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SYNTHESIS OF CARBOHYDRATE DERIVATIVES CONTAINING VINYLIC THIOETHER GROUPS[1]

S. HANESSIAN AND A. P. A. STAUB
Department of Chemistry, University of Montreal, Montreal, Quebec (Canada)
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ABSTRACT

The reaction of methyl 4,6-*O*-benzylidene-3-*O*-(methylsulfonyl)-2-*S*-phenyl-2-thio-α-D-altropyranoside (**3**) with 1,5-diazabicyclononene in methyl sulfoxide affords the corresponding 2-vinyl thioether **4** in high yield. Reaction of the isomeric 3-phenylthio-2-methanesulfonate **11** under the same conditions affords methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**5**) with elimination of both substituents. With sodium hydride in dimethoxyethane **11** gives the expected vinyl thioether **12** in which the phenylthio substituent is at C-3. These base-catalyzed elimination reactions in methyl 4,6-*O*-benzylidene-α-D-altropyranosides containing diaxial phenylthio and methylsulfonyl substituents appear to be highly dependent on the location of substituents and the solvent. Under the same experimental conditions, the 3-phenylthio-2-methanesulfonate system behaves markedly differently from the conformationally and configurationally related 2-phenylthio-3-methanesulfonate system. Elimination is also effected with 1,2-*O*-isopropylidene-3,5-di-*O*-(methylsulfonyl)-6-*S*-phenyl-6-thio-α-D-glucofuranose (**18**), which gives the corresponding 6-phenylthio-5,6-ene derivative (**19**).

INTRODUCTION

One of the more convenient methods for the introduction of a thioether group in a carbohydrate derivative involves the opening of a suitable epoxide ring with an alkylthiolate anion. Conformationally rigid molecules, such as methyl 2,3-anhydro-4,6-*O*-benzylidene-hexopyranosides, usually react stereoselectively, as in the classical procedure for preparation of deoxy sugars[2] through subsequent desulfurization with Raney nickel. The thioethers[3] most commonly prepared have been methylthio[4], ethylthio[5], and benzylthio ethers[6], which lend themselves not only to reductive desulfurization but also to neighboring-group reactions[7] via sulfonium ion intermediates.

To the best of our knowledge, phenylthio ethers of carbohydrates have not been reported, except for 1,2-*O*-isopropylidene-6-*S*-phenyl-6-thio-α-D-glucofuranose (**16**), which was described by Ohle and Mertens[8] in 1935. The phenylthio derivatives of carbohydrates are interesting in that the only proton α-disposed to the sulfur atom is

situated on the carbonydrate moiety. Many of interesting reactions of organic sulfur compounds involve initial abstraction of an α-proton. Furthermore, the behaviour of the phenylthio substituent in solvolytic, neighboring-group reactions is of interest in the carbohydrate series, because of the unique electronic and spatial characteristics of this substituent.

Our initial studies with the phenylthio ethers of carbohydrates are directed at the synthesis of vinylic phenylthio ethers[9] by suitable elimination reactions. These ethers provide potentially useful intermediates for photochemical reactions as well as free-radical and ionic ones, either as such, or at a higher oxidation state of sulfur.

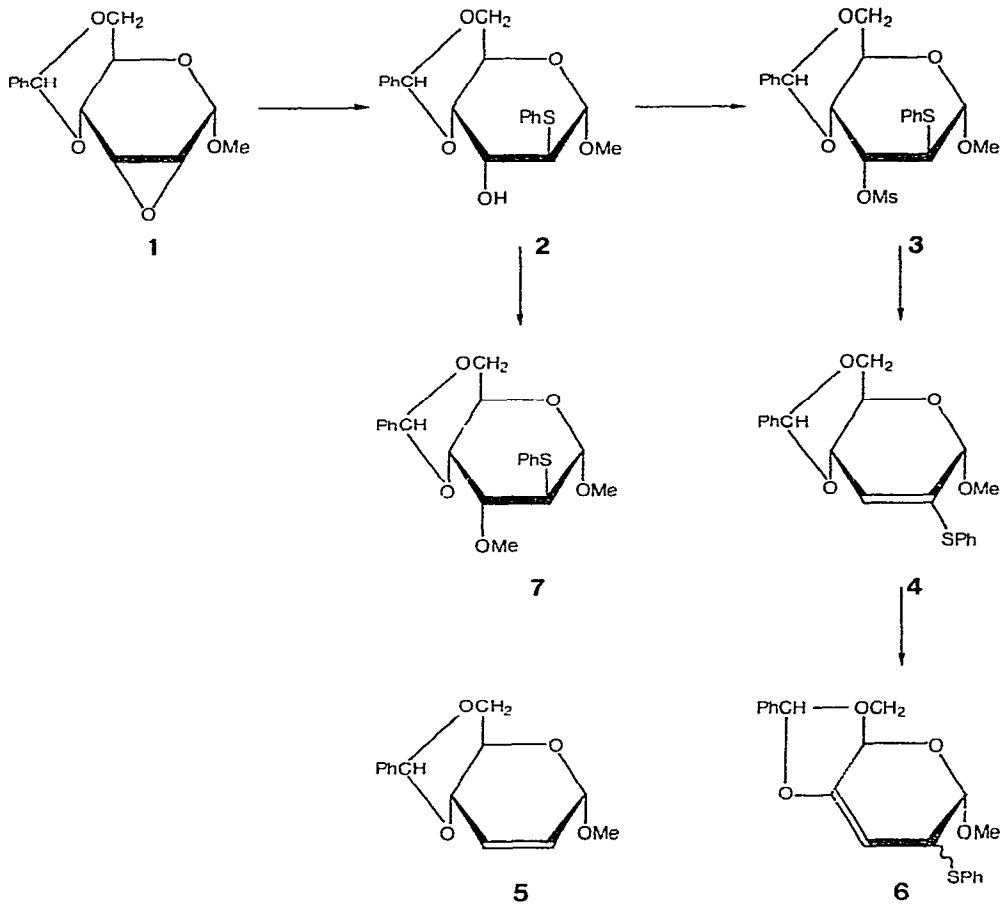
Brown and coworkers have described the synthesis of vinylic 2-benzylthio[10] and 2-methylthio[10] derivatives of the methyl 4,6-*O*-benzylidenehexopyranoside system. In this paper we disclose further results dealing with the synthesis and elimination reactions[9] of vicinally situated phenylthio and sulfonyloxy substituents in rigid and flexible systems.

