***trans*-2-(7-((*tert*-Butyldimethylsilyl)oxy)heptyl)-3-((*E*)-1-pentenyl)cyclopentanone (65)**: $bp_{0.1}$ 160 °C; IR (neat) 2950, 2920, 2850, 1735, 1440, 1245, 1090, 960, 825, 765, 740 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 5.49 (1 H, dt, J = 15, 7 Hz), 5.33 (1 H, dd, J = 15, 8 Hz), 3.58 (2 H, t, J = 7 Hz), 2.31 (2 H, m), 2.02 (5 H, m), 1.75 (1 H, m), 1.54 (2 H, m), 1.47 (2 H, m), 1.36 (2 H, m), 1.24 (8 H, br s), 0.88 (3 H, t, J = 7 Hz), 0.87 (9 H, s), 0.05 (6 H, s). Anal. Calcd for $C_{23}H_{44}O_2Si$: C, 72.57; H, 11.65. Found: C, 72.57; H, 11.83.

***trans*-2,3-Diphenylcyclopentanone (66)**: mp (hexane) 95 °C; IR (neat) 3060, 3020, 2960, 2920, 2860, 1950, 1870, 1740, 1595, 1480, 1440, 1385, 1275, 1130, 1110, 1070, 1025, 940, 905, 855, 750, 710, 690 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 7.14 (10 H, m), 3.46 (2 H, m), 2.67 (1 H, dd, J = 17, 8 Hz), 2.45 (2 H, m), 2.08 (1 H, m). Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.85; H, 6.82. This compound has been previously prepared.[40]

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Heteroatom-Directed Allylic Substitution and Rearrangement Reactions

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Alcoholic, phenolic, and thiolic nucleophiles attack 3-chloro-1-methoxypropene (1) exclusively at C-1 in the presence of *N,N*-diisopropylethylamine. The reaction is formally a highly regioselective S_N2' process. Some of the oxygen nucleophiles (e.g., methyl salicylate) react slowly under these conditions and give poor yields; however, the corresponding lithium alkoxides, formed by treating the alcohol with lithium bis(trimethylsilyl)amide, give good yields. Several of the mixed acrolein acetals made by this procedure can be produced independently by acid-catalyzed addition of the alcohols to methoxypropadiene. In contrast, acid-catalyzed addition of thiols to methoxypropadiene leads to 3-(arylthio)-1-methoxypropenes. Enolates derived from activated carbonyl compounds give C-alkoxyallylated products with **1**. The acrolein *O,S*-acetals **2f,g** were found to undergo acid-catalyzed rearrangement into enol ethers **3a,b**.

Substitution reactions involving allylic substrates are of interest for both mechanistic and synthetic reasons. The stereochemistry and the possible concertedness of the S_N2' reaction continue to provoke discussion of allylic substitution mechanisms.[1-11] New synthetic applications in the area include Stork's S_N2' thiolate and alkoxide cyclizations and Kang's silicon-directed regiospecific alkylations of allylic halides.[12,13] We report here a new type of regiospecific allylic substitution which is formally a heteroatom-directed S_N2' reaction. We have also discovered a new method for the α-alkoxyallylation of activated carbonyl compounds that complements the methods recently reported by Coates.[14] In addition, we find that acid-catalyzed rearrangement of acrolein *O,S*-acetals gives 1-methoxy-3-(arylthio)propenes. Hoffmann and Kemper have reported the utility of such propenes in the synthesis of methoxy-substituted homoallylic alcohols.[15]

Results and Discussion

Treatment of an ether solution of 3-chloro-1-methoxypropene (**1**) with alcohols or thiols in the presence of *N,N*-diisopropylethylamine gives mixed acetals of acrolein **2**. If the nucleophile is a thiol (Table I, entries 8 and 9),

$$\underset{\mathbf{1}}{ClCH_2CH{=}CHOCH_3} \rightarrow \underset{\mathbf{2}}{CH_2{=}CHCH(OCH_3)R}$$

the reaction is complete within 5 min at −78 °C. The crude oils obtained after workup appear to be at least 90% pure by NMR. There is no indication in the NMR of the normal S_N2 products. Table I (entries 1, 3, 4, 5, 7) shows that phenols, in addition to primary, secondary, and tertiary alcohols, can be used. Some of the oxygen nucleophiles react sluggishly. Methyl salicylate, for example, gives only a 10% yield under these conditions. However, if the lithium salt is generated before the addition of **1**, the yield increases to 83%. Similarly, the yield improves from 77% to 92% if methyl thiosalicylate is subjected to the same conditions.

None of the acetals in Table I have been reported previously. Hoff, Brandsma, and Arens have prepared 3-methoxy-3-ethoxypropene, a mixed acetal, by acid-catalyzed addition of ethanol to methoxypropadiene.[16] They employed a 4-h reflux period with *p*-toluenesulfonic acid as the catalyst. These authors report that the mixed acetal was contaminated with the symmetrical acetals: $CH_2{=}$

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Table I. Acetals 2 and Enol Ethers 3

entry	product	R	method	yield, %
1	**2a**	$O(CH_2)_3CH_3$	A[a]	66 (36)[b]
2	**2a**	$O(CH_2)_3CH_3$	B	(54)
3	**2b**	$OC(CH_3)_3$	A	50 (25)
4	**2c**	$OCH(CH_3)_2$	A	48 (24)
5	**2d**	OPh	A	52 (46)
6	**2d**	OPh	B	(59)
7	**2e**	O-2-$(CH_3O_2C)C_6H_4$	A	(83)
8	**2f**	SPh	A	84 (70)
9	**2g**	S-2-$(CH_3O_2C)C_6H_4$	A	84 (77)
10	**2g**	S-2-$(CH_3O_2C)C_6H_4$	C	(92)
11	**3a**	SPh	D	(62)
12	**3a**	SPh	E	(71)
13	**3b**	S-2-$(CH_3O_2C)C_6H_4$	D	(72)
14	**3b**	S-2-$(CH_3O_2C)C_6H_4$	E	(82)
15	**3c**	$(EtO_2C)_2CHCH_2CH$=$CHOCH_3$	C	78 (46)[c]
16	**3d**	$(EtO_2C)_2C(Ph)CH_2CH$=$CHOCH_3$	C	85 (64)[c]

