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Sulfur as a Regiochemical Control Element. Synthesis of 2-Alkoxy(acyloxy)-3-alkyl(aryl)thiobuta-1,3-dienes

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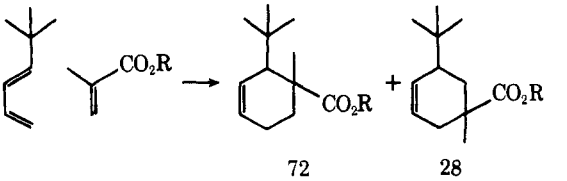
Abstract: The internal competition between substituents in the 2,3 positions of a diene—one being a sulfur and the other an oxygen substituent—is discussed. To examine this question, a general approach to 2-alkoxy(acyloxy)-3-alkyl(aryl)thiobuta-1,3-dienes has been developed. Bromocyclobutanone undergoes displacement with sulfur nucleophiles without competing rearrangements of the benzylic acid type. These compounds have been O-alkylated and O-acylated to give 1-alkoxy(acyloxy)-2-alkyl(aryl)thiocyclobutenes. Thermal opening of the cyclobutenes, preferably by the technique of flash vacuum pyrolysis, gave the desired dienes normally in overall yields of 35–67%.

While the generalization of the reaction between a conjugated diene and an olefin to form a substituted cyclohexene adduct was formulated in 1928,[1,2] this fundamental and broad reaction continues to mystify chemists. Many features such as those dealing with stereochemistry are well understood, but many aspects still remain aloof. For example, the observation of endo addition has been rationalized by (1) inductive (van der Waals or dipolar) forces,[3] (2) charge transfer,[4] (3) secondary bonding forces,[5] (4) favorable geometry for overlap,[6] and (5) secondary orbital interactions.[7]

Even more unsettled is the question of regiochemistry, which has been claimed to be "the biggest unsolved problem in the field".[8] Simple electronic effects do not greatly affect regioselectivity. Thus, both an electron-donating (e.g., 2-ethoxy-1,3-butadiene)[2d] and an electron-withdrawing substituent (e.g., 2-cyano-1,3-butadiene)[9] on the diene lead to the same



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orientation with a dienophile such as acrylic ester. Steric factors do not overwhelm the reaction as illustrated in eq 1.[2d]

A frontier orbital PMO approach has been highly successful in explaining many features of the Diels–Alder reaction including regioselectivity.[10,11] Various levels of sophistication have been used and a very large number of reactions are correctly "predicted" by this approach. In its simplest version, only the HOMO–LUMO pair of frontier orbitals is considered and the regiochemistry evolves from consideration of the terminal

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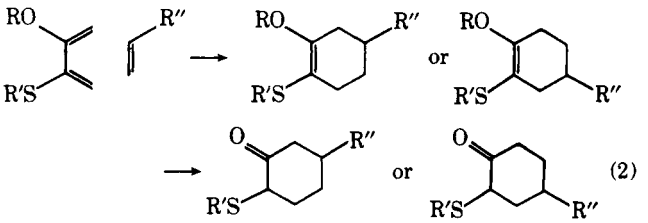
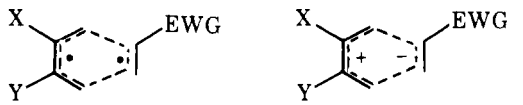
coefficients of both reactants. In some instances, consideration of secondary orbital interactions in addition to the primary bonding centers is invoked to explain regiochemistry. Bachler and Mark concluded that, in addition to these molecular orbital considerations, charge-transfer interactions and steric effects of the substituents on both the diene and dienophile are also involved.[12] The effect of Lewis acid catalysts has been rationalized in the context of this theoretical approach.[13] Clearly, the regiochemistry of concerted thermal cycloadditions is among the less understood phenomena of these exceptionally important reactions.

Our interest in the role of sulfur in synthesis led us to consider an annulative approach to sulfur-substituted cyclohexyl derivatives. Thus, β-keto sulfides, versatile building blocks,[14] can be envisioned to arise from a 2,3-disubstituted diene as shown in eq 2. It is immediately apparent that the question of



(2)

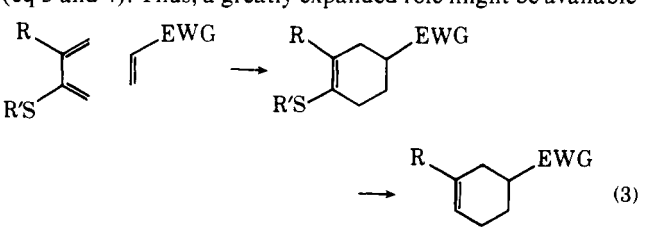
regiochemistry arises. The answer to such a question is not obvious since both sulfur[15] and oxygen[2] substituents are normally potent directing groups in dienes in which only one is present. A simplified working hypothesis considers two extremes for the transition state of the Diels–Alder reaction, a diradical form **1** and a polar form **2**. To the extent that the



1 **2**

diradical form dominates, since sulfur better stabilizes an adjacent radical center compared to oxygen,[16] sulfur should dominate the regiochemistry. On the other hand, to the extent that polar factors dominate, it is more debatable whether oxygen or sulfur should dominate. While solvolysis work suggests that oxygen can better stabilize a positive charge,[17] ion cyclotron resonance studies of hydride donation in the gas phase suggest that sulfur can better stabilize a positive charge.[18] We felt that the solution data would probably be more applicable to the situation at hand so that the prediction was that oxygen would dominate the regiochemistry if polar factors dominate.

