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Synthesis of DL-Methyl Meromycolate

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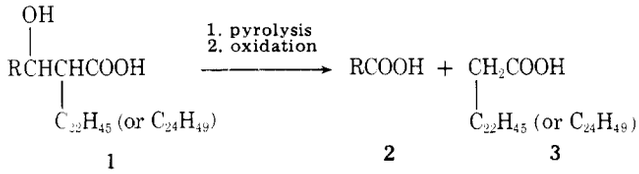
A flexible total synthesis is reported of a biscyclopropane methyl meromycolate, a product derived from the tuberculosis bacterium. The approach was to synthesize two major sections separately, namely, the bistrimethylenedithiol derivative of 10-oxo-*cis*-13,14-methylenedotriacontanal and the ethylene glycol acetal of 22-bromo-*cis*-19,20-methylenedocosanal, and then to combine them just before the final stages.

Degradation of the cell wall of tuberculosis organisms has given a number of products, among which is a family of lipids collectively called "mycolic acids".[1] These are all high molecular weight carboxylic acids **1** with a long straight chain at the carboxylic α position and a hydroxy group at the β position. Pyrolysis of mycolic acid (**1**) produces an aldehyde plus



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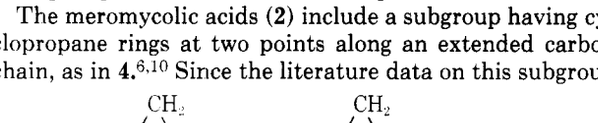
either tetracosanoic or hexacosanoic acid (**3**). Oxidation of the aldehyde ("meromycolaldehyde"), generally with silver oxide, yields the corresponding meromycolic acid (**2**).[2-9] We wish to contribute to this area by developing flexible total syntheses leading to meromycolates of assured structure. Not only would these be available for reference and comparison but they would also be used for the synthesis of mycolic acids as well as larger liposaccharide cell wall components.

The meromycolic acids (**2**) include a subgroup having cyclopropane rings at two points along an extended carbon chain, as in **4**.[6,10] Since the literature data on this subgroup



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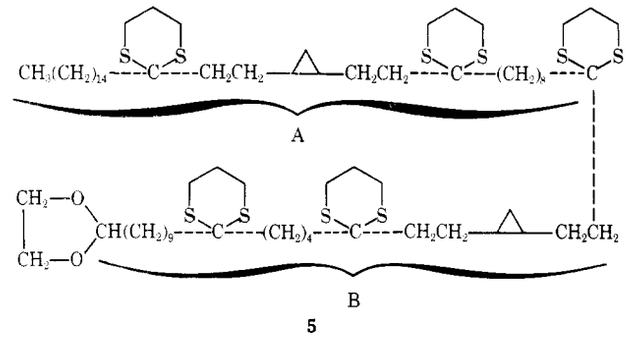
provide a defensible basis for the structural assignment, we took this kind of meromycolic acid as our first synthesis target. Different sets of x, y, z values in **4** have been reported for the most abundant component in the samples investigated.[11] We chose the set $x = 17$, $y = 14$, $z = 17$,[12] because the corresponding meromycolic acid is representative, and because it has in fact been obtained as a degradation product. The present paper reports our work, which has for the first time furnished a large molecular weight synthetic meromycolate of unequivocal structure.

To assemble the pieces that would give meromycolic acids **4** we first tried the mixed Kolbe anodic coupling process,[13] which proved not to be satisfactory. Alkylation of metalated 1,3-dithianes[14] gave much better results, and we relied on the dithiane method throughout the synthesis. Formulation **5** shows the fragments contributing carbon atoms to the meromycolic ester selected as the synthesis target (**4**: $x = 17$, $y = 14$, $z = 17$). Moieties A and B were constructed separately—the dotted lines indicate the several bonding points—and then were combined to give the complete carbon skeleton. The cyclopropane rings in the two parts were both introduced in the form of the same 3,4-methylenehexane unit, specifically as compound **16**, whose synthesis is described below.



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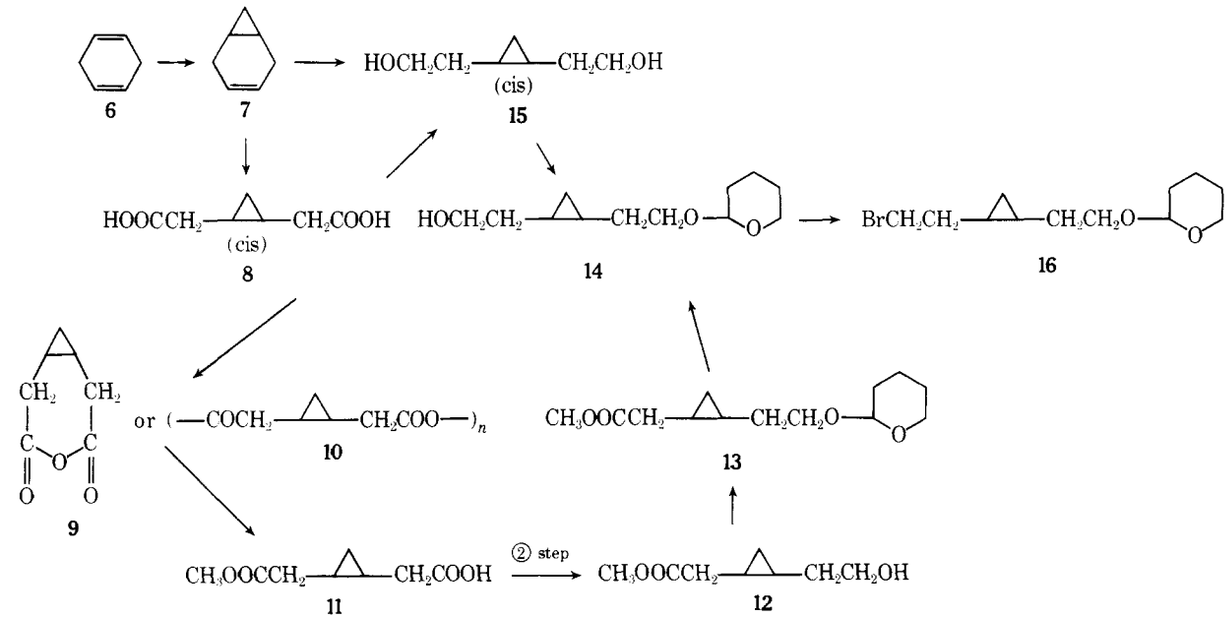
Synthesis of the Cyclopropane Portion (16). Norcarene (**7**), from 1,4-cyclohexadiene (**6**), can be converted by ozonolysis to *cis*-1,2-cyclopropanediacetic acid (**8**).[15] It was expected that anhydride formation from diacid **8** would give cyclic anhydride **9**, which would acylate methanol without complication to give half-ester **11** as the sole product. The half-ester was, in fact, obtained but only as a 2:1:1 mixture with the corresponding diester and diacid. This result is consistent with the formulation of the acid anhydride as a linear polymer **10** instead of the cyclic monomer **9**. The separated half-ester **11** was converted to the ester–acid chloride and then reduced with borohydride to ester alcohol **12**. Reaction with dihydropyran furnished intermediate **13**, which with lithium aluminum hydride gave alcohol **14**. Further conversions provided the properly functionalized tetrahydopyranyl–alkyl bromide synthon **16**. An alternate pathway called for direct sodium borohydride reduction of the ozonide from norcarene (**7**) to diol **15**, which could also be obtained from diacid **8**. The diol treated with dihydropyran under controlled conditions gave the desired monotetrahydropyranyl derivative **14** in modest single-pass conversions (35%) though in high yield when corrected for the recovered, reusable materials.[16] The shorter path via diol **15** was preferred.

