19.7 mg, 25%) as a colorless oil, $[\alpha]_D$ +21.2° (c 1.69, EtOH) (lit.[15] $[\alpha]_D$ +21.7° (c 0.75, 95% EtOH)).

(2*R*)-2-*tert*-Butyl-5-deuterio-6-methyl-2*H*,4*H*-1,3-dioxin-4-one (5-Deuterio-1). (2*R*)-5-Bromo-2-*tert*-butyl-6-methyl-2*H*,4*H*-1,3-dioxinone[6] (700 mg, 2.8 mmol) was dissolved in benzene (15 mL); 10% Pd/C (375 mg) and Et_3N (0.4 mL, 2.8 mmol) were added, and the mixture was stirred under D_2 for 2 h. The suspension was filtered, and the residue was purified by flash chromatography (eluant hexane/ether, 3:1) to give the deuteriated dioxinone 5-deuterio-**1** (385 mg, 80%) as a solid. According to the ^{1}H NMR and the MS analyses, the isotopic purity was ≥95%. For the analytical data of the 5-H compound, see ref 6.

(2*R*,5*S*,6*R*)-2-*tert*-Butyl-5-deuterio-6-methyl-1,3-dioxan-4-one (10). 5-Deuterio-**1** (182 mg, 1.06 mmol) was dissolved in ethyl acetate (14 mL). 10% Pd/C (60 mg) was added, and the mixture was stirred for 22 h under a hydrogen atmosphere (26 atm). The suspension was filtered and evaporated, and the residue was purified by flash chromatography (eluant hexane/ether, 3:1) to give **10** (173 mg, 94%) as a solid. According to the ^{1}H NMR and the MS analyses, the isotopic purity was ≥95%. For the analytical data of the 5-H compound see ref 19.

X-ray Analysis. All intensity measurements were carried out with an ENRAF NONIUS CAD4 diffractometer with a graphite monochromator (Mo Kα radiation, A = 0.7107 Å). The structures were solved by[97] SHELX 86 and refined with the use of the X-RAY 72 system.[98]

Acknowledgment. We thank Dr. M. Demuth (MPI Mülheim), Dr. J. Winkler (University of Chicago) and Prof. Ch. Kanega (Tohoku University) for informing us about unpublished results concerning structure and photoreactivity of dioxinones prior to publication.[22-24] The help of Prof. J. D. Dunitz, Prof. M. Dobler, Dr. W. B. Schweizer, M. Egli, and Th. Maetzke with the X-ray crystal structure analyses, data-file searches, and molecular modeling is gratefully acknowledged. We thank Dr. Y. Noda for carrying out some experiments, Dr. B. Jaun and B. Brandenberg for the NMR spectra and for their help with the interpretation of the NOE measurements. Continuous financial support by the Sandoz AG (Basel) and generous gifts of the biopolymer PHB by MBL (Billingham) and of pivalaldehyde by the BASF AG (Ludwigshafen) are gratefully acknowledged.

Supplementary Material Available: Tables containing crystallographic data, atomic coordinates and displacement parameters, and bond lengths and angles of **11** and **12**, calculated coordinates, net charges, and overlap populations (9 pages). Ordering information is given on any current masthead page.

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Facilitation of Electrochemical Oxidation of Dialkyl Sulfides Appended with Neighboring Carboxylate and Alcohol Groups†

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Abstract: The electrochemical oxidation of variously 2-substituted 6-(methylthio)bicyclo[2.2.1]heptanes in acetonitrile was studied by using cyclic voltammetry. Three compounds, endo acid salt **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g**, were found to oxidize much more easily in the presence of trace amounts of bromide ion. Controlled potential electrolysis of endo acid salt **1h** in the presence of 2,6-di-*tert*-butylpyridine and a small amount of water gave endo acid sulfoxide **5a**. Such oxidation in the presence of ^{18}O-labeled water led to the incorporation of the label into the oxygen atoms of both the sulfoxide and carboxylate moieties of endo acid sulfoxide **5a**. This result suggested the intermediacy of acyloxysulfonium salt **6**. This salt was prepared by bromine oxidation of endo acid salt **1h** at low temperatures, characterized spectroscopically, and hydrolyzed to endo acid sulfoxide **5a**. Controlled potential electrolysis of endo primary alcohol **1c** and endo tertiary alcohol **1g** in the presence of 2,6-di-*tert*-butylpyridine produced the corresponding alkoxysulfonium salts **7a** and **7b**, respectively. These data are interpreted in terms of bromide catalysis of the thioether oxidation with neighboring carboxylate or alcohol participation.

Electrochemical evidence, which supported the hypothesis that certain groups proximate to a sulfur atom of a thioether but not bonded to it facilitate the oxidation at sulfur by neighboring group participation, was communicated.[1] That is, the peak potential for oxidation of dialkyl sulfides appended with neighboring carboxylate or alcohol moieties was over 500 mV more cathodic than that for control compounds. The overall 2e$^-$ oxidation was suggested to occur with concomitant bond formation between an

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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Table I. Anodic Oxidation of Norbornyl Derivatives by Cyclic Voltammetry

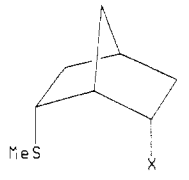
compd	E_p[a]	compd	E_p[a]
1a	1.20	**2a**	1.28
1b	1.21	**2b**	1.29
1c	0.56[c]	**2c**	1.20
1d	0.85	**2d**	1.40
1e	0.98	**2e**	1.20
1f	1.12	**2f**	1.42
1g	0.57[c]	**2g**	1.25
1h[b]	0.65[c]	**2h**[b]	1.28
3a	1.31	**4a**	1.31
3b	1.32	**4b**	1.27

[a] Peak potentials of first oxidation peak determined at a Pt electrode (1 cm^2), 0.1 V/s scan rate, and measured in acetonitrile, 0.1 M (n-Bu_4NClO_4 versus Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode). [b] Salt of acids prepared by adding 2,6-di-*tert*-butylpyridine to a solution of the corresponding carboxylic acid. [c] This peak is not observed in the absence of trace amounts of bromide ion.

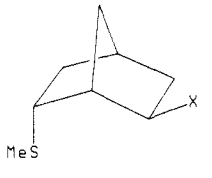
oxygen atom of the neighboring group and the sulfur atom undergoing oxidation. However, the detailed mechanism for this process was not elucidated. This paper presents the full details of the previously communicated work and convincing evidence for the mechanism of the facilitated electrochemical oxidations. This mechanism involves catalysis of the oxidation by bromide ion and neighboring carboxylate or alcohol group participation in the oxidation of these compounds with bromine.

