Diastereoselective Oxidations of a Thioether Appended with a Neighboring Carboxylic Acid Group

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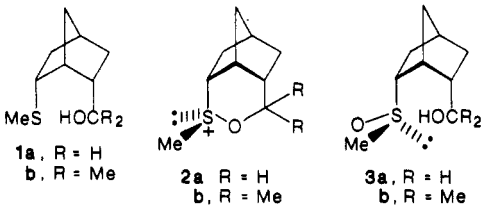
Diastereoselective oxidations of endo acid **5a**, 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, and endo ester **5b**, methyl 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylate, with the bromine complex of 1,4-diazabicyclo[2.2.2]octane in aqueous acetic acid to the corresponding sulfoxides are reported. The relative stereochemistry of the major diastereomeric product obtained by such oxidation of endo acid **5a** was unequivocally established by X-ray crystallographic analysis. Endo acid sulfoxide **7a** crystallizes in the monoclinic space group $P2_1/c$ with $a = 8.554$ (1) Å, $b = 8.989$ (2) Å, $c = 12.575$ (2) Å, $\beta = 98.64$ (1)°, and $Z = 4$. The structure was solved by direct methods. Full-matrix least-squares refinement led to a conventional R factor of 0.038 after several cycles of anisotropic refinement. The predominant sulfoxide formed in the oxidation of endo acid **5a** and endo ester **5b** with the bromine complex of 1,4-diazabicyclo[2.2.2]octane is of the opposite diastereomeric series. This difference in stereochemistry is ascribed to neighboring-group participation in the oxidation of endo acid **5a** by the carboxylate moiety. Diastereoselective oxidations of endo acid **5a** and endo ester **5b** with *m*-chloroperoxybenzoic acid to the corresponding sulfoxides are reported. The results suggest that the carboxylic acid group does not direct attack by the peracid on the thioether.

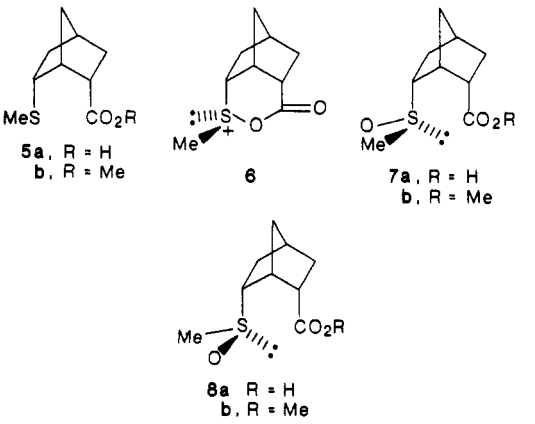
Recently, we reported the highly diastereoselective oxidations of a thioether to the corresponding sulfoxide controlled by a neighboring hydroxyl group.[1,2] Specifically, endo primary alcohol **1a**, 2-*endo*-(hydroxymethyl)-6-*endo*-(methylthio)bicyclo[2.2.1]heptane, on treatment with



tert-butyl hypochlorite followed by mercury(II) chloride gave alkoxysulfonium salt **2a**, *S*-methyl-2-thionia-3-oxatricyclo[3.3.1.^{1,5}1^{7,9}]decane, with high diastereoselectivity. Base-promoted hydrolysis of this salt yielded sulfoxide **3a**, 2-*endo*-(hydroxymethyl)-6-*endo*-(methylthio)bicyclo-[2.2.1]heptane *S*-oxide, exclusively. Similarly, such oxidation of endo tertiary alcohol **1b**, 2-*endo*-(1-hydroxy-1-methylethyl)-6-*endo*-(methylthio)bicyclo[2.2.1]heptane, selectively gave alkoxysulfonium salt **2b**, 4,4-dimethyl-*S*-methyl-2-thionia-3-oxatricyclo[3.3.1.^{1,5}1^{7,9}]decane (although with less diastereoselectivity than with endo primary alcohol **1a**), which on base-promoted hydrolysis provided sulfoxide **3b**,[2] 2-*endo*-(1-hydroxy-1-methylethyl)-6-*endo*-(methylthio)bicyclo[2.2.1]heptane *S*-oxide. However, oxidation of endo primary alcohol **1a** with *m*-chloroperoxybenzoic acid produced the other diastereomeric sulfoxide (i.e., **4a**) with a diastereomer ratio of 16:1. Such high diastereoselectivity in hydroxyl-controlled peracid oxidation of a sulfide to sulfoxide has subsequently been exploited in transferring chirality from a chiral auxiliary to a vinyl sulfide by De Lucchi et al.[3] The resulting optically active vinyl sulfoxides were used to advantage as dienophiles in asymmetric Diels–Alder addition to cyclopentadiene. This paper presents our studies on the stereochemistry of oxidation of endo acid **5a**,[4] 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, in which a neighboring carboxyl group can mediate the oxidation at sulfur, and the corresponding methyl ester **5b**,[4] methyl 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylate.

