Synthesis and Conformation of 4,4,5,5-Tetramethyl-1,2-dithiane Mono-*S*-oxide[1]

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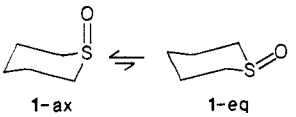
The synthesis of the title compound (**6**), an interesting subject for the study of anomeric and other conformational effects, was attained from ethyl isobutyrate in eight steps, with an overall yield of 11%. The synthetic route described herein involved the crucial displacement of both neopentylic tosylate groups in 2,2,3,3-tetramethyl-1,4-butanediol ditosylate; while several standard procedures led to the formation of unexpected products, purified potassium thioacetate in hexamethylphosphoramide afforded the required dithioacetate derivative. The mechanistic implications of the well- and bad-behaved reactions are discussed. From the results of variable-temperature NMR experiments it is concluded that the axial conformer of **6** dominates the equilibrium to such an extent that no contribution of the equatorial isomer is recorded. This result suggests a $\Delta G^\circ \geq 3.0$ kcal/mol for the conformational equilibrium of the parent 1,2-dithiane mono-*S*-oxide.

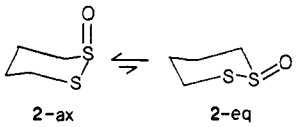
Introduction

The well-established preference by most substituents to occupy the equatorial orientation in a cyclohexane ring[2] is occasionally reversed in substituted heterocycles. The best known example is the anomeric effect;[3] i.e., the tendency of an electronegative substituent to assume the axial rather than equatorial orientation at C(1) of a pyranoid ring. This conformational effect was discovered by Edward[4a] and by Lemieux and Chu.[4b] A few years later, the also classical papers of Johnson and Martin showed that the S=O group prefers an axial arrangement in thiane oxide (**1**).[5] A quantitative determination of the equilibrium depicted in eq 1 was accomplished by Lambert and Keske,[6] suggesting a conformational free energy difference of 0.175 kcal/mol.



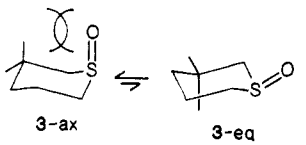
(1)

That the substitution of an α-methylene group by sulfur in **1** (to give the cyclic thiosulfinate **2**) results in a greater predominance of the axial conformer (eq 2) was first proposed by Harpp and Gleason in 1971[7] and confirmed by several research groups in the early 1980s.[1,8] In fact,



(2)

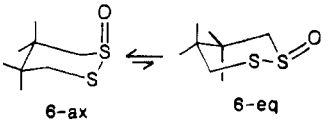
the equilibrium **2**-ax $\rightleftharpoons$ **2**-eq is so much tilted to the left that the participation of the equatorial isomer is too small to permit a quantitative measurement of the equilibrium constant. However, it has been demonstrated by Lambert et al.[9] that the introduction of a *gem*-dimethyl group at C(3) in thiane oxide **1** (to give **3**) strongly disfavors the axial conformer (eq 3). Because the participation of **3**-ax



(3)

in eq 3 was found to be less than 5% [ΔG°(**3**-eq $\rightleftharpoons$ **3**-ax) $\geq$ 1.7 kcal/mol] and because ΔG°(1-eq $\rightleftharpoons$ 1-ax) = 0.2 kcal/mol, Lambert estimated that the repulsive, syn-diaxial Me/S=O interaction is worth at least 1.9 kcal/mol.[9,10]

In this paper we describe the preparation of 4,4,5,5-tetramethyl-1,2-dithiane mono-*S*-oxide (**6**), the rationale being that the syn-diaxial Me/S=O interaction in **6**-ax will produce an equilibrium closer to unity in eq 4, therefore



(4)

allowing a more precise determination of the conformational preference of the S=O group in **6** and, indirectly, in **2**. As it turned out, the preparation of **6** was not trivial and afforded a wealth of interesting, potentially useful synthetic data, which deserve description. The results of the conformational analysis of **6** are also presented here, although a detailed discussion of the signal assignments, as well as additional solvent effects and shift reagent experiments, will be published separately.[11]

Results and Discussion

Preparation of Diethyl Tetramethylsuccinate (9). Among the several literature procedures,[12] the method of Brocksom et al.[12b] (treatment of the lithium enolate of ethyl isobutyrate with 0.5 equiv of iodine) was initially

(1) Conformational Preference of the S=O Group. 2. For part 1, see: Juaristi, E.; Guzmán, J.; Kane, V. V.; Glass, R. S. *Tetrahedron* **1984**, *40*, 1477–1485.

(2) Cf. Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199–222.

