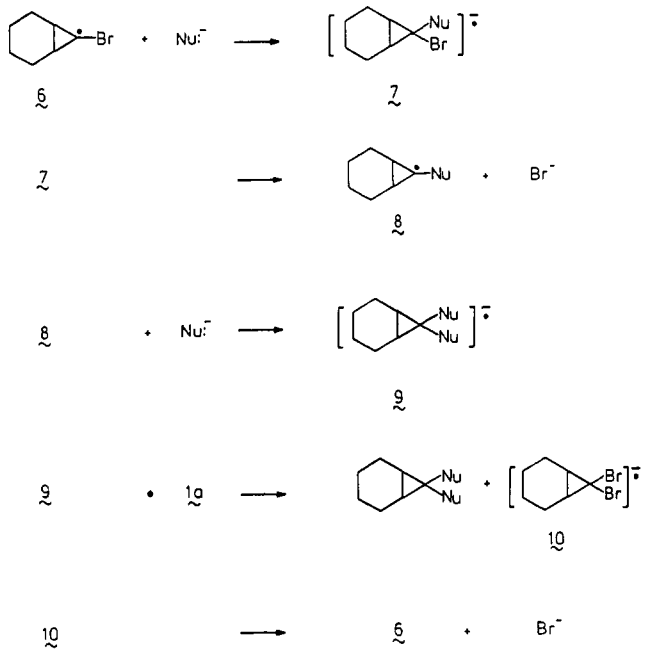
Scheme I



The initiation and termination steps are not clear. One possibility for initiation is photolytic cleavage of a C–Br bond. Compounds **1a**, **1i**, and **1j** all have weak tailing absorptions near the wavelengths of irradiation. Another possibility is an electron transfer from the nucleophile to the halo compound in much the same way as has been suggested for aryl halides.[4,8]

The proposed chain mechanism accommodates the inhibition of the reaction by Tempo and the phenomenon of photostimulation. An efficient intramolecular electron transfer and fragmentation, converting **7** → **8**, also accords with the fact that monosubstituted products were not found in the reaction mixtures.

An analogous chain mechanism with fewer propagation steps is consistent with the experimental data from **1i** and **1j**.

Acknowledgment. Support by the Australian Research Grants Scheme and the University of Adelaide Special Research Grants Program is gratefully acknowledged.

Registry No. **1a**, 2415-79-4; **1b**, 58681-16-6; **1e**, 91842-48-7; **1h**, 91842-51-2; **1i**, 1121-40-0; **1j**, 1121-41-1; **11**, 91842-52-3; (*Z*)-**3**, 91842-49-8; (*E*)-**3**, 91842-50-1.

(8) Hoz, S.; Bunnett, J. F. *J. Am. Chem. Soc.* **1977**, *99*, 4690–99.
(9) The possibility that the substitution of the *second* bromine occurs by an elimination–addition process cannot be excluded on the basis of the present data.

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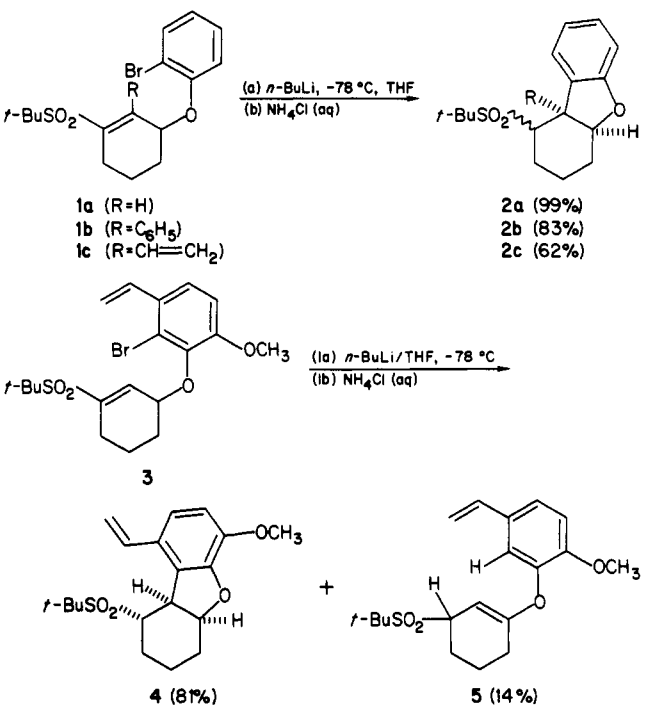
Tandem Intramolecular Conjugate Addition/Intramolecular Alkylation Reactions of Substituted Vinyl Sulfones