Results and Discussion

Endo acid **5a** was oxidized to the corresponding sulfoxide with the bromine complex of 1,4-diazabicyclo-[2.2.2]octane in aqueous acetic acid by the procedure of Oae and co-workers.[5,6] The mixture of diastereomeric



sulfoxides obtained in 72% yield was analyzed by ^{1}H NMR spectroscopy. A 7:1 ratio of diastereomers **7a** and **8a**, 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid *S*-oxide, was produced. The major diastereomer was obtained pure by fractional recrystallization.

(1) Glass, R. S.; Setzer, W. N.; Prabhu, U. D. G.; Wilson, G. S. *Tetrahedron Lett.* **1982**, *23*, 2335.
(2) Glass, R. S.; Hojjatie, M.; Setzer, W. N.; Wilson, G. S. *J. Org. Chem.* **1986**, *51*, 1815.
(3) De Lucchi, O.; Marchioro, C.; Valle, G.; Modena, G. *J. Chem. Soc., Chem. Commun.* **1985**, 878. De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457.
(4) Glass, R. S.; Duchek, J. R.; Prabhu, U. D. G.; Setzer, W. N.; Wilson, G. S. *J. Org. Chem.* **1980**, *45*, 3640.
(5) Oae, S.; Ohnishi, Y.; Kozuka, S.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 364.
(6) Oxidation of salts of endo acid **5a** by bromine at low temperature gives the (acyloxy)sulfonium salt, which provides the sulfoxide acid on hydrolysis: Glass, R. S.; Petsom, A.; Coleman, B. O.; Duchek, J. R.; Hojjatie, M.; Klug, J.; Wilson, G. S., unpublished results.

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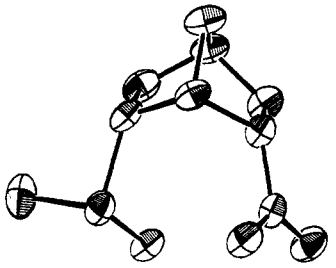


Figure 1. ORTEP[24] drawing of endo acid sulfoxide **7a**. The hydrogen atoms are not shown. Thermal ellipsoids are drawn to enclose 50% of the probability distribution.

Table I. Crystal Data[a] for Endo Acid Sulfoxide 7a

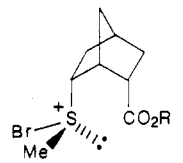
mol formula	$C_9H_{14}O_3S$
mol wt	202.27
space group	$P2_1/c$[b]
a, Å	8.554 (1)
b, Å	8.989 (2)
c, Å	12.575 (2)
β, deg	98.64
Z	4
d_{obsd}, g cm^{-3}	1.42[c]
d_{calcd}, g cm^{-3}	1.41
cryst color, shape	colorless, block
cryst dimens, mm	0.38 × 0.22 × 0.25
no. unique data	2204
no. obsd data	1483
abs coeff [$\mu(\lambda)$], cm^{-1}	3.0

[a] Standard deviation of the least significant figure is given in parentheses. [b] Space group was determined by systematic absences [$0k0$, k = 2n + 1; $h0l$, l = 2n + 1] and subsequent least-squares refinement. [c] Density was determined by the flotation method using a solution of carbon tetrachloride and pentane.

Its relative stereochemistry was unequivocally established as **7a** by X-ray crystallographic analysis.