(3) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

(4) (a) Edward, J. T. *Chem. Ind. (London)* **1955**, 1102–1104. (b) Lemieux, R. U.; Chu, N. J. *Abstracts of Papers*, 133rd National Meeting of the American Chemical Society, San Francisco; American Chemical Society: Washington, DC, 1958; N-31.

(5) (a) Johnson, C. R.; McCants, D. *J. Am. Chem. Soc.* **1964**, *86*, 2935–2936. (b) Martin, J. C.; Uebel, J. J. *Ibid.* **1964**, *86*, 2936–2937.

(6) Lambert, J. B.; Keske, R. G. *J. Org. Chem.* **1966**, *31*, 3429–3431.

(7) Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1971**, *36*, 1314–1316.

(8) (a) Bass, S. W.; Evans, S. A. *J. Org. Chem.* **1980**, *45*, 710–715. (b) Takata, T.; Iida, K.; Oae, S. *Heterocycles* **1981**, *15*, 847–850.

(9) Lambert, J. B.; Bailey, D. S.; Mixan, C. E. *J. Org. Chem.* **1972**, *37*, 377–382.

(10) Comparison of the conformational equilibria of 1,3-oxathiane mono-*S*-oxide a(**4**) and 5,5-dimethyl-1,3-oxathiane mono-*S*-oxide (**5**) led Anteunis and Van Acker to propose that the magnitude of the syn-diaxial Me/S=O interaction is smaller: 1.3 kcal/mol; see: Van Acker, L.; Anteunis, M. *Tetrahedron Lett.* **1974**, 225–228.

(11) Juaristi, E.; Cruz-Sánchez, J. S.; Petsom, A.; Glass, R. S. manuscript submitted to *Tetrahedron*.

(12) (a) Bickel, A. F.; Water, W. A. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 312. (b) Brocksom, T. J.; Petragnani, N.; Rodrigues, R.; La Scala-Teixeira, H. *Synthesis* **1975**, 396–397. (c) Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009–2012.

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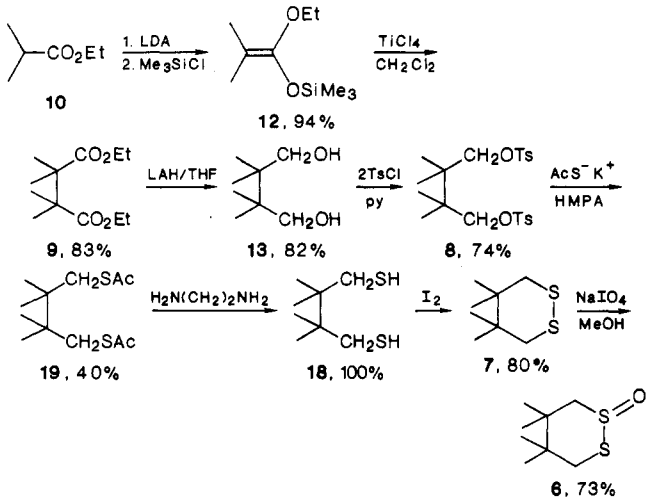
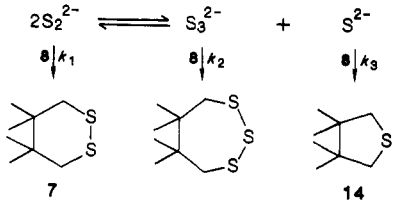
Scheme I[a]



[a] Reagents that did not effect displacement of the tosylate groups in 8: Na_2S_2 in DMF; Na_2CS_3 in HMPA; AcS^-K^+ in EtOH; $C_6H_5CH_2S^-Na^+$ in HMPA.

Scheme II



chosen; however, in our hands this method afforded **9** in a scant 8% yield. Attention was turned then to the method of Inaba and Ojima.[12c] Treatment of ethyl isobutyrate with lithium diisopropylamide (LDA) and chlorotrimethylsilane produced derivative **12** in 94% yield; $TiCl_4$-mediated dimerization provided the desired product in 83% yield (Scheme I).

Preparation of 2,2,3,3-Tetramethyl-1,4-butanediol Ditosylate (8). Reduction of diester **9** with lithium aluminum hydride (LAH) afforded the diol **13** as expected; the yield of this reaction was 62% in diethyl ether as solvent,[13a] but it was improved to 82% in tetrahydrofuran (THF).[13b]

Ditosylate **8** was then formed in 74% isolated yield from diol **13** and tosyl chloride according to the usual procedure.[14]

Preparation of 4,4,5,5-Tetramethyl-1,2-dithiane (7). The displacement reaction of the neopentylic tosylates in **8** proved to be the crucial step in the synthesis; of course, leaving groups at neopentylic positions are known to react slowly with otherwise good nucleophiles.[15]