Results and Discussion

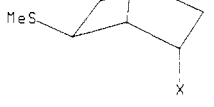
Anodic oxidation of 2-substituted 6-(methylthio)bicyclo-[2.2.1]heptanes **1–4** was studied by cyclic voltammetry in anhydrous acetonitrile. A full description of the synthesis and



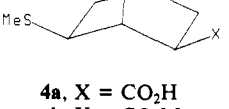
1a, X = CO_2H
b, X = CO_2Me
c, X = CH_2OH
d, X = $CONH_2$
e, X = $NHCO_2Et$
f, X = COSMe
g, X = CMe_2OH
h, X = CO_2^- $[2,6\text{-}(t\text{-}Bu)_2C_5H_4N]^+$



2a, X = CO_2H
b, X = CO_2Me
c, X = CH_2OH
d, X = $CONH_2$
e, X = $NHCO_2Et$
f, X = COSMe
g, X = CMe_2OH
h, X = CO_2^- $[2,6\text{-}(t\text{-}Bu)_2C_5H_4N]^+$



3a, X = CO_2H
b, X = CO_2Me



4a, X = CO_2H
b, X = CO_2Me

characterization of compounds **1–4** has been described elsewhere.[2,3] All of the oxidations are electrochemically irreversible even at scan rates up to 50 V/s. The peak potentials presented in Table I have been determined under a standard set of conditions. All of the peaks are well-defined. The peak potentials for most of the sulfides occur in the range expected for the oxidation of dialkyl sulfides.[4] However, the salts of endo carboxylic acid **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g** oxidize unusually easily. Thus the endo acid salt **1h** has an anodic peak potential 630 and 550 mV more cathodic than that of exo acid salt **2h** and endo acid **1a**, respectively; endo primary alcohol **1c** oxidizes at a peak potential 640 mV more cathodic than that of exo primary alcohol **2c**, and endo tertiary alcohol **1g** shows an anodic peak potential 680 mV less positive than that of exo tertiary alcohol **2g**. These unusually facile oxidations require the presence of at least traces of bromide ion. Commercially available tetra-*n*-butylammonium perchlorate and tetrafluoroborate contained sufficient amounts of bromide ion as an impurity that the unusual anodic peaks were observed when these salts were used as the supporting electrolyte. Neutron activation analysis of the commercially available tetra-*n*-butylammonium perchlorate indicated 70.8 ppm of bromide. This corresponds to a concentration of 3×10^{-5} M bromide ion in a solution 0.1 M in supporting electrolyte. However, when lithium or sodium perchlorate, both of which are bromide free by neutron activation analysis, were used as supporting electrolytes, endo acid salt **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g** showed a single anodic peak with peak potentials of 1.19, 1.03, and 1.08 V, respectively. Addition of lithium bromide resulted in the appearance of anodic peaks at 0.65, 0.56, and 0.57 V, respectively. The peak potential for oxidation of a 0.1 mM solution of lithium bromide in acetonitrile 0.1 M in lithium perchlorate determined at a Pt electrode (1 cm^2), with 0.1 V/s scan rate, was 0.57 V. Nevertheless, the amounts of lithium bromide added to endo acid salt **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g**, or the trace amounts present in commercial grade tetra-*n*-butylammonium perchlorate were insufficient to account for the amount of anodic current measured. The current flow was consistent with overall $2e^-$ oxidation of the sulfide. Since the peak potentials observed are close to that for oxidation of bromide ion to bromine in this system,[5] the bromide ion catalyzes the oxidation of the sulfide.[6] That is, the bromide ion is oxidized to bromine; the bromine then oxidizes the sulfide and in turn is reduced to bromide; the bromide ion is reoxidized electrochemically to continue this cycle. As long as the reduction of bromine by the sulfide is fast it will appear as if the sulfide is directly oxidized at a diffusion-controlled rate. Only the sulfides appended with appropriate neighboring groups show this remarkable behavior. Related examples of indirect electrooxidation mediated by bromide ion are the oxidation of alcohols to carbonyl compounds in the presence of thioethers,[6] the oxidation of amines to nitriles,[7] and the oxidation of aldehydes to esters.[8]

To gain more insight into these anodic oxidations, the controlled potential electrolysis of endo acid salt **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g** was studied. Electrolysis of endo acid salt **1h** at a controlled potential of 0.86 V, in the presence of a small amount of water and excess 2,6-di-*tert*-butylpyridine yielded the endo acid sulfoxide **5a** as a 3:2 mixture of diastereomers and an apparent "n" value, the number of electrons (or Faradays) per mole of substance electrolyzed,[10] of 1.7. The minor diastereomer was the same as the major isomer produced in the diastereoselective oxidation of endo acid **1a** with *m*-chloroperoxybenzoic acid,[8] as proven by comparison of the corresponding pure sulfoxide esters **5b** separated by preparative HPLC.

If electrochemical oxidation of endo acid salt **1h** occurs with participation, the two-electron oxidation product is acyloxy-

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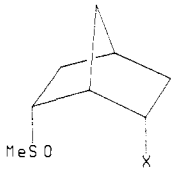
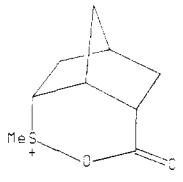
(4) Cottrell, P. T.; Mann, C. K. *J. Electrochem. Soc.* **1969**, *116*, 1499.
(5) Bromide ion shows two oxidation peaks in acetonitrile at a platinum electrode due to the following reactions: (1) $3Br^- \rightleftharpoons Br_3^- + 2e^-$; (2) $2Br_3^- \rightleftharpoons 3Br_2 + 2e^-$ Magno, F.; Mazzochini, G. A.; Bontempelli, G. *J. Electroanal. Chem.* **1973**, *47*, 461. Casalbore, G.; Mastragostino, M.; Valcher, S. *Ibid.* **1977**, *77*, 373. Casalbore, G.; Mastragostino, M.; Valcher, S. *Ibid.* **1978**, *87*, 411. Under our conditions the two oxidation peaks occurred at +0.6 and +0.8V.
(6) Bromide-ion catalysis of the electrooxidation of *n*-octyl methyl sulfide has been reported: Shono, T.; Matsumura, Y.; Hayashi, J.; Mizoguchi, M. *Tetrahedron Lett.* **1980**, *21*, 1867, in which the product then mediates the oxidation of secondary alcohols to ketones.
(7) Shono, T.; Matsumura, Y.; Inoue, K. *J. Am. Chem. Soc.* **1984**, *106*, 6075.
(8) Shono, T.; Matsumura, Y.; Hayashi, J.; Inoue, K.; Iwasaki, F.; Itoh, T. *J. Org. Chem.* **1985**, *50*, 4967.
(9) Glass, R. S.; Petsom, A.; Wilson, G. S. *J. Org. Chem.* **1987**, *52*, 3537.
(10) Bard, A. J.; Faulkner, L. R. In *Electrochemical Methods. Fundamentals and Applications*; Wiley: New York, 1980, pp 370–428.