RESULTS AND DISCUSSION

The readily available methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[11] (**1**) (see Scheme I) was treated with sodium thiophenoxide in refluxing 2-methoxyethanol. A major product was formed (t.l.c.) after 1.5 h and consisted of methyl 4,6-*O*-benzylidene-2-*S*-phenyl-2-thio-α-D-altropyranoside[9] (**2**), obtained as a pale-yellow syrup which was used directly for further transformations because it decomposed within a few days at room temperature. The minor products formed in the preparation of **2** did not interfere with subsequent steps. Definitive proof for the attachment of the phenylthio group at C-2 was obtained by methylation of **2** to give the crystalline 3-methyl ether **7**, followed by reductive desulfurization. The product thus obtained was identical with methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*ribo*-hexopyranoside[4a]. Authentic material was obtained by methylation of methyl 4,6-*O*-benzylidene-2-deoxy-D-*ribo*-hexopyranoside[4a].

Mesylation of **2** afforded the crystalline 3-methanesulfonate (**3**) in good yield[9]. Treatment of **3** with 1,5-diazabicyclo[4.3.0]-5-nonene[12a] (DBN) or 1,5-diazabicyclo-[5.4.0]-5-undecene[12b] (DBU) in methyl sulfoxide and heating for 2.5 h at 85° caused elimination to give crystalline methyl 4,6-*O*-benzylidene-3-deoxy-2-*S*-phenyl-2-thio-α-D-*erythro*-hex-2-enopyranoside[9] (**4**) in over 80% yield. Traces of the isomeric derivative **12** and the olefin **5** were also present in the mother liquors. The presence of a vinylic phenylthio grouping was evident from i.r. data (1610 cm^{-1}, C=C–SPh), n.m.r. data (see Experimental), and the characteristic u.v. maximum of the conjugated system. Chemical proof was provided by studies on allylic isomerization to the isomeric enol ether derivative[9] **6** in the presence of base, and by Raney nickel desulfurization to the known[13] olefinic derivative **5**.

It is noteworthy that attempted elimination of **3** in the presence of sodium in dimethoxyethane led to a mixture of the expected product **4** and the isomeric enol ether **6**. Using this same system, Brown and coworkers[10] had demonstrated that

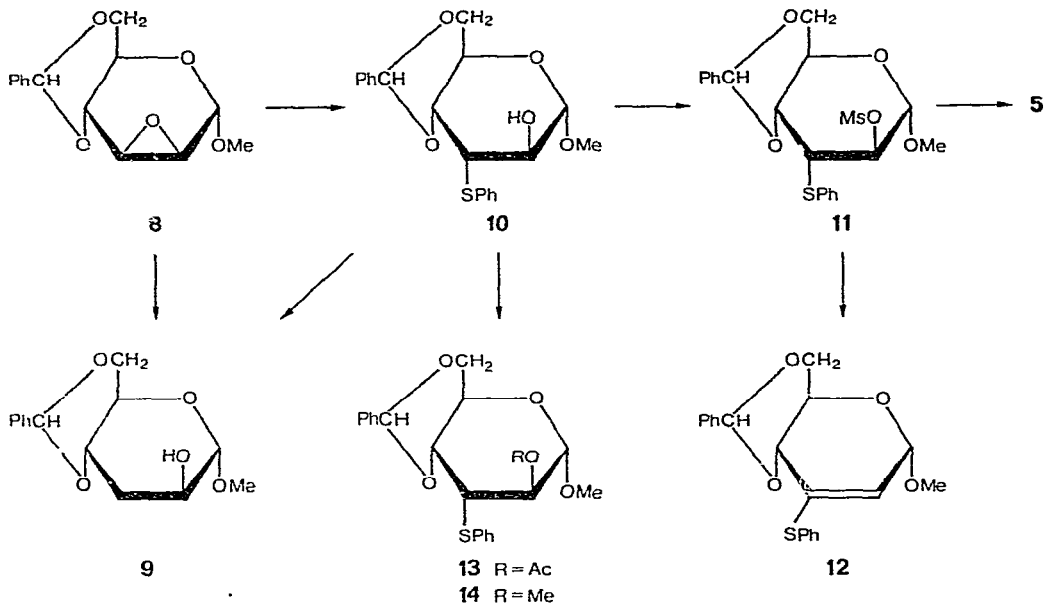


Scheme I

methyl 2-*S*-benzyl-4,6-*O*-benzylidene-3-*O*-methyl-2-thio-α-D-altropyranoside gave, in addition to the two olefins corresponding to **4** and **6**, a glycal derivative formed by elimination of the aglycon. In our studies, a better leaving group at C-3 (mesyloxy *versus* methoxy), was explicitly chosen, to promote the formation of **4** and to avoid formation of the glycal. DBN appears to be an excellent base for effecting selective eliminations of this type without causing allylic rearrangement.

The strong tendency for elimination of a *trans*-situated substituent in structures such as **3** was reflected in the relative ease of elimination in refluxing benzene containing sodium hydrogen carbonate. Actually, mother liquors from the preparation of **2** and **3** always contained small quantities of the elimination product **4**. The elimination reactions of **3** are summarized in Table I.

The studies were then extended to 3-phenylthio derivatives (see Scheme II). Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[14] (**8**) reacted with sodium thiophenoxide to afford the expected crystalline, methyl 4,6-*O*-benzylidene-3-



Scheme II

TABLE I

ELIMINATION REACTIONS OF METHYL 4,6-*O*-BENZYLIDENE-3-*O*-(METHYLSULFONYL)-2-*S*-PHENYL-2-THIO-α-D-ALTROPYRANOSIDE

Reaction of **3** *with*	*Product (yield)*			
	4	**5**	**6**	**12**
DBN in DMSO	72%	trace		trace
DBU in DMSO	86%	trace		trace
$NaHCO_3$ in benzene	15%	trace		
Na in DME	~18%[a]		~14%[a]	

[a]Determined by the integrated areas of characteristic peaks in the n.m.r. spectrum.

