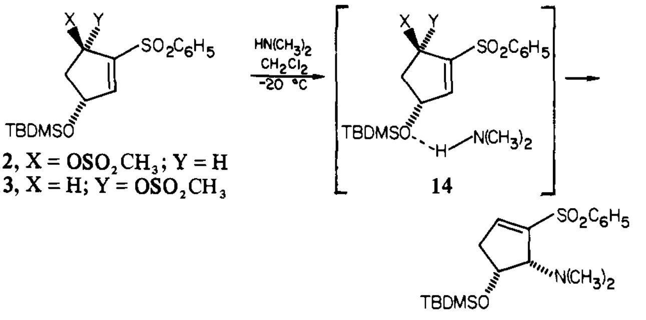

12, X = OSO_2CH_3; Y = H
13, X = H; Y = OSO_2CH_3

14

15 (92%)

Apparently the silyloxy group is facilitating a directed addition via intermediate **14** in this polarized S_N2' Lawton-type reaction.[13,14] Conversion of **15** to *d*-**2** (98%) was accomplished as previously described,[2] thus affording an overall yield of 46% from the "unnatural" enantiomer *l*-**1**.

We also find that the enantiomeric sulfide alcohols *l*-**1** and *d*-**1** serve as superb starting materials for providing a pair of enantiomeric cross-conjugated epoxy vinyl sulfones in the context of a separate project directed toward the synthesis of lathrane-type diterpenes.[15] For example, treatment of sulfone alcohol **10** with diisopropylethylamine (1.1 equiv) in the presence of methanesulfonyl chloride (1.2 equiv) in methylene chloride affords the crystalline mesylate *l*-**16** [mp 131-132 °C; $[\alpha]^{25}{}_D$ -148° (*c* 2.00, $CHCl_3$), 89%].[7] Reaction of *l*-**16** with solid sodium hydroxide (3 equiv) cleanly effects β elimination of the mesyloxy group to generate the epoxy vinyl sulfone *l*-**17** [mp 118-120 °C, $[\alpha]^{25}{}_D$ -30° (c 1.50, $CHCl_3$), 89%).[7] The enantiomeric epoxy vinyl sulfone *d*-**17** may also be simply prepared from the same sulfide alcohol *l*-**1** (Scheme II). Alcohol-directed epoxidation[2] affords an epoxy alcohol which upon treatment with methanesulfonyl chloride and diisopropylethylamine produces mesylate *l*-**18** [mp 168-171 °C, $[\alpha]^{25}{}_D$ -39.5° (*c* 2.00, $CHCl_3$), 77%].[16] Conversion of *l*-**18** to *d*-**17** [mp 119-121 °C, $[\alpha]^{25}{}_D$ +29° (*c* 2.00, $CHCl_3$), 94%] via β elimination was accomplished by treatment with excess aqueous 10% sodium hydroxide solution. Naturally, application of the same series of reactions on the enantiomeric sulfide alcohol *d*-**1** ultimately also affords the chiral epoxy vinyl sulfones *d*-**17** and *l*-**17** in an enantioconvergent[9] manner (*d*-**1** → *d*-**16** → *d*-**17**; *d*-**1** → *d*-**18** → *l*-**17**).[15]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (PRF 9941 AC-1, 11617-AC1). We also thank the National Institutes of Health for their generous support of this research (CA-19689, Ca-21840). The ^{13}C NMR used in this investigation was obtained on the departmental CFT-20 instrument provided by NSF Grant 7842. We thank the Purdue University Biological Magnetic Resonance Laboratory for access to the 360-MHz ^1H NMR spectrometer (NIH RR01077).

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(13) For a discussion of the effects of leaving group stereochemistry in the normal S_N2' reaction, see R. M. Magid, *Tetrahedron*, **36**, 1901 (1980), and references contained therein.

(14) For S_N2' reactions of polarized olefins, see (a) S. Mitra and R. G. Lawton, *J. Am. Chem. Soc.*, **101**, 3097 (1979); (b) D. J. Dunham and R. G. Lawton, *ibid.*, **93**, 2074 (1971). See also: (c) R. D. Clark, *Synth. Commun.*, **9**, 325 (1979); (d) R. H. Wollenberg, *Tetrahedron Lett.*, **21**, 3139 (1980); (e) A. B. Smith, III, B. A. Wexler, and J. S. Slade, *Tetrahedron Lett.*, **21**, 3237 (1980). (f) N. H. Cromwell, D. S. Soriano, and E. Doomes, *J. Org. Chem.*, **45**, 4983 (1980); (g) T. Takahashi, K. Hori, and J. Tsuji, *Tetrahedron Lett.*, **22**, 119 (1981).