An ORTEP drawing[24] of **7a** is shown in Figure 1, and crystal data for this compound are given in Table I. This structural study reveals several interesting features. The norbornyl ring skeleton is significantly distorted from the C_{2v} symmetry of the parent hydrocarbon. There is an unsymmetrical contra twist, C(+−),[7] of the norbornyl system. This twisting can be seen from the C(1)–C(2)–C(3)–C(4) and C(4)–C(5)–C(6)–C(1) torsion angles of +8.0 and −3.4°, respectively. This twisting is similar to that observed for endo acid **5a**[4] and endo primary alcohol sulfoxide **4a**.[1,8] The packing of racemic endo acid **5a** showed that one enantiomer is hydrogen bonded to the other enantiomer via reciprocal hydrogen bonding of the carboxylic acid moieties.[4] Similarly, the packing of racemic endo acid sulfoxide **7a** shows that one enantiomer is hydrogen bonded to the other but the carboxylic acid moiety of one enantiomer is hydrogen bonded to the sulfoxide oxygen of the other enantiomer. Hydrogen bonding between the alcohol moiety of one enantiomer and the sulfoxide oxygen of the other enantiomer was observed in endo primary alcohol sulfoxide **4a**.[1,8]

The structure of the major diastereomer produced by oxidation of endo acid **5a** is that expected based on analogy with the results with endo primary alcohol **1a**.[1,2] That is, steric effects control the direction of attack[1,2] by bromine to give bromosulfonium salt **9a**[9] selectively. Backside displacement by the neighboring carboxylate group leads to (acyloxy)sulfonium salt **6**. This salt, unlike the alkoxysulfonium salts **2a** and **2b** produced by *tert*-butyl hypochlorite oxidation of endo primary alcohol **1a** and endo



9a, R = H
b, R = Me

tertiary alcohol **1b**, respectively, cannot be isolated,[10] but their relative stereochemistries are the same. Hydrolysis of (acyloxy)sulfonium salt **6**, *S*-methyl-2-thionia-3-oxa-4-oxotricyclo[3.3.1.^{1,5}1^{7,9}]decane, with inversion of stereochemistry at sulfur[10] provides the observed sulfoxide. In support of this mechanism are the results obtained on similar oxidation of endo ester **5b**. In this case, neighboring-group participation is precluded. Treatment of endo ester **5b** with the bromine complex of 1,4-diazabicyclo[2.2.2]octane in aqueous acetic acid gave the corresponding sulfoxides in a 71% yield as a 1:10 mixture of diastereomers **7b** and **8b**, methyl 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylate *S*-oxide, as determined by ^{1}H NMR spectroscopic analysis. The structure and stereochemistry of the minor isomer was unequivocally established by comparison with the ester prepared from pure endo acid sulfoxide **7a** and diazomethane. The major diastereomeric endo ester sulfoxide **8b** was obtained pure by fractional recrystallization and was fully characterized.

These results on the oxidation of endo ester **5b** are consistent with those of endo acid **5a** in that steric effects control the direction of attack by bromine on the endo ester **5b** to give bromosulfonium salt **9b**. However, neighboring-group participation is precluded in this case unlike that of the acid. Thus, water[5,9] attacks bromosulfonium salt **9b** with inversion of configuration at sulfur to give endo ester sulfoxide **8b** preferentially.[9] This sulfoxide is the ester of the *diastereomer* of the predominant sulfoxide obtained by bromine oxidation of endo acid **5a**. This result supports the suggestion that neighboring-group participation forming (acyloxy)sulfonium salt **6** occurs in the oxidation of endo acid **5a**.

Our interpretation of the results obtained on bromine oxidation of endo acid **5a** and endo ester **5b** presumes that product formation is kinetically controlled. Since halide ions in strong acid are known to isomerize sulfoxides,[11] we decided to test whether equilibration occurs under our reaction conditions in aqueous acetic acid. The following experiments were therefore carried out. A sample of endo acid **5a** was oxidized as before with the complex of bromine and 1,4-diazabicyclo[2.2.2]octane in aqueous acetic acid. The reaction mixture was then divided into three equal portions. One portion of this product was worked up as usual. The second portion was allowed to stand at room temperature for 18 h and then worked up in the usual way. To the third portion was added a known amount of the minor endo acid sulfoxide **8a**. This mixture was allowed to stand for 18 h and then worked up. Analysis of all of these portions by ^{1}H NMR spectroscopy revealed that there was no detectable isomerization. A similar experiment with endo ester **5b** showed that no significant isomerization of endo ester sulfoxides occurred under these conditions.