[a] Method A. The alcohol, phenol, or thiol was treated with 3-chloro-1-methoxypropene in ether at −78 °C in the presence of *N,N*-diisopropylethylamine. Method B. The alcohol, phenol, or thiol was treated with methoxypropadiene in ether at 0 °C in the presence of methanesulfonic acid. Method C. The lithium anion of the nucleophile was preformed by using lithium bis(trimethylsilyl)amide and then 3-chloro-1-methoxypropene was added. Method D. The thiol was added to methoxypropadiene in ether at −70 °C in the presence of CF_3SO_3H. Method E. The *O,S*-acetal in ether at −70 °C was treated with CF_3SO_3H. [b] The first figure represents the yield before low temperature vacuum distillation. The products appear to be approximately 90% pure by NMR before distillation. The second figure (in parentheses) is the distilled yield. Considerable amounts of the more volatile ethers are lost to the cold trap. The vacuum distillation was employed as a precaution against disproportionation. [c] These products contain varying amounts of the corresponding regioisomers. Comparison with the compounds Coates[14] has reported indicates that the *Z* isomer is not present, however. The figure in parentheses is the yield of the alkoxyallylation product shown. The preceding figure is the combined yield of both regioisomers.

$CHCH(OCH_3)_2$ and CH_2=$CHCH(OC_2H_5)_2$. This disproportionation is probably due to their acidic reaction conditions, although it may also occur in the atmospheric pressure distillations used in their workups, the distillation glassware serving as the acid catalyst. Our base-catalyzed method minimizes formation of the symmetrical acetals; however, as a precaution we purified the products of our initial experiments by fast low temperature distillation through base-washed glassware. We found that fractional distillation at atmospheric pressure does sometimes yield a symmetrical acetal as a small high boiling fraction even when our reaction conditions are used.

We have found that it is possible to catalyze the synthesis of some of these mixed acetals from methoxypropadiene with methanesulfonic acid at 0 °C. The reaction is complete in minutes at this temperature. The acid-catalyzed method does not seem to work with tertiary alcohols however. We have confirmed the structures of acetals **2a,d** by this alternative synthesis. Disproportionation was not observed under these conditions.

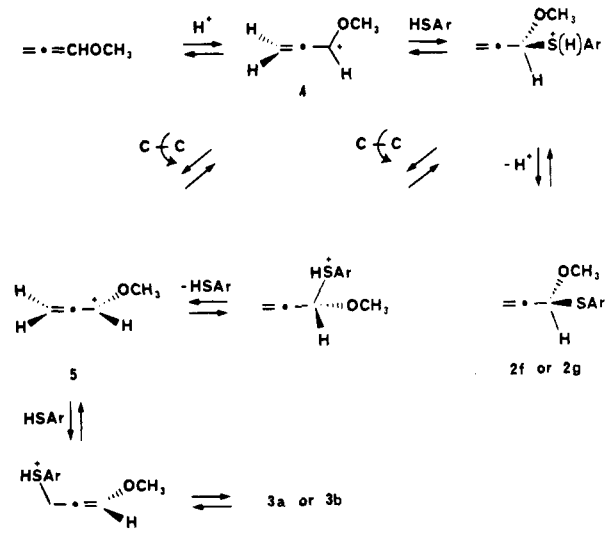
The *O,S*-acetals **2f,g** also have not been reported previously. No trace of S_N2 products was found in these syntheses. Attempts to form these *O,S*-acetals by methanesulfonic acid catalyzed addition of the thiol to methoxypropadiene gave a mixture of the thioacetal **2f,g** and the corresponding rearrangement product **3a,b**. However,

RCH_2CH=$CHOCH_3$

3a, R = phenylthio
3b, R = 2-carbomethoxyphenylthio

if trifluoromethanesulfonic acid is used with careful temperature control, these enol ethers can be generated cleanly. The *E* isomer is formed almost exclusively. A trace of the *Z* isomer is barely detectable in the ^1H NMR. Hoffmann and Kemper[15] generated (*E*)-$PhSCH_2CH$=$CHOCH_3$ using the same reagents but somewhat different conditions (HBF_4, −20 °C, CH_2Cl_2/ether).

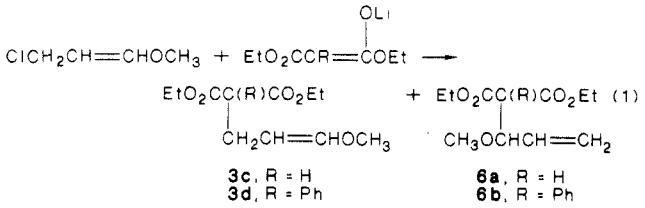
Scheme I



The mechanism of the acid-catalyzed enol ether formation may involve prior formation of the acetal and then subsequent rearrangement (Scheme I). Alternatively, the nucleophile may attack the intermediate allylic carbocation on the unsubstituted terminus. Note that the prior formation of acetal **2f,g** may suggest that interception of the initially formed secondary alkoxycarbocation **4** is faster than the C–C bond rotation which forms the allylic carbocation **5**. On the the other hand, if the allylic carbocation **5** is the reactive intermediate, it seems unlikely that it would undergo faster attack on the unsubstituted terminus than on the alkoxy-substituted terminus due to resonance stabilization of the positive charge by the oxygen. Thus both cations **4** and **5** would be expected to preferentially react on the alkoxy-substituted carbon. Therefore, formation of the enol ether product would require reversible generation of the allylic carbocation **5** from the initially formed acetal **2f,g** or direct formation from **4** via **5**. Apparently, the enol ether **3a,b** is the thermodynamically favored product since **3a,b** does not produce any acetal **2f,g** under these conditions (CH_3SO_3H, 0 °C, ether). But **2f,g** made under basic conditions, when treated with the much stronger acid CF_3SO_3H at −78 °C does give **3a,b**.[17] Neither acetal **2f** nor **2g** gives its corresponding enol ether at 0 °C in CH_3SO_3H. These observations suggest that the mixture of products seen in the CH_3SO_3H reactions reflects kinetic trapping of an intermediate alkoxyallyl carbocation. We have never seen any evidence that *O,O*-acetals can rearrange as do the *O,S*-acetals. This implies that the acetal must contain the proper heteroatom (sulfur) in order for the enol ether to form.