S-phenyl-3-thio-α-D-altropyranoside (**10**) in 85% yield. The location of the phenylthio substituent was established by Raney-nickel desulfurization, which gave the known, crystalline methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside[15] (**9**). Acetylation of **10** with acetic anhydride in pyridine afforded a highly crystalline monoacetate (**13**). Methylation of **10** with methyl iodide in the presence of silver oxide and *N*,*N*-dimethylformamide[16,17] afforded the crystalline methyl 4,6-*O*-benzylidene-2-*O*-methyl-3-*S*-phenyl-3-thio-α-D-altropyranoside (**14**). Methylation of **10** with methyl iodide and silver oxide in the absence of *N*,*N*-dimethylformamide afforded, in addition to **14**, a 9% yield of the starting epoxide* **8**. The unexpected formation of **8** was the *first in a series of unusual reactions* associated with the

*The silver oxide used in these experiments afforded a neutral suspension in water. Older batches of silver oxide also led to the formation of the epoxide **8**.

3-phenylthio altrosides of structure **10**, which were unique and were not observed in the case of the configurationally and conformationally related 2-phenylthioaltrosides of general structure **2**.

To our knowledge, this represents the first example of the formation of an epoxide during the methylation of a secondary hydroxyl group having a *trans*-orientation to a vicinal thioether group. The possibility of formation of **8** via a sulfonium-salt intermediate[18], with subsequent attack by the C-2 hydroxyl group was discounted, since treatment of methyl 4,6-*O*-benzylidene-2-*O*-methyl-3-*S*-phenyl-3-thio-α-D-altropyranoside (**14**) with methyl iodide and silver oxide gave only unchanged starting material. To explore the possibility of a silver ion-assisted loss of the phenylthio grouping, a solution of **10** or **14** in 1,2-dimethoxyethane was treated with silver oxide under conditions simulating methylation. In each case only unchanged starting material was recovered.

Mesylation* of **10** gave the crystalline methyl 4,6-*O*-benzylidene-2-*O*-(methylsulfonyl)-3-*S*-phenyl-3-thio-α-D-altropyranoside **11**. Treatment of **11** with DBN in methyl sulfoxide as in the case of **3** afforded (unexpectedly) methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**5**) in 65% yield. Loss of both mesyloxy and phenylthio substituents had occurred instead of the normal elimination, which would have given methyl 4,6-*O*-benzylidene-2-deoxy-3-*S*-phenyl-3-thio-α-D-*erythro*-hex-2-enopyranoside (**12**). The latter was formed only in trace amounts. The same results were obtained with DBU in methyl sulfoxide. The elimination reactions of **11** are summarized in Table II.

TABLE II

ELIMINATION REACTIONS OF METHYL4,6-*O*-BENZYLIDENE-2-*O*-(METHYLSULFONYL)-3-*S*-PHENYL-3-THIO-α-D-ALTROPYRANOSIDE (**11**)

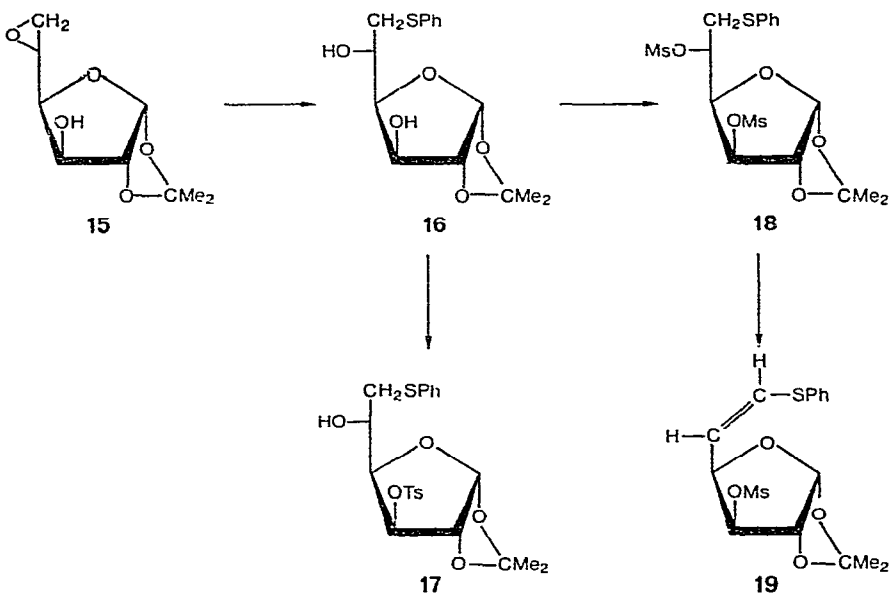
Reaction of **11** *with*	*Product (yield)*		
	4	**5**	**12**
Na in DME	trace		70%
NaH in DME	trace		68%
DBN in Me_2SO	trace	65%	trace
DBU in Me_2SO	trace	40%	trace

The high dependence of the nature of product(s) on the solvent was demonstrated by performing the elimination reaction in 1,2-dimethoxyethane instead of

*The relative reactivities, in terms of neighboring-group effects of the phenylthio ether group and alkyl or aralkylthio groups[7], during sulfonylations of a vicinal, trans-oriented hydroxyl group, are noteworthy. In most cases the sulfonylation products are devoid of sulfonate groups but contain chlorine (in the case of methane- and *p*-toluenesulfonyl chlorides) instead. This is due to the intermediate formation of epithiosulfonium salts, which are opened with retention of configuration by the strongest nucleophile in the medium, namely chloride ion. The sulfonylation of compounds **2** and **10** without detectable chlorination, reflects the much lower nucleophilicity of the phenylthio ether group under the reaction conditions, as compared with alkylthio ethers.

methyl sulfoxide. The products were **5**, the expected olefin **12**, and a small proportion of the isomeric **4**, which is formed by initial rearrangement[19] of the methanesulfonate **11**. In the presence of sodium methoxide in methanol a mixture of **5** and **12** was produced. The desired 3-phenylthio olefin **12** was obtained in 70% yield by performing the elimination reaction in 1,2-dimethoxyethane containing sodium or sodium hydride. The nature of the solvent as well as the base thus plays an important role in determining the type of elimination undergone by the 3-phenylthio altroside derivative **11**. A single mechanism cannot be proposed that would explain these variations in the case of **11** and its unique behaviour compared with the isomeric **3** under a given set of conditions. The intermediacy of sulfonium salts, especially in methyl sulfoxide, could be suggested, but the different results obtained in the case of **3** and **11** require detailed conformational and configurational considerations. Mechanistic aspects of these elimination reactions particularly with regard to the role of the ring proton α- to the sulfur atom, are under continued study.