(15) See J. C. Saddler, P. L. Fuchs, *J. Am. Chem. Soc.*, following paper in this issue for the use of these chiral cross-conjugated epoxyvinyl sulfones.

(16) The relatively poor yield (77%) of mesylate *l*-**18** simply reflects the ease of the *l*-**18** → *d*-**17** transformation. Simply treating crude mesylate *l*-**18** with sodium hydroxide affords an overall yield of 87% from the epoxy alcohol.

Enantiospecific Syntheses of γ-Substituted Enones: Organometallic S_N2' Conjugate-Addition Reactions of Epoxy Vinyl Sulfones[1]

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Received December 1, 1980

We have previously shown that γ-oxygenated vinyl sulfones **1a**,**b**, (R^1 = H) can serve as doubly charge-inverted ynone synthons (**2**).[2] The key reaction involves the conjugate addition of "hard" anions ($pK_a > 25$), such as organolithium species, to vinyl sulfones to yield an α-sulfonyl stabilized anion which is further alkylated in situ. Oxidation of the adducts followed by β elimination of the phenylsulfinic acid affords α,β-difunctionalized enones **3** (R^1 = H) in very good overall yields (Scheme I).[2]

In the context of our efforts directed toward the total synthesis of Lathrane-type diterpenes (**16**–**18**), we sought to extend this strategy to provide for the enantiospecific incorporation of an additional alkyl moiety (R^1) in the γ position of enone **3**. The specific reaction required involves the S_N2' conjugate-addition reaction of an organometallic species with epoxy vinyl sulfone **4a** (formally a *triply* charge-inverted ynone synthon **5**).

Initial experiments directed toward this goal were not especially encouraging. Treatment of racemic **4a**[3] with methyllithium (1.0 equiv) in THF at -78 °C afforded a mixture of three products after aqueous workup: γ-sulfonylcyclopentenone (**7**)[4,5] (presumably via [1,5] hydrogen migration on the intermediate **6** resulting from γ deprotonation of vinyl sulfone **4a**) as well as a mixture of the conjugate-addition products **8** and **9** in a 4:1 ratio (Scheme II).[4] Additional experimentation revealed that the unwanted deprotonation reaction could be completely avoided and that the relationship between the entering organometallic reagent and the newly forming allylic alcohol moiety could be established in a stereocontrolled fashion. For example, reaction of chiral epoxy vinyl sulfone *l*-**4a**[3] with methyllithium (1.05 equiv) in the presence of lithium perchlorate[6] in a 1:1 mixture of methylene chloride and diethyl ether at -78 °C for 20 min cleanly affords a 95:5 mixture of *d*-**8**/*d*-**9** [$[\alpha]^{25}{}_D$ = +48.5° (*c* 2.25, $CHCl_3$), 81%].[4,7,8] Alternatively, addition of trimethylaluminum (1.5 equiv in hexane) to a -78 °C suspension of methylcopper (1.5 equiv) followed by epoxy vinyl sulfone *l*-**4a** and slowly warming the reaction to 0 °C over 20 min affords the *anti*-allyl alcohol *d*-**9** [$[\alpha]^{25}{}_D$ +88° (*c* 2.76, $CHCl_3$), 80%] uncomtaminated with the *syn*-allyl alcohol *d*-**8** within the limits of detection.[4,7,8] Repetition of the last two reactions with the equally readily available dextrorotatory enantiomer of epoxy vinyl sulfone **4a**[3] naturally affords the enantiomers of **8** and **9** (*d*-**4a** → [A] → *l*-**8**; *d*-**4a** → [B] → *l*-**9**). The stereochemical results obtained with these two reactions suggest

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† Graduate Research Associate; David Ross Fellow, 1978-1980; Texaco Fellow, 1980-1981.

‡ A. P. Sloan Fellow, 1977-1979.

(1) Syntheses via vinyl sulfones. 7. For paper 6 see ref 3.