Interest in the possibility that sulfur would dominate the regiochemistry (i.e., sulfur would serve the role of a regiochemical control element) is heightened by the realization that 1,3 (meta) substituted compounds may become available via a Diels–Alder reaction due to the ease of desulfurization (eq 3 and 4). Thus, a greatly expanded role might be available



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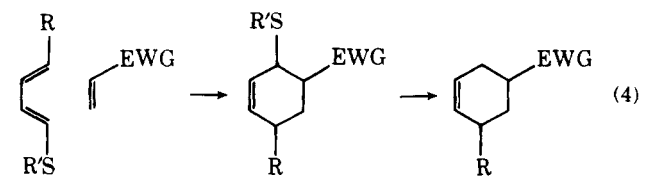
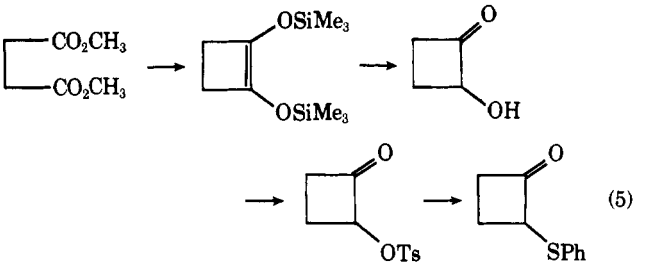


(4)

for the Diels–Alder reaction because, in addition to the normal ortho–para orientation, the meta orientation would now be in hand. Furthermore, the question of the generality of sulfur playing such a role in the broad class of thermal cycloaddition reactions and in either reaction partner opens a new avenue for investigation. In this paper we wish to report the synthesis of 2-R-*O*,3-R′-*S*-buta-1,3-dienes and in the following paper on their cycloaddition.[19,20]

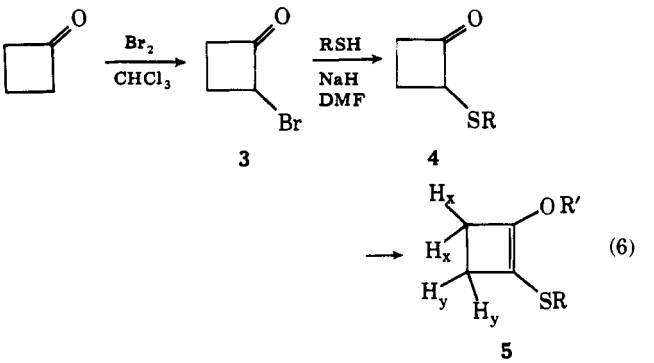
Synthesis of 2-Disubstituted Cyclobutenes

2,3-Dialkoxy-1,3-butadienes are available from 1,3-butadiene utilizing an alkoxymercuration reaction as a key step.[21] More recently, the applicability of the acyloin reaction to succinate esters has allowed the synthesis of 1,2-dialkoxycyclobutenes and by thermolysis the corresponding 2,3-dialkoxy-1,3-butadiene.[22] This latter approach appears more promising as a route to sensitive dienes since the diene could be generated under conditions for its reaction with a dienophile in the event that it should prove too reactive to isolate. Thus, we investigated the conversion of 2-hydroxycyclobutanone, available from dimethyl succinate as outlined in eq 5, to 2-



(5)

phenylthiocyclobutanone.[23] Difficulties encountered in obtaining 2-hydroxycyclobutanone on large scale and on converting it into the phenylthiocyclobutanone led us to concentrate our efforts on an alternative as outlined in eq 6, especially



3 **4**

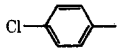
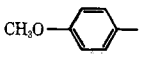
(6)

5

since cyclobutanone is conveniently available on relatively large scale from phenylthiocyclopropane and formaldehyde.[24]

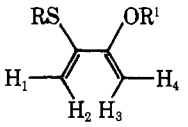
Reproducible yields of **4** are obtained only when the bromide **3**[25] is purified by distillation and is used immediately, and when contact of **3** with metal (e.g., syringe needles) is avoided. Conia utilized a similar procedure to prepare 2-phenoxycyclobutanone and observed disproportionation of the product.[25] Although such a disproportionation might be expected to be even more important in the sulfur analogue, it was not generally observed. Only in the case of substitution with 4-chlorophenylthiolate were products that might have involved disproportionation detected. Addition of a catalytic amount of tetra-*n*-hexylammonium iodide eliminated these side products from the reaction. The semibenzylic acid rearrangement, which in principle could compete with nucleophilic substitution under the reaction conditions, was not observed. It should also be mentioned that the direct sulfenylation of cyclobutanone with diphenyl disulfide was examined. Presumably, disproportionation was a major headache under these conditions since only 2,4-bis(phenylthio)- and 2,2,4-tris(phenylthio)cyclobu-

Table I. Preparation of 2,3-Disubstituted 1,3-Butadiene

entry	R	% yield **4**	R′	% yield **5**	% yield **6**	series
1	Ph	90–95	CH_3	45–60	98	**a**
2	Ph	90–95	CH_3CO	85	98	**b**
3		71	CH_3	57	95	**c**
4		61–85	CH_3CO	75–85	95	**d**
5		73	CH_3	87	84	**e**
6	$HOCH_2CH_2$	92	*a*	45	*b*	**f**

[a] In this case, an intramolecular cyclization leads to **9**. [b] The instability of the diene led to only poor yields on attempted isolation. Thus, in this case, the diene was normally generated and trapped with a dienophile.

Table II. ^1H NMR Data of Dienes[a]

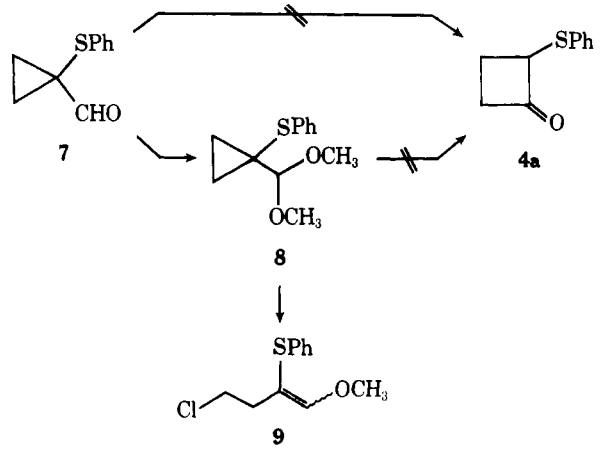


diene	R	R′	δ_1	δ_2	δ_3	δ_4
6a	Ph	CH_3	5.37	6.01	4.17	4.83
6b	Ph	$COCH_3$	5.44	5.84	4.88	5.36
6c	4-ClC_6H_4	CH_3	5.40	6.00	4.16	4.75
6d	4-$CH_3OC_6H_4$	$COCH_3$	5.50	5.50	4.94	5.02
6e	$C_3H_3N_2$	CH_3	5.89	6.36	4.24	4.90
6f	$-CH_2CH_2-$		5.09	5.42	4.10	4.31

[a] All chemical shifts are in parts per million downfield from internal Me_4Si. Spectra were recorded in $CDCl_3$ at 100 MHz.

tanone were obtained in low yields. Table I summarizes the α-thio-substituted cyclobutanones obtained.