In 1935 Ohle and Mertens[8] reported the synthesis of 1,2-*O*-isopropylidene-6-*S*-phenyl-6-thio-α-D-glucofuranose **16** by pyridine-catalyzed ring-opening of the epoxide[14,20] **15** with thiophenol in refluxing benzene. In our hands, this procedure gave at best, a 70% yield of the desired **16**. Ring-opening with sodium thiophenoxide in methoxyethanol gave crystalline **16** in 87% yield. Mesylation of this product afforded the crystalline dimethanesulfonate **18**. Tosylation, on the other hand, gave a crystalline monotosyl derivative **17**, in which the tosyloxy function was at C-3 as evidenced from the n.m.r. spectrum. Elimination of the C-5 mesyloxy group in **18** in the presence of DBN or DBU in methyl sulfoxide afforded a 46% yield of the corre-



Scheme III

sponding crystalline olefin, 5-deoxy-1,2-*O*-isopropylidene-3-*O*-(methylsulfonyl)-6-*S*-phenyl-6-thio-α-D-*xylo*-hex-5-enofuranose (**19**).

Elimination was also effected with sodium or sodium hydride in DME in 65% yield. No elimination was observed in the presence of triethylamine or morpholine. The conformational flexibility of the side chain in **18**, consequently the favorable orientation of the eliminated group, could well account for the formation of **19** under a variety of basic conditions. A *cis* stereochemistry for **19** is proposed based on n.m.r. spectral data. Attempted desulfurization led to a mixture of products that could not be separated. A compound related to **19**, namely 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-*S*-methyl-6-thio-D-*xylo*-hex-5-enofuranose has been prepared[21] by a Wittig type of reaction and is reported to have the *cis* stereochemistry.

EXPERIMENTAL

General. — Melting points are uncorrected. N.m.r. spectra were obtained in chloroform-*d* (unless otherwise stated) at 60 or 100 MHz, with tetramethylsilane as internal standard. I.r. spectra were recorded with a Beckman IR-8 instrument. V.p.c. analyses were performed by using a 3% Ov-17 column packing (Applied Science Labs., State College, Pa.). T.l.c. was performed on Silica gel GF_{250} (Merck) and the spots were detected with a solution containing 5% each of ammonium molybdate, sulfuric acid and phosphoric acid[22], after heating the plates at 110°. Sulfur-containing compounds were also detected with a 0.05M sulfuric acid solution containing 1% of potassium permanganate. Conventional processing signifies drying organic solutions over anhydrous sodium sulfate, filtration, and evaporation under diminished pressure.

Methyl 4,6-O-benzylidene-2-S-phenyl-2-thio-α-D-altropyranoside[9] (**2**). — A solution containing 6.5 g (24.6 mmoles) of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[11] (**1**) in 250 ml of dry 2-methoxyethanol was treated with 4 g (30 mmoles) of sodium thiophenoxide and the solution was heated for 1.5 h at 80–90° in an atmosphere of nitrogen. After cooling to 0°, the solution was neutralized with M acetic acid and concentrated to dryness by coevaporation of toluene. The resulting yellow syrup was dissolved in dichloromethane, the solution was washed with water, and the organic layer processed in the usual manner to give **2** as a yellow syrup (9.5 g quantitative), which consisted predominantly of one spot on t.l.c. (30:15:0.2 chloroform–2,2,4-trimethylpentane–methanol). Traces of the olefinic product **4** were also present. The syrup was stored at 0° and was used within a few days because of its tendency to decompose.

Methyl 4,6-O-benzylidene-3-O-(methylsulfonyl)-2-S-phenyl-2-thio-α-D-altropyranoside[9] (**3**). — Methanesulfonyl chloride (6.2 g, 54 mmoles) was added dropwise and with stirring to a cold solution of **2** (8 g, 21.4 mmoles) in 90 ml of dry pyridine. After 24 h at 5°, the mixture was added dropwise to a cold solution of 0.4M sodium hydrogen carbonate. The resulting gum was separated by decantation, dissolved in dichloromethane; the solution was washed successively with M hydrochloric acid, M sodium

hydrogen carbonate, and water. Processing of the organic phase in the usual manner afforded a syrup that crystallized from ether–pentane to give 6.78 g (70%) of **3**. Recrystallization from absolute ethanol gave pure **3**, m.p. 130–131°, $[\alpha]_D^{25}$ +79.5° (*c* 0.994, $CHCl_3$); n.m.r. data (100 MHz) τ 5.14 (singlet, H-1), 4.92 (quartet, *J* 1.2 Hz, H-3), 4.41 (singlet, –CHPh), 6.65 (singlet, OMe), 7.15 (singlet, OSO_2Me).

Anal. Calc. for $C_{21}H_{24}O_7S_2$: C, 55.73; H, 5.34; S, 14.17. Found: C, 55.88; H, 5.30; S, 14.12.

Methyl 4,6-O-benzylidene-3-O-methyl-2-S-phenyl-2-thio-α-D-altropyranoside[9] (**7**). — A. *Methylation with methyl iodide and silver oxide.* To a solution of **2** (1.500 g, 4 mmoles) in 10 ml of methyl iodide was added portionwise 2 g of silver oxide*. The mixture was first stirred for 1.5 h at room temperature and then for 10 h under reflux. The salts were removed by filtration, the solids were throughly extracted with chloroform, and the filtrate was concentrated to give a yellow syrup that crystallized from ether–hexane to give a semi-crystalline gum, which was filtered and dried under vacuum; yield 1.21 g (78%). After two recrystallizations from absolute ethanol, the product had m.p. 84.5–85.5°, $[\alpha]_D^{29}$ +73.2° (*c*, 2.63, $CHCl_3$); n.m.r. data (60 MHz) τ 4.42 (singlet, –CHPh), 5.40 (singlet, H-1), 6.51 (singlet, C-3 methoxyl), 6.62 (singlet, C-1 methoxyl).