5a, X = CO_2H
b, X = CO_2Me
c, X = CH_2OH
d, X = CMe_2OH

sulfonium salt **6**, which is expected to hydrolyze to endo acid sulfoxide **5a**. Acyloxysulfonium salts have been proposed as



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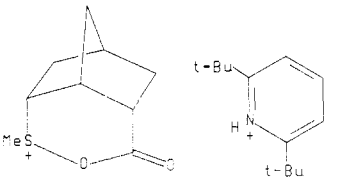
intermediates in other reactions such as the reaction of sulfoxides with anhydrides and acid chlorides[11] and carboxylate-catalyzed oxidation of thioethers by iodine.[12] Cyclic acyloxysulfonium salts have been suggested as intermediates in the reduction and racemization of various sulfoxide carboxylic acids with appropriate geometry,[13] acid-catalyzed hydrolysis of a sulfimide carboxylic acid,[14] the reaction of *o*-carboxyphenyl sulfoxides with acetic anhydride,[15] and the reaction of 2-(phenylsulfinyl)benzoic acid with trifluoromethanesulfonic anhydride, in which case the corresponding acyloxysulfonium triflate has been isolated.[16] Acyloxysulfuranes, which are closely related to acyloxysulfonium salts, have also been prepared and isolated.[16,17] Solutions of acyloxysulfonium salt **6** were prepared by chemical methods in order to determine its properties. Treatment of the 18-crown-6 complex of the potassium salt of endo acid **1a** in acetonitrile at −40 °C with bromine followed by silver tetrafluoroborate resulted in the precipitation of 2 formula weight equiv of silver bromide. The bromine-free oxidation product in solution showed a carbonyl stretching frequency in the infrared at 1828 cm^{-1}, which is in the range expected for acyloxysulfonium salt **6**.[16] The absorption due to the methyl protons in the ^1H NMR spectrum of this salt overlapped with the large absorption due to the protons of 18-crown-6, which is also present in the solution. To avoid this overlap, endo acid salt **1h** was used in the bromine oxidation instead of the 18-crown-6 complex of the potassium salt of endo acid **1a**. The ^1H NMR spectrum of the oxidation product obtained in this manner showed absorption in the expected region due to the methyl protons at δ 3.1 ppm. However, the infrared spectrum of this material exhibited absorption due to carbonyl stretching at 1714 cm^{-1} rather than at 1828 cm^{-1}. This lower frequency absorption is apparently due to the hydrogen bonding between the carbonyl oxygen of acyloxysulfonium salt **6** and the 2,6-di-*tert*-butylpyridinium ion as shown in **7**.[18] If 2,6-di-*tert*-butyl-



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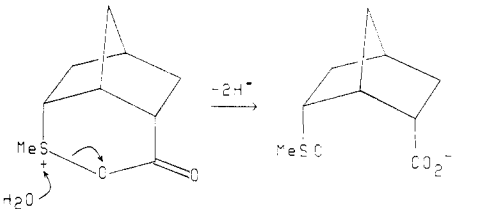
pyridinium trifluoromethanesulfonate is added to a solution of acyloxysulfonium salt **6** prepared from the 18-crown-6 complex of the potassium salt of endo acid **1a**, an infrared absorption appears at 1714 cm^{-1} and that at 1828 cm^{-1} diminishes. Hydrolysis of this oxidation product provided endo acid sulfoxide **5a** in good yield. Although acyloxysulfonium salt **6** was stable at low temperatures in acetonitrile solution, it undergoes decomposition rapidly when warmed to 0 °C or above in solution. The hydrolysis of acyloxysulfonium salt **6** to endo acid sulfoxide **5a** and its thermal instability, presumably undergoing Pummerer rearrangement,[11] are in accord with literature precedent.

To find out whether acyloxysulfonium salt **6** is formed on anodic oxidation of endo acid salt **1h**, it must be trapped as soon as it is formed. Controlled potential electrolysis of endo acid salt **1h** in the presence of water was already shown to give endo acid sulfoxide **5a**. To provide compelling evidence for the intermediacy of the acyloxysulfonium salt in the anodic oxidation of endo acid salt **1h**, the controlled potential electrolysis was repeated in the presence of ^{18}O-labeled water and excess 2,6-di-*tert*-butylpyridine. The endo acid sulfoxide **5a** was isolated as a 3:2 mixture of diastereomers in 68% yield. This mixture was converted to the corresponding methyl esters **5b**, which were separated into each pure diastereomer by HPLC on silica gel. Analysis of each diastereomeric endo ester sulfoxide **5b** by mass spectroscopic analysis showed ^{18}O incorporation into the oxygen atoms of both the sulfoxide and ester moieties in the ratio of approximately 2:1, respectively, for both diastereomers. These results suggest that acyloxysulfonium salt **6** formed in this electrolysis and of endo acid salt hydrolyzed to endo acid sulfoxide **5a** by nucleophilic attack competitively at sulfur and the carbonyl group, as expected. That is, nucleophilic attack by ^{18}O-labeled water on the sulfur atom displacing carboxylate (1) results in formation of endo acid



(1)

sulfoxide **5a** with ^{18}O incorporation into the sulfoxide oxygen. In addition, nucleophilic attack by ^{18}O-labeled water at the acyl carbon generating a tetrahedral intermediate followed by expulsion of the sulfoxide moiety results in ^{18}O incorporation into the

(11) Acyloxysulfonium salts have been suggested as intermediates in the Pummerer reaction (Block, E. *Reactions of Organosulfur Compounds*; Academic: New York, 1978, pp 154–162) and in the oxidation of alcohols with dimethyl sulfoxide and acid anhydride mixtures: Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214; **1967**, *89*, 2416. Reaction between dimethyl sulfoxide and acetic anhydride to give the corresponding acyloxysulfonium salt is an unfavorable equilibrium so that the acyloxysulfonium salt cannot be directly observed by ordinary NMR monitoring: Varkey, T. E.; Whitfield, G. F.; Swern, D. *J. Org. Chem.* **1974**, *39*, 3365.

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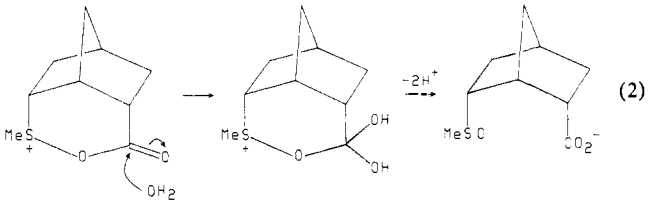
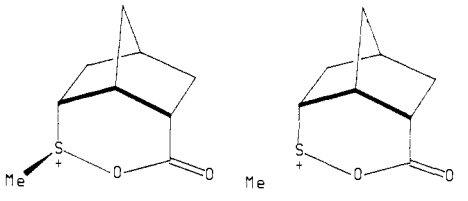
(18) A referee pointed out that the observed shift ascribed to hydrogen bonding effects is unusually large. Indeed the carbonyl stretching frequency for carboxylic acid esters has been previously reported to shift 20–50 cm^{-1} due to hydrogen bonding: Yasuda, N.; Nakamura, A.; Tsuboi, M. *J. Heterocycl. Chem.* **1987**, *24*, 303 and references therein. However, the carbonyl stretching frequencies of ethyl acetate and methyl isobutyrate, which occur at 1736 and 1735 cm^{-1}, respectively, in acetonitrile, both shift to approximately 1619 cm^{-1} (117 and 116 cm^{-1} shifts, respectively) on addition of 2,6-di-*tert*-butylpyridinium trifluoromethanesulfonate (a broad absorption of this salt also occurs at 1619 cm^{-1} and must be subtracted to reveal the shifted carbonyl stretching frequencies). The difference between our results and those obtained previously may be due to the use of a hydrogen-bond donor in which the hydrogen atom is attached to a positively charged nitrogen atom, thereby resulting in stronger hydrogen bonds, instead of a neutral nitrogen or oxygen atom.