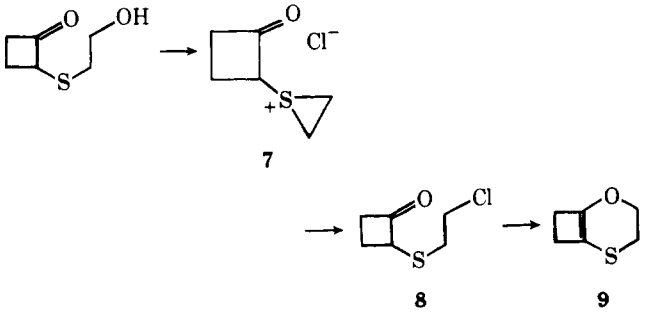
In an ancillary study, the use of a ring expansion reaction[27] was considered since it was known that 1-methoxycyclopropanecarboxaldehyde rearranged to 2-methoxycyclobutanone upon treatment with acid.[28] 1-Phenylthiocyclopropanecarboxaldehyde (**7**)[29] was readily available by quenching 1-phenylthiocyclopropyllithium[30] with DMF. Unlike the methoxy derivative, **7** showed no inclination to rearrange to **4a**. To provide more driving force for rearrangement, we converted **7** to its acetal under forcing conditions (CH_3OH, $(CH_3)_2NCH(OCH_3)_2$, TsOH, reflux). Treatment of acetal **8** with TsOH or BF_3–ether in hot benzene (with or without molecular sieves), TFA–TFAA, or aqueous $HClO_4$ in methylene chloride either led to recovered starting material or destroyed it. On the other hand, treatment with trimethylsilyl chloride–TsOH or $TiCl_4$ gave a clean product but only that resulting from ring opening, i.e., **9**. The failure of **7** to rearrange in contrast to the methoxy series must be a kinetic problem since both reactions involve similar structural changes. The kinetic problem may be due to the difference in ability for sulfur to stabilize a positive charge compared to oxygen.



O-Alkylation was accomplished by treating the β-keto sulfide **4** with sodium hydride and dimethyl sulfate at −40 °C, the temperature being particularly critical (see Table I). Below −40 °C the rate was too slow and above −40 °C the enolate appeared to decompose at an appreciable rate. The reaction was consistent on small scales (~10 mmol) but led to erratic yields on attempts to scale up to 100 mmol. Formation of **5a** appeared to be especially sensitive, and it was prepared only on about a 2-mmol scale. The methyl enol ethers were stable only for a few days at −16 °C and thus normally were prepared in small-scale reactions (≤5 mmol) and used directly. It is interesting to note that C-alkylation was not an important complication, whereas C-methylation was normally the major product upon alkylation of 2-phenylthiocyclohexanone with methyl iodide.[31] While conformational differences between a four- and six-membered ring may be cited as part of the reason for the different regiochemistry of alkylation, we do not have a good explanation at present.

In contrast to the alkylation reaction, O-acylation proceeded in good yields routinely even on large scale (see Table I). The β-keto sulfide, dissolved in triethylamine, was treated with acetic anhydride at room temperature. The enol acetates **5** (R′ = CH_3CO) were stable at −20 °C for several weeks without noticeable decomposition.

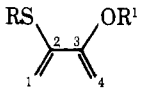
In the special case of **4** (R = CH_2CH_2OH), formation of the cyclobutene **7** entailed consecutive treatment with thionyl chloride in chloroform and then addition of triethylamine.[32] Apparently, an intermediate chloride, either **7** or **8**, was formed



in the initial treatment with thionyl chloride which then cyclizes to give the desired cyclobutene **9**.

The cyclobutenes exhibited double bond stretching vibrations at 1623 ± 2 cm^{-1} for the enol ethers **5a,c,e** (except for **5f**, which had this absorption at 1680 cm^{-1}) and at 1655 ± 5 cm^{-1} for the enol esters. The protons of the ethylene group appeared as an AA′BB′ pattern centered at δ 2.65 ± 0.08 in the enol ethers and δ 2.90 ± 0.01 in the enol acetates for H_x (see eq 6) and at a position for H_y that varied not only with the oxygen substituent but also with the sulfur substituent (see Experimental Section).

Table III. ^{13}C NMR Data of Dienes[a]



diene	R	R′	δ_1	δ_2	δ_3	δ_4	$\delta_1 - \delta_2$	$\delta_3 - \delta_4$
6a	Ph	CH_3	117.5	138.5	157.6	86.5	21.0	71.1
6b	Ph	$COCH_3$	119.0	136.6	150.4	106.6	17.6	43.8
6c	4-ClC_6H_4	CH_3	120.0	137.8	157.9	86.4	17.8	71.5
6d	4-$CH_3OC_6H_4$	$COCH_3$	115.1	139.0	150.4	105.6	24.0	44.8
6e	$C_3H_3N_2$	CH_3	126.1	133.4	158.6	86.1	7.3	72.5

[a] All chemical shifts are in parts per million downfield from internal Me_4Si. Spectra were recorded in $CDCl_3$ at 15.1 MHz.

Generation of Dienes

The thermal ring opening was accomplished in three ways: (1) in solution, (2) through a packed hot tube, and (3) via flash vacuum pyrolysis. The high reactivity of the dienes made their generation in solution unsuitable except for in situ trapping by a dienophile (see the accompanying paper). To use a vertically mounted hot tube packed with glass helices, deactivation of the surface by addition of *O,N*-bis(trimethylsilyl)acetamide and triethylamine was required. Using a 2.5 × 42 cm column under a stream of nitrogen (~550 mL/min), a temperature of ~350 °C effected complete ring opening. The yields of the dienes varied with nitrogen flow, temperature, cleanliness of the glass helices, purity of the starting cyclobutene, and rate of addition.