We also investigated the reaction of activated carbonyl compounds with 3-chloro-1-methoxypropene (eq 1). The principal products formed in these reactions (**3c,d**) are the apparent result of simple S_N2-type C-alkylation of the

(17) Reaction time and temperature are critical in these rearrangements. The enol ethers are sensitive to further reaction giving, in the case of **3a**, a mixture of 1,3-bis(phenylthio)-1-methoxypropane and 1,1-dimethoxy-3-(phenylthio)propane. The structures of these compounds were confirmed by independent synthesis from **3a**.



preformed enolates. The side products **6a,b** result from a formal S_N2' C-alkylation. The more hindered enolate (R = Ph) favors the enol ether product **3d** over the isomeric olefin **6b** by 3 to 1, whereas the ratio of **3c** to **6a** is 1.2 to 1.

Although apparently the result of direct S_N2 alkylation of the enolates, **3c,d** could arise via *O*-alkylation of the enolate by the methoxy-substituted carbon of the allylic chloride followed by Claisen rearrangement. Low temperature quenching and workup of the reaction does not give the product of *O*-alkylation on C-1 of 3-chloro-1-methoxypropene. However, from literature precedents,[18] the rearrangement may well be rapid even at 0 °C. Thus, despite our precautions we may not be able to observe the intermediate and therefore cannot exclude this pathway on this basis alone.

Butyllithium reacts with **1** to give an approximately equimolar mixture of (*E*)-1-methoxyheptene and 3-methoxyheptene. Obviously, no Claisen pathway is available in this case and the result suggests the lack of any inherent alkylation regioselectivity with carbon nucleophiles.

The low temperatures and basic conditions of this reaction complement the conditions that Coates has reported for achieving alkoxyallylations of similar substrates.[14] The use of preformed enolates with **1** gives only *E* enol ethers, whereas Coates' method gives *E*/*Z* mixtures. Unfortunately, without a sterically hindered nucleophile regioselectivity is not good, but the necessary separation of isomers can be achieved by fractional distillation.

At present we cannot distinguish between a concerted S_N2' mechanism or a stepwise pathway for any of these substitutions. In the case of the concerted mechanism the methoxy substituent would increase the atomic orbital coefficient at C-1 in the LUMO of 3-chloro-1-methoxypropene. This would enhance the reaction rate at this carbon in comparison to an allylic chloride lacking a heteroatom substituent. On the other hand, if a stepwise mechanism is involved, one would expect the methoxy substituent to bear a considerable fraction of the positive charge in the intermediate alkoxyallyl carbocation and thereby to direct the nucleophile to C-1 also. Thus, either a concerted or a stepwise mechanism could explain the high regioselectivity observed.

We note in this connection that Bordwell has argued against the existence of the S_N2' mechanism.[9] Allylic halides with electron-withdrawing substituents at C-1 seem unreactive to substitution. He contends that electron-withdrawing substituents would increase the likelihood of an S_N2' process since electron repulsion between the π bond and the nucleophile would be reduced.

However, the simple FMO argument presented above seems to imply that electron-withdrawing substituents would decrease the coefficients of the LUMO at C-1 and that the S_N2' pathway might be disfavored. Moreover, Bach[1] argues that the π–n HOMO–HOMO interaction between the olefin and the nucleophile "is responsible for frontier orbital narrowing that elevates a filled orbital, the 'effective HOMO', closer to the LUMO." Electron-donating substituents might be expected to reinforce this FMO narrowing, while electron-withdrawing groups could work against it. Calculations testing such substituent effects would be of interest.[19]

Aside from these theoretical arguments, two observations suggest that the S_N2' pathway may be preferred over a process involving cation intermediates. Firstly, the acid-catalyzed addition of thiols to methoxypropadiene discussed above very likely involves an intermediate alkoxyallyl carbocation. This reaction gives a 1 to 1 mixture of products resulting from attack of the thiol on either end of the putative carbocation intermediate. This result is in marked contrast to the regioselectivity exhibited by **1** in its reaction with thiols. Moreover, this regioselectivity occurs under conditions (low temperature and a nonionizing solvent) which are not conducive to carbocation formation. Secondly, 3-bromo-1-methoxypropene, generated at the same temperature and in the same solvent as **1**, undergoes reaction with thiophenol to give a 3.5 to 1 mixture of **2f** and **3a**. Presumably the bromo analogue is more likely to undergo substitution through a cation intermediate or a cation-like transition state than is **1** because bromide is a better leaving group than is chloride.

Of course, allylic bromides are prone to allylic rearrangement.[20] We have not excluded the possibility that a mixture of bromides is formed at −78 °C which subsequently undergoes direct displacement of bromide by the thiol. It is unlikely however that the major product **2f** could have formed this way since this would imply that **7** would be favored over **8** in the equilibrium mixture, or that the interconversion between **7** and **8** in ether at −78 °C is much faster than bromide displacement by thiol.

$CH_2{=}CHCH(Br)OCH_3$ (**7**) $\qquad$ $BrCH_2CH{=}CHOCH_3$ (**8**)

Conclusion

Mixed acrolein acetals and *O,S*-acetals can be prepared cleanly from 3-chloro-1-methoxypropene. Some of these mixed acetals can also be made by carefully controlled acid-catalyzed addition of alcohols to methoxypropadiene. Low temperature alkoxyallylation of stabilized enolates is also possible with this reagent.