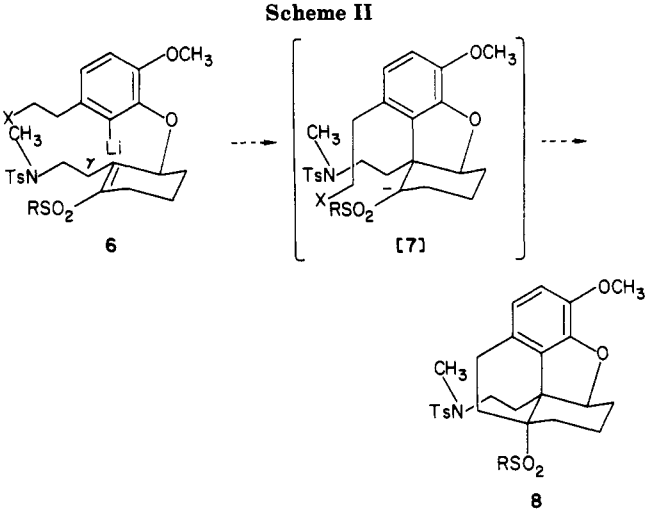
Summary: The title process can successfully be used to construct polycyclic ring systems.

Sir: In connection with our synthetic program it became desirable to develop a method to effect the intramolecular

Scheme I



Scheme II

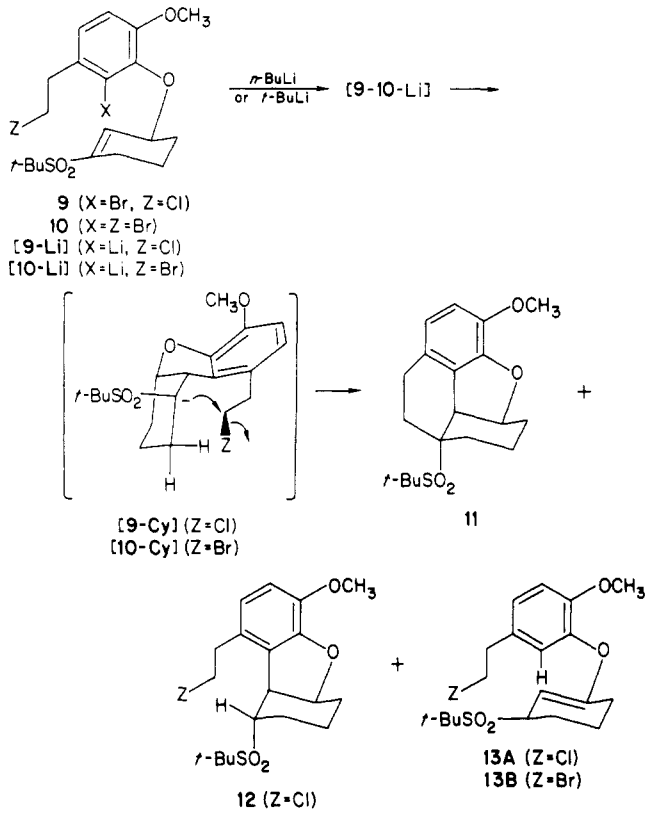


conjugate addition of aryloxy anions to β-functionalized vinyl sulfones.[1] In order to test this concept a series of three vinyl sulfones **1a–c** were prepared[2–4] and subjected to transmetalation with *n*-butyllithium in THF at −78 °C, (Scheme I). Quenching the resulting α-sulfonyl anion after 15 min at −78 °C efficiently produces the tricyclic adducts **2a–c** as a diastereomeric mixture at the sulfone center.[4–6]