Flash vacuum pyrolysis proved to be a more efficient and convenient technique. The apparatus was described in detail previously.[33] A temperature of ~350 °C was required for complete conversion and the yields were normally ≥95% (see Table I). Before thermolysis, 2,6-di-*tert*-butyl-4-methylphenol (BHT) was placed in the collecting bulb to stabilize the diene as it collected. 2-Methoxy-3-(2′-pyrimidylthio)-1,3-butadiene required deactivation of the apparatus with *O,N*-bis(trimethylsilyl)acetamide and extremely pure samples of the precursor cyclobutene for consistently high yields. For the pyrolysis of the oxathiene **9**, a temperature of 325 °C was employed. The diene **6f** could not be obtained without substantial decomposition or, if the temperature was lowered, without recovering a large portion of cyclobutene. Nonetheless, Diels–Alder reactions could be performed with diene of this quality to give adducts in ≥40% yields.

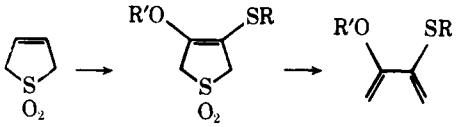
Since the dienes required the presence of stabilizer (BHT) to store for any time, combustion analyses were not possible. However, high-resolution mass spectra could be obtained on the pure dienes except for **5a** and **5f** and elemental composition established in this way. These two dienes were too unstable in the absence of BHT so were not kept (in the case of **5a**) or available (in the case of **5f**) in the pure state. Their structures were further supported by spectral analysis (see Experimental Section for infrared spectral data). Table II summarizes the ^1H NMR shifts for the butadiene portions. The chemical shifts reflect somewhat the electronic nature of the substituents. Thus, increasing the electronegativity of the sulfur substituent, cf. **6a** or **6c** with **6e**, causes downfield shifts of ~0.51 and 0.36 ppm for H_1 and H_2, respectively, suggesting that the major effect is due to the interaction of the substituent with the π system. A similar situation exists for H_3 and H_4, where changes of ~0.72 and 0.36 ppm are observed in switching from methoxy to acetoxy. Note that the change of the sulfur substituent has a negligible effect on H_3 and H_4, and the change of the oxygen substituent has a negligible effect on H_1 and H_2.

The ^{13}C NMR shifts show these trends more dramatically and the data is summarized in Table III. The absorptions for C(1) and C(2) are virtually independent of the oxygen substituent and those for C(3) and C(4) of the sulfur substituent. Here one sees even the minor changes in the substituent reflected in noticeable shifts. Thus, $\delta_1 - \delta_2$ decreases more or less systematically as the substituent changes from more electron donating, e.g., **6d**, to more electron withdrawing, e.g., **6e**. An approximately 30-ppm change in $\delta_3 - \delta_4$ is observed in going from methoxy to acetoxy. Clearly, these substituents have a major and systematic effect on the electron distribution in the diene—an effect that probably should be mirrored in their cycloadditions.

Discussion

A versatile synthesis of 2-alkoxy(acyloxy)-3-alkyl(aryl)-thio-1,3-butadienes from cyclobutanone in overall yields of 35–67% is in hand. The current cost of cyclobutanone leads us to prepare it. Of the available methods for its synthesis, we find it most convenient to use the acid-catalyzed rearrangement of 1-hydroxymethyl-1-phenylthiocyclopropane.[24] In the presence of BHT, the dienes appear to be stable at 0 °C for several weeks. The acetoxy dienes are considerably more stable than the methoxy dienes. For synthetic applications, the acetoxy dienes are recommended. Normally, we prefer to utilize the diene directly. Thus, the cyclobutenes serve as a convenient storage point. One advantage of this method is the fact that the cyclobutenes can be used directly in the cycloadditions and preclude having to preform the diene. The mild conditions that unmask the diene make it compatible with a wide array of substrates. Another feature of this approach is the flexibility in modifying the substituents at sulfur and oxygen.

A totally different approach from sulfolene has also been considered. Thus far, all attempts to suitably functionalize the



double bond have been fruitless. At present, the cyclobutene method indeed appears to be the method of choice to these very valuable conjunctive reagents. In the following paper, we describe their cycloadditions.

Experimental Section

General. All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were obtained as solutions in the indicated solvent on a Beckman IR-8 or a Perkin-Elmer 267 spectrophotometer. NMR spectra were determined in the indicated solvent on a Jeolco MH-100 (100 MHz) or a Bruker WH270 (270 MHz) instrument; chemical shifts are reported in parts per million downfield from tetramethylsilane (Me_4Si). ^{13}C NMR spectra were determined in the indicated solvent on a Jeolco FX-60 (15.1 MHz) instrument; chemical shifts are reported in parts per million downfield from Me_4Si. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; addition of b indicates a broadened pattern. Coupling constants are given in hertz. Mass spectra were recorded on an AEI-MS-902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 mA unless otherwise specified. Melting points were obtained on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Labora-

Table IV. Experimental Details for Displacement by Sulfide[k]

entry	2-bromocyclobutanone, wt (mmol)	RSH (wt, mmol)	NaH dispersion, wt, mmol	DMF, mL	product (wt, yield)
1	4.5 g (30)	PhSH (3.63 g, 33)	1.26 g,[a] 30	30	**4a**[b] (5.09 g, 95%)
2	4.95 g (30.0)	4-ClC_6H_4SH (4.31 g, 30.0)	1.14 g,[c] 30.0	50[d]	**4c**[e] (4.5 g, 71%)
3[j]					
4	4.7 g (31.5)	$C_4H_3N_2SH$ (3.54 g, 31.5)	1.21 g,[c] 31.5	40	**4e**[f] (4.13 g, 73%)
5	1.0 g (6.7)	$HOCH_2CH_2SH$ (680 mg, 8.0)	352 mg,[g] 7.35	7[h]	**4f**[i] (905 mg, 92%)