(2) (a) P. C. Conrad and P. L. Fuchs, *J. Am. Chem. Soc.*, **100**, 346 (1978); (b) J. C. Saddler, P. C. Conrad, and P. L. Fuchs, *Tetrahedron Lett.*, 5079 (1978).

(3) J. C. Saddler, R. E. Donaldson, and P. L. Fuchs, *J. Am. Chem. Soc.*, preceding paper in this issue.

(4) All new compounds exhibit satisfactory ^1H NMR, ^{13}C NMR, mass, exact mass spectra refer to isolated material of >95% purity.

(5) Although γ-sulfonylcyclopentenone (**7**) and hydroxy dienyl sulfone (**10**) are undesired side products in the context of the study described in this paper, they represent highly functionalized intermediates of obvious synthetic potential. Both **7** and **10** can easily be prepared [**4a** + $(C_2H_5)_3N/(C_2H_5)_3N \cdot HCl/CH_2Cl_2$ → **7**, 65%; **4b** + LDA/THF/-78 °C → **10**, 50%].

(6) E. C. Ashby and S. A. Noding, *J. Org. Chem.*, **44**, 4371 (1979).

(7) MnO_2 oxidation of the 95% pure *d*-**8** yields an enone [$[\alpha]^{25}{}_D$ -8.7° (*c* 0.70, $CHCl_3$) identical in all respects, except sign of rotation, with that derived from the more pure *d*-**9** [$[\alpha]^{25}{}_D$ +9.3° (c 0.70, $CHCl_3$)].

(8) The relative stereochemistries of **8**, **9**, and **11**, **12** were assigned by europium shift studies.

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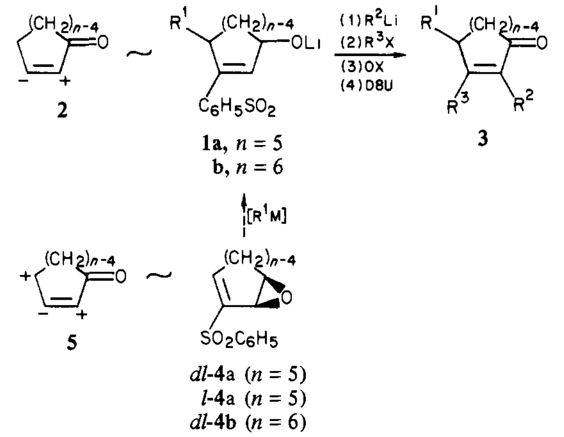
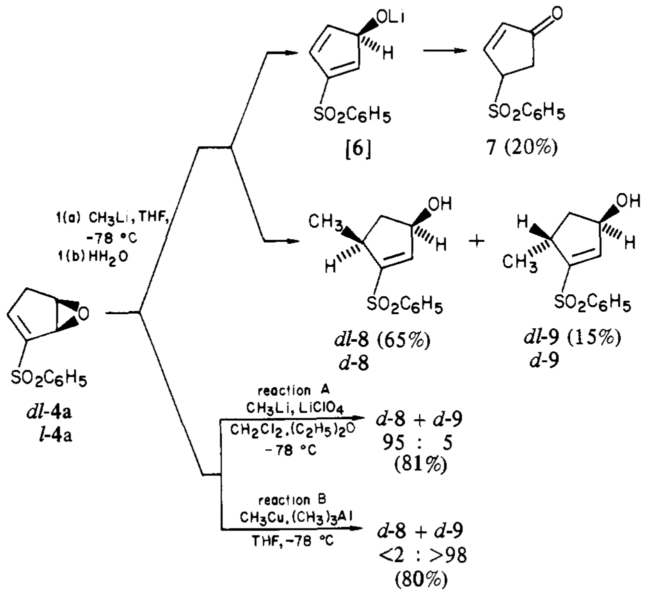
Scheme I