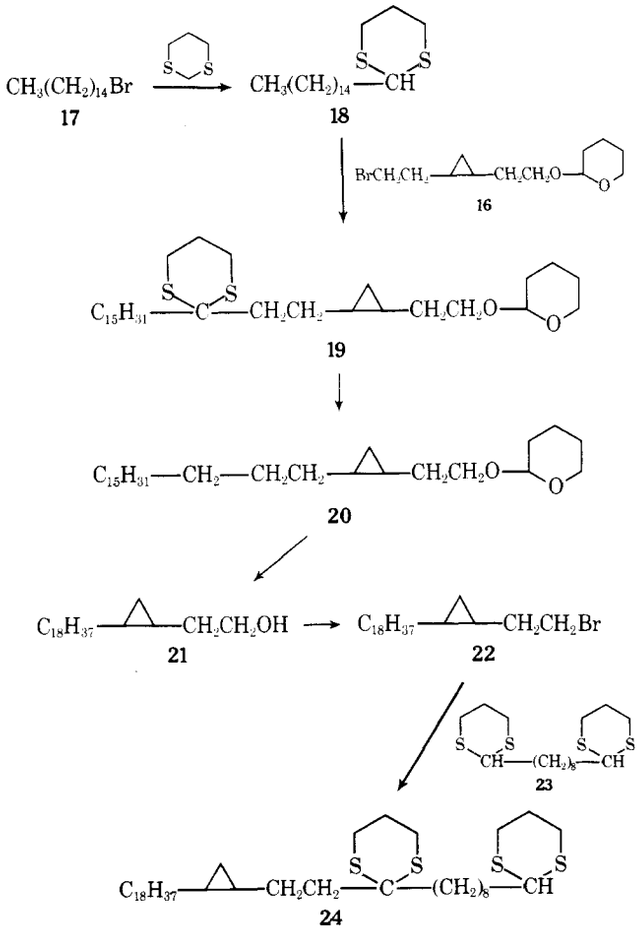
Fragment **16** provides all the asymmetric centers of the finished meromycolic acid. In the present work we used racemic **16** and so obtained an optically inactive final product. In work to be continued we plan to insert the resolved forms

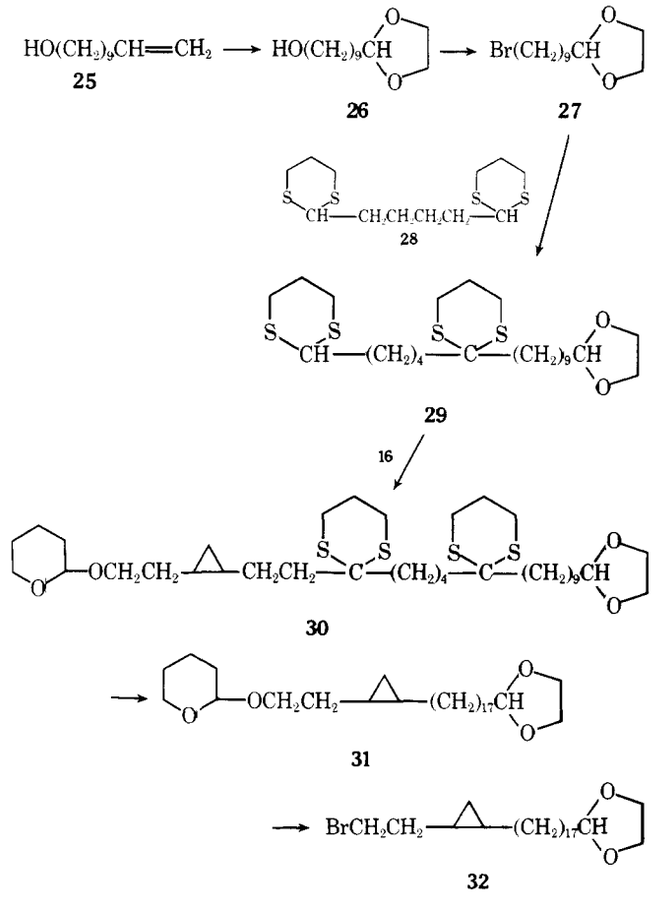


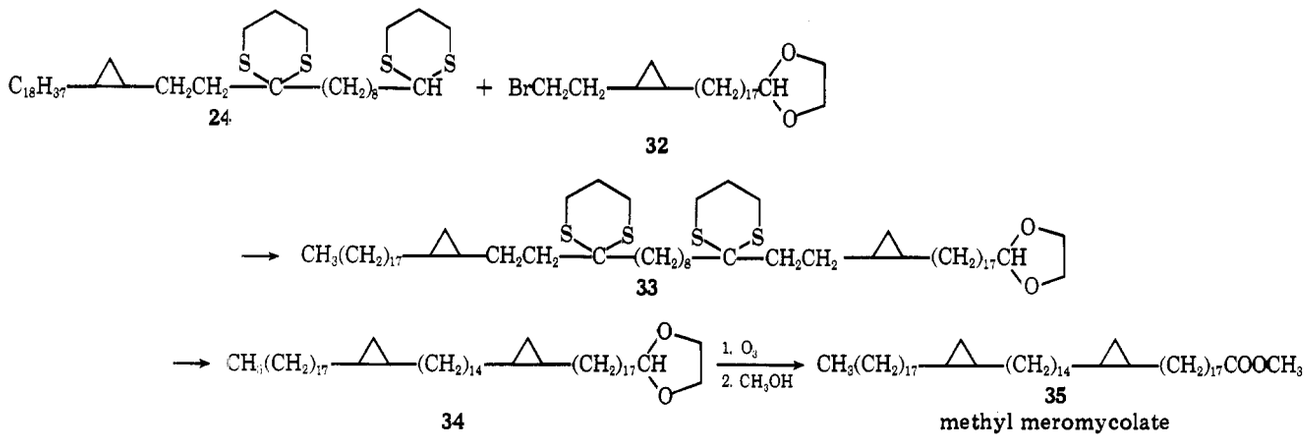
of **16**, and thus, by ringing the changes with the two enantiomers, to arrive at the optically active forms of meromycolic acid **4**.

Synthesis of the Methyl End (5-A or 24) of Meromycolic Acid. 2-Pentadecyl-1,3-dithiane (**18**) was obtained by alkylating the lithio derivative of 1,3-dithiane with pentadecyl bromide (**17**). A second alkylation, this time with the cyclopropane-containing bromide **16**, afforded the 2,2-disubstituted dithiane **19** which, after desulfurization with Raney nickel[17] to **20**, was hydrolyzed to *cis*-3,4-methylenedocosanol (**21**) and then converted to the corresponding bromide **22**. Finally, bisdithiane derivative **23** was monoalkylated with this bromide to **24**, which was one of the two major sections (**5-A**) making up the meromycolic acid product. A variation by which the chain was extended by alkylating bisdithiane **23** not with **22** but instead with the bromide corresponding to **19** was explored. However, removing six atoms of sulfur at once from the trisdithiane in the last stages of the synthesis was disadvantageous, and this approach was not pursued.

Synthesis of the Carboxyl End (5-B or 32) of Meromycolic Acid. At first we planned to synthesize this part of the molecule with the terminal vinyl group carried through in place of carboxyl. Oxidation at the last stage would cleave the double bond and develop the acid group. This approach was dropped when model experiments indicated that the vinyl







group would be saturated during the intermediate Raney nickel desulfurizations.[18]

The synthesis that was realized started with the ozonolysis of 10-undecenol (**25**) to 10-hydroxydecanal, which was converted directly to acetal **26**. The chain was extended by six carbon atoms by coupling the corresponding bromide **27** with bisdithianyl derivative **28**. A second alkylation, this time with the cyclopropane synthon **16**, led to intermediate **30**. To complete the sequence, the bisdithiane molecule **30** was desulfurized to **31** and the tetrahydropyranyl end of the chain was transformed to bromide, as in **32**. In the acid-catalyzed removal of the tetrahydropyranyl group, the problem of avoiding loss of the aldehyde blocking group at the far end of the chain was solved simply by including high concentrations of ethylene glycol in the reaction mixture.

Synthesis of Methyl Meromycolate (35). Coupling of the lithio derivative of bisdithiane intermediate **24** with alkyl bromide **32** gave the expected product **33**. A minor heterogeneity was more conveniently removed in the next step, after desulfurization, than at this stage. An unexpected complication was encountered in the desulfurization step. The product, biscyclopropane **34**, requires a ratio of 0.5 for the nuclear magnetic resonance signals at δ 0.85 (*C*-methyl) and 0.55 ppm (cyclopropane H's cis to each other). The fact that the observed ratio was greater than 0.5 indicated extra methyl groups and (or) fewer cyclopropane rings. Hydrogenolysis of the cyclopropane rings would account for this result. The presence of extra hydrogen atoms in the desulfurization product, which turned out to be a mixture, was confirmed when mass spectra showed molecular peaks not only at *m/e* 840 as calculated for **34** but also at *m/e* 842. Recrystallizations from dilute methylene chloride solutions separated the mixture cleanly into a higher melting material (mp 69–72 °C), taken as the desired product **34**, and a lower melting material (mp 45–49 °C), taken as the overreduced product. Mass spectra on the separated fractions confirmed the assignments, since the higher melting materials (**34**) had a molecular peak at *m/e* 840 and no significant peak at *m/e* 842, while the lower melting material showed a molecular peak at *m/e* 842 but practically nothing at *m/e* 840.