(1) Syntheses via Vinyl Sulfones. 12. For paper 11, see, R. E. Donaldson, J. C. Saddler, S. Byrn, A. T. McKenzie, and P. L. Fuchs, *J. Org. Chem.*, 48, 2167 (1983). Morphine Support Studies. 4. For previous papers in this series see (a) D. L. Barton, P. C. Conrad, and P. L. Fuchs, *Tetrahedron Lett.*, **21**, 1811 (1980); (b) J. Ponton, P. Helquist, P. C. Conrad, and P. L. Fuchs, *J. Org. Chem.*, **46**, 118 (1981); (c) P. R. Hamann and P. L. Fuchs, *J. Org. Chem.*, 48, 914 (1983).
(2) Syntheses of **1a–c** and **3** were smoothly accomplished by S_N2 displacement of the γ-mesyloxy vinyl sulfones with lithium *o*-bromophenolate in NMP or by Mitsunobu [*Synthesis*, 1 (1981)] coupling of the γ-hydroxy vinyl sulfones with *o*-bromophenol.[3,4]
(3) Synthesis of 2-bromo-3-styryl-6-methoxyphenol was effected in 49% overall yield from isovanillin by bromination/protection as the MOM-aryl ether/phase-transfer Wittig/deprotection.[4]
(4) The experimental procedure for these compounds will be fully described in a subsequent full paper.
(5) All new compounds have been fully characterized by NMR, ^{13}C NMR, exact mass, and/or combustion analysis.

0022-3263/84/1949-3865$01.50/0

Scheme III

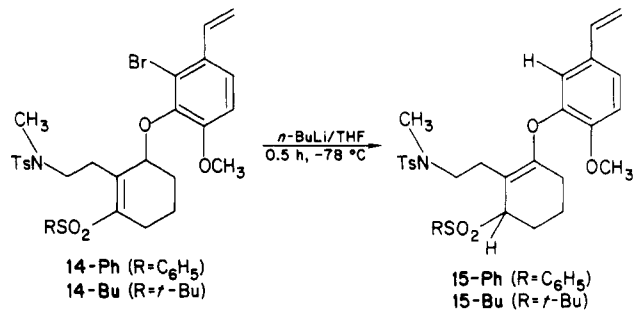


Similar transmetalation of the more highly functionalized γ-aryloxy vinyl sulfone **3**[2-5] afforded a mixture of the expected furan derivative **4** (81%) contaminated with the debrominated, deconjugated allyl sulfone **5** (14%). Although we had not previously observed any deconjugation product analogous to **5**, the full significance of this observation was soon to become highly apparent.

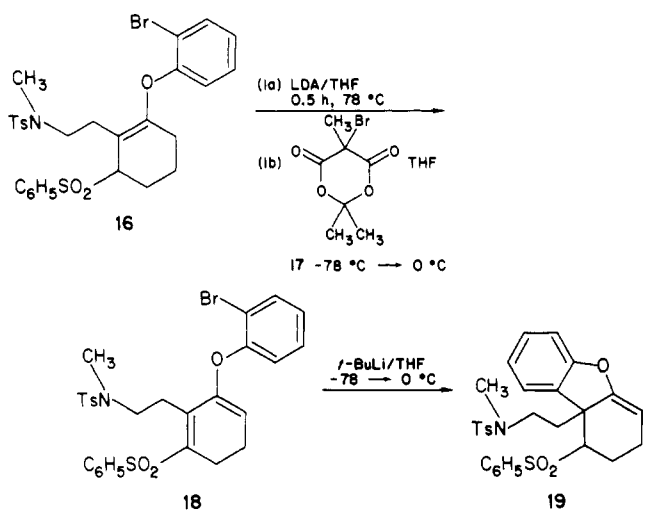
Armed with the above results we wished next to answer two basic questions: Could this reaction be employed when the substituent at the β position of the vinyl sulfone bore acidic γ-hydrogens as well as a δ leaving group [cf. **6**] and whether the intermediate α-sulfonyl anion [**7**] produced in such an addition could be made to suffer further intramolecular alkylation[7] (Scheme II) to directly yield tetracyclic material [**8**]?

Before addressing the key reaction of the β-substituted substrate **6**, it was deemed prudent to ascertain the scope and limitations of the tandem intramolecular conjugate addition/intramolecular alkylation reaction with simpler (β-hydrogen) systems.[8] To that end, transmetalation of the β-haloethyl-substituted vinyl sulfones **9** and **10** with 2 equiv of *tert*-butyllithium[13] at −78 °C followed by quenching of the reaction after 5 min provided a useful contrast (Scheme III). In the case of the β-chloroethyl substrate **9**, a pair of products in the ratio of 3:1 were isolated in 91% yield after purification. The major product was shown to be the *mono*cyclized β-chloroethyl sulfone **12** (69%), while the minor product was the deconjugated