carboxylate moiety as shown in mechanism 2. Indeed hydrolysis



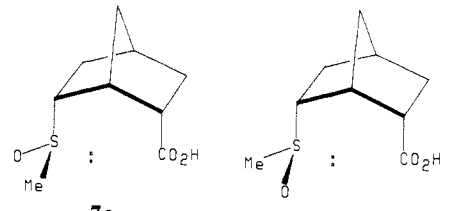
(2)

of the chemically prepared solution of acyloxysulfonium salt **6** at −25 °C with ^{18}O-labeled water in the presence of 2,6-di-*tert*-butylpyridine resulted in the formation of endo acid sulfoxide **5a** in 96% yield with ^{18}O incorporation into both the sulfoxide and carboxylate moieties. In this case as in the controlled potential electrolysis of endo acid salt **1h**, both diastereomic endo acid sulfoxides **5a** are formed in a 3:2 ratio. The diastereomers were separated by HPLC after conversion to the corresponding methyl esters. The ^{18}O label was incorporated into each of the diastereomers. To account for ^{18}O incorporation in the sulfoxide and carboxylate moieties of both diastereomeric endo acid sulfoxides, both diastereomeric acyloxysulfonium salts **6** are suggested to form. Indeed, examination of the ^1H NMR spectrum of the chemically prepared acyloxysulfonium salt **6** showed two methyl absorbances in the ratio of 66:34. The major diastereomer is suggested to have structure **6a** in analogy with studies on endo alcohol **1c** discussed later in this paper. Therefore, the minor isomer is **6b**. Attack by water on acyloxysulfonium **6** at sulfur



6a **6b**

according to mechanism 1 is assumed to result in inversion of configuration at sulfur[11] whereas attack at carbon according to mechanism 2 results in retention of configuration at sulfur. Therefore, attack by ^{18}O-labeled water at sulfur of diastereomer **6a** produces the major diastereomeric endo acid sulfoxide **7a** with ^{18}O-labeled sulfoxide. The same endo acid sulfoxide is produced



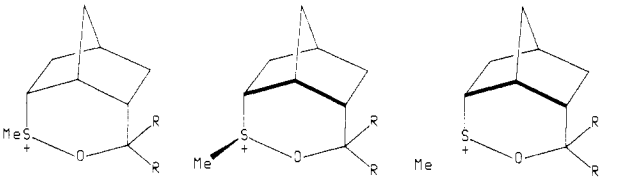
7a **7b**

with ^{18}O-labeled carboxylate by water attack on carbon of the minor diastereomer acyloxysulfonium salt **6b**. Similarly, the minor diastereomeric endo acid sulfoxide **7b** forms with ^{18}O-labeled sulfoxide by water attack on the sulfur atom of the minor acyloxysulfonium salt diastereomer **6b** and ^{18}O-labeled carboxylate by water attack on carbon of acyloxysulfonium salt diastereomer **6a**. The ratio of diastereomeric endo acid sulfoxides **5a** was determined by ^1H NMR analysis and the ^{18}O labeling determined quantitatively in each isomer by the methods already discussed. Such experimental results combined with the mechanistic rationale yield a 3:2 ratio of the diastereomeric acyloxysulfonium salts **6a** and **6b**, respectively. This compares favorably with the ratio of diastereomeric alkoxysulfonium salts obtained by ^1H NMR analysis of the chemically prepared solution at low temperature. Furthermore, the ratios of water attack at sulfur versus carbon for acyloxysulfonium salt diastereomers **6a** and **6b** are 74:26 and 78:22, respectively. These results provide indirect but compelling evidence for the intermediacy of acyloxysulfonium salt **6** in the anodic oxidation of endo acid salt **1h**.

It is conceivable that in the electrochemical experiment the ^{18}O label in the carboxylic acid moiety arises not by water attack on the acyloxysulfonium salt as shown in (2) but rather by oxygen exchange between the carboxyl and sulfoxide oxygens. That is, only sulfoxide-labeled product is initially produced, which then scrambles its oxygen label with the carboxylic group (most likely during the acidic workup conditions). To preclude this possibility, both sulfoxide carboxylic acid **5a** selectively labeled in the sulfoxide moiety and a sample selectively labeled in the carboxylic acid group were synthesized, as outlined below, and were dissolved in a solution containing the components present at the end of the controlled potential electrolysis and unlabeled water. Workup and mass spectroscopic analysis of the isolated endo ester sulfoxide **5b** as before revealed no significant interchange of the ^{18}O label between the sulfoxide and carboxylic acid moieties or loss of label.

Sulfoxide carboxylic acid **5a** labeled with ^{18}O in the carboxylic acid moiety was prepared as follows. Acid-catalyzed hydrolysis of acyl imidazolide **1**, X = CO (1-imidazole), in ^{18}O-labeled water provided **1a** with high incorporation of the ^{18}O label into the carboxylic acid group. Oxidation with *m*-chloroperoxybenzoic acid yielded sulfoxide carboxylic acid **5a**, selectively labeled in the carboxylic acid moiety, in high yield in a 4:1 ratio of diastereomers.[9] Preparation of sulfoxide carboxylic acid **5a** labeled in the sulfoxide moiety was accomplished in two steps. Oxidation of ester **1b** with the diazabicyclo[2.2.2]octane·$2Br_2$ complex in acetic acid containing ^{18}O-labeled water[9,19] afforded the corresponding ^{18}O-labeled sulfoxide. Saponification gave sulfoxide carboxylic acid **5a** with the ^{18}O label in the sulfoxide group.

Controlled potential electrolysis of endo primarily alcohol **1c** at 0.65 V in the presence of 2,6-di-*tert*-butylpyridine gave an "*n*" value[10] of 1.9. Analysis of the electrolysis solution by ^1H NMR spectroscopy suggested the presence of alkoxysulfonium salt **8a** as a 76:24 mixture of diastereomers **9a** and **10a**, respectively,[3,20] formed in a combined yield of 90%. The mixture was hydrolyzed

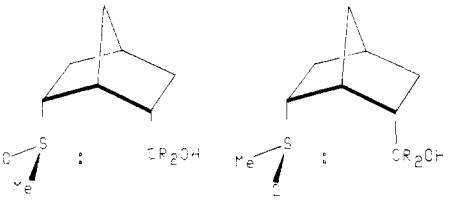


8a, R = H
b, R = Me

9a, R = H
b, R = Me

10a, R = H
b, R = Me

with aqueous base to provide the diastereomeric endo primary alcohol sulfoxides **11a** and **12a**, which were separated by HPLC and shown to be identical with authentic samples. Similarly,



11a, R = H
b, R = Me

12a, R = H
b, R = Me

controlled potential electrolysis of endo tertiary alcohol **1g** in anhydrous acetonitrile at 0.6 V in the presence of 2,6-di-*tert*-butylpyridine and a trace amount of bromide ion gave an "*n*" value[10] of 1.9. ^1H NMR spectroscopic analysis of the solution showed the formation of alkoxysulfonium salts **8b** in 85% yield as a 45:55 mixture of diastereomers **9b** and **10b**, respectively.[3] These results constitute examples of neighboring group participation by an alcohol moiety in the electrochemical oxidation of a thioether.