[a] 57% NaH dispersion in mineral oil used for this run. [b] May be further purified by TLC with 10–40% ether in hexane. [c] 63% NaH dispersion in mineral oil used for this run. [d] For this reaction, 10–15 mg of tetra-*n*-hexylammonium iodide added after generation of sodium 4-chlorobenzenethiolate. [e] Purified by LC as described in the general example. [f] Product directly recrystallized from ether, mp 67–68 °C. [g] 50% NaH dispersion in mineral oil used for this run. [h] 1,2-Dimethoxyethane used as solvent at room temperature for 2 h. [i] May be further purified by TLC with 5% CH_3OH in $CHCl_3$. [j] For preparation of **4d** see text. [k] Spectral data follow. **4a**: IR ($CHCl_3$) 1790, 1480, 1440 cm^{-1}; NMR ($CDCl_3$) δ 1.6–2.1 (1 H, m), 2.2–2.6 (1 H, m), 2.8–3.2 (2 H, m), 4.40 (1 H, dd, J = 7.8, 7.6 Hz), 7.1–7.5 (5 H, m). Calcd for $C_{10}H_{10}OS$: 178.0452. Found: 178.0452. **4b**: IR ($CHCl_3$) 1790, 1470 cm^{-1}; NMR ($CDCl_3$) δ 1.6–2.05 (1 H, m), 2.10–2.70 (1 H, m), 2.85–3.20 (2 H, m), 4.32 (1 H, t, J = 6.8 Hz), 7.1–7.5 (4 H, m). Calcd for $C_{10}H_9ClOS$: 212.0063. Found: 212.0074. **4e**: IR ($CHCl_3$) 1790, 1560, 1380 cm^{-1}; NMR ($CDCl_3$) δ 2.3–2.7 (2 H, m), 3.1–3.4 (2 H, m), 4.7 (1 H, dd, J = 9, 8 Hz), 6.98 (1 H, t, J = 5.5 Hz), 8.48 (2 H, d, J = 5.5 Hz). Calcd for $C_8H_8N_2OS$: 180.0357. Found: 180.0353. Anal. ($C_8H_8N_2OS$): C, H, N, S. **4f**: IR ($CHCl_3$) 3600–3300, 1780, 1725, 1385 cm^{-1}; NMR ($CDCl_3$) δ 1.65–3.50 (7 H, m), 3.60–4.1 (2 H, m), 4.22 (1 H, dd, J = 10, 7 Hz). Further characterized as its trimethylsilyl ether: IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.12 (9 H, s), 1.6–2.1 (1 H, m), 2.2–2.7 (1 H, m), 2.7–3.0 (2 H, m), 3.12 (2 H, bt, J = 8 Hz), 3.76 (2 H, bt, J = 8 Hz), 4.23 (1 H, dd, J = 9, 7 Hz). Calcd for $C_9H_{18}O_2SSi$: 218.0791. Found: 218.0794.

tories, Ann Arbor, Mich. Thin layer or preparative thick layer (1.5 mm) plates were made of E. Merck AG Darmstadt silica gel PF-254 or Brinkmann silica gel P/UV-254 no. 66 and activated by drying at 140 °C for 2 h. Removal of material from the silica gel was accomplished by successive washings with ether or ethyl acetate. The term LC is used for high- (or medium-) pressure solid-liquid chromatography and refers to the use of a standard 2.5 (i.d.) × 100 cm column with a precolumn filter of 1.5 (i.d.) × 25 cm dimensions, both of which were packed with 32–63 μm Woelm silica gel and preequilibrated with the indicated solvent mixture. The system utilized a single-stage constant flow pump at approximately 22 mL/min.

In experiments requiring dry solvents, ether, tetrahydrofuran, dioxane, and dimethoxyethane were distilled from sodium benzophenone ketyl. Benzene, toluene, methylene chloride, dimethylformamide, triethylamine, xylene, hexane, and pyridine were distilled from calcium hydride. Acetic anhydride was distilled from 5 mol % quinoline. Apparatus for experiments requiring anhydrous conditions was dried by flaming in a stream of nitrogen.

Preparation of 2-Bromocyclobutanone. Following the method of Conia et al. 16.6 g (103 mmol) of bromine in 20 mL of chloroform was reacted with 7.26 g (103 mmol) of cyclobutanone in 100 mL of chloroform to give 14.3 g (92%) of 2-bromocyclobutanone, bp 75–79 °C (15 mm) (lit.[25] bp 82–84 °C (18 mm)).

Displacement by Sulfide. Preparation of 2-(4′-Methoxyphenylthio)cyclobutanone (4d). Sodium hydride oil dispersion (50%, 1.06 g (528 mg), 22.0 mmol) was washed twice with hexane, suspended in anhydrous dimethylformamide (35 mL), and cooled to approximately 0 °C (ice bath). To the stirred slurry was added 4-methoxythiophenol (3.94 g, 28.0 mmol) dropwise over 1 h. When the solution became clear, 2-bromocyclobutanone (3.30 g, 22.2 mmol) was added dropwise over 15 min. The resulting solution was stirred at 0 °C for 1 h. The solution was then poured into ether and water, washed with cold (0 °C) 1 M aqueous potassium hydroxide and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was homogeneous by TLC and could normally be used without further purification. In this case, the residual oil was purified by LC (column length 100 cm, inner diameter 2.5 cm, 15% ether in hexane) to give yields of 2.81–3.91 g (61–85%) of 2-(4′-methoxyphenylthio)cyclobutanone as a clear, pale yellow oil: IR ($CHCl_3$) 1790, 1590, 1490, 1460, 1440 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.6–2.0 (1 H, m), 2.1–2.5 (1 H, m), 2.7–3.0 (2 H, m), 3.70 (3 H, s), 4.17 (1 H, d of d, J = 8.0, 7.9 Hz), 6.72 (2 H, d, J = 9 Hz), 7.32 (2 H, d, J = 9 Hz); mass spectrum *m/e* (%) 210 (3.2), 209 (7.4), 208 (58), 180 (11), 168 (11), 167 (25), 166 (100), 165 (27), 151 (44), 147 (16), 140 (20), 139 (86), 135 (31), 125 (15), 124 (15), 123 (10), 121 (47), 108 (18), 107 (16), 97 (13), 96 (24), 95 (19), 77 (15), 70 (20), 69 (22), 65 (17), 64 (11), 63 (17), 53 (12), 50 (10), 45 (43), 42 (21), 41 (29). Calcd for $C_{11}H_{12}O_2S$: 208.0558. Found: 208.0558.