Scheme IV



Scheme V



enol ether **13A** (23%). The complementary reaction of the β-bromoethyl substrate **10** afforded a 73% yield of the bis-cyclized product **11** along with deconjugated enol ether **13B** (and decomposition products derived therefrom). Warming the cold solution from the reaction of **9**, presumably containing intermediate [**9-Cy**], does afford a poor yield of the bis-cyclized adduct **11** in addition to a number of uncharacterized side products. This observation is in accord with our earlier observations in simpler systems regarding the intramolecular alkylation of (β-haloethyl) arenes with α-sulfonyl anions.[7]

With these results in hand it was time to examine changing cyclization reaction with a vinyl sulfone bearing alkyl substitution in the β position. Metalation of **14-Ph**[4,5,9] with *n*-butyllithium at −78 °C rapidly produced a new product in high yield (Scheme IV). Purification of this labile material on silica gel was always attended by substantial material loss, but a 55% yield of the deconjugated enol ether **15-Ph** could be isolated in one instance.[4,5,10]

(6) The yield of **2c** was somewhat reduced by isolation of 17% of starting material **1a** by the use of a nominal 0.9 equiv of *n*-butyllithium in this reaction; a deficiency of butyllithium was essential to prevent subsequent 1,6-addition of the butyl group to the dienyl sulfone moiety.

(7) J. Ponton, P. Helquist, P. C. Conrad, and P. L. Fuchs, *J. Org. Chem.*, **46**, 118 (1981).

(8) The phenols necessary for these reactions were prepared from the bromostyrene[3] in standard fashion. Synthesis of the two β-haloethyl-substituted, γ-aryloxy vinyl sulfones **9**[4,5] and **10**[4,5] from the γ-hydroxy vinyl sulfone and the two phenols was smoothly effected by the Mitsunobu coupling procedure (93–97%).

(9) Synthesis of **14-Ph** and **14-Bu** was accomplished as follows: Using the protocol of Piers,[9a] the monoanion of 1,5-dimethoxycyclohexa-1,3-diene was sequentially treated with *p*-toluenesulfonylaziridine,[9b] methyl iodide, and aqueous hydrochloric acid to afford a cyclohexane-1,3-dione bearing a β-sulfonyl amidoethyl group in the 2-position (82% overall yield).[4,5] Conversion of this material to its enol mesylate[9c] followed by addition–elimination with sodium benzenesulfinate (or *tert*-butyl thiolate followed by MCPBA oxidation) provided the corresponding β-sulfonyl enones. Dibal reduction followed by conversion to the mesylate and displacement with the lithium salt of bromostyrylphenol in NMP produced the γ-aryloxy, β-substituted vinyl sulfones **14-Ph** and **14-Bu**.[4,5] (a) E. Piers and J. R. Grierson, *J. Org. Chem.*, **42**, 3755 (1977); (b) M. Kojima, T. Kawakita, and K. Kudo, *Yakusaku Zasshi*, **92**, 465 (1970). [*Chem. Abstr.*, **77**:151711y]; (for a two-step procedure, see G. S. Bates and S. Ramaswamy, *Can. J. Chem.*, **58**, 716 (1980)); (c) C. J. Kowalski and K. W. Fields, *J. Org. Chem.*, **46**, 197 (1981).

(10) While the initial NMR of the crude reaction product shows this enol ether to be present in high yield, purification by chromatography on silica gel results in the formation of substantial amounts of the substituted phenol and enone which result from acid-catalyzed hydrolysis of the enol ether.

Deprotonation at the γ-aryloxy position was a result of >95% of *intramolecular* proton exchange from the initially formed aryl anion; this was unambiguously demonstrated by repeating the metalation reaction on a 1:1 mixture of labeled precursors.[4] Because it had been previously observed in acyclic cases that the deconjugation of *phenyl* vinyl sulfones is a more facile process than *tert-butyl* vinyl sulfones,[11] and because our previous successful intramolecular conjugate additions had all employed the *tert*-butyl sulfones, it was felt that the solution to the deconjugation problem might lie with substrate **14-Bu**.[4,5,9] Unfortunately, this was not the case; metalation of **14-Bu** with *n*-butyllithium also afforded the product of deconjugation, allyl sulfone **15-Bu**.[10] While it appears that the factors which control the fate of a β-substituted, transmetalated γ-aryloxy vinyl sulfone with regard to the intramolecular proton transfer remain to be more clearly defined, it seems likely that conformational factors at the aryloxy anion stage are of crucial importance.