1-Methoxy-3-(arylthio)propenes are now generally available. The utility of functionalized propenes of this type in the synthesis of methoxy-substituted homoallylic alcohols has been demonstrated.[15] The sulfoxide of **3a** is a synthon for several functional groups. These results will be reported separately.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 700 or 137 IR spectrometer. Proton NMR spectra were obtained on a Varian T-60 by using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. Mass spectral determinations were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility. Analyses were performed by MicAnal Organic Microanalysis. Melting points were obtained on a Fisher-Johns hot stage apparatus or

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a Thomas-Hoover oil immersion apparatus. Melting and boiling points are both uncorrected. Tetrahydrofuran and ether were distilled from sodium and benzophenone. All strong base reactions were done under a positive pressure of nitrogen. Hexamethyldisilazane (Aldrich) was distilled from BaO through a 25-cm column packed with glass helices. The fraction boiling at 120–123 °C was collected. Kugelrohr distillations employed the apparatus available from Aldrich Chemical Company. Fractional distillations employed a 25-cm column packed with glass helices. Refractive indices were recorded on an Abbe refractometer equipped with a recirculating water bath. Organic reagents were purchased from Aldrich Chemical unless otherwise noted. Ratios of geometric and regioisomers formed were determined by NMR. Spectral and physical data were not necessarily obtained from the experimental run described.

Preparation of 3-Chloro-1-methoxypropene (1). This compound was prepared by the method of Hoff and Brandsma.[21] The molarity of the resulting solution was checked gravimetrically by precipitation of AgCl. Thus, to ethanolic $AgNO_3$ (32 mL of a 0.209 M solution) was added a 10-mL aliquot of freshly prepared 3-chloro-1-methoxypropene in ether. The solution was filtered by gravity and the filter paper washed with ethanol. The paper containing the AgCl precipitate was spread out on a watch glass and dried to constant weight on a steam bath. The molarity of the chloropropene solutions are reproducibly found to be 0.62 M (within 5% of the theoretical 0.631 M). It is crucial that the AgCl precipitated in this procedure be white. If the chloropropene gives a yellow precipitate, the nucleophilic displacement reactions described below fail.

Preparation of Lithium Bis(trimethylsilyl)amide. A stock solution was prepared from a solution of hexamethyldisilazane (4.64 mL, 22 mmol) in THF (15 mL) cooled to −78 °C under nitrogen to which *n*-butyllithium (22 mmol, 14.86 mL of a 1.48 M solution in hexane) was added. The resulting solution was taken to be 0.64 M.

Preparations of Acrolein Acetals 2. Method A. To the alcohol or thiol (24.8 mmol) was added neat *N,N*-diisopropylethylamine (24.8 mmol, 4.32 mL). The mixture was cooled to −78 °C and a 40-mL (24.8 mmol) aliquot of an ethereal solution of 3-chloro-1-methoxypropene was then added by syringe. After 0.5 h the bath was removed and the mixture was allowed to come to room temperature over the course of 2 h. Alternatively, the reaction mixture was stored overnight at −20 °C prior to workup. The crude reaction mixture was poured into 40 mL of water. The organic layer was separated and then washed three times with 20 mL of water, once with 10% NaOH (if either a phenol or thiol was a reactant), and then once with brine. The ether solution was dried over $MgSO_4$, filtered, and reduced via rotatory evaporation to an oil.

Method B. A catalytic amount of methanesulfonic acid (0.104 g, 1.1 mmol) was added dropwise over a 1-min interval to a solution of 1-methoxypropadiene (0.431 g, 0.50 mL, 5.9 mmol) and the alcohol (5.9 mmol) in 20 mL of ether at 0 °C. The solution was stirred at 0 °C for 30 min to 2 h depending on the alcohol as noted below. Then *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmole) was added dropwise over a 1-min interval. The solution was warmed to 25 °C and then washed three times with water, twice with 10% NaOH (if a thiol or a phenol was a reactant), and once with brine. The ether solution was then dried over $CaCl_2$, filtered, and then reduced by rotatory evaporation to an oil.

Preparation of 3-Butoxy-3-methoxypropene (2a). Method A gave 2.37 g (66%) of a colorless oil, pure by NMR, which was subjected to Kugelrohr distillation (30–56 °C/0.2 mm) yielding 1.30 g (36%) of **2a**: n^{20}_D 1.4123; IR (neat, cm^{-1}) 1060 (C–O); ^1H NMR δ 5.87 (ddd, J = 17, 10, 4.5 Hz, 1 H, C*H*=CH_2), 5.33 (m, 2 H, CH=C*H*$_2$), 4.83 (m, 1 H, CH_3OCHO), 3.5 (m, 2 H, OCH_2), 3.33 (s, 3 H, OCH_3), 1.53 (m, 4 H, $CH_2CH_2CH_3$), 0.97 (m, 3 H, CH_2CH_3); mass spectrum, m/e 143 (M^+ – H), 113 (M^+ – OCH_3), 71 (M^+ – $OCH_2CH_2CH_2CH_3$); high resolution mass spectrum, calcd for $C_8H_{15}O_2$ 143.1072, found 143.1073. An analytical sample was prepared by fractional distillation: bp 140–144 °C; n^{24}_D 1.4094. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.47; H, 11.30.

Method B. After 2 h of stirring in the presence of acid, the reaction was quenched and worked up as detailed above to give a colorless oil. Kugelrohr distillation gave 0.39 g (54.2%) of the product.

Preparation of 3-*tert*-Butoxy-3-methoxypropene (2b). Method A gave 1.78 g (50%) of a colorless oil pure by NMR. Kugelrohr distillation (25 °C/0.2 mm) gave 0.91 g (25%) of product: n^{20}_D 1.4067; IR (neat, cm^{-1}) 1075, 1019 (C–O); ^1H NMR δ 5.87 (ddd, J = 17, 10, 5 Hz, 1 H, C*H*=CH_2), 5.33 (m, 2 H, CH=C*H*$_2$), 5.10 (m, 1 H, CH_3OCHO), 3.25 (s, 3 H, CH_3), 1.28 (s, 9 H, $(CH_3)_3CO$); mass spectrum, m/e 143 (M^+ – H), 129 (M^+ – CH_3); high resolution mass spectrum, calcd for $C_8H_{15}O_2$ 143.1072, found 143.1076. An analytical sample was prepared by fractional distillation: bp 123–125 °C; n^{23}_D 1.4042. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.67; H, 11.33.