The remaining examples are summarized in Table IV.

Preparation of 1-Methoxy-2-phenylthiocyclobutene (5a). To ~139 mg (~3.5 mmol) of oil-free potassium hydride (obtained by washing 492 mg of a ~28% mineral oil dispersion) at −40 °C were added sequentially 2 mL of dry DMF and 0.3 mL (3 mmol) of dimethyl sulfate. (Caution. The temperature must be carefully controlled; otherwise a vigorous reaction can occur at this point.) A solution of 360 mg (2 mmol) of 2-phenylthiocyclobutanone in 6 mL of dry DMF was added over a 20-min period, during which time the reaction mixture became bright yellow and evolved hydrogen gas. The solution was allowed to warm to 0 °C and then poured into 100 mL of 0.05 N aqueous potassium hydroxide and the product extracted with hexane (sometimes brine added to disperse emulsions). The organic layer was washed with water and brine, dried (K_2CO_3), and evaporated in vacuo to give 363 mg of crude product. The products from two consecutive runs were combined and distilled via a Kugelrohr apparatus at 85 °C (0.03 mm) to give 486 mg (64%). Repetition of this reaction using 4 g (100 mmol) of potassium hydride, 12.6 g (100 mmol) of dimethyl sulfate, and 11.0 g (61 mmol) of 2-phenylthiocyclobutanone gave 9.96 g (85%) of crude product which, after Kugelrohr distillation at 75–95 °C (0.1 mm), gave 4.80 g (41%) of product. IR (CCl_4): 1623, 1482, 697 cm^{-1}. NMR (CCl_4): δ 2.1–2.25 (2 H, m), 2.48–2.65 (2 H, m), 3.84 (3 H, s), 6.8–7.1 (5 H, m). Calcd for $C_{11}H_{12}OS$: 192.0609. Found: 192.0606. Anal. ($C_{11}H_{12}OS$): C, H, S.

Preparation of 1-Methoxy-2-(4′-chlorophenylthio)cyclobutene (5c). Potassium hydride oil suspension (25%, 800 mg (200 mg), 5.00 mmol), washed twice with pentane, was suspended in anhydrous DMF (4 mL) and cooled to −45 °C (aqueous calcium chloride, dry ice bath). A solution of 2-(4′-chlorophenylthio)cyclobutanone (395 mg, 1.86 mmol) in DMF (1 mL) was added to the stirred slurry at −45 °C and then stirred for 1.5 h. Dimethyl sulfate (0.7 mL, 0.82 g, 8.0 mmol) was added via syringe. The calcium chloride/dry ice bath was replaced with a methanol/wet ice bath (−10 °C). Stirring was continued at −10 °C for 2 h and then the reaction was quenched by the addition of 0.5 N aqueous potassium hydroxide (20 mL). The solution was exhaustively extracted with hexane. The combined organic portions were washed with water and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (20% ether in hexane) to give 240 mg (57%) of 1-methoxy-2-(4′-chlorophenylthio)cyclobutene as a clear oil: R_f 0.85 (two elutions); IR ($CHCl_3$) 1620, 1470 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (2 H, dd, J = 4, 3 Hz), 2.66 (2 H, dd, J = 4, 3 Hz), 3.90 (3 H, s), 7.0–7.3 (4 H, m). Calcd for $C_{11}H_{11}ClOS$: 226.0219. Found: 226.0214.

Preparation of 1-Methoxy-2-(2′-pyrimidylthio)cyclobutene (5e). Sodium hydride oil dispersion (63%, 305 mg (192 mg), 8.0 mmol) was

washed twice with hexane and suspended in a mixture of dimethylformamide (8 mL) and dimethyl sulfate (1.14 mL, 1.52 g, 12.0 mmol). The slurry was cooled to approximately 0 °C (ice bath). A solution of 2-(2′-pyrimidylthio)cyclobutanone (960 mg, 5.32 mmol) in 3 mL of dimethylformamide was added to the stirred slurry dropwise over 30 min and stirring continued for an additional 3 h. The reaction mixture was poured into 100 mL of ethyl acetate and 50 mL of 0.5 N aqueous potassium hydroxide and stirred for 1 h. The phases were separated and the aqueous portion was back-extracted with ethyl acetate. The combined organic portions were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (50% ether and 1% triethylamine in hexane) to give 893 mg (87%) of 1-methoxy-2-(2′-pyrimidylthio)cyclobutene as a clear oil, R_f 0.8 (four elutions). IR ($CHCl_3$): 1625, 1560, 1545, 1380, 1305 cm^{-1}. NMR ($CDCl_3$): δ 2.4 (2 H, dd, J = 4.0, 3.5 Hz), 2.72 (2 H, dd, J = 4.0, 3.5 Hz), 3.92 (3 H, s), 7.0 (1 H, t, J = 5 Hz), 8.52 (2 H, d, J = 5 Hz). Calcd for $C_9H_{10}N_2OS$: 194.0514. Found: 194.0517.

Preparation of 1-Acetoxy-2-phenylthiocyclobutene (5b). Acetic anhydride (1.5 mL) was added to a stirred solution of 2-phenylthiocyclobutanone (172 mg, 0.98 mmol) in anhydrous triethylamine (2 mL) at room temperature. After 12 h, the reaction mixture was poured into a separatory funnel containing ether and saturated aqueous sodium carbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (20% ether in hexane) to give 182 mg (85%) of 1-acetoxy-2-phenylthiocyclobutene as a clear oil, R_f 0.55. IR ($CHCl_3$): 1775, 1660, 1580, 1480, 1455 cm^{-1}. NMR ($CDCl_3$): δ 2.00 (3 H, s), 2.30 (2 H, dd, J = 4.5, 4.0 Hz), 2.90 (2 H, dd, J = 4, 3 Hz), 7.0–7.4 (5 H, m). Calcd for $C_{12}H_{12}O_2S$: 220.0558. Found: 220.0556.