Cyclic disulfides are conveniently prepared by the method of Hutchins et al.,[16] who employ sodium sulfide and sulfur to generate in situ disulfide dianion. When this procedure was applied to ditosylate **8**, thiolane **14** instead of dithiane **7** was obtained. This result is best explained by considering that S_2^{2-} is formed as a mixture of polysulfides and sulfide itself;[17] whereas the product-determining nucleophile with most dihalides and ditosylates is S_2^{2-},[16] it appears that hindered **8** is kinetically more reactive toward S^{2-} (i.e., $k_3 \gg k_1, k_2$ in Scheme II).[18]

Scheme III

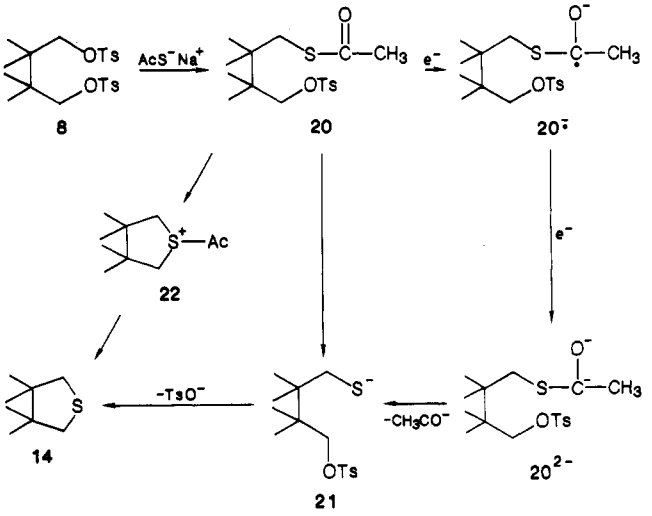


Table I. Yield of Thiolane 14 as a Function of Sodium Concentration in the Reaction of Ditosylate 8 with Thioacetic Acid and Sodium in Hexamethylphosphoramide[a]

entry	8, equiv	CH_3COSH, equiv	Na, equiv	yield of 14, %
1	1	2	0.5	18
2	1	2	1.5	64
3	1	2	3.0	~100

The use of sodium trithiocarbonate for the incorporation of the sulfur atoms[19] was then explored. Reaction of ditosylate **8** with Na_2CS_3, prepared according to the method of Jordis and Rudolf,[20] at 100 °C during 3 h gave no evidence of the formation of cyclic trithiocarbonate **17**.

Attention was turned then to the use of ethanolic potassium thioacetate[19,21] for the conversion of **8** to the dithioacetate **19**; hydrolysis of **19** would afford the required dithiol **18**. Disappointingly, however, no reaction at all was observed between **8** and ethanolic potassium thioacetate, under refluxing conditions after 48 h. The lack of success in this reaction is again ascribed to the stern requirements inherent to the displacement of neopentylic substrates.[15] It is known that highly dipolar solvents such as hexamethylphosphoramide (HMPA) facilitate the substitution reaction of hindered reagents.[22] Thus HMPA was substituted for ethanol. At the same time, the thioacetate anion was generated from thioacetic acid and sodium metal, in order to avoid the presence of water in the medium: it has been recently shown that H_2O in HMPA is a good nucleophile.[23]

Unexpectedly, treatment of ditosylate **8** with 2 equiv of thioacetic acid and 2 equiv of sodium metal in HMPA produced the five-membered sulfide **14** in 70–80% yield.

(13) (a) Sowinsky, A. F.; Whitesides, G. M. *J. Org. Chem.* **1979**, *44*, 2369–2376. (b) Levisalles, J.; Rudler, H.; Villemin, D. *J. Organometal. Chem.* **1980**, *193*, 69–82.

(14) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. I, pp 1179–1181.

(15) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; p 13.

(16) Eliel, E. L.; Rao, V. S.; Smith, S.; Hutchins, R. O. *J. Org. Chem.* **1975**, *40*, 524–526.

(17) Schmidt, M.; Siebert, W. In *Comprehensive Inorganic Chemistry*; Bailar, J. C., Jr., Emeleus, H. J., Nyholm, R., Trotman-Dickerson, A. F., Eds.; Pergamon: Oxford, 1973; Vol. 2, pp 837–838.

(18) Thiolane **14** and its sulfoxide derivative **16** were independently prepared by treatment of **8** with sodium sulfide (**8** → **14**) and subsequent oxidation with sodium periodate (**14** → **16**); see the Experimental Section.

(19) Wardell, J. L. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: New York, 1974; Chapter 4.

(20) Jordis, U.; Rudolf, M. *Phosphorus and Sulfur* **1984**, *19*, 279–283.

(21) Cf. Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807–1816.

(22) See, for example: Holtz, H. D.; Stock, L. M. *J. Am. Chem. Soc.* **1965**, *87*, 2404–2409.