Preparation of 3-Isopropoxy-3-methoxypropene (2c). Method A gave 1.53 g (48%) of a colorless oil, pure by NMR, which was subjected to Kugelrohr distillation (20 °C/0.8 mm) to give 0.76 g (24%) of the product: n^{20}_D 1.4022; IR (neat, cm^{-1}) 1125, 1070, 1030 (C–O); ^1H NMR δ 5.87 (ddd, J = 17, 10, 5 Hz, 1 H, C*H*=CH_2), 5.30 (m, 2 H, CH=C*H*$_2$), 4.87 (m, 1 H, CH_3OCHO), 3.90 (qn, J = 6 Hz, 1 H, $(CH_3)_2CHO$), 3.30 (s, 3 H, OCH_3), 1.20 (d, J = 6 Hz, 3 H, CH_3CHCH_3), 1.15 (d, J = 6 Hz, 3 H, CH_3CHCH_3); mass spectrum, m/e 131 (M^+ + H), 129 (M^+ – H), 99 (M^+ – OCH_3), 71 (M^+ – $OCH(CH_3)_2$); high resolution mass spectrum, calcd for $C_7H_{15}O_2$ 131.1072, found 131.1074. An analytical sample was prepared by fractional distillation: bp 113–114 °C; n^{20}_D 1.4000. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.71; H, 11.13.

Preparation of 3-Phenoxy-3-methoxypropene (2d). Method A gave 2.10 g (52%) of a colorless oil, pure by NMR, which was subjected to Kugelrohr distillation (52–70 °C/0.2 mm), yielding 1.87 g (46%) of the product: n^{20}_D 1.5052; IR (neat, cm^{-1}) 1600, 1590 (Ph), 1495, 1235, 1080 (C–O); ^1H NMR δ 7.17 (m, 5 H, Ph), 6.03 (ddd, J = 17.5, 10, 4 Hz, 1 H, C*H*=CH_2), 5.53 (m, 2 H, CH=C*H*$_2$), 5.37 (m, 1 H, CH_3OCHO), 3.40 (s, 3 H, CH_3O); mass spectrum, m/e 164 (M^+), 133 (M^+ – OCH_3), 71 (M^+ – OPh); high resolution mass spectrum, calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0835. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.35.

Method B. After being stirred for 30 min in the presence of acid as described above, the reaction was quenched and worked up to give 0.574 g (59%) of a colorless oil, pure by NMR.

Preparation of 3-Methoxy-3-(2-carbomethoxyphenoxy)propene (2e). Method A above gave 2.77 g of a yellow-green oil which was subjected to Kugelrohr distillation (77–90 °C/0.3 mm), yielding 2.02 g (83%) of **2e**: n^{20}_D 1.5172; IR (neat, cm^{-1}) 1725 (C=O), 1600, 1580 (Ph), 1120, 1075 (C–O); ^1H NMR δ 7.83–6.75 (m, 4 H, Ph), 6.05 (ddd, J = 17, 10, 3 Hz, 1 H, C*H*=CH_2), 5.70 (m, 2 H, CH=C*H*$_2$), 3.38 (m, 1 H, CH_3OCHO) 3.88 (s, 3 H, CO_2CH_3), 3.40 (s, 3 H, OCH_3); mass spectrum, m/e 222 (M^+), 191 (M^+ – OCH_3); high resolution mass spectrum, calcd for $C_{12}H_{14}O_4$ 222.0892, found 222.0890. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.82; H, 6.41.

Preparation of 3-(Phenylthio)-3-methoxypropene (2f). Method A gave 3.75 g (84%) of a light yellow oil which was subjected to Kugelrohr distillation (72–90 °C/0.3 mm), yielding 3.14 g (70%) of product: n^{20}_D 1.5600; IR (neat, cm^{-1}) 1660, 1645, 1585 (Ph), 1490, 1110, 1080 (C–O); ^1H NMR δ 7.33 (m, 5 H, Ph), 5.90 (ddd, J = 17, 10, 4 Hz, 1 H, C*H*=CH_2), 5.20 (m, 2 H, CH=C*H*$_2$), 5.03 (m, 1 H, CH_3OCHS), 3.53 (s, 3 H, CH_3O); mass spectrum, m/e 180 (M^+), 109 (M^+ – CH_2=CHCHOCH$_3$), 71 (M^+ – SPh); high resolution mass spectrum, calcd for $C_{10}H_{12}OS$ 180.06088, found 180.0609. Anal. Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71. Found: C, 66.85; H, 6.85.

Preparation of 3-Methoxy-3-[(2-carbomethoxyphenyl)thio]propene (2g). Method A gave 4.95 g (84%) of a light yellow oil, pure by NMR, which was subjected to Kugelrohr distillation (114–126 °C/0.1 mm), yielding 4.54 g (77%) of the product: n^{20}_D 1.5682; IR (neat, cm^{-1}) 1720 (C=O), 1640, 1590, 1565 (Ph), 1120, 1060 (C–O); ^1H NMR δ 7.90–7.03 (m, 4 H, Ph), 5.97 (ddd, J = 18, 10, 4 Hz, 1 H, C*H*=CH_2), 5.37 (m, 2 H, CH=C*H*$_2$), 5.20 (m, 1 H, CH_3OCHS), 3.92 (s, 3 H, CO_2CH_3), 3.50 (s, 3 H, OCH_3); mass spectrum, m/e 238 (M^+), 207 (M^+ – OCH_3), 167 (M^+ – CH_2=CHCHOCH$_3$); high resolution mass spectrum, calcd for $C_{12}H_{14}O_3S$ 238.06635, found 238.0665. Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48;

(21) Hoff, S.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 845.

H, 5.92. Found: C, 60.33; H, 6.03.

Method C. To lithium bis(trimethylsilyl)amide (11.0 mmol, 17.25 mL of a 0.64 M stock solution) was added at −78 °C neat methyl thiosalicylate[22] (11.0 mmol, 1.85 g). The solution was warmed until the precipitate had dissolved and then recooled to −78 °C. Then 3-chloro-1-methoxypropene (14.9 mmol, a 24-mL aliquot of a 0.62 M solution in ether) was added. The flask was allowed to warm to room temperature over the course of 0.5 h. The solution was then washed twice with water, twice with 10% NaOH, and once with brine and then dried over $MgSO_4$. The solvent was removed by rotatory evaporation and the residual oil distilled by Kugelrohr to give 2.53 g (92%) of the product.