Oxidation of endo ester **5b** with *m*-chloroperoxybenzoic acid results in an 89% yield of a 4:1 mixture of diastereomeric sulfoxides **7b** and **8b**. As expected,[1,2,12] the

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(8) Setzer, W. N. Ph.D. Dissertation, University of Arizona, 1981.
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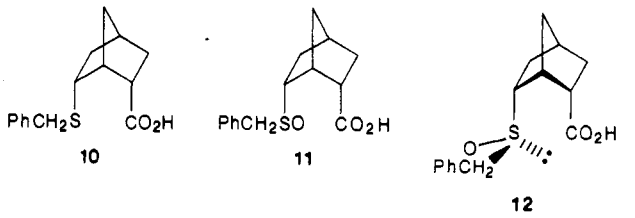
(11) For leading references, see: Wilson, G. E., Jr., *Tetrahedron* **1982**, *38*, 2597.

peracid attacks the sulfur atom from the same, sterically less hindered, direction as bromine, yielding predominantly diastereomer **7b**.[13] Since there is inversion of configuration in the hydrolysis of the bromosulfonium salt **9b**, the predominant sulfoxide is the diastereomer of that preferentially produced in the peracid oxidation. Thus, either diastereomeric endo ester sulfoxide can be selectively synthesized.

Treatment of endo acid **5a** with *m*-chloroperoxybenzoic acid in dichloromethane gives the corresponding diastereomeric sulfoxides in 82% yield and a 5:1 ratio of diastereomers **7a** and **8a**. The predominant diastereomer is the *same* as that produced by bromine oxidation of the endo acid **5a**. This predominant diastereomer is also of the same diastereomeric series as that produced by peracid oxidation of endo ester **5b**. This is surprising because of the results obtained with endo primary alcohol **1a**. In this case, *m*-chloroperoxybenzoic acid oxidation in dichloromethane gave predominantly the opposite diastereomer as oxidation with *tert*-butyl hypochlorite followed by alkaline hydrolysis.[1,2] To account for the stereochemistry in the peracid oxidation it was suggested[1] that the peracid is hydrogen bonded to the alcohol moiety and thereby directs attack on the sulfur atom from the more hindered direction. Similar hydrogen bonding to the peracid is expected for the carboxylic acid moiety in endo acid **5a**. Indeed, peracid oxidation of sulfides to sulfoxides directed by a carboxylic acid group has been reported.[15] The authors offered two alternatives for the basis of this directing effect. Hydrogen bonding between the carboxyl group and peracid was one possibility, and the other was prior formation of a diacyl peroxide intermediate. By analogy, oxidation of another carboxyl-substituted sulfide was similarly suggested to be subject to such control by the carboxylic acid.[16] However, other geometric factors were also suggested to account for this diastereoselective oxidation. We suggest that the reason the carboxylic acid moiety in endo acid **5a** does not hydrogen bond to the peracid and direct attack on sulfur from the more hindered direction is that it preferentially forms a very strong hydrogen-bonded carboxylic acid dimer. The crystal structure studies on endo acid **5a**[4] clearly show such hydrogen bonding in the solid state. More importantly, molecular weight determinations of endo acid **5a** in dichloromethane,[17] the solvent used for the oxidation, show it to be a dimer in solution.

Johnsson and Allenmark[18] reported that oxidation of endo acid **10**, 6-*endo*-(benzylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, with peracetic acid in acetone–ethyl ether produced one diastereomeric sulfoxide **11**, 6-*endo*-(benzylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid *S*-oxide. However, these workers were unable to assign the stereochemistry of this sulfoxide. We, therefore, oxidized endo acid **5a** under their conditions using peracetic acid in acetone–diethyl ether. The corresponding sulfoxide was obtained in 84% yield with a diastereomer ratio of 5:1 as determined by ^{1}H NMR spectroscopic analysis, in which diastereomer **7a** predominated. This result is the same as that obtained with *m*-chloroperoxybenzoic acid in dichloromethane. By analogy, we suggest that the structure of the predominant sulfoxide produced on oxidation of endo acid **10** is sulfoxide **12**.



Experimental Section

All melting points are uncorrected and were taken in microscope slides with a Thermolyne melting point apparatus. IR spectra were obtained on a Perkin-Elmer 983 infrared spectrometer. ^{1}H NMR spectra were measured at 250 MHz with a Bruker WM 250 NMR spectrometer on samples dissolved in deuteriochloroform with chloroform (assigned a chemical shift of δ 7.24) as the internal standard. Mass spectra were done at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE (National Science Foundation Regional Instrumentation Facility). Preparative-layer chromatography was done on 8 × 8 in. glass plates prepared with Merck HF-254 (Type 60) silica gel (Brinkmann Instruments, Inc.) on an absorbent layer 0.75 mm thick. HPLC was performed with an Altex/Beckman 110A pump and a Spectra Physics Model 8400 UV/vis detector.