Why the cyclopropane ring breaks during the Raney nickel desulfurization of bisdithiane **33** is not clear. In preliminary model experiments, exposing *cis*-1,2-dipropylcyclopropane[19] to Raney nickel under the conditions used in the desulfurization of **33** did not effect the ring and allowed recovery of more than 90% of unchanged material. Nor was there any sign of cyclopropane ring cleavage in the Raney nickel desulfurization of intermediates **19**, nor of **30**. The only obvious difference is the higher molecular weight of compound **34**.

The last stages in the synthesis were to be accomplished by hydrolyzing acetal **34** to meromycolaldehyde and then oxidizing the aldehyde to meromycolic acid. Preliminary work showed that the ethylene glycol acetal of decanal could be smoothly hydrolyzed under mildly acidic conditions that had no effect on either *cis*-1,2-dipropylcyclopropane or on methyl *cis*-9,10-methyleneoctadecanoate. Despite these favorable results, no conditions could be found that allowed an uncomplicated hydrolytic unmasking of acetal **34**. Either no reaction occurred or unmanageable mixtures developed.[20] This behavior jibes with the cyclopropane hydrogenolysis in the preceding step in indicating unusual sensitivity to ring cleavage. Possibly in a molecule as large as **34** intramolecular forces can fold the molecule in a way that strains the ring(s). Also, the acetal may be buried in a hydrocarbon region of low dielectric, which could hinder access to the hydrolysis catalyst as well as to the polar water molecule.

Rather than switching to more readily hydrolyzable acetals, we tried an ozonolysis procedure which has been used to oxidize acetals to esters.[21] When applied to acetal **33**, this process smoothly formed the expected hydroxyethyl meromycolate ester. Direct base-catalyzed ester interchange then converted the hydroxyethyl ester to the end product, methyl meromycolate (**35**). The properties determined for the product are fully consistent with formulation **35**, and we regard this structure as secure.

In work to be continued we plan to carry the synthesis through with optically active cyclopropane synthons **16** so as to reach individual, chirally homogeneous, methyl meromycolates.[22] These will be compared with the appropriate degradation methyl meromycolate. They will also be elaborated to mycolic acid[23] and then further to more complex molecules.[24]

Experimental Section

General. Melting points and boiling points are uncorrected. Most of the nuclear magnetic resonance curves were determined with a 60-MHz instrument, with chloroform replacing tetramethylsilane as a reference compound whenever it was necessary to avoid interference with the high-field signal for cyclopropane hydrogen. When ether or tetrahydrofuran was used as reaction solvent, they were distilled over lithium aluminum hydride and collected directly in the reaction flask. Solvents were removed from solutions of temperature-sensitive material by using a rotary evaporator under reduced pressure with the heating bath maintained at or below the temperature specified. Thin layer chromatography made use of commercial silica gel plates impregnated with a fluorescent material enabling visualization with ultraviolet light. Iodine vapor and, for molecules containing divalent sulfur, a spray of 1% palladous chloride in 6 N hydrochloric acid were also useful. Analyses for elements were reported by Galbraith Laboratories, Inc., Knoxville, Tenn.

Norcarene (7).[25] A mixture of 52 g (0.53 mol) of anhydrous powdered cuprous chloride, 35 g (0.53 mol) of 20-mesh granulated zinc, and 150 ml of anhydrous ether was stirred and refluxed for 75 min in a moisture-protected apparatus. 1,4-Cyclohexadiene (25 g, 0.31 mol) mixed with 71 g (0.27 mol) of diiodomethane was added, and the suspension was stirred and refluxed for 21 h. Appropriate processing gave 5.2 g (50% when corrected for recovered 1,4-cyclohexadiene) of norcarene (**7**), bp 112–116 °C. Use of norcarene containing small amounts of 1,4-cyclohexadiene in the next step offered no great disadvantage.

1,2-*cis*-Cyclopropanediacetic Acid (8) from Norcarene (7). The ozonolysis procedure of Weinstein and Sonnenberg[15] was modified in a number of ways. Ozone in oxygen was passed through a 10% solution of norcarene (7) in methanol at 0 °C until the effluent gases oxidized hydriodic acid to iodine. After all volatiles were stripped away (temperature below 15 °C), the viscous residue was allowed to react with 30% hydrogen peroxide in formic acid first at room temperature and then for a short time at 50 °C. The crude product from the reaction mixture, when triturated with two parts of ethyl acetate, gave white prisms of *cis*-1,2-cyclopropanediacetic acid (8), mp 130–132 °C (lit.[15] mp 131–133 °C). The yields ranged from 50 to 65%.

Half Methyl Ester 11 of *cis*-1,2-Cyclopropanediacetic Acid. A mixture of the diacid 8 (3.0 g, 0.019 mol) and *N,N'*-dicyclohexylcarbodiimide (3.9 g, 0.019 mol) in 30 ml of absolute tetrahydrofuran was stirred at 0 °C for 1 h and then at room temperature for 3 h. The precipitate was separated and rinsed with tetrahydrofuran (15 ml). Distillation of solvent at temperatures no higher than 30 °C left the acid anhydride **9** or **10** of *cis*-1,2-cyclopropanediacetic acid as a viscous orange oil: ir (film) 1820 and 1750 cm^{-1} but no carboxyl hydroxyl absorption and no C=N stretch vibration at 2125 cm^{-1}.

The crude anhydride was stirred at 25 °C with 35 ml of absolute methanol for 20 h in a moisture-free system. After distilling away excess methanol (temperature no higher than 30 °C), the oily residue was diluted with 10 ml of anhydrous ether and the mixture was filtered to remove some insoluble dicyclohexylurea. All volatiles were stripped, and the residue was distilled to yield about 2 g (50–60%) of colorless half-ester **11:** bp 98–100 °C (0.10 mm) [lit.[26] bp 150–155 °C (6 mm); 141–142 °C (3 mm)]; mp below 25 °C; ir (film) 3675–2400, 1740, 1710 cm^{-1}; NMR (CCl_4) δ 3.6 (s, 3, $COOCH_3$), 2.4–2.2 (m, 4, 2 CH_2COO), 1.5–0.5 ppm (m, 4, cyclopropane H's). In a 25% solution the one-proton signal for carboxyl H appeared at δ 9.0 ppm; in a 15% solution it appeared at δ 12 ppm.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.59; H, 7.31.

Diacid **8** remained in the pot as residue, whereas dimethyl *cis*-1,2-cyclopropanediacetate distilled from the reaction mixture at bp 89 °C (0.1 mm) in about 25% yield: ir (film) 1735 cm^{-1}; NMR (CCl_4) δ 3.7 (s, 6, 2 $COOCH_3$), 2.36 (d, J = 6 Hz, 4, 2 CH_2COO), 1.5–0.6 ppm (m, 4, cyclopropane H's).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.89; H, 7.53.

Similar results were obtained when acetic anhydride was substituted for dicyclohexylcarbodiimide, or when the diacid was taken in very low concentration. With acetyl chloride as reagent, the methanolysis product was practically all diester, presumably the result of traces of hydrogen chloride. When sodium methoxide (1.5 mol) in hot or cold tetrahydrofuran was used in place of methanol with the anhydride formed with dicyclohexylcarbodiimide, the 2:1:1 mixture was again obtained. All attempts at purifying the anhydride failed. Distillation at temperatures up to 160 °C (0.1 mm) gave no volatile product and left an intractable brown gum in the flask.

Methyl 6-Hydroxy-*cis*-3,4-methylenehexanoate (12). Oxalyl chloride (2.2 g, 0.017 mol) was added in one portion to a moisture-protected solution of half-ester **11** (2.0 g, 0.011 mol) in 20 ml of dry benzene. After stirring the solution at 25 °C for 3 h, all volatiles were stripped away at temperatures below 45 °C. The pale-yellow residual ester–acid chloride dissolved in 10 ml of dry dioxane was added over 5 min to a stirred mixture of sodium borohydride (0.88 g, 0.023 mol) in 30 ml of dioxane. Stirring was continued for 20 h. The mixture was treated dropwise with 10 ml of water and then brought to pH 4 with sulfuric acid. The dioxane together with some water was distilled off at reduced pressures, and the product was then extracted thoroughly with ether. Removing ether from the dried extracts left a pale yellow oil (ca. 1.9 g). Repetition of this procedure starting with 2.1 g of the half-ester gave about the same results. Distillation of the combined products through a short column furnished 3.0 g (79%) of colorless hydroxy ester **12:** bp 73–75 °C (0.15 mm); ir 3400, 3055, 1735 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (t, J = 7 Hz, CH_2O–), 3.6 (s, $COOCH_3$), 3.33 (s, 1, OH), 2.33 (d, J = 6.8 Hz, 2, CH_2COO), 1.78–0.53 ppm (m, 6, cyclopropane H's plus CH_2CH_2OH). The combined integration for the first two signals corresponded to five protons.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.70; H, 8.94. Found: C, 60.88; H, 8.99.