(23) Hutchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360–1362.

Likely mechanisms for this reaction are presented in Scheme III. Monothioacetate **20** appears as the logical precursor to the final product. Conversion of **20** to **14** could proceed via the sulfonium intermediate **22**, but no thioacetic anhydride ($CH_3COSCOCH_3$) was detected in the crude product;[24] this observation apparently discards also the direct conversion of monothioacetate **20** to thiolate **21**. A more plausible pathway for the **20** → **21** transformation is via an electron-transfer mechanism involving radical anion **20**$^{\bullet-}$ (Scheme III).

Support for this reasoning is obtained both from the literature and from additional experimental data: (1) the thioacetate group is a good acceptor of electrons as indicated by its low reduction potential,[25] (2) credible sources of electrons are the sodium metal or the diamidophosphite anion $[Na^+OP^-(NMe_2)_2]$ which is probably formed in the reaction medium,[26,27] (3) radical anions derived from ketones and other carbonylic compounds are easily reduced to the dianion, which then cleaves with loss of the R–CO$^-$ ion,[28] (4) deficiency of sodium in the reaction lowered the yield of **14**, whereas an excess of sodium increased it (Table I), and (5) development of the reaction in the presence of *p*-dinitrobenzene, a well-known radical inhibitor,[29] led to significantly lower yields of **14**.

At this point it was obvious that the presence of sodium (or any other metal) in the reaction medium should be prevented. Therefore, potassium thioacetate was prepared from thioacetic acid and ethanolic potassium hydroxide; subsequent concentration of the reaction mixture afforded crystalline $CH_3COS^-K^+$, which was filtered, washed with dry THF, and dissolved in HMPA. Addition of ditosylate **8** and heating to ca. 100 °C during 3.5 h successfully led to the formation of the desired dithioacetate **19** in 40% isolated yield (Scheme I).

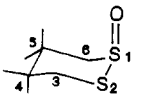
Preparation of 4,4,5,5-Tetramethyl-1,2-dithiane Mono-*S*-oxide (6). Aminolysis[21] of dithioacetate **19** was achieved in quantitative yield by treatment with ethanolic ethylenediamine (Scheme I).

The oxidation of dithiol **18** to **7** was first carried out with lead acetate and sulfur following the procedure of Cragg and Weston.[30] However, the conversion took place with a total yield of only 5% (two steps). Much better results were obtained with a more conventional oxidation with iodine[31] (Scheme I).

The oxidation of dithiane **7** to the final product (**7** → **6**) was accomplished with sodium periodate under the conditions suggested by Johnson and Keiser[32] (Scheme I). Sulfoxide **6** was purified by flash column chromatography[33] and sublimed at reduced pressure to furnish the pure product in 73% yield.

Summary of Synthetic Work. Scheme I summarizes the reactions and yields of pure, isolated products, starting from ethyl isobutyrate to the tetramethyl-1,2-dithiane monosulfoxide **6**. Eight distinct steps were required in this route, which afforded the final product in an overall yield of 11%.

Table II. 250-MHz ^{1}H NMR Chemical Shifts (ppm) for 6



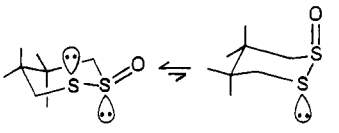
nuclei	solvent (temp, °C)	
	$CDCl_3$ (22)	CD_2Cl_2 (−80)
H(3ax)	3.78	3.68
H(3eq)	2.32	2.29
axial CH_3–C(4)	1.14	1.03
equat CH_3–C(4)	1.07	0.97
axial CH_3–C(5)	1.39	1.26
equat CH_3–C(5)	0.95	0.85
H(6ax)	2.90	2.84
H(6eq)	2.95	2.91

The unsuccessful reactions discussed in the text were as important as the successful ones since they provide a deeper understanding of the chemistry of the system, in particular the requirements and consequences of substitution reactions at highly hindered positions.

Conformation of 4,4,5,5-Tetramethyl-1,2-dithiane 1-Oxide (6). Table II summarizes the 250-MHz ^{1}H NMR spectrum of **6**. The very large difference in chemical shifts for the hydrogens at C(3) ($\Delta\delta$ = 1.45 ppm) can only be reasonably attributed to a *predominantly axial conformation* in eq 4, in which H(3ax) experiences a strong deshielding effect by the syn-diaxial sulfinyl group.[34]

In an attempt to observe different signals for the individual conformers in **6**-ax ⇌ **6**-eq, the spectrum was recorded at −80 °C in CD_2Cl_2. The proton spectrum (Table II) is the same at this temperature and room temperature ($\Delta\delta$ for all hydrogens ≤0.1 ppm). This information indicates that the participation of **4**-equatorial in the equilibrium is not significant: K in eq 4 ≥ 95/5; $\Delta G°$ ≥ 1.7 kcal/mol. Because the CH_3/S=O syn-diaxial interaction present in **6**-ax amounts to at least 1.3 kcal/mol,[9,10] the conformational free energy difference in the equilibrium **2**-ax ⇌ **2**-eq is estimated as $\Delta G°$ ≥ 3.0 kcal/mol.