Scheme II



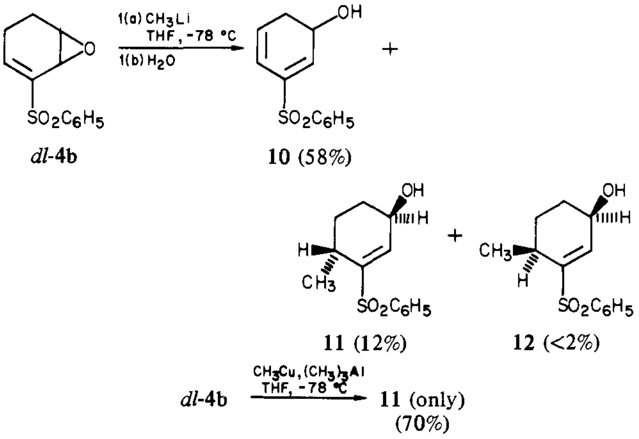
that in noncoordinating solvents (reaction A), methyllithium is undergoing a directed addition via chelation to either the epoxide or possibly an epoxide–lithium perchlorate complex,[6] whereas with the methylcopper/trimethylaluminum reaction (reaction B), presumably a highly THF-solvated epoxide–trimethylaluminum complex is formed which presents no opportunity for coordination with the methylcopper, and addition to the less sterically encumbered α face ensues.

The homologous six-membered cross-conjugated epoxy vinyl sulfone *dl*-**4b**[9] was investigated less extensively. With this substrate the γ-deprotonation reaction was an even more severe problem under the methyllithium/THF conditions, yielding a 5:1 mixture of dienyl alcohol **10**[4,5] and *trans*-δ-methyl allyl alcohol **11** (Scheme III).[4,8] *cis*-δ-Methyl allyl alcohol **12** was not present, within the limits of detection (360-MHz ^{1}H NMR).[8,10] Treatment of **4b** under the conditions of reaction A provided a complex mixture of products in which **10** was still the major species present. Reaction B was far more successful, affording only allyl alcohol **11** to the complete exclusion of the deprotonation product **10**.[11]

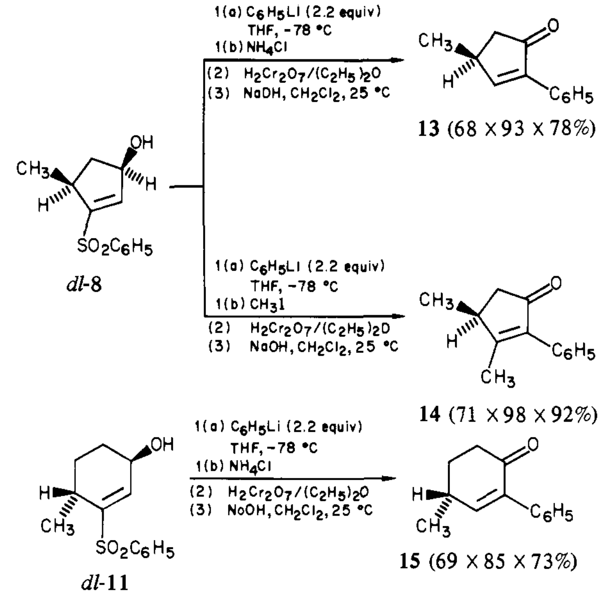
Racemic substrates **8** and **11** could be easily converted to enones **13**–**15** by using essentially the procedure originally developed for the parent γ-hydroxy vinyl sulfones (Scheme IV).[2]

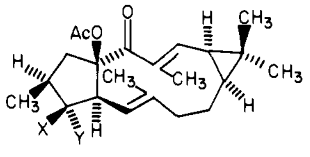
Having demonstrated the viability of cross-conjugated epoxy vinyl sulfones **4a,b** as triply charge-inverted ynone synthons in simple systems (**13**–**15**), we next turned our attention to the lathrane-type diterpenes jolkinol C (**16**),[12] jolkinol D (**17**),[12] and bertyadionol D (**18**).[13]

Scheme III

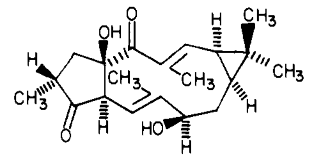


Scheme IV





16, X = Y = O
17, X = OH; Y = H



18

One potential entry to these systems, as outlined for jolkinol C (**16**), could be via an intraannular, enolate-promoted 1,4-fragmentation reaction of tetracyclic **19** (Scheme V).[14] Access to **19** (through enone **20**) would then require the union of the two chiral pieces **21** (*l*-**9** as its monolithium salt) and dithioacetal anion **22**.

Preparation of dithioacetal reagent **22** was easily accomplished. The chiral aldehyde **23**[15] (97.5 mmol) was dissolved in liquid sulfur dioxide (270 mL) at -45 °C and treated with dry gaseous HCl for 20 min. The sulfur dioxide was allowed to evaporate to afford

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[9] See ref 3, footnote 8.