***cis*-3,4-Methylene-1,6-hexanediol (15) from Norcarene (7).** Ozonized oxygen was bubbled into a solution of 3-norcarene (3.1 g, 0.033 mol) in 40 ml of absolute chloroform at −78 °C until the effluent gases began to release iodine from aqueous potassium iodide. After the excess ozone was swept out in a stream of oxygen, the stirred mixture at 0 °C was treated with sodium borohydride (9.9 g, 0.26 mol) in 70 ml of 1:1 ethanol–water over a period of 1 h. Stirring was continued for 18 h at room temperature. Acidification to pH 2 with dilute sulfuric acid was followed by thorough extraction with chloroform. The dried extracts were fractionated through a short-path column to give *cis*-3,4-methylene-1,6-hexanediol (**15,** 2.6 g, 70%) as a colorless, viscous liquid: bp 88–89 °C (0.005 mm) [Vogel et al.[15] report bp 136–137 °C (0.01 mm)]; ir (neat) 3500–3300 cm^{-1}; NMR ($CDCl_3$) δ 4.45 (s, 2, 2 OH), 3.67 (t, J = 6 Hz, 4, 2 CH_2O), 1.7–1.3 (broad m, 4, 2 CH_2CH_2O), 0.7 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (broad m, 1, cyclopropane H cis to substituents). The 4.45-ppm signal disappeared when D_2O was introduced.

The same diol product **15** was obtained by reducing *cis*-1,2-cyclopropanediacetic acid (**8**) or its dimethyl ester with lithium aluminum hydride in tetrahydrofuran.

Monotetrahydropyranyl Derivative 14 of *cis*-3,4-Methylene-1,6-hexanediol. A. From Diol 15. To a solution of diol **15** (3.0 g, 0.023 mol) in dry dichloromethane (120 ml) at 3 °C was added a cold solution of dihydropyran (1.9 g, 0.023 mol) in tetrahydrofuran (30 ml) and then 20 mg of *p*-toluenesulfonic acid in 5 ml of tetrahydrofuran. The mixture was stirred for 1 h at 3 °C and then for 5 h at 10 °C. Triethylamine (0.5 g) was added before removing almost all of the volatiles (temperature below 45 °C). Extraction with pentane removed the tetrahydropyranyl derivatives and left practically pure unchanged diol **15** as a second phase. Distillation of the material in the pentane gave 2.8 g (36% conversion) of the desired monotetrahydropyranyl derivative **14,** bp 100–109 °C (0.003 mm). This product gave a single spot on a TLC plate (ether): ir 3500 cm^{-1}; NMR ($CDCl_3$) δ 4.40 (broad s, 1, tetrahydropyranyl OCHO), 1.4 (broad s, 10, CH_2's next to cyclopropane plus tetrahydropyran 3, 4, and 5 positions), 0.5 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (broad m, 1, cyclopropane H cis to alkyls). Also evident was a multiplet at δ 3.45 (CH_2OTHP plus the tetrahydropyran 6-methylene) topped by a triplet (J = 6 Hz, CH_2OH) and accompanied by a singlet at 3.35 ppm (OH), which together integrated for 7 protons. The 3.35 ppm signal vanished when D_2O was added.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.10; H, 10.36.

B. From Methyl 6-Hydroxy-*cis*-3,4-methylenehexanoate (12). A mixture of ester alcohol **12** (1.0 g, 6.3 mmol), 0.78 g (9.5 mmol) of dihydropyran, and 30 mg of *p*-toluenesulfonic acid in 30 ml of benzene was stirred at 25 °C for 1 day. The mixture was washed with dilute aqueous sodium hydroxide, dried, and then stripped of all volatile material to give 1.5 g of the tetrahydropyranyl derivative **13** of ester alcohol **12.**

A solution of product **13** in ether (10 ml) was added under nitrogen to lithium aluminum hydride (0.5 g, 12 mmol) suspended in 30 ml of ether, and the mixture was stirred at room temperature for 1 day. Excess reagent was decomposed by adding 10 ml of water dropwise to the reaction mixture cooled to below 0 °C followed by 30 ml of 5% aqueous sodium hydroxide. The aqueous layer was extracted thoroughly with ether, and the combined, dried, ether solutions were stripped of all solvent at temperatures no higher than 40 °C to leave the monotetrahydropyranyl derivative **14** as a faintly yellow oil (1.4 g).

Tetrahydropyranyl Bromo Derivative 16. The general procedure as detailed in the preparation of bromo intermediate **27** was followed. Monotetrahydropyranyl derivative **14** (2.6 g, 0.012 mol) in pyridine (25 ml) plus 2.6 g (0.014 mol) of *p*-toluenesulfonyl chloride gave rise to 5.0 g of the corresponding tosylate as a pink oil: ir free of absorption at 3600–3300 cm^{-1}; NMR, consistent with the presence of the tosylate group.

Anhydrous lithium bromide (3.4, 0.039 mol) with 3.2 g of the monotosylate of derivative **14** in 240 ml of dry acetone gave crude product **16,** which on distillation yielded 1.84 g (85% from **14**) of homogeneous (thin layer chromatography with benzene) tetrahydropyranyl derivative **16** of 6-bromo-*cis*-3,4-methylenehexanol: bp 82–92 °C (0.01 mm); NMR ($CDCl_3$) δ 4.45 (broad s, 1, tetrahydropyranyl OCHO), 3.5 (m, 3 CH_2O), 3.30 (t, J = 6 Hz, CH_2Br), 1.5 (broad s, 10, CH_2's next to cyclopropane ring plus CH_2's at tetrahydropyran 3,4,5 positions), 0.6 (m, 3, cyclopropane H's cis to each other), −0.2 ppm (m, 1, cyclopropane H cis to alkyls). The combined integration for the 3.5 and 3.3 ppm signals corresponded to six protons.

Anal. Calcd for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.63; Br, 28.82. Found: C, 51.69; H, 7.80; Br, 28.64.

The bromo compound deteriorated at room temperature and was routinely stored at 5 °C. The triphenylphosphine–*N*-bromosuccinimide conversion[27] of alcohol **14** to bromide **16** was not satisfactory; the tetrahydropyran ring was attacked to some extent, and the mixture was difficult to purify. When lithium chloride was substituted for lithium bromide, the chloride corresponding to bromide **16** was formed. To check this last process the tetrahydropyranyl protecting

group was removed by exposure to 95% alcohol containing a trace of *p*-toluenesulfonic acid, whereupon 6-chloro-*cis*-3,4-methylenehexanol was obtained.

2-Pentadecyl-1,3-dithiane (18) by Alkylating Dithiane with Pentadecyl Bromide (17).[28] After preparing 2-lithio-1,3-dithiane by metalating 1,3-dithiane (1.24 g, 10.3 mmol) at −30 to −20 °C with butyllithium (10.5 mmol in 2.33 M hexane solution) in 50 ml of absolute tetrahydrofuran, pentadecyl bromide (3.00 g, 10.3 mmol) was injected, and the alkylation was allowed to proceed for 1.5 h and then for 20 h at −7 °C. Water (10 ml) was added and volatiles were removed at reduced temperature (<50 °C). The alkylation product was extracted with ether, and the ether solution was washed thoroughly with water and with dilute aqueous alkali before drying. On crystallization of the crude product from chloroform–methanol, white plates of 2-pentadecyl-1,3-dithiane (**18**, 2.73 g, 80%), mp 44–45.5 °C, homogeneous according to thin layer chromatography (10:1 pentane–ether), was obtained: ir ($CHCl_3$) 2900, 905 cm^{-1}; NMR ($CDCl_3$) δ 4.02 (t, J = 6.0 Hz, 1, dithiane SCHS), 2.97–2.72 (m, 4, 2 CH_2S), 2.25–1.90 (m, dithiane 4-CH_2), 1.27 (broad band, linear CH_2's), 0.92 ppm (t, J = 6.8 Hz, CH_3C). Integration from 2.25–0.92 indicated 33 protons as required.