Preparation of 1-Acetoxy-2-(4′-methoxyphenylthio)-1-cyclobutene (5d). Acetic anhydride (6 mL) was added to a stirred solution of 2-(4′-methoxyphenylthio)-1-cyclobutanone (1.27 g, 6.1 mmol) in anhydrous triethylamine (6 mL) at room temperature. After 14 h, the solution was then diluted with ether (100 mL), washed with saturated aqueous sodium carbonate and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by LC (column length 100 cm, inner diameter 2.5 cm, 10% ether in hexane) to give 1.14–1.29 g (75–85%) of 1-acetoxy-2-(4′-methoxyphenylthio)-1-cyclobutene, a clear oil. IR ($CHCl_3$): 1770, 1650, 1590, 1490, 1460, 1367 cm^{-1}. NMR ($CDCl_3$): δ 2.05 (3 H, s), 2.24 (2 H, t, J = 4.0 Hz), 2.91 (2 H, t, J = 4.0 Hz), 3.80 (3 H, s), 6.79 (2 H, d, J = 9.0 Hz), 7.30 (2 H, d, J = 9.0 Hz). Calcd for $C_{13}H_{14}O_3S$: 250.0664. Found: 250.0657.

Preparation of 2,3-Cyclobutene-1,4-oxathiin (5f). Thionyl chloride (1.60 mL, 2.62 g, 22.0 mmol) was added via syringe to a stirred solution of 2-(2′-hydroxyethylthio)cyclobutanone (2.60 g, 17.8 mmol) in chloroform (30 mL) at room temperature. After 1 h, dropwise addition of anhydrous triethylamine (1.0 mL, 0.73 g, 7.2 mmol) to the stirred reaction mixture caused an immediate exothermic reaction. The reaction mixture was maintained at reflux by the dropwise addition of a second aliquot of triethylamine (5.30 mL, 3.84 g, 38.0 mmol) over 30 min. It was allowed to cool to room temperature without external cooling and then poured into a separatory funnel containing pentane (250 mL) and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated by distillation through a 10-cm Vigreux column. The residual oil was distilled at reduced pressure to give 1.06 g (47%) of 2,3-cyclobutene-1,4-oxathiin as an oil, bp 55–56 °C (2.5 mm). IR (CCl_4): 1680, 1450, 1410, 1370 cm^{-1}. NMR (CCl_4): δ 2.3–2.5 (2 H, m), 2.7–3.1 (4 H, m), 4.2–4.4 (2 H, m). Calcd for C_6H_8OS: 128.0296. Found: 128.0300.

Preparation of Dienes. Preparation of 2-Acetoxy-3-(4′-methoxyphenylthio)-1,3-butadiene (6d). 1-Acetoxy-2-(4′-methoxyphenylthio)-1-cyclobutene (133 mg, 0.53 mmol) was distilled at reduced pressure (1.0 mm) through a horizontally mounted quartz tube (inner diameter 5 mm) preheated to 350 °C. The product condensed immediately upon leaving the hot zone into the collecting bulb which contained 2,6-di-*tert*-butyl-4-methylphenol (25 mg). The entire tube was cooled and then thoroughly rinsed with methylene chloride. The combined rinsings were concentrated in vacuo to give 129 mg (97%) of 2-acetoxy-3-(4′-methoxyphenylthio)-1,3-butadiene suitable for use without further purification. In this case, purification by preparative TLC (50% ether in hexane) gave 124 mg (93%) of 2-acetoxy-3-(4′-methoxyphenylthio)-1,3-butadiene as a clear, straw-colored oil, R_f 0.45. The scale of the reaction could be increased without a decrease in yield or purity. For example, reaction of 1.0 g (4.0 mmol) of 1-acetoxy-2-(4′-methoxyphenylthio)-1-cyclobutene gave 0.96 g (96%) of 2-acetoxy-3-(4′-methoxyphenylthio)-1,3-butadiene of high purity. IR ($CHCl_3$): 1768, 1590, 1490, 1365 cm^{-1}. NMR ($CDCl_3$): δ 2.16 (3 H, s), 4.94 (1 H, bs), 5.02 (1 H, bs), 5.49 (2 H, bs), 6.84 (2 H, d, J = 8 Hz), 7.34 (2 H, d, J = 8 Hz). ^{13}C NMR ($CDCl_3$): 168.2 (s), 159.8 (s), 150.4 (s), 139.0 (s), 134.5 (d), 122.8 (s), 115.1 (t), 114.9 (d), 105.6 (t), 55.2 (q) ppm. Calcd for $C_{13}H_{14}O_3S$: 250.0664. Found: 250.0672.

Table V. Experimental Details for Preparation of Dienes[d]

entry	cyclobutene (wt, mmol)	temp, °C	diene (wt, yield)	BHT, mg
1	**5a**	see text		
2	**5b** (68 mg, 0.31)	350	**6b**[a] (64 mg, 94%)	10
3	**5c** (240 mg, 1.06)	350	**6c**[b] (225 mg, 94%)	25
4	**5d**	see text		
5	**5e** (200 mg, 1.03)	350	**6e**[c] (168 mg, 84%)	40
6	**5f**	see text		