(19) Oae, S.; Ohishi, Y.; Kazuika, S.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 364.
(20) Glass, R. S.; Setzer, W. N.; Prabhu, U. D. G.; Wilson, G. S. *Tetrahedron Lett.* **1982**, *23*, 2335.

Since the electrochemical oxidation of endo acid salt **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g** occurs via bromide ion catalysis, chemical oxidation of these compounds with bromine under similar conditions should give the same products and, particularly, comparable ratios of diastereomers. As already discussed in the case of endo acid salt **1h**, both electrochemical and bromine oxidation followed by hydrolysis afforded endo acid sulfoxide **5a** in a 60:40 and 66:34 ratio of diastereomers respectively. Treatment of endo primary alcohol **1c** with bromine followed by silver perchlorate gave alkoxysulfonium salt **8a** with a ratio of 80:20 of diastereomers **9a**:**10a** as determined by ^{1}H NMR spectroscopy.[3,20] Hydrolysis of the mixture with aqueous base yielded endo primary alcohol sulfoxide diastereomers **11a** and **12a** in a ratio of 80:20, respectively.[3,20] Similarly, treatment of endo tertiary alcohol **1g** with bromine followed by silver perchlorate gave alkoxysulfonium salt **8b** with an 38:62 ratio of diastereomers **9b** and **10b**, respectively.[3,20] Hydrolysis of the mixture with aqueous base afforded the corresponding endo tertiary alcohol sulfoxides **11b** and **12b** as a 2:3 mixture, respectively, in 91% yield. These sulfoxides were also separated by HPLC. The results compare favorably with those obtained by electrochemical oxidation and support the suggestion that the bromine generated electrochemically reacts with endo acid salt **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g**.

In summary, anodic oxidation of thioethers exhibit a peak at ca. 0.6 V when bromide ion and a neighboring carboxylate or alcohol moiety are present. These oxidations produce acyloxy- or alkoxysulfonium salts in which there is a bond between sulfur and oxygen. Such participation in the oxidation of thioethers by halogen has been reported before in other systems using different methods. Klein and Stollar[21] on the basis of stereochemical studies suggested that 4-hydroxy groups participate in the oxidation of thianes with wet bromine. Hirschon et al.[22] reported alcohol participation in the aqueous iodine oxidation of 5-hydroxythiacyclooctane, 4-hydroxythiacyclohexane, and 4-hydroxy-4-methylthiacyclohexane on the basis of stereochemical and kinetic studies. In addition, the bridged alkoxysulfonium salt formed in iodine oxidation of 5-hydroxythiacyclooctane was isolated and characterized. On the other hand, oxidation of *o*-(methylthio)-benzoic acid with aqueous iodine was reported by Tagaki et al.[23] to involve general base not nucleophilic catalysis by the carboxylate group. This result contrasts with the reports that the acceleration in the oxidation of thioethers to sulfoxides with aqueous iodine by mono- and dicarboxylate ions is due to intermolecular nucleophilic catalysis.[12,24]

Experimental Section

Cyclic Voltammetry. Voltammograms were measured on solutions approximately 10^{-3} M in dialkyl sulfide and 0.1 M in tetra-*n*-butylammonium perchlorate, which served as supporting electrolyte, in acetonitrile with a Ag/0.10 M $AgNO_3$ in acetonitrile reference electrode. A 1.0-cm^2 platinum flag, which was heated to incandescence in a flame prior to each run, served as the working electrode, and the data were collected with a cyclic scan rate of 0.1 V/s. The electrochemical apparatus was purged with nitrogen, and the experiment was run under the flow of nitrogen or assembled and used in a Vacuum Atmosphere Model HE-113-210 Dry Box equipped with an HE-493 Dri-Train purification system. The electrochemical instrumentation, data acquisition, and data processing systems have been described previously.[25]

Controlled Potential Electrolysis of 6-*endo*-(Methylthio)bicyclo-[2.2.1]heptane-2-*endo*-carboxylate (1h). A sample of endo acid **1a** (40 mg, 0.215 mmol), 2,6-di-*tert*-butylpyridine (124 mg, 0.645 mmol), ^{18}O-enriched water (5.0 mg, 0.25 mmol), and tetra-*n*-butylammonium tetrafluoroborate (1.644 g, 10 mmol), dissolved in anhydrous acetonitrile (100 mL), was exhaustively electrolyzed at a constant potential of 0.86 V versus a Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode. When the current decayed to 0.1% of its initial value, 35.85 Coulombs had passed. This corresponds to an "*n*" value of 1.7.

The solution from the controlled potential electrolysis was lyophilized. The residue was dissolved in acetonitrile/water (1:1) and chromatographed (HPLC) on a Nucleosil C18 column (8 × 25 mm, 1:1 acetonitrile/water as eluant, 2.2 mL/min flow rate). The fractions eluted were monitored by UV absorption at 220 nm, and the fraction corresponding to 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid *S*-oxide (**5a**) by retention time was collected. A peak with the same retention time as starting endo acid **1a** was observed, and its absorbance corresponded to 4.0 mg of endo acid **1a** (10% unreacted). This fraction was lyophilized and rechromatographed with acetonitrile/water (9:1) to separate the supporting electrolyte. The fraction corresponding to sulfoxide acid **5a** was collected and lyophilized to give sulfoxide acid **5a** (26.5 mg, 68%). Analysis by ^{1}H NMR revealed the two diastereomeric sulfoxides **5a** in a ratio of 3:2.

The sulfoxide acid **5a** was dissolved and treated with excess diazomethane solution in ethyl ether. The reaction mixture was concentrated to an oil, dissolved in acetonitrile/methanol (19:1) and chromatographed (HPLC) on silica gel (Lichrosorb SI 100, 4 × 25 cm, 19:1 acetonitrile/methanol as eluant, 2 mL/min flow rate). The fractions eluted were monitored by UV absorption at 220 nm. The fractions corresponding to each of the diastereomeric sulfoxide esters **5b** were collected separately. Their ratio determined by UV absorption was 67:33. The ^{18}O content and distribution in each isomer was determined by mass spectroscopic analysis.

Major sulfoxide ester **5b**: 218 ($M^+ + 2$, 4352), 216 (M^+, 3668), 155 (13 732), 153 (20 728). Computation of ^{18}O distribution: %^{18}O incorporation = [intensity 218/(intensity 216 + 218)] × 100 = [4352/(3668 + 4352)] × 100 = 54; intensity of 153 + 155 peaks from ^{18}O-enriched sulfoxide ester = I = (intensity 153 + 155) × 0.54 = (20 728 + 13 732) × 0.54 = 18 608; %^{18}O enrichment of CO_2Me in sulfoxide ester = [(I − intensity 155)/I] × 100 = [(18 608 − 13 732)/18 608] × 100 = 26.