Dichloromethane was purchased from EM Science, Gibbstown, NJ, and distilled from calcium hydride before use. *m*-Chloroperoxybenzoic acid was obtained from Aldrich Chemical Co., Milwaukee, WI, and it contained 80% of peracid by iodometry.[19] The 1,4-diazabicyclo[2.2.2]octane–bromine complex (DABCO·2Br$_2$) was prepared according to the method of Oae et al.[5] with 1,4-diazabicyclo[2.2.2]octane purchased from Aldrich. A diazomethane solution in diethyl ether was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide obtained from Aldrich with a Diazald kit purchased from the same source.[20]

Oxidation of Endo Acid 5a with the 1,4-Diazabicyclo[2.2.2]octane–Bromine Complex. A sample of DABCO·2Br$_2$ complex (41 mg, 0.09 mmol) was added to a solution of endo acid **5a** (22 mg, 0.12 mmol) in 70% aqueous acetic acid (5 mL). The mixture was stirred for 10 min, and the solvent was removed under reduced pressure [50 °C (10 Torr)] with a rotary evaporator. ^{1}H NMR spectroscopic analysis of the crude product using piperonal as internal standard indicated a mixture of endo acid sulfoxides (72% yield) with a 7:1 ratio of diastereomers **7a** and **8a**.

The crude product was triturated with dichloromethane (3 × 10 mL) and filtered. The dichloromethane solution was concentrated, and the resulting solid residue was recrystallized twice from diethyl ether–dichloromethane to afford the major endo acid sulfoxide **7a**: mp 185–186 °C; IR (KBr) 3200–2200 (br O–H str), 2976, 2951, 2914, 1740 (C=O), 1310, 1266, 1248, 1234, 1014, 1004 (S=O), 981, 947, 933, 766, 736, 702, 682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.55–1.70 (2 H, m), 1.75–2.20 (4 H, m), 2.48 (1 H, br s), 2.80 (3 H, s), 2.85 (1 H, m), 2.88 (1 H, br s), 3.16 (1 H, m).

A pool of the enriched minor endo acid sulfoxide from several experiments was subjected to a repetitive recrystallization to obtain the pure minor endo acid sulfoxide **8a**: mp 192–194 °C; IR (KBr) 3504, 3451 (OH from water of crystallization), 3200–2200 (br O–H), 2963, 2537, 1715 (C=O), 1650, 1453, 1425, 1346, 1308, 1215, 1128, 978 (S=O), 935, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.05 (1 H, m), 1.56 (1 H, br d, J = 9 Hz), 1.68 (1 H, br d, J = 9 Hz), 1.74–2.00 (3 H, m), 2.45 (1 H, br s), 2.61 (3 H, s), 2.94 (1 H, m), 3.14 (1 H, m), 3.30 (1 H, br s).

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(13) Hydrogen bonding between the peracid and ester moiety in which the peracid is the hydrogen bond donor is not important in the oxidation of the sulfide. Such hydrogen bonding would direct the oxygen from the sterically more hindered direction and produce diastereomer **8b**. In this regard it is known that in epoxidation of allylic alcohols with peracids the hydroxy group, which can act as a hydrogen bond donor, directs the peracid syn to itself, whereas if the alcohol is esterified, attack occurs anti to this moiety, which can no longer be a hydrogen bond donor, only an acceptor.

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(15) Undheim, K.; Greibrokk, T. *Acta Chem. Scand.* **1970**, *24*, 3429.

(16) Johnsson, H.; Allenmark, S. *Chem. Scr.* **1975**, *8*, 216.

(17) The molecular weight of endo acid **5a** in dichloromethane was found to be 343 at 30 °C and at a concentration of 23.6 mg/mL by Huffman Laboratories, Inc., Golden, CO.