Anal. Calcd for $C_{19}H_{38}S_2$: C, 68.99; H, 11.61; S, 19.40. Found: C, 69.19; H, 11.76; S, 19.54.

Formation of Intermediate 19 by Coupling 2-Pentadecyl-1,3-dithiane (18) with Bromide 16. The alkylation process was carried out in a scrupulously dry three-necked flask under a small positive pressure of argon or nitrogen dried by passage through a tower of calcium sulfate. Tetrahydrofuran (50 ml) was distilled directly from lithium aluminum hydride into the flask, which already contained 2-pentadecyl-1,3-dithiane (**18**, 455 mg, 1.5 mmol) and triphenylmethane (3 mg). With stirring and with the reaction flask at −30 °C (solid CO_2 in ethanol) 0.8 ml of 2.25 M butyllithium in hexane (1.8 mmol) was injected by syringe through a stopple. The argon inlet needle was withdrawn, and the sealed reaction mixture was stirred for 3.5 h at −30 to −20 °C. The pink triphenylmethide color, detected after about 10 min, reached a maximum intensity after approximately 0.5 h.

Again under argon, 300 mg (1.08 mmol) of the tetrahydropyranyl derivative of 6-bromo-*cis*-3,4-methylenehexanol (**16**) was injected, and the mixture, which became colorless after a few minutes, was stirred at −30 to −20 °C for 1 h.

Water (2 ml) was added, after which the mixture was concentrated at 40 °C. The pale yellow oily residue was shaken with water (50 ml) and several portions of ethyl acetate. The ethyl acetate extract was rinsed with water, dried, and evaporated to furnish the alkylation product **19** (736 mg). Preparative layer chromatography, using benzene as the developing solvent and ultraviolet light for visualization, separated this product into a faster moving fraction (R_f 0.7), which proved to be unchanged pentadecyldithiane (**18**, 175 mg, 0.53 mmol), and a slower moving fraction (R_f 0.4), which was the desired product **19** (474 mg, 83% based on bromo compound **16**). Analytical thin layer chromatography showed a single spot with trace impurities: NMR ($CDCl_3$) δ 4.40 (broad s, 1, tetrahydropyranyl OCHO), 3.5 (m, 4, 2 CH_2O), 2.60 (m, 4, 2 CH_2S), 2.0–1.1 (m, 41, as against 40 calculated, cyclic and linear CH_2's), 0.70 (t, J = 5 Hz, CH_3C), 0.5 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (m, cyclopropane H cis to alkyls). The integration of the last three signals corresponded to seven protons as required by formulation **19**.

***cis*-3,4-Methylenedocasanol (21) by Desulfurization and Hydrolysis of Intermediate 19.** Activated Raney nickel (ROC/RIC Inc.) stored under water was washed in succession with ten portions of water, six of 95% alcohol, six of absolute alcohol, and eight of cyclohexane. A vigorously stirred 70 °C solution of dithiane **19** (960 mg, 1.83 mmol) in cyclohexane (80 ml) was treated at 15-min intervals with 10-, 5-, and 2.5-g portions of this Raney nickel in hexane. Fifteen minutes after the last portion was added, the solids (still pyrophoric) were separated by filtration through diatomaceous earth (Celite), and were rinsed several times with warm cyclohexane. Removing solvent from the combined filtrates left 620 mg of colorless oil. To remove the remaining sulfur, this oil, redissolved in 60 ml of cyclohexane, was treated as before with a fresh portion of Raney nickel (3 g). The resulting colorless, sulfur-free dihydropyran derivative **20** of *cis*-3,4-methylenedocosanol (600 mg) had the following properties: ir, no absorption at 3600–3300 cm^{-1}; NMR ($CDCl_3$) δ 4.50 (broad s, 1, OCHO), 3.50 (m, 4, 2 CH_2O), 1.70–1.10 (m, ca. 42, CH_2's), 0.80 (t, J = 6 Hz, CH_3C), 0.5 (broad s, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls). The integration value of the 0.8–0.5 ppm signals corresponded to six protons.

To remove the tetrahydropyranyl protecting, the oily product **20** was allowed to stand for 18 h at room temperature in a solution of ethanol (50 ml), water (2 ml), and 11 N hydrochloric acid (1 ml). After 1 ml of triethylamine was added, the mixture was stripped of volatiles at temperatures no higher than 50 °C. Some water was added, and the product **21** was extracted into ethyl acetate. The extract, rinsed twice with water, dried, and stripped of all solvent, left *cis*-3,4-methylenedocosanol (**21**) as a colorless residue weighing 520 mg (85%): mp 50–51 °C; homogeneous according to thin layer chromatography using 1:5 ether–benzene as developing solvent; NMR ($CDCl_3$) δ 3.65 (t, J = 6 Hz, 2, CH_2O), 2.05 (s, 1, OH), 1.5–1.1 (s with shoulder, 36, linear CH_2's), 0.80 (t, J = 6 Hz, CH_3C), 0.55 (broad s, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls). Integration of the 0.8 and 0.55 ppm signals indicated six protons; the 2.05 ppm signal for hydroxyl disappeared when D_2O was added.

Anal. Calcd for $C_{23}H_{46}O$: C, 81.58; H, 13.69. Found: C, 81.31; H, 13.93.

***cis*-3,4-Methylenedocosanyl Bromide (22).** The general procedure by which the alcohol was tosylated and then transformed to bromide was similar to that described for the conversion of alcohol **26** to bromide **27**. *cis*-3,4-Methylenedocosanol (**21**, 520 mg, 1.54 mmol) in 8 ml of pyridine freshly distilled from solid potassium hydroxide was treated with 382 mg (2.0 mmol) of tosyl chloride. The resulting white solid *cis*-3,4-methylenedocosanyl tosylate (650 mg, 86% yield) showed no infrared absorption in the 3600–3300-cm^{-1} region but did show nuclear magnetic resonance signals at δ 7.33 and 7.77 ppm. A solution of this tosylate (630 mg, 1.28 mmol) in dry acetone (50 ml) containing 600 mg of lithium bromide (6.9 mmol) was refluxed for 3 h. Isolation of the bromide product **22** made use of chloroform for extraction instead of ethyl acetate. The *cis*-3,4-methylenedocosanyl bromide (**22**, 520 mg of 87% from the alcohol) was obtained as a straw-colored oil liquid at room temperature but solid at 0 °C. Thin layer chromatography (benzene solvent) showed one major spot as well as some very faint extra spots: NMR ($CDCl_3$) δ 3.42 (t, J = 5 Hz, 2, CH_2Br), 1.1 (s with shoulder at 1.5, 36, linear CH_2's), 0.85 (t, J = 6 Hz, CH_3C), 0.55 (s, cyclopropane H's cis to each other), −0.25 ppm (m, 1, cyclopropane H cis to alkyls). Integration from 0.85 to 0.55 ppm indicated 6.5 protons as against the required 6 protons. The mass spectral equal-intensity peaks at *m/e* 400 and 402 corresponded to the molecular formula, $C_{23}H_{45}Br$. No peaks were noted at higher *m/e* values.

1,4-Bisdithianylbutane (28) and 1,8-Bisdithianyloctane (23).[28] 1,3-Dithiane (3.34 g, 0.0278 mol) in 80 ml of tetrahydrofuran containing 12.4 ml of 2.33 M butyllithium in hexane (0.029 mol) was allowed to stand at −40 to −20 °C for 1.25 h. After 1,4-dibromobutane was added, the mixture was stirred at the same temperature for 2 h and then allowed to stand at −7 °C for 20 h. The crude product, on recrystallization from chloroform–methanol, furnished 3.32 g (81%) of 1,4-bisdithianylbutane (**28**) in two crops, both with mp 103–103.5 °C. The product showed only a single spot on thin layer chromatography (either with 5:1 pentane–ether or with chloroform): ir ($CHCl_3$) 2900, 905 cm^{-1}; NMR ($CDCl_3$) δ 4.04 (t, J = 6 Hz, 2, 2 SCHS), 3.03–2.73 (m, 8, 4 CH_2S), 2.35–1.30 ppm (m, 12, all other H's).

Anal. Calcd for $C_{12}H_{22}S_4$: C, 48.86; H, 7.54; S, 43.60. Found: C, 48.89; H, 7.74; S, 43.43.