Minor sulfoxide ester **5b**: 218 ($M^+ + 2$, 1440), 216 (M^+, 1291), 155 (6284), 153 (8820). Computation of ^{18}O distribution %^{18}O incorporation = [intensity 218/intensity (216 + 218)] × 100 = [1440/(1292 + 1440)] × 100 = 53; intensity of 153 + 155 peaks from ^{18}O-enriched sulfoxide ester = I = (intensity 153 + 155) × 0.53 = (8820 + 6284) × 0.53 = 8005; %^{18}O enrichment of CO_2Me in sulfoxide ester = [(I − intensity 155)/I] × 100 = [(8005 − 6284)/8005] × 100 = 22.

Controlled Potential Electrolysis of 2-*endo*-(Hydroxymethyl)-6-*endo*-(methylthio)bicyclo[2.2.1]heptane (1c). A sample of endo primary alcohol **1c** (50 mg, 0.29 mmol) and 2,6-di-*tert*-butylpyridine (0.14 mL, 0.62 mmol) were dissolved in an 0.1 M solution of sodium perchlorate in anhydrous acetonitrile (50 mL). A portion of an 0.1 M solution of lithium bromide in anhydrous acetonitrile (50 μL, 5 μmol) was added to this solution. The solution was exhaustively electrolyzed at a constant potential of +0.65 V versus a Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode. The total charge corresponded to an "*n*" value of 1.9. The solution was concentrated to dryness under reduced pressure using a rotary evaporator and a bath temperature of 40–50 °C. The residue was repeatedly triturated with ethyl acetate. The combined extracts (50 mL) were filtered and concentrated to dryness with a rotary evaporator. The residue was washed with diethyl ether (2 × 10 mL) and dried with a rotary evaporator to give a white solid (136 mg), which was analyzed by ^{1}H NMR spectroscopy. Such analysis of a solution of this material in deuteriochloroform with piperonal as an internal standard revealed alkoxysulfonium salt **8a** formed in 90% yield as a mixture of diastereomers **9a** and **10a** in a 76:24 ratio. This mixture was further purified by preparative HPLC with a Nucleosil C-18 column (8 mm × 25 cm), eluting with acetonitrile at 1.5 mL/min flow rate, and monitoring with a UV detector set at 230 nm. The fraction with a retention time of 5.7 min was collected, and its ^{1}H NMR spectrum was identical with that of a mixture of **9a** and **10a** obtained by bromine oxidation of endo primary alcohol **1c**. The mixture of diastereomers **9a** and **10a** was also hydrolyzed by dissolving in 10% aqueous sodium hydroxide solution. The solution was saturated with sodium chloride and repeatedly extracted with dichloromethane. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered, and concentrated to a solid, which was chromatographed with HPLC techniques on a Nucleosil C-18 column (8 mm × 25 cm), eluting with acetonitrile/water (95:5) with a flow rate of 2.2 mL/min, and using a UV detector set at 220 nm. Two peaks with retention times of 4.5 and 5.8 min were eluted and separately collected. These samples were analyzed by ^{1}H NMR spectroscopy at 250 MHz and found to be identical with the known diastereomeric sulfoxide alcohols **11a** and **12a**, respectively.

Controlled Potential Electrolysis of 2-*endo*-[1-(Methylhydroxy)-ethyl]-6-*endo*-(methylthio)bicyclo[2.2.1]heptane (1g). A sample of endo tertiary alcohol **1g**[3] (73 mg, 0.37 mmol) and 2,6-di-*tert*-butylpyridine (0.17 mL, 0.75 mmol) were dissolved in an 0.1 M solution of sodium perchlorate in anhydrous acetonitrile (50 mL). A portion of a 0.1 M

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(22) Hirschon, A. S.; Beller, J. D.; Olmstead, M.; Doi, J. T.; Musker, W. K. *Tetrahedron Lett.* **1981**, *22*, 1195. Hirschon, A. S.; Doi, J. T.; Musker, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 725.
(23) Tagaki, W.; Ochiai, M.; Oae, S. *Tetrahedron Lett.* **1968**, 6131.
(24) Higuchi, T.; Gensch, K.-H. *J. Am. Chem. Soc.* **1966**, *88*, 5486.
(25) Langhus, D. L.; Wilson, G. S. *Anal. Chem.* **1979**, *51*, 1139.

solution of lithium bromide in anhydrous acetonitrile (50 μL, 5 μmol) was added to this solution. The solution was electrolyzed as that described for endo primary alcohol **1c**. The total charge corresponded to an "*n*" value of 1.9. The solution was worked up as in the electrolysis of endo primary alcohol **1c**, and the solid obtained was dissolved in acetonitrile-d_3 and analyzed by ^{1}H NMR spectroscopy. This analysis revealed the formation of alkoxysulfonium salt **8b** in 85% yield as a mixture of diastereomers **9b** and **10b** in a ratio of 45:55. Further purification by HPLC gave a sample whose ^{1}H NMR spectrum was identical with that of a mixture of **9b** and **10b** obtained by bromide oxidation of endo tertiary alcohol **1g**.

Oxidation of Endo Primary Alcohol 1c with Bromine Followed by Hydrolysis. A solution of endo primary alcohol **1c** (172 mg, 1.00 mmol) and 2,6-di-*tert*-butylpyridine (286 mg, 1.40 mmol) dissolved in anhydrous acetonitrile (6 mL) was placed under an argon atmosphere and cooled to −35 °C. A solution of bromine (51 μL, 1.0 mmol) in anhydrous acetonitrile (2 mL) was added with stirring over 10 min. After completion of the addition, the yellow solution was stirred at −35 °C for 1 h, and then anhydrous silver perchlorate (414 mg, 2.00 mmol) was added. After being stirred for 1 h at −35 °C, the mixture was allowed to warm to room temperature and stirred for 30 min at this temperature. The mixture was filtered, and the precipitate was washed with acetonitrile (10 mL). The combined filtrates were concentrated under reduced pressure to a solid (165 mg): ^{1}H NMR (CD_3CN) δ 1.2–3.9 (m, ring protons), 3.29 (s, CH_3S), 3.44 (s, CH_3S), 4.22, 4.27, 4.42, 4.62 (two overlapping AB systems, CH_2O). Analysis of this ^{1}H NMR spectrum showed an 80:20 mixture of diastereomeric alkoxysulfonium salts **8a**.

This mixture of alkoxysulfonium salts was dissolved in distilled acetonitrile (5 mL), and a solution of sodium hydroxide (40 mg, 1.0 mmol) in distilled water (2 mL) was added. The mixture was stirred at room temperature for 30 min. Distilled water (15 mL) was then added, and the acetonitrile was removed under reduced pressure. The aqueous solution was then lyophilized to a white solid (100 mg, 86%), which was chromatographed by preparative HPLC with use of a Lichrosorb SI 100 column (4.6 mm × 25 cm), eluting with acetonitrile (flow rate of 1.5 mL/min) and monitoring with a UV detector set at 230 nm. The major diastereomer **11a** eluted with a retention time of 3.8 min (71 mg, 71%): mp 96–98 °C; IR (KBr) 3240 (OH), 1055 (SO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75–3.05 (m, ring protons), 2.70 (s, SCH_3), 3.83 (m, CH_2O). The minor diastereomer **11b** eluted with a retention time of 4.2 min (23 mg, 23%): mp 109–111 °C; IR (KBr) 3310 (OH), 1045 (SO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.65–3.1 (m, ring protons), 2.49 (s, SCH_3), 3.83 (m, CH_2O).