[a] Yield after TLC isolation using 40% ether in hexane, R_f ~0.5. [b] Yield after TLC isolation using 20% ether in hexane, R_f ~0.8. [c] Yield after TLC isolation using 8% acetone in chloroform. [d] Spectral data of dienes follow. **6b**: IR ($CHCl_3$) 1760, 1640, 1575, 1475, 955, 890 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (3 H, s), 4.90 (1 H, bs), 5.36 (1 H, bs), 5.50 (1 H, bs), 5.68 (1 H, bs), 7.0–7.4 (5 H, m); ^{13}C NMR (15.1 MHz, $CDCl_3$) 168.3 (s), 150.4 (s), 136.6 (s), 133.8 (s), 130.5 (d), 129.0 (d), 127.0 (d), 119.0 (t), 106.6 (t), 20.6 (q) ppm. Calcd for $C_{12}H_{12}O_2S$: 220.0558. Found: 220.0545. **6c**: IR ($CHCl_3$) 1610, 1560, 1465, 910 cm^{-1}; NMR ($CDCl_3$) δ 3.52 (3 H, s), 4.17 (1 H, b, J = 3 Hz), 4.76 (1 H, bd, J = 3 Hz), 5.36 (1 H, bs), 6.00 (1 H, bs), 7.1–7.35 (4 H, m); ^{13}C NMR (15.1 MHz, $CDCl_3$) 157.9 (s), 137.8 (s), 133.4 (s), 133.3 (s), 131.6 (d), 129.0 (d), 120.0 (t), 86.4 (t), 55.4 (q) ppm. Calcd for $C_{11}H_{11}ClOS$: 226.0221. Found: 226.0221. **6e**: IR ($CHCl_3$) 1610, 1545, 915 cm^{-1}; NMR ($CDCl_3$) δ 3.76 (3 H, s), 4.30 (1 H, bd, J = 1.5 Hz), 4.96 (1 H, bd, J = 1.5 Hz), 5.98 (1 H, bs), 6.44 (1 H, bs), 7.04 (1 H, t, J = 5 Hz), 8.54 (2 H, d, J = 5 Hz); ^{13}C NMR ($CDCl_3$) 158.6 (s), 157.4 (d), 133.4 (s), 126.1 (t), 117.0 (d), 116.2 (s), 86.1 (t), 55.6 (q) ppm. Calcd for $C_9H_{10}N_2OS$: 194.0514. Found: 194.0508.

The remaining examples are summarized in Table V except for **6a** and **6f**, which are presented in detail.

Preparation of 2-Methoxy-3-phenylthiobuta-1,3-diene (6a). A vertically mounted glass column (length 45 cm, inner diameter 2 cm) packed with glass helices was heated to approximately 335 °C (internal thermocouple) and maintained with a nitrogen flow of 550 mL/min. The glass surfaces were deactivated by rinsing with *O,N*-bis(trimethylsilyl)acetamide (2 mL). The column was then equipped with two consecutive U-tube traps at the exit. Each trap, maintained at −78 °C, was filled with glass beads and 20 mg of BHT as stabilizer. A solution of 480 mg (2.5 mmol) of cyclobutene **5a** in 10 mL of hexane was dropped through the hot tube over 10 min. The column was washed with an additional 10 mL of hexane while hot and, after cooling, with ether. The contents of the traps were combined and the traps washed with additional ether. The combined organic layers were concentrated in vacuo to give 478 mg (99%) of diene containing 40 mg of BHT. The diene was pure by spectral analysis. Attempts to chromatograph the diene led only to decomposition. IR (CCl_4): 1580, 1550, 1485, 930, 912 cm^{-1}. NMR (CCl_4): δ 3.58 (3 H, s), 4.17 (1 H, bd, J = 2 Hz), 4.83 (1 H, bd, J = 2 Hz), 5.36 (1 H, bs), 6.01 (1 H, bs), 7.0–7.4 (5 H, m).

Preparation of 2,3-Bis(methylene)-1,4-oxathiin (6f). Using the procedure for **6a**, 275 mg (2.15 mmol) of 2,3-cyclobutene-1,4-oxathiin (**5f**) in 5 mL of hexane gave 270 mg of residue which, by NMR, was a mixture of the desired diene **6f**, starting material, and decomposition products. Attempted purification led to substantial decomposition. Diene of this quality was utilized in Diels–Alder reactions. For example, reaction with *N*-phenylmaleimide gave the adduct in 55% yield (see accompanying paper). Spectroscopic data for the mixture was recorded. IR (CCl_4): 1620, 1430, 870 cm^{-1}. Partial NMR (CCl_4):

δ 5.42 (1 H, s), 5.09 (1 H, s), 4.31 (1 H, s), 4.10 (1 H, s).

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Sulfur as a Regiochemical Control Element. Cycloadditions of 2-Alkoxy(acyloxy)-3-alkyl(aryl)thiobuta-1,3-dienes

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Abstract: The cycloadditions of 2-methoxy-3-phenylthiobuta-1,3-diene, the 4′-chlorophenylthio and 2′-pyrimidylthio derivatives, and 2-acetoxy-3-phenylthiobuta-1,3-diene and its 4′-methoxyphenylthio derivative with unsymmetrical dienophiles are examined. The effect of silica gel, boron trifluoride etherate, and magnesium bromide on the regiochemistry is probed. In situ generation of the diene from the precursor cyclobutene and cycloaddition is a promising technique for sluggish dienophiles such as cyclohex-2-en-1-one. The use of a cisoid diene, 2,3-dimethylene-1,4-oxathiin, has also been examined. By variation of the substituents and use of thermal vs. Lewis acid catalysis, either sulfur or oxygen dominance of regiochemistry is possible. The former, combined with desulfurization, offers an approach to 1,3-substituted cyclohexanes via cycloaddition chemistry—a type of substitution not available in the normal Diels–Alder reaction. Thus, sulfur serves as a regiochemical control element. Rationalization of these results in terms of current concepts is presented. The frontier-orbital approach modified by consideration of charge-transfer (polar) interactions best accounts for the results. The site of complexation of the Lewis acids in these reactions also appears open to question.

The introduction of heteroatom-substituted dienes as cycloaddition partners has allowed the creation of cyclohexanes with functional groups in masked forms. For example, 2-methoxybuta-1,3-diene[1] is the equivalent of $-CH_2C(O)CH_2CH_2-$ and 1,1-dithiobuta-1,3-dienes[2] are the equivalent of $-COCH{=}CHCH_2-$. The synthesis of 1-methoxy-3-trimethylsiloxybuta-1,3-diene[3] has led to several creative applications in complex synthesis. In our program to expand the horizons of β-keto sulfides in synthesis, we sought cycloaddition routes to them.[4,5] As outlined in the previous paper, this has led to synthesis of 2-alkoxy(acyloxy)-3-alkyl(aryl)thiobuta-1,3-dienes and the theoretical question regarding re-

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