Preparation of (*E*)-1-Methoxy-3-(phenylthio)propene (3a). Method D. From Methoxypropadiene and CF_3SO_3H. Trifluoromethanesulfonic acid (0.885 g, 5.90 mmol) was added dropwise over a 5-min period to a solution of methoxypropadiene (0.413 g, 5.90 mmol) and thiophenol (0.650 g, 5.9 mmol) in 20 mL of ether at −60 °C. The temperature was kept below −55 °C throughout the addition. The solution was stirred 30 min and then *N,N*-diisopropylethylamine (0.776 g, 6.00 mmol) was added dropwise over a 5-min period. The solution was warmed to 25 °C and washed twice with water, then twice with 10% NaOH, and then once with brine. The ether solution was dried over $CaCl_2$, filtered, and reduced to a yellow oil by rotatory evaporation. Kugelrohr distillation (92–125 °C/0.1 mm) gave 0.66 g (62%) of the product: n^{26}_D 1.6687; IR (neat, cm^{-1}) 1660, 1590 (Ph), 1470, 1220, 1140 (C–O); ^1H NMR δ 7.30 (m, 5 H, Ph), 6.33 (d, J = 13 Hz, 1 H, CH_3OCH=) 4.80 (dt, J = 13, 5 Hz, 1 H, OCH=$CHCH_2$), 3.50 (d, J = 8 Hz, 2 H, CH_2SPh) 3.48 (s, 3 H, OCH_3); mass spectrum, m/e 180 (M^+), 109 ($M^+ - CH_2$=CHCHOCH$_3$), 71 (M^+ − SPh); high resolution mass spectrum, calcd for $C_{10}H_{12}OS$ 180.06088, found 180.0608. Anal. Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71 Found: C, 66.37; H, 6.86.

Method E. From 3-Methoxy-3-(phenylthio)propene (2f). To a stirred solution of the acetal (1.03 g, 5.7 mmol) in 20 mL of ether at −78 °C was added triflic acid (0.10 mL, 1.10 mmol) dropwise. The mixture was stirred for 2 h and then quenched with an excess of triethylamine (0.20 mL, 1.4 mmol). The mixture was washed twice with water, once with 10% NaOH, and finally once with brine. The ether solution was dried over $MgSO_4$, filtered, and then reduced by rotatory evaporation. Kugelrohr distillation (80–85 °C/0.1 mm) gave 0.74 g (71%) of product.

Preparation of (*E*)-3-[(2-Carbomethoxyphenyl)thio]-1-methoxy-1-propene (3b). Method D. From Methoxypropadiene and CF_3SO_3H. This compound was prepared in the same manner as **3a**. However, the reaction temperature was kept at −70 °C and the volume of ether was 10 mL. The light yellow oil produced was subjected to Kugelrohr distillation (130–135 °C/0.1 mm) to yield 1.00 g (72%) of **3b** which slowly formed a gummy solid: mp 43–53 °C; IR (neat, cm^{-1}) 1720 (C=O), 1650, 1590 (Ar), 1460, 1130, 1060 (C—O); ^1H NMR δ 7.95 (br d, J = 7 Hz, 1 H, Ar), 7.47–6.97 (m, 3 H, Ar), 6.53 (d, J = 13 Hz, 1 H, CH_3OCH=), 4.83 (dt, J = 13, 7 Hz, 1 H, OCH=$CHCH_2$), 3.90 (s, 3 H, CO_2CH_3), 3.53 (d, J = 7 Hz, 2 H, ArSCH_2), 3.5 (s, 3 H, OCH_3); mass spectrum, m/e 238 (M^+), 207 ($M^+ - OCH_3$), 167 (M^+ − CH_2CH=CHOCH$_3$); high resolution mass spectrum, calcd for $C_{12}H_{14}O_3S$ 238.06635, found 238.0665. Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.37; H, 6.02.

Method E. From 3-Methoxy-3-[(2-carbomethoxyphenyl)thio]propene (2g). To the *O,S*-acetal (0.476 g, 2 mmol) in 5 mL of ether at −78 °C was added dropwise CF_3SO_3H (84.8 mg, 0.57 mmol). After 1 h of stirring, *N,N*-diisopropylethylamine (0.103 mL, 0.59 mmol) was added. The mixture was extracted twice with water, twice with 10% NaOH, and once with brine and then dried over $MgSO_4$. Solvent removal by rotatory evaporation and Kugelrohr distillation of the resulting oil gave 0.39 (82%) of (*E*)-3-[(2-carbomethoxyphenyl)thio]-1-methoxypropene.

Preparation of 3-Bromo-1-methoxypropene and Reaction with Thiophenol. To methoxypropadiene (3.50 g, 4.18 mL, 0.050 mol) in dry ether (160 mL) in a three-necked, 250-mL flask fitted with a Dewar condensor, a septum, and a fritted gas dispersion tube was added HBr (4.2 g, 0.052 mol) over a 3-min period. Both the flask and the condenser were cooled to −78 °C during the HBr addition. The HBr was delivered in portions from a lecture bottle (Matheson); the amount added was assumed to equal the weight difference of the lecture bottle. After 5 min of stirring at −78 °C, thiophenol (5.51 g, 5.14 mL, 0.050 mol) was added in one portion followed at once by *N,N*-diisopropylethylamine (10.5 mL, 0.060 mol). After 10 min the bath was removed and the mixture was allowed to warm for 20 min. The mixture was then extracted sequentially with H_2O (twice), 10% NaOH, and brine. The organic solution was dried over $MgSO_4$, filtered, reduced by rotatory evaporation, and then subjected to Kugelrohr distillation (72–87 °C/0.1 mm) to give 7.17 g (79.7%) of product consisting of a 3.5 to 1 mixture of acetal **2f** to trans enol ether **3a** by NMR analysis.