Oxidation of Endo Tertiary Alcohol 1g with Bromine Followed by Hydrolysis. A sample of endo tertiary alcohol **1g** (200 mg, 1.00 mmol) was oxidized by bromine (55 μL, 1.05 mmol) in the presence of 2,6-di-*tert*-butylpyridine (300 mg, 1.50 mmol) following the procedure outlined for the bromine oxidation of endo primary alcohol **1c**. Silver perchlorate (414 mg, 2.00 mmol) was added as outlined previously. Workup as before led to alkoxysulfonium salt **8b** (287 mg): ^{1}H NMR (CD_3SOCD_3) δ 1.12, 1.23 (dd, 1H), 1.36, 1.40, 1.60, 1.62 (s, CH_3C), 1.59–3.15 (m, ring protons), 3.20, 3.40 (s, CH_3S). Analysis of this spectrum showed a 38:62 ratio of diastereomeric alkoxysulfonium salts **8b**.

A solution of this material in acetonitrile (10 mL) was mixed with a 10% aqueous solution of sodium hydroxide and stirred at room temperature. The sample was neutralized, the acetonitrile was then removed under reduced pressure, and the resulting aqueous solution was lyophilized. The residue was triturated with chloroform. The chloroform extracts were filtered and then evaporated to give a white solid (198 mg, 91%): mp 129–133 °C, ^{1}H NMR ($CDCl_3$) δ 0.82–3.1 (m, ring protons), 1.04, 1.11, 1.24, 1.41 (s, CH_3C), 2.50, 2.55 (s, CH_3S), 4.9 (br, OH). Analysis of this ^{1}H NMR spectrum showed a mixture of diastereomeric sulfoxides **11b** and **12b** in a 2:3 ratio, respectively. This material was chromatographed by preparative HPLC with a Lichrosorb SI 100 column (4.6 mm × 25 cm), eluting with an acetonitrile/methanol gradient and monitoring with a UV detector. The minor isomer had a retention time of 3.0 min (67 mg, 33%): mp 132–134 °C; IR (KBr) 3445 (OH), 1048 (SO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79–3.00 (m, ring protons), 1.07, 1.24 (s, CH_3C), 2.48 (s, CH_3S), 5.0 (br s, 1H, OH). This sample was identical with that reported previously.[3] The major isomer had a retention time of 4.1 min (105 mg, 53%): mp 147–149.5 °C; IR (KBr) 3435 (OH), 1060 (SO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82–2.99 (m, ring protons), 1.14, 1.42 (s, CH_3C), 2.40 (s, CH_3S), 4.80 (br s, 1H, OH).

Endo Carboxylate K^+–18-Crown-6 Salt. A sample of endo acid **1a** (118 mg, 64 mmol) was dissolved in 0.420 M potassium hydroxide in 95% ethanol (1.52 mL, 64 mmol). A sample of 18-crown-6 (168 mg, 64 mmol) was added, and the mixture was stirred at room temperature for 1 h. The solution was then concentrated under reduced pressure, and the solid obtained was recrystallized from ethyl acetate/hexane to give the salt as white needles: 175 mg (57%); mp 234–235 °C; IR (KBr) 1571 (CO_2^-) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4–3.2 (m with s at 2.2, 11 H), 3.64 (s, 24 H, OCH_2). Anal. Calcd for $C_{21}H_{36}O_8SK\cdot1.5H_2O$: C, 49.10; H, 7.46; S, 6.24. Found: C, 49.02; H, 7.62; S, 6.38.

***S*-Methyl-4-oxo-2-thionia-3-oxatricyclo[5.2.1.0^{5,9}]decane (6). Method A.** To a sample of endo carboxylate K^+–18-crown-6 prepared as above (113 mg, 0.231 mmol), dissolved in anhydrous acetonitrile (5.0 mL), and cooled to −40 °C under a nitrogen atmosphere was added bromine (11.0 μL, 34 mg, 0.215 mmol). The solution rapidly decolorized, and on addition of a 0.245 M solution of silver tetrafluoroborate in acetonitrile (1.89 mL, 0.46 mmol) a precipitate formed. The solution was filtered at −35 °C, and the precipitated silver bromide was washed, dried, and weighed: 83.5 mg, 96% yield. An IR spectrum of the filtrate at −35 °C showed absorption at 1828 cm^{-1} (C=O). A solution of 2,6-di-*tert*-butylpyridine (20 μL, 20 mg, 10 mmol) and trifluoromethanesulfonic acid (9.4 μL, 16 mg) in acetonitrile (1 mL) was added portionwise under anhydrous conditions to the IR sample at −35 °C. The intensity of the absorption peak at 1828 cm^{-1} diminished, and absorption appeared at 1713 cm^{-1}. Ultimately the absorption at 1828 cm^{-1} almost completely disappeared, and there was strong absorption at 1713 cm^{-1}. The ^{1}H NMR spectrum was taken at −35 °C on a similarly prepared sample in acetonitrile-d_3: endo carboxylate K^+–18-crown-6 (10 mg, 0.02 mmol), in acetonitrile-d_3 (2 mL), bromine (2.7 μL, 8.5 mg, 0.053 mmol), silver tetrafluoroborate (21.1 mg, 0.106 mmol) in acetonitrile-d_3 (1 mL) filtered into an NMR tube at −35 °C (silver bromide precipitated 22 mg, 99%): ^{1}H NMR δ 1.5–3.1 (m, ring H), 3.2–3.4 (br, CH_2O).

Method B. To a stirred solution of endo acid **1a** (30 mg, 0.16 mmol) dissolved in acetonitrile-d_3 (2 mL) under a nitrogen atmosphere was added 2,6-di-*tert*-butylpyridine (32 mg, 0.16 mmol). After being stirred for 1 h the solution was transferred to a filtration apparatus cooled to −35 °C. Bromine (8.3 μL, 29 mg, 0.16 mmol) was added followed by a solution of silver tetrafluoroborate (63 mg, 32 mmol) in acetonitrile-d_3 (2 mL). A precipitate formed, and the solution was filtered. The precipitated silver bromide weighed 64 mg, and the ^{1}H NMR spectrum of the filtrate was measured at −35 °C: ^{1}H NMR (CD_3CN) δ 1.5 (s, 18 H, *t*-Bu), 2–3.1 (m, ring H), 3.2 (s, 3 H, CH_3), 7.9–8.5 (m, 3 H, Ar H). A solution was prepared similarly in acetonitrile, and its IR spectrum was measured at −35 °C: IR (CH_3CN) 1713 cm^{-1}.