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X-ray Single-Crystal Structure Study of Endo Acid Sulfoxide 7a. Crystals of the major diastereomeric endo acid sulfoxide **7a**, obtained by fractional recrystallization of the product obtained by oxidation of endo acid **5a** with the DABCO·$2Br_2$ complex, suitable for X-ray crystallographic analysis were grown by slow vapor diffusion of a solution of the compound in nitromethane with diethyl ether. A crystal (0.38 × 0.22 × 0.25 mm) was sealed in a glass capillary and mounted on a Syntex $P2_1$ autodiffractometer. The automatic centering and least-squares routines were carried out on 25 reflections, and the cell constants determined by least-squares treatment of these reflections are given in Table I. The monoclinic space group was determined from systematic absences to be $P2_1/c$ (No. 14). The θ–2θ data collection technique was used, and data were collected to a maximum 2θ of 55.0°. The data with $F \geq 3\sigma(F)$ were used in the calculations. The data were reduced to F_o and $\sigma(F_o)$. Lorentz and polarization corrections were applied to the data. Three standards monitoring every 46 reflections indicated no decay.

The structure was solved by direct methods using the SDP-PLUS program package. Using default parameters, a total of 13 atoms were located. The hydrogen atoms bonded to carbon atoms were visible in the first difference map. These hydrogen atoms were included at idealized positions. In subsequent refinements they were restrained to ride on the atom to which they are bonded, with fixed isotropic thermal parameters. The hydrogen atom of the carboxylic acid was evident in a subsequent difference map. This hydrogen atom was included at the position found in the difference map and restrained to ride on its oxygen atom with fixed isotropic thermal parameter. The structure was refined by full-matrix least-squares techniques[21] by using neutral-atom scattering factors[22] with anomalous dispersion terms[23] included for all atoms. The final cycle of refinement included 118 variable parameters and yielded unweighted (R) and weighted (R_w) agreement factors of 0.038 and 0.046, respectively. The standard deviation of an observation of unit weight was 1.42.

Oxidation of Endo Ester 5b with the 1,4-Diazabicyclo[2.2.2]octane–Bromine Complex. A sample of DABCO·$2Br_2$ complex (36 mg, 0.08 mmol) was added at once to a stirred solution of endo ester **5b**[4] (34 mg, 0.17 mmol) in 80% aqueous acetic acid (1 mL). The reaction mixture was stirred until it became homogeneous (ca. 2–3 min). The solvent was then removed under reduced pressure with a rotary evaporator. Analysis of the residue by ^{1}H NMR spectroscopy revealed endo ester sulfoxide as the 1:10 mixture of diastereomers **7b** and **8b**. This residue was dissolved in diethyl ether and filtered. The filtrate was concentrated and chromatographed on a preparative layer of silica eluting with 10% methanol in ethyl acetate to give endo ester sulfoxide (26 mg, 71% yield). Recrystallization by vapor diffusion of pentane into a diethyl ether solution of this material afforded diastereomerically pure endo ester sulfoxide **8b**. This material was identical (mp, mmp, ^{1}H NMR, IR) with endo ester sulfoxide **8b** prepared and isolated in pure form from the reaction of endo ester **5b** with *m*-chloroperoxybenzoic acid described below.

Stability of Endo Acid Sulfoxide to Equilibration. A sample of the DABCO·$2Br_2$ complex (46 mg, 0.11 mmol) was added at once to a stirred solution of endo acid **5a** (25 mg, 0.13 mmol) in 80% aqueous acetic acid (15 mL). This mixture was stirred at room temperature for 10 min, and then three portions of this solution each 3 mL were pipetted into three 10-mL round-bottom flasks. The first portion was evaporated to dryness and analyzed by ^{1}H NMR spectroscopy after dissolving in deuteriochloroform and using dichloromethane as an internal standard. Such analysis revealed endo acid sulfoxide **7a** (5.5 mg) and endo acid sulfoxide **8a** (0.55 mg), giving a ratio of diastereomers of 10:1. The second portion was stirred at room temperature for 18 h. The solvent was then evaporated and the sample analyzed by ^{1}H NMR spectroscopy as done for the first portion. This analysis showed the ratio of **7a** to **8a** to be 9.8:1. To the third portion was added pure endo acid sulfoxide **8a** (2 mg) to give initially a ratio of **7a** to **8a** of 2.1:1. This mixture was stirred at room temperature for 18 h and then the solvent removed by rotary evaporation. The residue was analyzed by ^{1}H NMR spectroscopy as before to give a ratio of 2.3:1 for **7a** and **8a**.