[10] Oxidation of **11** by the method of Brown [H. C. Brown, C. P. Garg, and K. Liu, *J. Org. Chem.*, **36**, 387 (1971)] yields 4-methyl-3-(phenylsulfonyl)cyclohex-2-en-1-one (89%) which affords a 1:6 mixture of **11** and **12** upon DIBAL reduction.

[11] Tris(phenylthio)boron also served equally well as Lewis acid in place of trimethylaluminum in the **4b** → **10** reaction.

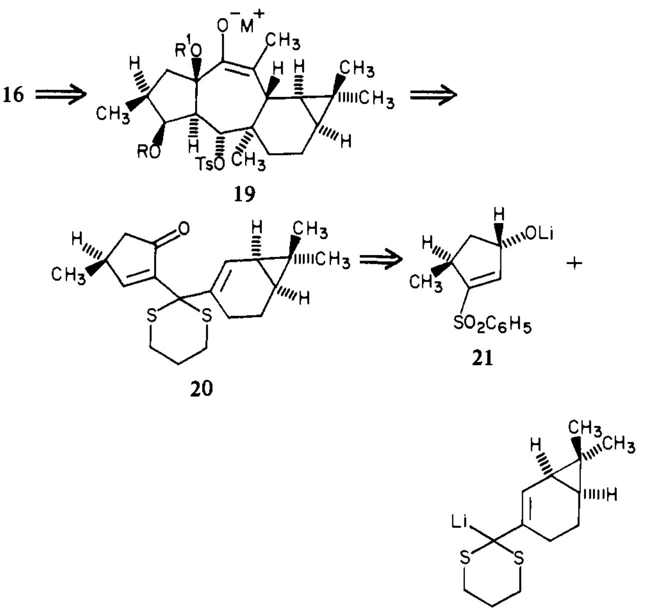
[12] D. Uemara, K. Nobuhara, Y. Nakayama, Y. Shizuri, and Y. Hirata, *Tetrahedron Lett.*, 4593 (1976).

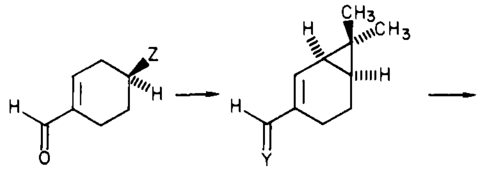
[13] E. L. Ghisalberti, P. R. Jerreries, and R. F. Toia, *Tetrahedron*, **34**, 233 (1978).

[14] D. A. Clark and P. L. Fuchs, *J. Am. Chem. Soc.*, **101**, 3567 (1979).

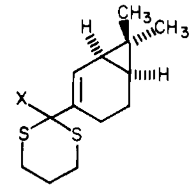
[15] L. A. Champon and Co. Ltd: $[\alpha]^{25}_{D}$ -121° (c 10.0, CHCl$_3$).

Scheme V

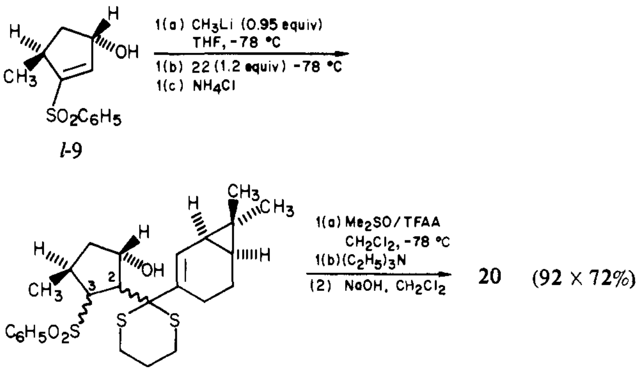




23, $Z = CCH_3{=}CH_2$ 25, Y = 0
24a, $Z = C(CH_3)_2Cl$ 26, $Y = S(CH_2)_3S$
b, $Z = C(CH_3)_2Br$



26a, X = H
22, X = Li
26b, X = D



20 (92 x 72%)