The unusual stability of **6**-ax (and **2**-ax) relative to **6**-eq (and **2**-eq) is probably the result of stereoelectronic effects. In particular, the anomeric effect[3] might be responsible for the antiperiplanar (diaxial) orientation of the S=O group and the lone pair of electrons at sulfur (eq 5). In addition, the destabilizing antiperiplanar arrangement of lone pairs in **6**-eq (and **2**-eq) as seen in eq 5 is also expected to be an important factor.[35]



(5)

Experimental Section

General Information. Melting points, determined with an Electrothermal apparatus, are uncorrected. Infrared (IR) spectra were recorded with a Nicolet MX-1-FT spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-390 and Bruker WM-250 spectrometers and are reported in ppm from internal tetramethylsilane (Me_4Si) on the δ scale. Data are reported as follows: chemical shift, multiplicity, coupling constants (hertz), integration. Carbon-13 NMR spectra were recorded on a JEOL FX-90Q (22.49 MHz) instrument operated in pulsed Fourier transform mode and locked on solvent

(24) Thioacetic anhydride gives a single line at δ 2.54; this signal is absent in the ^{1}H NMR spectrum of the crude product.
(25) Falsig, M.; Lund, H. *Acta Chem. Scand. B* **1980**, *34*, 591–595.
(26) Normant, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1046–1067.
(27) Cf. Bangerter, B. W.; Beatty, R. P.; Kouba, J. K.; Wreford, S. S. *J. Org. Chem.* **1977**, *42*, 3247–3251.
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(29) Russell, G. A.; Pecoraro, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 3331–3334.
(30) Cragg, R. H.; Weston, A. F. *Tetrahedron Lett.* **1973**, 655–656.
(31) Capozzi, G.; Modena, G. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: New York, 1974; Chapter 17.
(32) Johnson, C. R.; Keiser, J. E. *Organic Syntheses*; Wiley: New York, 1976; Collect, Vol. V, pp 791–793.
(33) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(34) Johnson, C. R.; Siegl, W. O. *J. Am. Chem. Soc.* **1969**, *91*, 2796–2797 and references therein.
(35) Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498–7505.

deuterium. Mass data were obtained on Hitachi Perkin-Elmer RMU-7H or Hewlett-Packard 5985-A spectrometers.

Flasks, stirring bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a dessicator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.[36] The BuLi employed was titrated according to the method of Juaristi et al.[37]

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

2-Propanone Ethyl Trimethylsilyl Ketal (12). Via the procedure of Inaba and Ojima,[12c] 40.44 g (0.4 mol, 56.24 mL) of diisopropylamine (freshly distilled over CaO) and 300 mL of dry THF were placed, under nitrogen in a 1000-mL round-bottom flask provided with a magnetic bar. The solution was cooled to 0 °C, and 0.42 mol (5% excess) of *n*-BuLi solution in hexane was added dropwise with stirring, which was continued for $^1/_2$ h at 0 °C. Ethyl isobutyrate (46.4 g, 0.4 mol, 53.59 mL) was then added and the reaction mixture was stirred at 0 °C for 1 h, before the addition of 85.6 g (0.787 mol, 100 mL) of chlorotrimethylsilane. Stirring was continued for an additional hour, then the suspended solids were filtered off, and the filtrate was concentrated in a rotary evaporator. The remaining yellowish liquid was distilled at reduced pressure (bp 29 °C/0.5 mmHg) so that 70.62 g (94% yield) of pure **12** was obtained: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 1.11 (t, J = 7.2 Hz, 3 H), 1.42 (s, 3 H), 1.47 (s, 3 H), 3.65 (q, J = 7.2 Hz, 2 H).