Stability of Endo Ester Sulfoxide to Equilibration. A sample of the DABCO·$2Br_2$ complex (107 mg, 0.25 mmol) was added at once to a stirred solution of endo ester **5b** (66 mg, 0.33 mmol) in 80% aqueous acetic acid (15 mL). This mixture was stirred at room temperature for 10 min, and then three portions of this solution each 3 mL were pipetted into three 10-mL round-bottom flasks. The first and second portions were treated and analyzed in the same way as the first and second portions from the preceding equilibration studies with the endo acid sulfoxide. Such analysis revealed a diastereomer ratio of **7b** to **8b** of 1:9.1 in the first portion and 1:9.7 in the second portion. To the third portion was added diastereomerically pure endo ester sulfoxide **7b** (3 mg) to give initially a ratio of **7b** to **8b** of 1:2.1. This mixture was stirred at room temperature for 18 h and then the solvent removed by rotary evaporation. The residue was analyzed by ^{1}H NMR spectroscopy as before to give a ratio of 1:2.6 for **7b** and **8b**.

Oxidation of Endo Acid 5a with *m*-Chloroperoxybenzoic Acid. A solution of *m*-chloroperoxybenzoic acid (27 mg, 0.16 mmol) dissolved in dichloromethane (5 mL) was added dropwise, with stirring, to a solution of endo acid **5a** (25 mg, 0.13 mmol) dissolved in dichloromethane (2 mL) cooled in an ice–water bath. After 1 h, the solution was concentrated to dryness with a rotary evaporator. ^{1}H NMR spectroscopic analysis of the residue using piperonal as an internal standard indicated an 82% yield of endo acid sulfoxide (12% unreacted starting endo acid **5a**) with a ratio of **7a** to **8a** of 5:1. This crude product was washed twice with diethyl ether, and the residue was recrystallized by slow vapor diffusion of diethyl ether in a solution of the material dissolved in dichloromethane to provide pure **7a** identical with the material prepared previously.

Oxidation of Endo Ester 5b with *m*-Chloroperoxybenzoic Acid. A solution of *m*-chloroperoxybenzoic acid (46 mg, 0.27 mmol) in dry dichloromethane (5 mL) was added dropwise to a stirred solution of endo ester **5b** (45 mg, 0.23 mmol) in dichloromethane (2 mL) cooled in an ice–water bath. After 1 h, dichloromethane was evaporated under reduced pressure on a rotary evaporator. ^{1}H NMR spectroscopic analysis of the crude product in $CDCl_3$ using piperonal as an internal standard indicated 89% yield of the endo ester sulfoxide with a ratio of isomers **7b** to **8b** of 4:1. About 7% of the starting material was left unreacted.

The crude material was subjected to preparative TLC on a silica gel plate eluting with 10% methanol in ethyl acetate to afford endo ester sulfoxide (39 mg, 80%; R_f 0.26) as a colorless, viscous liquid. This liquid was subjected to HPLC on a 10-μm silica column (250 × 4.6 mm), using 5% methanol in acetonitrile as eluant. The flow rate was set at 1 mL/min, and the UV detector was operated at 230 nm. The appropriate peak was collected for **7b**, which was obtained as a colorless, viscous liquid: IR (neat) 2956, 2882, 1729 (C=O), 1454, 1434, 1344, 1310, 1291, 1267, 1249, 1206, 1125, 1023 (S=O), 941, 759, 720, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.55–2.16 (6 H, m), 2.47 (1 H, br s), 2.62 (3 H, s), 2.82 (1 H, m), 2.85 (1 H, br s), 3.04 (1 H, m), 3.64 (3 H, s); MS, m/e calcd for $C_{10}H_{16}O_3S$ 216.0820, found 216.0818.

Diastereomer **8b** was collected as a colorless crystalline solid: mp 128–128.5 °C; IR (KBr) 2989, 2962, 2913, 2882, 1724 (C=O), 1434, 1411, 1344, 1322, 1312, 1237, 1199, 1131, 1046, 1032, 1006, 757, 712, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.99 (1 H, ddd, J = 2.2, 7.3, 12.8 Hz), 1.57 (1 H, dd, J = 2, 10 Hz), 1.67 (1 H, dd, J = 2, 10 Hz), 1.74–2.01 (3 H, m), 2.44 (1 H, br s), 2.45 (3 H, s), 2.98 (2 H, m), 3.24 (1 H, br s), 3.76 (3 H, s); MS, m/e calcd for $C_{10}H_{16}O_3S$ 216.0820, found 216.0823.