Anal. Calc. for $C_{21}H_{24}O_5S$: C, 64.89; H, 6.22; S, 8.24. Found: C, 64.73; H, 6.13; S, 8.33.

B. *Methylation by the Kuhn procedure*[16,17]. A suspension of silver oxide (4.65 g) and **2** (3.74 g, 10 mmoles) in 65 ml of *N,N*-dimethylformamide and 1.85 g (30 mmoles) of methyl iodide was stirred for 3 days at room temperature. The solids were filtered and the filtrate was evaporated in the presence of butyl alcohol to eliminate most of the solvent. The final residue was dissolved in chloroform, the solution was washed with water, and processed to give a syrup that crystallized. Trituration with ethanol afforded the product **7** (2.69 g, 69%) identical in all respects with a sample prepared according to procedure *A*.

Reductive desulfurization of **7** in the presence of excess Raney nickel[25] afforded a syrup that showed one main component by t.l.c. Isolated by preparative t.l.c. it was found to be identical with methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*ribo*-hexopyranoside[4a], m.p. 88–90°, $[\alpha]_D^{25}$ +111° (*c* 1.05, $CHCl_3$). This product exhibited a single sharp peak by v.p.c. analysis.

Methyl 4,6-O-benzylidene-3-deoxy-2-S-phenyl-2-thio-α-D-erythro-hex-2-enopyranoside[9] (**4**). — *A. Elimination with 1,5-diazabicyclo[4.3.0]-5-nonene (DBN.)* A solution containing 2.9 g of **3** (6.4 mmoles) and 5.5 ml of DBN[12a] in 100 ml of dry methyl sulfoxide was heated for 2.5 h at 80° in an atmosphere of nitrogen. The solution was cooled to room temperature, diluted with 300 ml of dichloromethane, and washed with water (3 × 75 ml), followed by 0.5M acetic acid, aqueous sodium hydrogen carbonate, and finally with water. Drying and processing of the organic layer afforded a syrup that crystallized from abs. ethanol to give **4** as colorless crystals (1.8 g, 72%).

*A product of Anachemia Chemical Ltd., Montreal. The silver oxide was lot No. 960722.

Additional product, traces of starting material, and the olefins **5** and **12**, were also present in the mother liquors as evidenced by t.l.c. (10:5:0.06 chloroform–2,2,4-trimethylpentane–methanol). An analytical product was obtained by recrystallization from abs. ethanol, m.p. 144–145°, $[\alpha]_D^{25}$ −84.5° (*c*, 1.04 $CHCl_3$); λ_{max}^{EtOH} 246 nm (ε 7.4×10^3); $M^{\cdot+}$ 356, *m/e* 325 ($M-OCH_3$); λ_{max}^{KBr} 1610 cm^{-1} (C=CSPh); n.m.r. data (60 MHz) τ 4.23 (apparent singlet, H-3), 4.49 (singlet, –CHPh), 5.19 (singlet, H-1), 6.55 (singlet, C-1 methoxyl).

Anal. Calc. for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.65; S, 8.99. Found: C, 67.11; H, 5.44; S, 8.88.

Reductive desulfurization of this product afforded a crystalline mixture consisting of starting material and the expected olefin **5**. The latter was obtained crystalline after preparative t.l.c. m.p. 116–117°; reported[13] m.p. 119–120°.

B. Elimination in the presence of 1,5-diazabicyclo[5.4.0]-5-undecene (DBU). A solution containing 1.44 g (3.2 mmoles) of **3** and 2.75 ml of DBU[12b] in 50 ml of dry methyl sulfoxide was heated for 2.5 h at 80° in an atmosphere of nitrogen. The deep yellow solution was processed as in the case of DBN to give a 86% yield of crystalline **4**, m.p. 143–144°. Investigation of the mother liquors by t.l.c. indicated the presence of traces of **5**.

C. Elimination in the presence of sodium hydrogen carbonate in benzene. A suspension containing 50 mg of **3** and 100 mg of sodium hydrogen carbonate in 5 ml of dry benzene was refluxed and the progress of the elimination was followed by t.l.c. After 72 h there were formed the product **4** (15%) and a trace of the olefin **5**. Starting material still preponderated.

D. Elimination in the presence of sodium in 1,2-dimethoxyethane (DME). A solution containing 452 mg of **3** (1 mmole) and 56 mg (2.4 mg atom) of finely cut sodium in 25 ml of dry DME was refluxed for 12 h. After cooling the solution, ethanol (20 ml) was added and the resulting fine suspension was allowed to settle. The supernatant solution was decanted, evaporated to dryness, the residue was washed with cold water, and dissolved in dichloromethane. Processing of this solution in the usual manner gave a semi-crystalline, syrup that was triturated with ethanol and pentane. Recrystallization of the product from the same solvent mixture gave 118 mg (32%) of a mixture of **4** and the isomeric **6** (as evidenced by t.l.c., and n.m.r. spectra); n.m.r. data (60 MHz) τ 4.23 (H-3 in **4**), 4.49 (singlet, –CHPh), 4.68 (H-3 in **6**), 5.03 (H-1 in **6**, doublet, $J_{1,2}$ 4 Hz), 5.19 (H-1 in **4**, singlet), 6.57 (C-1 methoxyl protons in **6**), 6.56 (C-1 methoxyl protons in **4**).

Methyl 4,6-O-benzylidene-3-S-phenyl-3-thio-α-D-altropyranoside (**10**). — Sodium thiophenoxide (1.40 g, 10 mmoles) was added to a solution containing 2.326 g (8.8 mmoles) of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[21] (**8**) in 40 ml of 2-methoxyethanol. After stirring for 3 h at 80–90° under nitrogen the cold solution was neutralized with M acetic acid and evaporated to dryness. The residue was dissolved in dichloromethane (250 ml), the solution was washed with water, and processed in the usual manner to give a crystalline solid. Recrystallization from hot ethanol containing a few ml of pentane gave the pure product; yield 2.8 g (85%),

m.p. 139–140°. Another recrystallization afforded an analytical sample, m.p. 140–141°, $[\alpha]_D^{29}$ −39.7° (*c* 3, $CHCl_3$); λ_{max}^{KBr} 3450 cm^{-1} (OH); n.m.r. data (60 MHz) τ 5.90 (broad singlet, half-width, 3 Hz, H-1), 4.38 (singlet, –CHPh), 6.57 (singlet, C-1 methoxyl).