Hydrolysis of Acyloxysulfonium Salt 6. To a sample of acyloxysulfonium salt **6** in acetonitrile, prepared according to method B with endo acid **1a** (30 mg, 0.16 mmol) as starting material and separated from silver bromide, was added ^{18}O-labeled water (0.3 mL, 15 mmol) at −25 °C. The solution was allowed to warm to room temperature slowly, and the acetonitrile was removed under reduced pressure. Distilled water (5 mL) was added, and the solution was passed through a column of ion-exchange resin in the acid form (Dowex 50W-X8). The acidic fractions were collected, combined, and lyophilized to give a yellow solid (30.5 mg). This solid was dissolved in anhydrous dichloromethane and treated with excess diazomethane solution in diethyl ether at −20 °C. The solution was warmed to room temperature, washed with a saturated aqueous solution of sodium bicarbonate, and dried with anhydrous magnesium sulfate. The mixture was filtered and concentrated on a rotary evaporator to a light yellow liquid (32 mg). This material was chromatographed by HPLC on a silica gel column (Lichrosorb SI 100, 25 cm × 4.6 mm) and eluting with a 95:5 acetonitrile/methanol solution. The flow rate was 2 mL/min, and the UV detector was set at 205 nm. Two peaks were detected at 4.6 and 5.8 min in a ratio of 70:30, and each was collected. Spectroscopic data for the major diastereomer of sulfoxide ester **5b**: ^{1}H NMR ($CDCl_3$) δ 1.5–3.3 (m, ring protons), 2.67 (s, 3 H, $CH_3S(O)$), 3.70 (s, 3H, CO_2CH_3); MS, *m/e* 218, 216, 203, 153, 139, 67. Spectroscopic data for the minor diastereomer of sulfoxide ester **5b**: ^{1}H NMR ($CDCl_3$) δ 0.95–3.24 (m, ring protons), 2.45 (s, 3 H, $CH_3S(O)$), 3.85 (s, 3 H, CO_2CH_3); MS, *m/e* 218, 216, 203, 153, 139, 121, 67.

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Registry No. 1a, 64887-93-0; **1b**, 64887-94-1; **1c**, 64887-95-2; **1d**, 74036-60-5; **1e**, 64887-96-3; **1f**, 74036-61-6; **1g**, 91631-95-7; **1h**, 91631-94-6; **2a**, 64937-41-3; **2b**, 64937-42-4; **2c**, 64937-43-5; **2d**, 74080-75-4; **2e**, 64937-44-6; **2f**, 74080-76-5; **2g**, 91738-66-8; **2h**, 91738-65-7; **3a**, 74080-77-6; **3b**, 74080-78-7; **4a**, 74080-79-8; **4b**, 74080-80-1; **5a**, 114613-40-0; **5b**, 114672-85-4; **5c**, 114613-41-1; **5d**, 114672-86-5; **6**, 64887-98-5; **9a**, 82993-10-0; **9b**, 101835-84-1; **10a**, 114613-42-2; **10b**, 101835-87-4; 2,6-(*t*-Bu)$_2$C$_5$H$_3$N, 585-48-8; Br$^-$, 24959-67-9.

Supplementary Material Available: General experimental section, preparations of carboxyl ^{18}O-labeled endo acid **1a**, carboxyl

^{18}O-labeled sulfoxide carboxylic acid **5a**, sulfoxide ^{18}O-labeled sulfoxide ester, and sulfoxide ^{18}O-labeled endo acid **5a**, control experiments with carboxyl ^{18}O-labeled endo acid sulfoxide **5a**, sulfoxide ^{18}O-labeled endo acid sulfoxide **5a**, carboxyl ^{18}O-labeled endo acid sulfoxide **5a**, and sulfoxide ^{18}O-labeled endo acid sulfoxide **5a**, and Table II of mass spectral data for control experiments (8 pages). Ordering information is given on any current masthead page.

Chiral and Achiral Formamidines in Synthesis. The First Asymmetric Route to (-)-Yohimbone and an Efficient Total Synthesis of (±)-Yohimbone†

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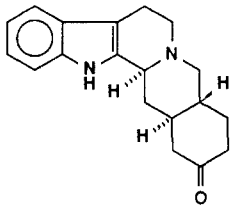
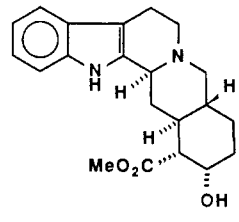
Abstract: An asymmetric synthesis of (-)-yohimbone from chiral formamidines is presented. The synthetic pathway intercepts a previously reported route to yohimbenone (**6**) reported by Winterfeldt. An investigation of the [3,3]-rearrangement involving iminium salts **8** and **9** reveals that this process loses its stereochemical integrity since when optically active **7** is used as the starting material, only racemic **6** is obtained. Removal of the keto group by reduction to **19**, however, allows the ring closure to yohimbenone to proceed with complete conservation of chirality. Thus, the [3,3]-rearrangement was circumvented in going from **19** to **21** and **22**. This latter sequence proceeded by a Pictet-Spengler-Grieco ring closure rather than the [3,3]-rearrangement. The asymmetric synthesis of (-)-yohimbone was accomplished in 11 steps in 17% overall yield. Furthermore, a racemic synthesis of yohimbone, **1**, was also performed with achiral formamidine **25** and was carried out in six steps in 38% overall yield.

Our continuing studies utilizing achiral and chiral formamidines[1] as vehicles for elaboration of secondary amines (Scheme I) has led to a number of approaches to various alkaloid systems. To date we have demonstrated the total synthesis of racemic indole[2] and isoquinoline[3] alkaloids as well as asymmetric total syntheses of indole,[4] morphine,[5] and isoquinoline[6] alkaloids. A total synthesis of (+)-anisomycin[7] has also been recently described. The underlying reasons for this powerful asymmetric process are still not completely understood, although recent reports[8,9] have examined the stereochemistry of the deprotonation and alkylation steps.

We present here the first report of an asymmetric total synthesis of yohimbone (**1**), a key member of the yohimboid class of alkaloids, and a product of the oxidative decarboxylation of yohimbine (**2**) historically the most important member of this group.[10] These complex and architecturally interesting systems



1, Yohimbone



2, Yohimbine

have been the subject of a vast number of chemical degradation and synthetic studies as well as pharmacological endeavors due to their important hypertensive activity. A recent report by Martin[11] details the historical efforts dedicated to this class of alkaloids. A general approach to the yohimboids (±)-reserpine and (±) α-yohimbine are reported in this highly informative paper. The basic strategy of Martin[11] and Wender[12] to reach the pentacyclic alkaloids, reserpine, and/or α-yohimbine (Scheme II) involved coupling of the preconstructued DE ring to tryptophyl bromide with all or some of the requisite stereocenters in place.

The approach to be described herein was based on our previous successes involving asymmetric alkylation of a carbanion adjacent to nitrogen (Scheme I), and we will demonstrate (vide infra) how both racemic and enantiomerically enriched (~99% ee) yohimbone (**1**) may be reached in a relatively few steps in good overall yields. The basic plan (Scheme III) was to employ the intact β-carboline (ABC rings) and via its carbanion **3** to alkylate with 3-methoxybenzyl bromide or give the benzylated adduct **4**. The latter was a pivotal intermediate in the syntheses of (±)-yohimbenone (**6**) described by Winterfeldt.[13] As the latter has shown, reduction of the enol ether **5** followed by cyclization with formaldehyde to give **6** posed a convenient test for our methodology. Reduction of the α,β-unsaturated ketone, yohimbenone (**6**), would

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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