Preparation of Ethyl (*E*)-2-Carbethoxy-5-methoxy-4-pentenoate (3c). To lithium bis(trimethylsilyl)amide (70.31 mL of a 0.64 M stock solution) at −78 °C was added dropwise diethyl malonate (Eastman, 7.21 g, 45.0 mmol), which had been washed with saturated $NaHCO_3$, dried, and then distilled. After stirring the mixture for 4.5 h, 3-chloro-1-methoxypropene (50 mmol in 130 mL ether) was added over 10 min. After 1 h at −78 °C, the mixture was allowed to warm to room temperature over a 1-h period. The mixture was washed twice with water, twice with 10% NaOH, and once with brine and then dried over $MgSO_4$. The solvent was removed by rotatory distillation and the oil (12.01 g, **6a:3c**, 1:1.2) was subjected to fractional distillation yielding four fractions: 1st (bp 74–77 °C/0.1 mm, 2.67 g, 25.8%, **6a**), 2nd (bp 81–84 °C, 1.12 g, 10.8%, **6a:3c**, 2.27:1), 3rd (bp 85.5–89 °C, 1.95 g, 18.8%, **6a:3c**, 1:7), 4th (bp 96–97.5 °C, 2.26 g, 21.6%, **3c**). The spectral data for the *E* isomer follows: n^{22}_D 1.4409; IR (neat, cm^{-1}) 1730 (C=O), 1655, 935 (C=C); ^1H NMR δ 6.40 (d, J = 13 Hz, 1 H, CH=$CHOCH_3$), 4.70 (dt, J = 13, 8 Hz, 1 H, CH=$CHOCH_3$), 4.21 (q, J = 7 Hz, 4 H, CH_3CH_2O), 3.5 (s, 3 H, CH_3O), 3.33 (m, 1 H, $CHCO_2Et$), 2.52 (t, J = 7 Hz, 2 H, $CHCH_2CH$=), 1.27 (t, J = 7 Hz, 6 H, CH_3CH_2O); mass spectrum, m/e 230 (M^+), 183 ($M^+ - H_2O^+C_2H_5$), 156 ($M^+ - HCO_2C_2H_5$); high resolution mass spectrum, calcd for $C_{11}H_{18}O_5$ 230.1154, found 230.1148. The spectral data for **6a** follows: n^{22}_D 1.4330; IR (neat, cm^{-1}) 1750 (C=O); ^1H NMR δ 6.10–5.13 (m, 3 H, CH=CH_2), 4.20 (2 overlapping q, J = 7 Hz, 4 H, CH_3CH_2O), 4.20 (obscured, 1 H, CH_3OCHCH=), 3.53 (d, J = 9 Hz, 1 H, $CHCO_2Et$), 3.30 (s, 3 H, CH_3O), 1.77 (2 overlapping t, J = 7 Hz, 6 H, CH_3CH_2O). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found (for 3rd): C, 57.10; H, 8.07.

Preparation of Ethyl (*E*)-2-Carbethoxy-2-phenyl-5-methoxy-4-pentenoate (3d). This compound was prepared as in the preceding case except that the diethyl phenylmalonate (Eastman) was used without further purification. Distillation by Kugelrohr (120–135 °C/0.1 mm) gave a 3:1 mixture of **3d** and the regioisomer, ethyl 2-carbethoxy-2-phenyl-3-methoxy-4-pentenoate (**6b**), in 85% yield. Fractional distillation gave the *E* isomer: bp 126–127 °C/0.1 mm; n^{23}_D 1.5000; IR (neat, cm^{-1}) 1730 (C=O), 1658, 939 (C=C), 1499, 727, 697 (Ph); ^1H NMR δ 7.37 (m, 5 H, Ph), 6.27 (d, J = 13 Hz, 1 H, CH=$CHOCH_3$), 4.68 (dt, J = 13, 7 Hz, 1 H, CH=CHO), 4.20 (q, J = 7 Hz, 4 H, CH_3CH_2O), 3.42 (s, 3 H, CH_3O), 2.90 (d, J = 8 Hz, 2 H, CH_2CH=C), 1.27 (t, J = 7 Hz, 6 H, CH_3CH_2); mass spectrum, m/e 306 (M^+), 236 (M^+ − CHCH=CHOCH$_3$), 71 ($M^+ - EtO_2CCPhCO_2Et$); high resolution mass spectrum, calcd for $C_{17}H_{22}O_5$ 306.14685, found 306.1451. The regioisomer **6b** was obtained as a mixture containing 33% of **3d**: bp 117–119 °C/0.1 mm; ^1H NMR δ 7.37 (m, 5 H, Ph), 5.87–4.93 (m, 3 H, CH=CH_2), 4.20 (obscured, 4 H, CH_3CH_2O) 4.20 (obscured, 1 H, CH_3OCHCH=), 3.27 (s, 3 H, CH_3O), 1.23 (t, J = 7 Hz, 6 H, CH_3CH_2). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found (for a 2.6:1 mixture of **3d:6b**): C, 66.79; H, 7.35.

Reaction of 3-Chloro-1-methoxypropene with Butyllithium. To a 20-mL (12 mmol) ethereal aliquot of 3-chloro-1-methoxypropene was added butyllithium (12 mmol, 8.11 mL of a 1.48 M solution in hexane) at −78 °C. After 0.5 h at −78 °C, the mixture was warmed to room temperature over 0.5 h. The mixture was washed sequentially with water (twice) and then brine. The organic solution was dried over $MgSO_4$ and filtered and then reduced in volume by rotatory evaporation to give 0.86 g (52%) of a hexane-contaminated oil. ^1H NMR showed the characteristic absorptions for (*E*)-1-methoxyheptene: δ 6.27 (d, J = 12 Hz, 1 H), 4.72 (dt, J = 12, 7 Hz). The characteristic pattern of a terminal vinyl group was seen between δ 6.00 and 4.92. The

(22) Prepared from thiosalicylic acid according to Clinton, R. O.; Laskowski, S. C. *J. Am. Chem. Soc.* **1948**, *70*, 3135.

ratio of enol ether to 3-methoxyheptene was 1:1. Additional purification was not attempted.