Diethyl Tetramethylsuccinate (9). Via the procedure of Inaba and Ojima,[12c] 1200 mL of methylene chloride (freshly distilled over $CaCl_2$) was placed under nitrogen in a 2000-mL round-bottom flask provided with a magnetic bar and addition funnel. 2-Propanone ethyl trimethylsilyl ketal (**12**, 70.65 g, 0.375 mol) was added and the solution was carefully treated with 74.83 g (0.394 mol, 43.25 mL) of $TiCl_4$, which had been previously diluted with 300 mL of methylene chloride. The resulting black solution was stirred under nitrogen for 2 h at room temperature and was then poured over ice and water (500 mL); the organic phase was separated, the aqueous one was extracted with 500 mL of CH_2Cl_2, and the organic extracts were combined, washed with three 500-mL portions of water, dried with anhydrous Na_2SO_4, and evaporated. The violet-colored liquid obtained was redissolved in 200 mL of CH_2Cl_2, treated with activated carbon, and filtered to afford a colorless liquid, which was concentrated to furnish 35.82 g (83% yield) of the desired product: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.19 (s, 12 H), 1.22 (t, J = 7.2 Hz, 6 H), 4.05 (q, J = 7.2 Hz, 4 H).

2,2,3,3-Tetramethyl-1,4-butanediol (13). Lithium aluminum hydride (6.49 g, 0.171 mol) and 340 mL of dry THF were placed under nitrogen in a 2000-mL round-bottom flask provided with a magnetic bar, condenser, and addition funnel. Diethyl tetramethylsuccinate (**9**, 35.82 g, 0.155 mol) and 160 mL of THF were placed in the addition funnel, and this solution was added dropwise to the one in the flask. The reaction mixture was heated to reflux under nitrogen for 24 h and then cooled to 0 °C before the sequential addition of 200 mL of water, 200 mL of 15% aqueous NaOH, and 630 mL of water; vigorous stirring was kept throughout this treatment. The resulting mixture was filtered and the filtrate extracted with three 200-mL portions of Et_2O. The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a white solid, which was recrystallized from hexane/$CHCl_3$ (95:5). The expected diol **13** was obtained in 82% yield (18.53 g) as fine white crystals: mp 209–211 °C (lit.[13a] mp 209.5–211.5 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.89 (s, 12 H), 3.40 (s, 4 H), 4.65 (s, 2 H); IR (KBr) 3300 (s), 2940 (s), 2880 (s), 1480 (s), 1378 (m), 1370 (m), 1152 (m), 1150 (s).

2,2,3,3-Tetramethyl-1,4-butanediol Ditosylate (8). Diol **13** (14.89 g, 0.102 mol) in 310 mL of pyridine was placed in a 500-mL round-bottom flask, and the solution was cooled to 0 °C before the slow addition of 58.36 g (0.306 mol) of *p*-toluenesulfonyl chloride. The reaction mixture was stirred for 30 min at 0 °C, and the resulting yellowish solution was kept in a refrigerator for 7 days. The mixture was then poured over ice and water (ca. 300 mL) and extracted with three 300-mL portions of $CHCl_3$. The chloroformic extracts were washed with three 200-mL portions of aqueous 25% hydrochloric acid and then with water (2 × 300 mL). The solution was dried over anhydrous $MgSO_4$ and concentrated to give a yellow liquid, which crystallized upon standing at room temperature. The desired ditosylate was purified by recrystallization from hexane/$CHCl_3$ (1:1); 34.47 g (74.4% yield) of **8** as white crystals were obtained: mp 110–111 °C (lit.[13a] mp 109.5–111 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.81 (s, 12 H), 2.43 (s, 6 H), 3.79 (s, 4 H), 7.35 (d, J_{AB} = 8.7 Hz, 4 H), 7.78 (d, J_{AB} = 8.7 Hz, 4 H); IR (KBr) 2950 (m), 2870 (m), 1600 (m), 1493 (m), 1475 (m), 1455 (m), 1380 (w), 1350 (s), 1190 (s), 1165 (s), 1100 (m), 963 (s), 855 (s), 820 (m), 668 (s), 660 (m), 558 (s), 483 (m).

Potassium Thioacetate. Potassium hydroxide (3.68 g, 65.7 mmol) was placed in a 250-mL round-bottom flask and dissolved in 50 mL of absolute ethanol. Thioacetic acid (65.8 mmol, 4.69 mL, 5 g) was added and the reaction mixture was stirred for 20 min at room temperature. The solvent was removed in a rotary evaporator to furnish a reddish, crystalline product, which was washed with dry THF until the crystals were only slightly yellow. This product was then dried at high vacuum to furnish pure potassium thioacetate (7.5 g, quantitative yield).

2,2,3,3-Tetramethyl-1,4-butanediol Dithioacetate (19). Hexamethylphosphoramide (30 mL) and 1.55 g (13.6 mmol) of freshly prepared potassium thioacetate were placed in a round-bottom flask provided with a magnetic stirrer. The mixture was stirred until the salt was completely dissolved, and then 3 g (6.6 mmol) of ditosylate **8** was added. The reaction mixture was then heated to 100 °C for 3.5 h, and the resulting dark-red solution was cooled in an ice bath and then poured over ice and water (ca. 60 mL) before extraction with three 50-mL portions of Et_2O. The ethereal extracts were washed with water (5 × 50 mL), dried over anhydrous Na_2SO_4, and evaporated to furnish a dark-red oil, which was purified by flash column chromatography[33] with benzene as eluent. The desired product (0.698 g, 40.3% yield) was isolated as a slightly yellow solid: mp 56–58 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.93 (s, 12 H), 2.35 (s, 6 H), 3.06 (s, 4 H).