The corresponding octane derivative **23** was prepared in an analogous way by using 22.6 mmol of butyllithium in hexane, 50 ml of tetrahydrofuran, 2.65 g (22.1 mmol) of 1,3-dithiane, and 3.00 g (11.0 mmol) of 1,8-dibromooctane. One crystallization of the product from chloroform gave 3.38 g (88%) of 1,8-bisdithianyloctane (**23**) as shiny white plates, mp 80–81.5 °C, showing a single spot on thin layer chromatography (5:1 pentane–ether): ir ($CHCl_3$) 2850, 905 cm^{-1}; NMR ($CDCl_3$) δ 4.09 (t, J = 6.8 Hz, 2, 2 SCHS), 3.10–2.75 (m, 8, 4 CH_2S), 2.25–1.15 ppm (m, 20, all other H's).

Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.77; H, 8.64; S, 36.58. Found: C, 54.86; H, 8.59; S, 36.73.

Intermediate 24 by Alkylation of Bisdithianyloctane (23) with *cis*-3,4-Methylenedocosanyl Bromide (22).[28] Metalation was accomplished by exposing bisdithianyloctane (**23**, 700 mg, 2.00 mmol) in 70 ml of tetrahydrofuran containing 5 mg of triphenylmethane to the action of butyllithium (2.1 mmol, 1.0 ml, of 2.1 M reagent in hexane) for 4 h at −20 °C. The pink solution was then treated with 510 mg (1.27 mmol) of *cis*-3,4-methylenedocosanyl bromide (**22**) in 10 ml of dry tetrahydrofuran, and the alkylation was allowed to proceed for 1.5 h. The crude reaction product was separated by preparative-plate chromatography (2:3 ligroin–benzene) into three bands, with R_f 0.7, 0.5, and 0.25. The slowest moving material proved to be unchanged 1,3-dithiane (356 mg, 1.02 mmol). The least polar fraction (R_f 0.7), recovered from the plate as a pale yellow oil (150 mg), was considered to be the dialkylation product; the integration ratio of the nuclear magnetic resonance signal at −0.3 ppm to that at 2.75 ppm (CH_2S's) came to 2:8, as required.

The fraction of intermediate polarity (R_f 0.5), isolated as a faintly yellow oil, was taken as the desired monoalkylation product **24.** This oily material (540 mg, 0.80 mmol), which did not solidify at ice-bath temperatures, showed a single spot on a thin layer chromatographic plate (1:1 ligroin–benzene) accompanied by some very faint trace spots: NMR ($CDCl_3$) δ 3.95 (t, J = 6 Hz, 1, SCHS), 2.75 (m, 8, 4 CH_2S), 2.1–1.3 (m), and 1.13 (s, 58, linear CH_2's plus 2 dithiane CCH_2C), 0.80 (t, J = 4 Hz, 3, CH_3C), 0.50 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls).

Ethylene Glycol Acetal 27 of 10-Bromodecanal. Ozone in oxygen was passed into a solution of 10-undecenol (5.0 g, 0.029 mol) in 50 ml of methanol at 0 °C for about 1 h, or until ozone was no longer absorbed. The excess ozone was blown out in a stream of nitrogen gas. Dimethyl sulfide (4.0 g, 0.065 mol) was added, and the solution was held at 0 °C for 0.5 h and then at 25 °C for 1 h. Crude 10-hydroxydecanal was obtained as a colorless oil after stripping away all volatiles at temperatures below 30 °C.

To prepare the corresponding acetal **26,** the crude product was stirred with 20 ml of ethylene glycol containing 20 mg of *p*-toluenesulfonic acid at room temperature for 18 h. The mixture was diluted with 200 ml of water and was extracted thoroughly with benzene. Fractionation of the dried extract gave 3.5 g (55%) of the ethylene glycol acetal **26** of 10-hydroxydecanal: bp 106–115 °C (0.004 mm); NMR ($CDCl_3$) δ 4.85 (t, J = 4 Hz, 1, OCHO), 3.91 (m, 4, ring CH_2's), 3.61 (t, J = 6 Hz, 2, $HOCH_2$), 2.68 (s, 1, OH), 1.3 ppm (broad s, 16, linear CH_2's). Thin layer chromatography (benzene) produced only one spot.

The alcoholic function was tosylated by dissolving the hydroxy acetal **26** (3.0 g, 0.014 mol) in 20 ml of carefully dried pyridine, cooling the solution to 3 °C, and then with stirring adding *p*-toluenesulfonyl chloride (3.5 g, 0.018 mol) that had been crystallized from petroleum ether. After 20 h at 0 °C, the tosylate of **26** could be isolated as a straw-colored oil (4.9 g, 94% from the hydroxy acetal): NMR ($CDCl_3$) δ 7.77 and 7.33 (two d's, J = 9 and 4 Hz, aromatic H's), 7.55 (impurity), 4.81 (t, J = 4 Hz, 1, OCHO), 4.00 (t, J = 6 Hz, CH_2OTs), 3.89 (m, ring CH_2's), 2.44 (s, 3, CH_3Ar), 1.90–1.10 ppm (m, 16, 8 linear CH_2's). Integration of the 4.00 and 3.89 ppm signals agreed with a total of six protons.

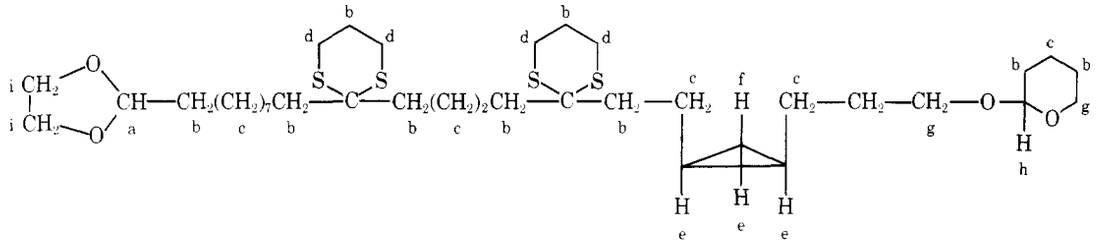
Without purification, the tosylate (4.5 g, 0.012 mol) was dissolved in 300 ml of acetone freshly distilled from anhydrous potassium carbonate, lithium bromide (4.7 g, 0.054 mol) dried at 100 °C for 1 day was added, and the solution was refluxed for 1.5 h. After suitable treatment, the reaction mixture furnished 2.2 g of 10-bromodecanal ethylene glycol acetal (**27**), bp 109–113 °C (0.017 mm). The yield from crude tosylate was 66%; the overall yield in the four-step process from 10-undecenol (**25**) was 34%. Thin layer chromatography of the distilled bromide **27** using benzene as solvent developed only a single spot. Interestingly, instead of the expected twin mass spectral molecular peaks at M − 1 and M + 1 (278 and 280), the peaks appeared at M − 2 and M (277 and 279), a result, presumably, of the molecule ion losing hydrogen readily from the OCHO grouping: NMR ($CDCl_3$) δ 4.84 (t, J = 4 Hz, 1, OCHO), 3.90 (m, 4, ring CH_2's), 3.40 (t, J = 6 Hz, 2, CH_2Br), 1.30 ppm (broad s, 16, 8 linear CH_2's).

Anal. Calcd for $C_{12}H_{23}BrO_2$: C, 51.62; H, 8.30; Br, 28.62. Found: C, 51.32; H, 8.22; Br, 28.86.

Bisdithiane Acetal 29 by Alkylation of 1,4-Bisdithianylbutane (28) with Bromo Acetal 27. A solution of 1,4-bisdithianylbutane (**28,** 1.00 g, 3.40 mmol) and triphenylmethane (3 mg) in 100 ml of tetrahydrofuran was treated at −25 °C with 1.70 ml of 2.2 M butyllithium in hexane (3.74 mmol) and, after 3.5 h, with bromo acetal **27** (0.600 g, 2.15 mmol). The reaction mixture was allowed to stand at −25 °C for 1.5 h. Processing essentially as before[28] afforded a pale yellow oil, which was chromatographed on a column of 60–200 mesh silica gel using benzene (1 l.) followed by 1:9 ether–benzene (0.5 l.) as developing solvents. The material eluted in the benzene fractions was unchanged 1,4-bisdithianylbutane (490 mg, 1.67 mmol). The material eluted with ether–benzene proved to be the desired alkylation product **29** (820 mg, 77% from the bromide **27**), showing a single spot on a thin layer chromatography plate (benzene): NMR ($CDCl_3$) δ 4.82 (t, J = 4 Hz, 1, OCHO), 4.10 (t, J = 4 Hz, SCHS), 3.90 (m, OCH_2CH_2O), 2.80 (m, 8, 4 CH_2-S), 2.1–1.3 ppm (complex, 33 vs. 30 calculated, all other CH_2's). Integration of the 4.10 and 3.90 ppm signals indicated five protons as required.