Anal. Calc. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.92; S, 8.56. Found: C, 63.89; H, 5.92; S, 8.45.

Methyl 2-O-acetyl-4,6-O-benzylidene-3-S-phenyl-3-thio-α-D-altropyranoside (**13**). — A solution of **10** (1 g) in 10 ml of dry pyridine was treated with 3 ml of acetic anhydride. After for 36 h at 5°, the solution was poured into ice–water with stirring, the crystalline product was filtered and washed with cold water; yield 1 g (90%), m.p. 124–126°. Recrystallization from the minimum volume of hot ether overnight afforded large rhomboid crystals at 5°; m.p. 115°, transformed into needles that melted at 127–128°, $[\alpha]_D^{27}$ −4.59° (*c* 2.8, $CHCl_3$); λ_{max}^{KBr} 1730 cm^{-1} (ester); n.m.r. data (60 MHz), τ 5.41 (broad singlet, half-width 3 Hz, H-1), 4.72 (quartet, $J_{1,2}$ 1.1 Hz, $J_{2,3}$ 2.5 Hz, H-2), 4.43 (singlet, –CHPh), 6.62 (singlet, C-1 methoxyl), 7.94 (singlet, acetate).

Anal. Calc. for $C_{22}H_{24}O_6S$: C, 63.44; H, 5.80; S, 7.69. Found: C, 63.65; H, 5.74; S, 7.67.

Methyl 4,6-O-benzylidene-2-O-methyl-3-S-phenyl-3-thio-α-D-altropyranoside (**14**). — *A. Methylation with methyl iodide–sodium hydride.* To a cooled solution containing 1.12 g (3 mmoles) of **10** and 1.6 g methyl iodide in 16 ml of 1,2-dimethoxyethane was added 0.16 g of sodium hydride in portions. When the addition was complete, a further 1.6 g of methyl iodide was added and the mixture was stirred for 2 h at room temperature. The yellow suspension was evaporated to dryness, the residue was suspended in ether, and the excess hydride was decomposed by dropwise addition of water. Processing the ethereal layer afforded a yellow syrup that was passed (in chloroform) through a short column containing Merck Silica gel GF. The resulting, colorless solution was evaporated to a syrup that crystallized after the addition of ethanol (0.5 ml); yield 0.5 g (60% based on recovered **10**, 0.3 g), m.p. 56–57°. Recrystallization from abs. ethanol afforded an analytical sample, m.p. 56–57°, $[\alpha]_D^{27}$ −4.76° (*c* 2.77, $CHCl_3$); n.m.r. data (60 MHz) τ 5.28 (broad singlet, half-width 3 Hz, H-1), 4.35 (singlet, –CHPh), 6.53 (singlet, C-1 and C-2 methoxylgroups).

Anal. Calc. for $C_{21}H_{24}O_5S$: C, 64.89; H, 6.22; S, 8.24. Found: C, 64.91; H, 6.30; S, 8.11.

B. Methylation by the Kuhn procedure[16,17]. A suspension of **10** (1.12 g, 3 mmoles), silver oxide (1.4 g, 6 mmoles) in 7 ml of *N,N*-dimethylformamide and 1.85 ml of methyl iodide was stirred in the dark for 36 h at room temperature. The solids were removed by filtration and the filtrate and washings were evaporated in the presence of butyl alcohol to remove most of the solvent and give a pale-yellow residue. This was dissolved in chloroform, the solution was washed with water, and processed to give a slightly colored, yellowish solid, (1 g) that was homogeneous by t.l.c. Recrystallization from abs. ethanol gave crystalline **14**.

C. Methylation with methyl iodide and silver oxide. Silver oxide (4.2 g,

18 mmoles) was added to a solution of **10** (2.24 g, 10 mmoles) in 10 ml of methyl iodide and the suspension was stirred at reflux. The reaction was complete after 7 h. The salts were filtered, washed with chloroform, and the filtrate and washings were taken to dryness to afford a crude, crystalline product (1.950 g) that was homogeneous by t.l.c. Recrystallization from hot abs. ethanol gave a first crop (370 mg, m.p. 144°) that consisted of pure methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**8**), as indicated by m.p., mixed m.p. (144°, lit.[20] 145.5°) i.r. and n.m.r. spectroscopy.

The mother liquors were concentrated to give a slightly yellow syrup (1.275 g) that consisted of pure **14**, free from the epoxide **8** as indicated by its n.m.r., spectrum which was identical with that of an analytical sample prepared by the method *A*.

*Desulfurization of methyl 4,6-*O*-benzylidene-3-*S*-phenyl-3-thio-α-D-altropyranoside* (**10**). — Raney nickel* (5 g) was deactivated by refluxing in acetone for 1 h. A solution of **10** (0.2 g, 0.55 mmole) in 10 ml of acetone was added to the cooled suspension and the mixture was heated for 6 h under reflux. After cooling to room temperature, the mixture was filtered, the catalyst was washed well with acetone and the filtrates and washings were evaporated to dryness. The residual syrup was repeatedly evaporated from small volumes of water to remove acetone condensation products. The final syrup was washed with petroleum ether (b.p. 30–60°) and triturated with 0.7 ml of ethanol. A crystalline product was obtained that had the same chromatographic behaviour as methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside[15] (**9**). Purification and separation from a small amount of unreacted **10** was achieved by preparative t.l.c. (10:5:0.08 chloroform–2,2,4-trimethylpentane–methanol) to give the product **9**; yield 0.1 g, m.p. 108–110° (undepressed upon admixture with authentic **9**); n.m.r. data (60 MHz) τ 5.47 (doublet, $J_{1,2}$ 1 Hz, H-1), 7.95 (multiplet, *J* 2 Hz and *J* 6.5 Hz, H-3), 4.40 (singlet, –CHPh), 6.59 (singlet, C-1 methoxyl), 7.55 (broad singlet, –OH).

Anal. Calc. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.36; H, 6.94.