27 (65%)

a quantitative yield of "crude" chloride **24a**[4,16] as a colorless oil. Tertiary halide **24a** was not further purified but dissolved in THF and added to a suspension of potassium *tert*-butoxide (107 mmol) in THF at 0 °C to afford a 94% yield of cyclopropyl aldehyde **25** $[[\alpha]^{25}_{\mathrm{D}}$ +120° (*c* 1.50, $CHCl_3$)].[4,17] Aldehyde **25** had been previously prepared (41% yield) in an analogous manner from the very labile tertiary bromide **24b** by Büchi.[17] Treatment of **25** with 1,3-propanedithiol in the presence of a catalytic amount of boron trifluoride etherate (0.08 equiv) in methlene chloride produced dithiane **26a**[4] $[[\alpha]^{25}_{\mathrm{D}}$ +26° (*c* 2.0, $CHCl_3$)] in 68% yield after purification by plug filtration on silica gel. Reaction of **26a** in THF at -78 °C with *n*-butyllithium for 1 h smoothly afforded anion **22** as evidenced by CH_3OD quenching studies to yield **26b** (90%).

Treatment of *l*-**9** in THF at -78 °C with methyllithium (0.95 equiv) affords a solution of **21** which is further reacted with **22** (1.2 equiv) and quenched with ammonium chloride to provide a 65% yield of sulfone alcohol **27** after chromatographic purification[4,18] (stereochemistry at C-2 and C-3 undefined). Swern oxidation[19] and base treatment then affords chiral enone $[[\alpha]^{25}_{\mathrm{D}}$ -48° (*c* 1.65, $CHCl_3$)].[4,20]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research (11617-AC1). The ^{13}C NMR used in this investigation was obtained on the departmental CFT-20 instrument provided by NSF Grant 7842. We thank the Purdue University Biological Magnetic Resonance Laboratory for access to the 360-MHz ^1H NMR spectrometer (NIH RR01077).

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[16] Olefin **25** was inert to HCl addition in numerous other solvents.

[17] G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Am. Chem. Soc.*, **91**, 6473 (1969). $[[\alpha]^{25}_{\mathrm{D}}$ 108° (*c* 4.0, $CHCl_3$)].

[18] A small amount (ca. 15%) of γ addition of heteroallyl anion **22** to vinyl sulfone **21** is also observed in this reaction.

[19] S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.*, **41**, 3329 (1976).

[20] Reaction of *dl*-**9** with chiral **22** followed by oxidation and elimination affords a mixture of enones which are diasteromeric at the γ-methyl position $[[\alpha]^{25}_{\mathrm{D}}$ 1.0° (*c* 0.95, $CHCl_3$)]. The only spectral characteristic which is diagnostic of this mixture is the quaternary vinyl carbon on the six-membered ring which can be observed in the ^{13}C NMR spectra. In the diastereomeric mixture this carbon appears as 1:1 pair of singlets at 134.9 and 134.7 ppm, while chiral enone **20** only exhibits the higher field peak. Control studies demonstrate that γ epimerization does not occur under the basic conditions necessary to β eliminate the phenylsulfinic acid in the synthesis of enone **20**.

Reaction of Allylically Substituted Enolates with Organometallic Reagents: A Convenient Source of Enolonium Ion Equivalents

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Received December 22, 1980

The importance of the enolate group in organic synthesis is largely attributable to its considerable service as a nucleophile in carbon–carbon bond-forming reactions.[1] We describe herein a new chemistry for allylically substituted enolates in which their classical role as a nucleophile in such reactions is reversed to that of an electrophile through a change only in reaction conditions.

The present study emerged from our interest in effecting the conversion of an α,β-epoxy ketone to an α-alkyl-β-hydroxy ketone, as generalized by **1** → **2** (Scheme I), with a starting substrate[2] whose attendant functionality attenuated the effectiveness of reductive alkylation methodology[3] and precluded the use of

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[†] A. P. Sloan Foundation Fellow, 1979–1981; Camille and Henry Dreyfus Teacher-Scholar Award Recipient, 1980–1985.

[1] d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979. House, H. O., "Modern Synthetic Reactions", W. A. Benjamin: Reading, MA, 1972; p 492 ff.

[2] Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 6340.

[3] (a) Szajewski, R. P. *J. Org. Chem.* **1978**, *43*, 1819. (b) McChesney, J. D.; Wypalek, A. F. *J. Chem. Soc., Chem. Commun.* **1971**, 542.