2,2,3,3-Tetramethyl-1,4-butanedithiol (18). Dithioacetate **19** (0.566 g, 2.16 mmol) and 3 mL of methanol were placed in a 10-mL round-bottom flask and treated with 0.18 g (3 mmol, 0.2 mL) of ethylenediamine in 2 mL of methanol. The reaction mixture was stirred for 5 min and then allowed to stand for 24 h before it was poured over 10 mL of H_2O and extracted with three 10-mL portions of Et_2O. The ethereal extracts were combined, dried over anhydrous Na_2SO_4, and evaporated to furnish a pale-yellow solid, which was used without further purification in the next reaction. The yield was quantitative (0.38 g): ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.97 (s, 12 H), 1.07 (t, J = 12.0 Hz, 2 H), 2.62 (d, J = 12.0 Hz, 4 H).

4,4,5,5-Tetramethyl-1,2-dithiane (7). Dithiol **18** (0.211 g, 1.185 mmol), 5 mL of water, and 10 mL of Et_2O were placed in a 25-mL round-bottom flask, and the mixture was stirred at 0 °C before the dropwise addition of an iodine (0.30 g, 1.185 mmol) solution in 5 mL of Et_2O. The resulting dark-red solution was stirred at 0 °C for 1 h and then enough saturated aqueous $NaHSO_3$ was added to decolorize the solution. Further dilution with water (15 mL) and extraction with three 50-mL portions of ether afforded, after the usual workup procedure, the crude product, which was sublimed (32 °C/0.5 mmHb) to furnish 0.167 g (80% yield) of the pure product: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.07 (s, 12 H), 2.70 (s, 4 H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 24.16, 35.54, 42.29.

4,4,5,5-Tetramethyl-1,2-dithiane 1-Oxide (6). Dithiane **7** (0.898 g, 5.102 mmol) in 40 mL of methanol was placed in a 100-mL round-bottom flask and cooled in an ice bath before the dropwise addition of 1.145 g (5.357 mmol) of $NaIO_4$ in 17 mL of water. The reaction mixture was stirred for 20 h at room temperature, filtered to remove the inorganic salts, and concentrated to near dryness before the addition of 50 mL of water and extraction with three 75-mL portions of $CHCl_3$. The chloroformic extracts were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator to furnish the crude product, which was purified by flash chromatography[33] with $CHCl_3$ as the eluant. The product was obtained as a white solid, which was then sublimed (80–85 °C/0.5 mmHg) to afford 0.718 g (73.4% yield) of pure monosulfoxide **6**: mp 187–189 °C; ^{1}H NMR (250 MHz, $CDCl_3$)

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δ 0.95 (s, 3 H), 1.07 (s, 3 H), 1.14 (s, 3 H), 1.40 (s, 3 H), 2.33 (d, J_{AB} = 14.7 Hz, 1 H), 2.89 (d, J_{AB} = 14.1 H), 2.92 (d, J_{AB} = 14.1 Hz, 1 H), 3.78 (d, J_{AB} = 14.7 Hz, 1 H); IR (KBr) 1062 cm^{-1} (s); MS, *m/e* 192 (M^+). Anal. Calcd for $C_8H_{16}OS_2$: C, 49.96; H, 8.38. Found: C, 50.25; H, 8.40.

3,3,4,4-Tetramethylthiolane (14). Sodium (0.152 g, 6.6 mmol), thioacetic acid (0.334 g, 4.4 mmol, 0.313 mL), and HMPA (20 mL) were placed in a 50-mL round-bottom flask and stirred at room temperature for 12 h before the addition of 1 g (2.2 mmol) of ditosylate **8**. The reaction mixture was heated to 100 °C for 12 h, poured over ice and water (ca. 100 mL), and extracted with three 60-mL portions of Et_2O. The ethereal extracts were washed with water (5 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated in a rotary evaporator to furnish a reddish solid (0.267 g, 100% yield), which was decolorized by distillation in a Kugelrohr apparatus, (40–44 °C/0.5 mmHg) to afford 0.238 g (89.2% yield) of the pure product **14**: ^1H NMR (90 MHz, $CDCl_3$) δ 0.98 (s, 12 H), 2.70 (s, 4 H).