*Methyl 4,6-*O*-benzylidene-2-*O*-(methylsulfonyl)-3-*S*-phenyl-3-thio-α-D-altropyranoside* (**11**). — A cooled solution containing 1 g (2.68 mmole) of **10** in 15 ml of dry pyridine was treated dropwise with 0.70 ml (8.5 mmoles) of methanesulfonyl chloride. The solution was kept for 36 h at 5°, excess reagent was decomposed by the addition of a few chips of ice and the solution was added dropwise with stirring to ice–water (150 ml). The resulting precipitate was filtered, washed with cold water, dissolved in dichloromethane, and the solution was again washed with water. Drying and evaporation afforded a syrup from which toluene was repeatedly evaporated below 40°. The resulting syrup crystallized from a mixture of ethanol–pentane to give 1.12 g (92%) of the methanesulfonate **11**; m.p. 100–101°. Recrystallization of a sample from ether afforded material having m.p. 101–102°, $[\alpha]_D^{26}$ −7.10° (*c* 3.40, $CHCl_3$); n.m.r. data (100 MHz, C_6D_6) τ 4.64 (singlet, –CHPh), 4.82 (broad singlet, H-2), 5.26 (singlet, (H-1), 7.00 (singlet, C-1 methoxyl), 7.87 (singlet, $-OSO_2Me$).

Anal. Calc. for $C_{21}H_{24}O_7S_2$: C, 55.73; H, 5.34; S, 14.17. Found: C, 55.58; H, 5.21; S, 14.22.

*Raney-nickel catalyst No. 28; W. R. Grace and Co., Pittsburg, Tennessee.

The product **11** needed to be manipulated with care, especially during recrystallization, because it rearranged upon slight heating[19].

*Methyl 4,6-O-benzylidene-2-deoxy-3-S-phenyl-3-thio-α-D-*erythro*-hex-2-enopyranoside* (**12**). — *A. Elimination in the presence of sodium in 1,2-dimethoxyethane.* A solution containing 0.52 g (1.15 mmole) of **11** and 30 mg (1.3 mmoles) of finely divided sodium metal in 30 ml of 1,2-dimethoxyethane was treated during 11 h under reflux in an atmosphere of nitrogen. After cooling to room temperature, 7 ml of ethanol were added to decompose excess sodium, the suspension was filtered, and the filtrate was evaporated to dryness. The residual solid was dissolved in dichloromethane, and the solution was washed with water and processed in the usual manner to give a pale yellow syrup that crystallized from ethanol–pentane; yield 0.285 g (70%). The product was contaminated by traces of the olefin **4**. Recrystallization was effected from abs. ethanol; m.p. 131.5–132.5°, $[\alpha]_D^{28}$ +62.7° (*c* 1.68, $CHCl_3$); λ_{max}^{KBr} 1625 cm^{-1} (C=C–SPh); n.m.r. data (60 MHz) τ 4.42 (broad singlet, –CHPh, 5.00 (unresolved multiplet, half-width 6 Hz, H-2), 5.16 (unresolved singlet, half-width 6 Hz, H-1), 6.65 (singlet, C-1 methoxyl).

Anal. Calc. for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.65; S, 8.99. Found: C, 67.16; H, 5.77; S, 9.08.

B. Elimination in the presence of sodium hydride in 1,2-dimethoxyethane. A mixture containing 0.3 g (0.67 mmole) of **11** and 31 mg of sodium hydride in 9 ml of 1,2-dimethoxyethane was refluxed for 2.5 h. Excess hydride was decomposed with a few drops of water and the solution was evaporated to dryness. The residue was taken up in 200 ml of dichloromethane, and the solution was washed with water and processed in the usual manner to give a colorless syrup that crystallized from absolute ethanol; yield 0.161 g (68%) of **12**. Trace amounts of **4** were also present as evidenced by t.l.c. (150:75:1 chloroform–2,2,4-trimethylpentane–methanol), Purification of a portion by preparative t.l.c. gave pure **12**, m.p. 129–131° (undepressed when mixed with an analytical sample of **12**).

C. Elimination in the presence of 1,5-diazabicyclo[4.3.0]-5-nonene (DBN) in 1,2-dimethoxyethane. A solution containing 80 mg of **11** and 0.15 ml of DBN in 4 ml of 1,2-dimethoxyethane was heated at 85° under nitrogen. After 5 h, t.l.c. examination revealed the presence of the three olefinic products **4**, **5**, and **12**.

D. Elimination in the presence of sodium methoxide in 1,2-dimethoxyethane. A solution containing 50 mg of **11** and 13.5 mg of sodium methoxide in 2 ml of 1,2-dimethoxyethane was heated for 19 h under reflux. Chromatographic examination revealed the presence of the three olefinic products **4**, **5**, **12** and another product that arises[19] from an initial rearrangement of **11**.

*Methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside* (**5**). — *A. Formation from* **11** *in the presence of DBN.* A solution containing 4.1 g (8.8 mmoles) of **11** and 7.6 ml of DBN in 135 ml of methyl sulfoxide was heated for 2.5 h at 80° in an atmosphere of nitrogen. The dark solution was poured into ice–water, the resulting solution was extracted with dichloromethane, and the organic phase was washed with water and then processed as usual. Evaporation afforded a dark syrup, which

crystallized after trituration with 1 ml of absolute ethanol to give 0.915 g of **5**, m.p. 119°. A second crop of product was obtained from the mother liquors after evaporation to dryness and extraction with hot petroleum ether (b.p. 30–60°); yield 0.235 g, m.p. 118–119°. The final mother liquors were chromatographed over a short column (15 cm) containing Silica Gel GF_{250} to give a further 0.231 g of product, m.p. 119–120°; reported[11] m.p. 119–120°; total yield, 65%.

B. Formation from **11** *in the presence of DBU.* A solution containing **11** (0.5 g, 1.1 mmole) and 1.1 ml of DBU in 18 ml of methyl sulfoxide was heated for 5.5 at 75–80° under nitrogen. The dark solution was diluted with 20 ml of dichloromethane, washed with water, diluted hydrochloric acid, and then with water, and the organic phase was processed in the usual manner to give a dark syrup that crystallized upon trituration with ethanol; yield 90 mg (40%), m.p. 117–118° (undepressed when mixed with authentic **5**). Recrystallization of a portion gave pure product, m.p. 119–120°.