Preparation of Authentic Endo Ester 7b. A solution of endo acid sulfoxide **7a** (18 mg, 0.09 mmol), from the same sample as that used for growing crystals for the X-ray structure determination, dissolved in dichloromethane (5 mL) was added dropwise, with stirring, to a solution of diazomethane in diethyl ether (50 mL) cooled in a dry ice–acetone bath. The reaction mixture was stirred and allowed to warm to room temperature overnight. The

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solvents were then removed with a rotary evaporator. ^{1}H NMR spectroscopic analysis of the residue indicated a quantitative yield of endo ester sulfoxide **7b**. This crude product was purified by chromatography on a preparative-layer plate of silica gel, eluting with 10% methanol in ethyl acetate. Pure endo ester sulfoxide (16 mg, 84% yield) was obtained in this way, and its ^{1}H NMR and IR spectra were identical with that of the material prepared previously.

Oxidation of Endo Acid 5a with Peracetic Acid. A sample of peracetic acid in ethyl acetate, whose peracid concentration was determined by iodometry[19] (15.9 mL, 0.30 mmol), was added dropwise to a stirred solution of endo acid **5a** (56 mg, 0.30 mmol) dissolved in a 1:1 mixture of diethyl ether and acetone (5 mL) and cooled in an ice–water bath. After completion of the addition, the solution was stirred and allowed to warm to room temperature overnight. The solvents were then removed under reduced pressure with a rotary evaporator to give a viscous liquid (159 mg). ^{1}H NMR spectroscopic analysis of this material in deuteriochloroform with dichloromethane as an internal standard indicated an 84% yield of endo acid sulfoxide with a diastereomer ratio of 5:1 of **7a** and **8a**. Crystallization of this material by slow vapor diffusion of diethyl ether into a dichloromethane solution provided crystalline **7a** identical with material obtained previously.

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Registry No. **5a**, 64887-93-0; **5b**, 64887-94-1; **7a**, 108919-47-7; **7b**, 108919-48-8; **8a**, 109009-38-3; **8b**, 109009-39-4.

Supplementary Material Available: Stereoscopic view of the packing of the molecules in the unit cell of endo acid sulfoxide **7a** and tables of final atomic positional and thermal parameters, bond lengths, bond angles, and selected torsion angle data (4 pages) (a listing of structure factor amplitudes is available from the authors). Ordering information is given on any current masthead page.

The Isoxazoline Route to the Hypocholesterolemic Agent Compactin: Use of the Isoxazoline as a 1,3-Diene Equivalent

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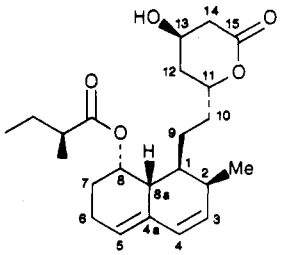
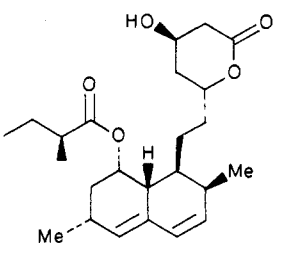
A total synthesis of the hypocholesterolemic agent compactin is described in which the hexahydronaphthalene portion of this molecule is constructed by an intramolecular nitrile oxide cycloaddition reaction. In the context of this synthesis, the isoxazoline ring system was found to serve as a useful 1,3-diene equivalent. The protocol developed for this conversion involves transformation of the isoxazoline to an allylic alcohol followed by regioselective dehydration using aluminum oxide. Molecular mechanics calculations on compactin-related octahydronaphthisoxazoles are also presented.

In 1976, an important new type of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor was isolated from the culture broth of the molds *Penicillium citrinum* and *Penicillium brevicompactum*. This compound compactin (1), also designated ML-236B,



compactin (1)



mevinolin (2)

is a competitive inhibitor of the rate-controlling enzyme in cholesterol biosynthesis.[1] The dihydroxy acid form of the structurally related product, mevinolin (2), has, moreover, been found to be one of the most potent HMG-CoA reductase inhibitors discovered.[2,3] Both compactin and mevinolin act as effective hypocholesterolemic agents in man and as such may find applications in treating atherosclerosis and coronary heart disease.[4]

Due to the significant biological activity of compactin, as well as our desire to investigate the use of the INOC (intramolecular nitrile oxide cycloaddition) reaction in the construction of decalins (a process in which for compactin the isoxazoline ring would serve as a 1,3-diene equivalent), we embarked on an effort to prepare this compound in the

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