3,3,4,4-Tetramethylthiolane 1-Oxide (15). Thiolane **14** (679 mg, 4.72 mmol) was oxidized following the same procedure used in the preparation of sulfoxide **6** (vide supra). The crude product was purified by flash chromatography[33] with AcOEt/hexane (1:1) as the eluant. Pure **15** (479 mg, 63.5% yield) was obtained as white, very hygroscopic crystals, whose melting point could not be reliably measured: ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (s, 6 H), 1.25 (s, 6 H), 2.67 (d, J_{AB} = 14.1 Hz, 2 H), 3.21 (d, J_{AB} = 14.1 Hz, 2 H); IR (KBr) 1487 (m), 1463 (m), 1412 (w), 1393 (m), 1381 (m), 1370 (w), 1197 (w), 1102 (m), 1030 (s), 1003 (m); MS, *m/e* 160 (M^+).[38]

Thioacetic Anhydride ($CH_3COSCOCH_3$). Thioacetic acid (7.45 g, 97.5 mmol, 6.99 mL) was placed in a 250-mL round-bottom flask provided with addition funnel and a Dewar condenser containing dry ice. Acyl chloride (13.86 mL, 195 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature and then to gentle reflux for 4 h. Distillation afforded in a first fraction the unreacted acyl chloride (21–22 °C/5 mmHg) and in the second fraction the desired product [55 °C/5 mmHg (lit.[39] bp 155–158 °C); 17.3 g, 75% yield]: ^1H NMR (90 MHz, $CDCl_3$) δ 2.54 (s).

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Registry No. **6**, 114763-95-0; **7**, 114763-96-1; **8**, 70178-81-3; **9**, 33367-54-3; **10**, 97-62-1; **12**, 31469-16-6; **13**, 10519-69-4; **14**, 114763-97-2; **15**, 114763-98-3; **18**, 114763-99-4; **19**, 114764-00-0; Me_3SiCl, 75-77-4; TsCl, 98-59-9; AcS^-R^+, 10387-40-3; $CH_3COSCOCH_3$, 3232-39-1; thioacetic acid, 507-09-5.

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A New and Stereospecific Synthesis of Cyclitols: (1,2,4/3)-, (1,2/3,4)-, and (1,3/2,4)-Cyclohexanetetrols

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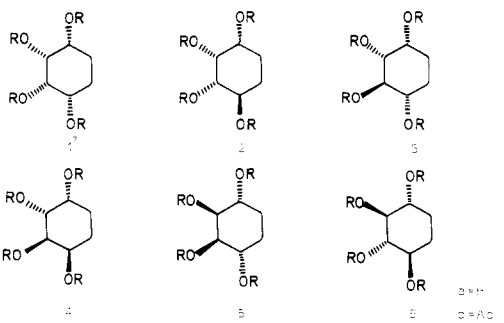
A new and stereospecific synthesis of (1,2,4/3)-, (1,2/3,4)-, and (1,3/2,4)-cyclohexanetetrols **3a**, **4a**, and **6a** is described. Syn and anti epoxy endoperoxides **9** and **10** were synthesized by epoxidation of endoperoxide **8** with *m*-chloroperbenzoic acid. Catalytic reduction of **9** and **10** gave the corresponding diols **13** and **15**. Triethylamine-catalyzed rearrangement afforded isomeric epoxy hydroxy ketones **17** and **18**. Reduction of the carbonyl group in **17** and **18** with $NaBH_4$ gave isomeric mixtures (**13** + **20**) and (**15** + **20**), respectively. All three possible epoxy diols (**13**, **15**, **20**) were converted to the corresponding epoxy diacetates and characterized by means of analytical methods. Epoxide opening was carried out in acidified water. Opening of **13** and **15** produced only one tetrol **3a**. Reaction of **21** with acidified water followed by acetylation gave a mixture of **4b** and **6b**.

Introduction

Zelinskii et al.[1] reported that 1,3-cyclohexadiene is converted into a tetrol by oxidation with permanganate. Nearly 20 years later Posternak and Friedli[2] proved that the product was DL-(1,2,3/4)-cyclohexanetetrol (**2a**). Reinvestigation by Sable et al.[3] confirmed this finding; they isolated in addition to **2a** small amounts of the isomeric (1,2,4/3) tetrol (**3a**) and the (1,2/3,4) tetrol (**4a**). Direct hydroxylation of 1,3-cyclohexadiene with monoperoxysuccinic acid gives a mixture of 3-cyclohexene-1,2-diol and (1,4/2,3)-cyclohexanetetrol (**5a**).[4] (1,3/2,4) tetrol (**6a**) has been synthesized by reduction of conduritol B[5a] and also by bromination of *vibo*-quercitol[5b] followed by catalytic reduction.



Studies of the reaction mechanism of hydroxylation of cyclic conjugated dienes[3,6] by permanganate have revealed

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