1,2-O-Isopropylidene-6-S-phenyl-6-thio-D-glucofuranose (**16**). — A mixture containing 1.6 g (8 mmoles) of 5,6-anhydro-1,2-*O*-isopropylidene-D-glucofuranose (**15**) and 1.2 g (9 mmoles) of sodium thiophenoxide in 45 ml of 2-methoxyethanol was refluxed for **1** h in an atmosphere of nitrogen. The cooled solution was neutralized with 4M acetic acid and evaporated to dryness to give a semi-crystalline syrup. The residue was taken up in 200 ml of dichloromethane, the solution was washed with water, and processed as usual to give a syrup that crystallized from ether–pentane. After being kept overnight at 5° the product was filtered to give 2.14 g (87%) of **16**, m.p. 80–82°; reported[8] m.p. 82°.

In another experiment, compound **16** was prepared according to the procedure described in the literature[8]. A solution containing **15** (2.1 g) and 1.2 g of thiophenol in 40 ml of benzene was refluxed for 24 h. The solution was evaporated to dryness and the resulting dark syrup was crystallized by trituration with petroleum ether (b.p. 30–60°); yield 2.55 g (70%); m.p. 80–81°.

1,2-O-Isopropylidene-3,5-di-O-(methylsulfonyl)-6-S-phenyl-6-thio-D-glucofuranose (**18**). — To a solution containing 1.4 g (4.5 mmoles) of **16** in 20 ml of pyridine, was added 2.10 ml (25 mmoles) of methanesulfonyl chloride with stirring at 0°. After 36 h at 5° the solution was poured into ice–water containing 50 ml of M sodium hydrogen carbonate. The resulting precipitate was filtered, washed with water, and dried to give the desired product **18**; yield, 2.03 g (97%); m.p. 92–93°. Recrystallization of a portion from ethanol gave pure material, m.p. 91.5–92.5°, $[\alpha]_D^{30}$ −32.7° (*c* 2.60, $CHCl_3$); n.m.r. data (60 MHz) τ 2.69 (multiplet, –SPh), 4.10 (doublet, $J_{1,2}$ 3.6 Hz, H-1), 4.95 (multiplet, H-3), 5.08 (doublet, H-2), 5.42 (quartet, $J_{4,5}$ 8.8 Hz, $J_{3,4}$ 3 Hz, H-4); 6.35 (quartet, $J_{6,6'}$ 15.4 Hz, $J_{5,6}$ 3.7 Hz, H-6), 6.79 (quartet, $J_{5,6'}$ 4.9 Hz, H-6'); 6.92 (singlet, C-3 OMs); 7.08 (singlet, C-5 OMs).

Anal. Calc. for $C_{17}H_{24}O_9S_3$: C, 43.58; H, 5.16; S, 20.53. Found: C, 43.46; H, 5.05; S.20.44.

1,2-O-Isopropylidene-6-S-phenyl-6-thio-3-O-p-tolylsulfonyl-D-glucofuranose (**17**). — A solution containing 0.5 g (1.6 mmole) of **16** in 10 ml of pyridine was treated with

1.9 g of tosyl chloride in small portions at 0°. After 36 h at room temperature the solution was treated with a few ml of water and after 30 min poured with stirring into ice–water. The gummy precipitate was separated by decantation, dissolved in dichloromethane, and the solution was washed with dilute acid, sodium hydrogen carbonate and finally with water. Processing of the organic phase in the usual manner afforded a crystalline product; yield 0.828 g (83%). Recrystallization from chloroform–ether–pentane afforded pure **17**, m.p. 145–146°, $[\alpha]_D^{26}$ −35.3° (*c* 1.87, $CHCl_3$); n.m.r. data (60 MHz) τ 2.3 (multiplet, aromatic), 4.04 (doublet, $J_{1,2}$ 3.6 Hz, H-1), 5.07 (doublet, $J_{3,4}$ 2.6 Hz, H-3), 5.29 (doublet, H-2), 5.65 (H-4, H-6,6'), 7.55 (singlet, tosyl $-CH_3$).

Anal. Calc. for $C_{22}H_{26}O_7S_2$: C, 56.6; H, 5.62; S, 13.75. Found: C, 56.47; H, 5.48; S, 13.66.

*5-Deoxy-1,2-O-isopropylidene-3-O-(methylsulfonyl)-6-S-phenyl-6-thio-*D*-xylo-hex-5-enofuranose* (**19**). — *A. Elimination in the presence of sodium in 1,2-dimethoxyethane.* To a solution of **18** (0.3 g, 0.64 mmole) in 10 ml of 1,2-dimethoxyethane was added 16 mg (0.7 mmoles) of finely cut sodium and the mixture was heated for 4 h at 56°. After cooling, the clear supernatant was decanted, evaporated to dryness, dissolved in dichloromethane, and the solution was washed with water. After processing the organic layer, a syrup was obtained that crystallized from ethanol to give 0.105 g (65%) of the product **19**, m.p. 109–110°, $[\alpha]_D^{30}$ −279° C 1.61, $CHCl_3$); λ_{max}^{KBr} 1610 cm^{-1} (C=C–SPh); n.m.r. data (60 MHz) τ 2.53 (singlet, –SPh), 3.29 (doublet, H-6), 3.86 (doublet, $J_{1,2}$ 4 Hz, H-1), 4.06 (quartet, $J_{5,6}$ 9.8 Hz, H-5), 4.64 (quartet, $J_{4,5}$ 7.2 Hz, H-4), 4.89 (doublet, $J_{3,4}$ 2.8 Hz, H-3), 5.05 (doublet, H-2), 6.87 (singlet, OSO_2–CH_3), 8.35, 8.58 (singlets, CMe_2).

Anal. Calc. for $C_{16}H_{20}O_6S_2$: C, 51.60; H, 5.41; S, 17.21. Found: C, 51.45; H, 5.30; S, 16.90.

B. Elimination in the presence of DBN in methyl sulfoxide. A solution containing 0.7 g (1.5 mmole) of **18** and 1.5 ml of DBN in 25 ml of methyl sulfoxide was heated for 2.5 h at 70°. The solution was diluted with dichloromethane, neutralized with M acetic acid, washed with water, and evaporated to dryness to afford an amber syrup. Trituration with ethanol gave the product (0.23 g, 46%), m.p. 108–109°.

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