Preparation of 1-Methoxy-1,3-bis(phenylthio)propane. To (*E*)-1-methoxy-3-(phenylthio)propene (0.30 g, 1.67 mmol) in 5 mL of methylene chloride was added thiophenol (0.35 mL, 3.4 mmol). Then methansulfonic acid (0.04 mL, 0.6 mmol) was added dropwise. The solution was stirred for 2 h in an ice bath at 0 °C. After stirring, the solution was quenched with an excess of triethylamine (0.09 mL, 0.63 mmol). The methylene chloride was then removed by rotatory evaporation and 15 mL of ether was added. The solution was then washed sequentially with 15 mL of water, 15 mL of 10% NaOH (twice), and 15 mL of brine. The ether solution was dried over calcium chloride, filtered, and reduced by rotatory evaporation. Kugelrohr distillation (201 °C/3 mm) gave 0.281 g of a clear thick oil (58%): ^{1}H NMR (CCl_4, δ) 7.17 (m, 10 H, 2 PhS), 4.70 (t, J = 6 Hz, 1 H, $CHOCH_3$) 3.4 (s, 3 H, $CHOCH_3$), 2.64 (t, J = 8 Hz, 2 H, $C_6H_5SCH_2$), 1.87 (q, J = 6 Hz, 2 H, SCH_2CH_2); IR (neat, cm^{-1}) 1587, 1470 (Ph), 1433 (CH_3), 1099 (C-O), 739, 690 (SPh). Anal. Calcd for $C_{16}H_{18}S_2O$: C, 66.16; H, 6.26. Found: C, 65.83; H, 6.05.

Preparation of 1,1-Dimethoxy-3-(phenylthio)propane. To (*E*)-1-methoxy-3-(phenylthio)propene (0.30 g, 1.67 mmol) in 25 mL of methanol was added methanesulfonic acid (0.04 mL, 0.6 mmol) dropwise. The solution was stirred for 21 h and then quenched with triethylamine (0.09 mL, 0.63 mmol). Methanol was then removed by rotatory evaporation and 20 mL of ether was added. The ether solution was washed twice with 20 mL of water and then dried over calcium chloride and filtered. The ether was removed by rotatory evaporation. Kugelrohr distillation (120 °C/3 mm) gave 0.289 g of clear oil (81%): ^{1}H NMR (CCl_4, δ) 7.23 (m, 5 H, C_6H_5S), 4.40 [t, J = 6 Hz, 1 H, $CH(OCH_3)_2$], 3.23 [s, 6 H, $CH(OCH_3)_2$], 2.87 (t, J = 8 Hz, 2 H, $C_6H_5SCH_2$-), 1.90 (dt, J = 6, 8 Hz, 2 H, $-SCH_2CH_2-$); IR (neat, cm^{-1}) 1587, 1477 (Ph), 2439 (CH_3), 1122, 1071 (C—O), 739, 690 (SPh). Anal. Calcd for $C_{11}H_{16}SO_2$: C, 62.22; H, 7.61. Found: C, 62.44; H, 7.33.

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1-Methoxyisobenzofuran from Base-Induced and Acid-Catalyzed Reactions of 1,3-Dihydro-1,3-dimethoxyisobenzofuran

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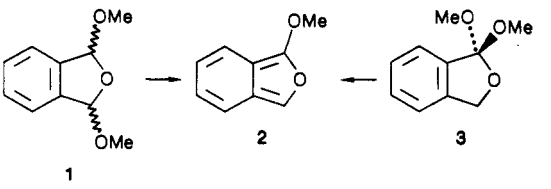
The title bis acetal (1) has been used in both acid-catalyzed and strong base induced procedures to generate 1-methoxyisobenzofuran (2). The acid-catalyzed reaction is not synthetically useful, since it requires forcing conditions and gives cycloadduct only with very reactive dienophiles (e.g., maleic anhydride). However, the $LiNR_2$-induced 1,4-elimination reaction of 1 yields isolable solutions of 2. This process is strongly solvent-dependent, being more rapid in THF than in diethyl ether, and very slow in hexane. The elimination exhibits syn selectivity in ether solvent, allowing the recovery of unreacted 1 enriched in the cis isomer. However, cis 1 also undergoes base-induced elimination to form 2, showing that an anti elimination pathway, although not favored, is energetically accessible. The utility of the base-induced method was demonstrated by the formation of the 3-lithiated derivative of 2, which was in turn converted to 1-methoxy-3-(trimethylsilyl)isobenzofuran. This derivative gave cycloadducts upon treatment with the dienophiles *N*-methylmaleimide and benzyne, the latter generated by dehydrohalogenation of bromobenzene.

Ortho esters such as **3** are useful precursors of 1-alkoxyisobenzofurans (e.g. **2**), in both acid-catalyzed[2,3] and base-induced[3,4] procedures. The 1-alkoxyisobenzofurans are generated as reactive intermediates under acidic conditions, while the base-induced method allows the preparation of solutions of **2** which have at least modest stability at ambient temperature.[5]

We were interested in exploring possible complementary approaches to **2** from the bis acetal **1**. In this paper we describe both acid-catalyzed and $LiNR_2$-induced reactions of **1**, which show that the conversion to **2** can occur. The acid-catalyzed reaction, although of mechanistic interest, appears to have little synthetic value. The base-induced procedure is more useful and also exhibits solvent-dependent stereoselectivity in the 1,4-elimination under certain conditions.



(1)

Results and Discussion

(a) Preparation of 1 and Identification of Stereoisomers. The substrate **1** was prepared by treatment of *o*-phthalaldehyde in methanol with an acid catalyst. This procedure resulted in the formation of the cyclic bis-acetal **1** along with a small amount of the less volatile acyclic bis-acetal, easily separated by vacuum distillation. The desired product **1** is a mixture of cis(meso) and trans (±) isomers **1c** and **1t**, as shown by the ^{1}H NMR spectrum, which exhibited distinctive singlets at 6.04 (major) and 6.3 ppm (minor isomer), with other features being very similar

(1) Formerly known as B. Mir-Mohamad-Sadeghy
(2) Contreras, L.; Slemon, C. E.; MacLean, D. B. *Tetrahedron Lett.* **1978**, 4237. See also: Contreras, L.; MacLean, D. B.; Faggiani, R.; Lock, C. J. L. *Can. J. Chem.* **1981**, *59*, 1247.
(3) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 2734.
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(5) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 1477.

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