Anal. Calcd for $C_{24}H_{44}O_2S_4$: C, 58.49; H, 9.00. Found: C, 58.41; H, 8.82.

Bisdithiane Intermediate 30 by Alkylation of Bisdithiane 29 with the Tetrahydropyranyl Derivative of 6-Bromo-*cis*-3,4-methylenehexanol (16).[28] The alkylation used 620 mg (1.2 mmol) of bisdithiane **29,** 5 mg of triphenylmethane, 75 ml of tetrahydrofuran, and 1.68 mmol of butyllithium (2.25 M hexane solution), followed after metalation was complete by 320 mg (1.15 mmol) of bromo compound **16.** The yellow, oily, crude product was purified by preparative layer chromatography with benzene as solvent. Appreciable unchanged bisdithiane starting material (**29**) was recovered (100 mg, 0.22 mmol) together with 605 mg (77% based on **16**) of the desired product **30.** Thin layer chromatography of this material showed a single spot accompanied by some very faint additional spots indicating the presence of trace impurities; NMR ($CDCl_3$) δ 4.8 (t, J = 4 Hz, 1, a), 4.6 (broad s, 1, h) 3.9 and 3.8 (two multiplets, 8, i and g), 2.8 (m, 8, d), 2.1–1.3 (m, 41.4 as compared to the required 42, c and b), 0.75 (broad s, 3, e), −0.2 ppm (m, 1, f).



Anal. Calcd for $C_{36}H_{64}O_4S_4$: C, 62.74; H, 9.36; S, 18.61. Found: C, 62.55; H, 9.22; S, 18.69.

Intermediate 31 by Desulfurization of Bisdithianyl Derivative 30. A solution of bisdithiane **30** (955 mg, 1.39 mmol) in 100 ml of cyclohexane was stirred at 70 °C with 9 g of Raney nickel prepared as described above. After 15 min, an additional 9 g of Raney nickel was added, and the mixture was stirred further for 15 min. The supernatant liquid was decanted from the solids and filtered directly through Celite. The still pyrophoric solids were rinsed several times with portions of hot cyclohexane. Evaporating the combined cyclohexane solutions at temperatures no higher than 45 °C left a colorless oil, which was redissolved in cyclohexane and stirred at 70 °C with fresh Raney nickel (4 g) and then, 15 min later, with a second 4-g portion of Raney nickel for an additional 15 min.

The sulfur-free product **31** was isolated as before as a solvent-free, colorless oil (390 mg) that solidified below 10 °C: ir, no peaks at 3600–3300 or at 1730 cm^{-1}; NMR ($CDCl_3$) δ 4.67 (t, J = 4 Hz, 1, dioxolane OCHO), 4.46 (broad s, 1, tetrahydropyran OCHO), 3.75 and 3.50 (complex, 8, 4 O-CH_2), 1.60–1.10 (complex, 45, undesignated H's), 0.50 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls). No olefinic signals appeared downfield from δ 4.67 ppm.

Ethylene Glycol Acetal 32 of 22-Bromo-*cis*-19,20-methylenedocosanal. The oily tetrahydropyranyl derivative **31** from two runs (750 mg, 1.56 mmol) was allowed to stand for 20 h at room temperature in a solution of 70 ml of tetrahydrofuran containing 2 ml of water, 4 ml of ethylene glycol, and 1 ml of 11 M hydrochloric acid. After addition of triethylamine (1 ml), the reaction mixture was stripped of volatile material at temperatures no higher than 50 °C. Water (60 ml) was added, and the product was extracted into ethyl acetate. The extract, washed with water, dried, and evaporated (<45 °C), left a colorless oil that crystallized to a white, waxy solid (726 mg), which was taken as the acetal of 22-hydroxy-*cis*-19,20-methylenedocosanal, ir 3500 cm^{-1} (no absorption at 1740–1720 cm^{-1}).

The alcohol in 15 ml of dry pyridine was tosylated by reaction with *p*-toluenesulfonyl chloride (480 mg, 2.51 mmol) over an 18-h period. The pale yellow tosylation product was purified by preparative layer chromatography (3% ether in benzene) followed by recrystallization of the solid fraction (540 mg) from ether. The silky white needles of the acetal tosylate (270 mg, 18% calculated from bisdithiane **30**) showed mp 69–70 °C; TLC (benzene) developed only a single spot. The mother liquor contained more of this tosylate (ca. 210 mg) plus about 50 mg of a second unidentified component.

Anal. Calcd for $C_{32}H_{54}O_5S$: C, 69.78; H, 9.88; S, 5.81. Found: C, 69.99; H, 9.75; S, 5.74.

A solution of crystalline tosylate (240 mg, 0.44 mmol) and anhydrous lithium bromide (250 mg, 2.87 mmol) in 25 ml of dry acetone

was stirred and refluxed for 3 h. The desired bromide **32** was isolated as a colorless oil (196 mg, 97%), mp ca. 20 °C; analysis by TLC (benzene) showed some very faint spots indicating traces of extraneous material; ir, no absorption maxima at either 3600–3300 or 1730 cm^{-1}; mass spectroscopy gave twin molecular peaks at *m/e* 458 and 460 corresponding to $C_{25}H_{47}BrO_2$; NMR ($CDCl_3$), all features satisfactory except that some of the high-field integrations deviated slightly from the expected value.

Completing the Carbon Skeleton (as in 33) by Alkylating Bisdithiane 24 with Bromide 32.[28] Bisdithiane **24** (670 mg, 1.0 mmol) was lithiated by exposure to butyllithium (0.55 ml of a 2.1 M solution in hexane, 1.1 mmol) in 70 ml of tetrahydrofuran containing 3 mg of triphenylmethane for 4 h at −25 to −15 °C. After bromide **32** (200 mg, 0.44 mmol) as a solution in 8 ml of tetrahydrofuran was added, the reaction was allowed to proceed for 1.5 h at −25 °C and for 16 h at −10 °C. The triphenylmethide pink color gradually faded and disappeared altogether in about 0.5 h. Isolation of product[28] gave a pale yellow oil, which was fractionated conveniently by preparative layer chromatography (benzene) into two bands. The faster moving material was unchanged bisdithiane **24** (388 mg, 0.58 mmol). The slower moving material, taken as the desired alkylation product **33,** was obtained as a viscous oil (360 mg, 82%) solidifying below 5 °C and showing only a single spot on thin layer chromatography. Although the nuclear magnetic resonance spectrum showed only the expected features, some discrepancy in the integration ratios pointed to the presence of impurity. Whatever the nature of this impurity, it did not disturb the calculated ratios corresponding to an intact dioxolane ring, two intact dithiane rings, and two cyclopropane rings. Thus the signal ratios at δ 4.75 (t, J = 4 Hz, OCHO), 3.80 (m, OCH_2CH_2O), 2.75 (m, 4 CH_2S's), and 0.55 ppm (broad s, cyclopropane H's cis to each other) came to 0.82:4.4:7.7:6.0, values that compared well with the required ratios of 1:4:8:6.

Attempted purification by gel filtration (Bio-beads 5 × 4 available from Bio-rad Laboratories and designed for molecular weights up to 1400) showed no sign of successful separation.

Formation of Intermediate 34 by Desulfurization of 33. The procedure was similar in general to that used in the desulfurization that led to *cis*-3,4-methylenedocosanol (**21**). Intermediate **33** (150 mg, 0.14 mmol) containing unidentified heterogeneity was stirred with Raney nickel (prepared as before) in cyclohexane solvent (25 ml) at 70 °C. The initial 3-g portion of Raney nickel was followed after 15 min with a second 3-g portion. Then, after 15 min, the reaction mixture was processed to recover the substrate, which was redissolved in cyclohexane (25 ml) and stirred again with Raney nickel (2 g) for 15 min. Product **34** was isolated as a white solid whose low solubility in most solvents presented problems. On analytical thin layer chromatography (benzene), this material developed two spots, R_f 0.45 and 0.55, both free of sulfur. The slower running component had the same R_f (0.45) as the starting material **33,** an observation suggesting that the R_f 0.45 fraction could be identified tentatively with the above-mentioned heterogeneity in the starting material, and further that the heterogeneity could not have contained sulfur.

Crystallizations of the white solid from 10 ml of acetone gave white, needlelike crystals of acetal **34** (70 mg, 60%), mp 66–70 °C, or from a different run, mp 60–75 °C. Preparative plate chromatography (benzene) was also effective in separating the contaminant from the desired product. Product **34** was soluble to only a very limited extent in chloroform, ether, dichloromethane, cyclohexane, or benzene. Thin layer chromatography on silica gel plates (carbon tetrachloride or benzene) produced a single spot. On an alumina plate (2:3 petroleum ether–benzene), the product showed two barely resolved spots; an alumina preparative plate did not give a clean separation. The infrared absorption spectrum was free of carbonyl absorption at 1730 cm^{-1}; and only the expected signals were seen on the nuclear magnetic resonance spectra ($CDCl_3$), including δ 3.90 (m, acetal OCH_2CH_2C) and 0.5 and −0.3 ppm (cyclopropane H's) peaks. Because of limited solubility and the resulting low intensity signals, integration was difficult. However, estimates of the ratio of methyl hydrogens (δ 0.85) to cis-cyclopropane H's gave values clearly greater than the 3:6 required for biscyclopropane **34.** High-resolution mass spectrometry (base peak at *m/e* 73 for the 2-dioxolane ion radical), with *m/e* peaks at 840 ($C_{58}H_{112}O_2$ as required for **34**) and 842 ($C_{58}H_{114}O_2$) clearly indicated the presence of material with two extra H's.

Eventually, successful separation was effected by recrystallizations from dilute (about 1%) dichloromethane solution. The less soluble white solid (25 mg), mp 69–72 °C, which precipitated at ice-bath temperatures, was taken as the desired product **34,** while the material from the mother liquor (ca. 23 mg), with mp 45–49 °C, was taken as the overreduced molecule. Thin layer chromatography of the separated fractions on either silica or alumina gave single spots, with the same respective R_f values; ir for the two materials was essentially identical.

Estimates based on the 100-MHz nuclear magnetic resonance curves of the two materials showed that the δ 0.56 ppm signal (cyclopropane H's cis to each other) for the higher melting material was considerably more intense than the same signal in the low-melting form; that in the higher melting product, the intensity ratio of the δ 0.56 ppm signal to the −0.3 to −0.4 ppm signal came close to 6:2, as required for compound **34;** that the ratio of the 0.8 (methyl H's) to 0.5 ppm signals was considerably lower in the high-melting product **34** than in the low-melting product; and that, in the curve for the higher melting form, repeated integrations for the OCH_2CH_2O signals at 3.90 ppm and the cyclopropane hydrogen signal at −0.35 ppm gave an average ratio of 4:2 (±20%), corresponding again to **34.**

Mass spectral analysis: calcd for the molecular mass of **34** ($C_{58}H_{112}O_2$), *m/e* 840.8662. Found: 840.8675, with no peak at 842 other than M + 2. Calcd for the molecular mass of $C_{58}H_{114}O_2$: *m/e* 842.8819. Found: 842.8820, with no significant peak at 840.

Methyl Meromycolate (35) from Acetal 34. At −65 °C, a saturated standardized solution of ozone in dichloromethane (0.7 ml containing 0.017 mmol) was added to a −40 °C solution of 5.0 mg (0.0059 mmol) of acetal **34** (mp 69–72 °C) in 10 ml of chloroform. After 5 min, another 0.6 ml of the cold ozone solution (total 0.033 mmol) was introduced, and the mixture was allowed to stand in the Dewar flask for 15 min. Removing all solvent at temperatures no higher than 0 °C left a white solid, which gave a single spot on thin layer chromatography running slower than the starting acetal, and which was taken as the desired hydroxyethyl meromycolate.

A solution of this solid in chloroform (4 ml) plus methanol (8 ml) containing potassium cyanide[29] (30 mg) was refluxed for 1.25 h, and then stripped of solvents at temperatures below 25 °C. The residue, to which a small volume of water was added, was extracted thoroughly with chloroform, and the chloroform extract was shaken with saturated salt solution before drying and removing solvent. The residual white solid was separated by preparative layer chromatography (0.25 mm layer, with benzene solvent) into methyl meromycolate (**35,** 1.9 mg, 0.0023 mmol, 40%) and unchanged starting acetal **34** (ca. 0.5 mg). Methyl meromycolate (**35**), mp 63–69 °C, showed only single spots on thin layer chromatography (alumina with benzene, or silica gel with either benzene or dichloromethane): ir ($CHCl_3$) 2930, 2850, 1735, 1440 cm^{-1}; NMR (at 100 MHz in dilute $CDCl_3$ solution with benzene as internal standard) δ 3.57 (s, CH_3O, 3.0–3.1), 2.22 (t, J = 7.5 Hz, $CH_2C{=}O$, 1.9–2.0), 1.2 (s, broad, CH_2's), 0.82 (t, J = 5 Hz, CH_3C), 0.54 (broad m, cyclopropane H's cis to each other), −0.36 ppm (m, cyclopropyl H's cis to alkyls, 1.9). From repeated instrument integrations, the ratio of the 3.57 to the −0.36 ppm signals was determined to be 3.1/1.9 (±6% av dev). The tailing from the intense δ 1.2 peak that reached under the 0.82 and 0.54 signals blocked attempts at integrating the latter two peaks. Mass spectral molecular peak: calcd for $C_{57}H_{110}O_2$ (**35**), *m/e* 826.8505; found, *m/e* 826.8503. A very low intensity peak (3% of height of the molecular peak) appeared at *m/e* 840 as the only unexpected feature in the fragmentation pattern.

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Registry No.—**6,** 592-57-4; **7,** 16554-83-9; **8,** 59014-42-5; **8** dimethyl ester, 54281-40-2; **8** polymer, 59014-43-6; **9,** 59014-44-7; **10,** 59043-33-3; **11,** 59014-45-8; **12,** 59014-46-9; **13,** 59014-47-0; **14,** 59014-48-1; **15,** 59014-49-2; **16,** 59014-50-5; **17,** 629-72-1; **18,** 59014-51-6; **19,** 59014-52-7; **20,** 59014-53-8; **21,** 59014-54-9; **21** tosylate, 59014-55-0; **22,** 59014-56-1; **23,** 59014-57-2; **24,** 59014-58-3; **25,** 112-43-6; **26,** 59014-59-4; **26** tosylate, 59043-32-2; **27,** 59014-60-7; **28,** 4883-04-9; **29,** 59014-61-8; **30,** 59014-62-9; **31,** 59014-63-0; **32,** 59014-64-1; **33,** 59014-65-2; **34,** 59014-66-3; **35,** 59014-67-4; diiodomethane, 75-11-6; dihydropyran, 110-87-2; 2-litho-1,3-dithiane, 36049-90-8; 1,3-dithiane, 505-23-7; 1,4-dibromobutane, 110-52-1; 1,8-dibromooctane, 4549-32-0; 10-hydroxydecanal, 22136-92-1; 22-hydroxy-*cis*-19,20-methylenedocosanal ethylene acetal, 59014-68-5; 22-hydroxy-*cis*-19,20-methylenedocosanal ethylene acetal tosylate, 59014-69-6.

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(28) The general procedure described for the alkylation of 2-pentadecyl-1,3-dithiane (**18**) with bromide **16** to form intermediate **19** was followed. In agreement with published results [E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Am. Chem. Soc.*, **96**, 1807 (1974); A. Streitwieser, Jr., and S. P. Ewing, *Ibid.*, **97**, 190 (1975)] we found that metalation of 1,3-dithiane itself was appreciably faster than metalation of monosubstituted 1,3-dithianes. We routinely and conveniently followed the course of the metalations by determining the nuclear magnetic resonance integration value for the proton(s) remaining at the dithiane 2 position after quenching aliquots with deuterium oxide. This assay also served to check the minimum concentration of our stock butyllithium in hexane, since when pure 1,3-dithiane was allowed to react (0.5 h, −30 °C) with 1 equiv of butyllithium as calculated from the concentration on the label and then quenched, the recovered dithiane showed a decrease in the δ 3.7 ppm signal (SCH_2S) from 2 to 1 (±5%). No sign of dideuteration was detected with an excess of butyllithium. Interestingly, the 2-monodeuterio-1,3-dithiane showed a one-proton triplet (J = 2 Hz) instead of a singlet at δ 3.7 ppm, a result attributable to proton–deuterium coupling (see Eliel et al.).
The progress of the alkylations generally was followed by thin layer chromatography, with drops taken directly from the reaction mixture and spotted on the plate. Benzene proved to be a useful developing solvent. For the most part, alkylations either of 2-unsubstituted or 2-monosubstituted dithianes gave good yields.
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