It was postulated that *removing the acidic γ proton* by changing the hybridization at the γ position would circumvent the intramolecular deprotonation problem that currently plagues the above reaction. In order to test this hypothesis, γ-aryloxy allyl sulfone **16**[4,5] was sequentially treated with LDA (intentionally utilizing an intermolecular variant of the deprotonation which defeated the currently constituted sp^3-hybridized series), followed by brominating agent **17**,[12] to afford dienol ether **18** in 93% yield (Scheme V). Transmetalation of **18** with 1.1 equiv of *tert*-butyllithium[13] at −78 °C produced the sensitive tricyclic enol ether **19**[4,5,14] after silica gel chromatography (49% overall from **16**).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also thank the NIH (CA 19689) for partial support of this project. We thank the Purdue University Biological Magnetic Resonance Laboratory (NIH RR01077) for access to the 470-MHz ^1H NMR spectrometer and the NSF (CHE 80-04246) for a departmental grant for a Varian XL200 spectrometer. P.R.H. would also like to thank Purdue University and Texaco for graduate fellowships.

Registry No. **1a**, 91880-09-0; **1b**, 91880-10-3; **1c**, 91880-11-4; **2a** (isomer 1), 91880-12-5; **2a** (isomer 2), 91880-27-2; **2b** (isomer 1), 91898-08-7; **2b** (isomer 2), 91880-28-3; **2c** (isomer 1), 91880-13-6; **2c** (isomer 2), 91880-29-4; **3**, 91880-14-7; **4**, 91880-15-8; **5**, 91880-16-9; **9**, 91880-17-0; **10**, 91880-18-1; **11**, 91880-19-2; **12**, 91880-20-5; **13A**, 91898-09-8; **13B**, 91898-10-1; **14**-Ph, 91880-21-6; **14**-Bu, 91880-22-7; **15**-Ph, 91880-23-8; **15**-Bu, 91880-24-9; **16**, 91880-25-0; **18**, 91880-26-1; **19**, 91880-30-7.

† Graduate Research Associate.

(11) J. Hine and M. J. Skoglund, *J. Org. Chem.*, **47**, 4766 (1982) and references contained therein.

(12) (a) B. M. Trost and L. S. Melvin, Jr., *J. Am. Chem. Soc.*, **94**, 1790 (1972); (b) **98**, 1204 (1976); (c) J. P. Marino, *J. Chem. Soc., Chem. Commun.* 861 (1973).

(13) (a) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972); (b) D. Seebach, H. Neumann, *Chem. Ber.*, **107**, 847 (1974).

(14) Initial attempts to simply effect the metalation/bromination/elimination sequence on compounds derived from **9** or **10** did not proceed as smoothly as with **16**. Research in this area is under investigation.

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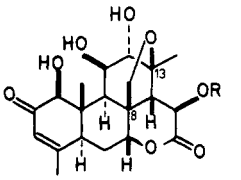
Synthetic Studies on Quassinoids: A Novel, General Method for the Elaboration of the C(8),C(13) Epoxymethano Bridge of Quassimarin

Summary: A novel, general method for the construction of the C(8),C(13) epoxymethano bridge of quassimarin and related quassinoids is described.

Sir: Our continuing interest in quassinoids[1] has led us to explore potential synthetic approaches to quassimarin (**1**) and related natural products [e.g., simalikalactone D (**2**)].

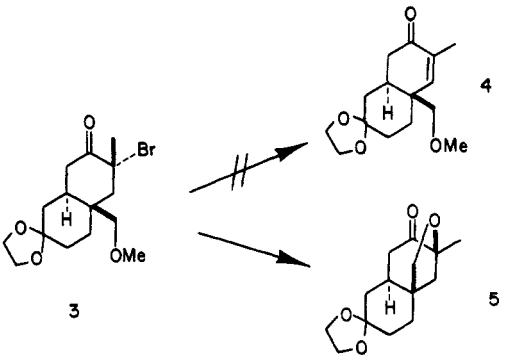


1 R = COC(OAc)(Me)Et

2 R = COCH(Me)Et

It was during the very early stages of our studies that we developed an efficient method for the construction of the C(8),C(13) epoxymethano bridge common to many naturally occurring quassinoids (cf. **1** and **2**).[2] We detail below the results of this investigation which have culminated in a general method for epoxymethano (ether) bridge formation.[3]

A few years ago in connection with an attempt to transform **3** into octalone **4**, bromo ketone **3**[4] was heated



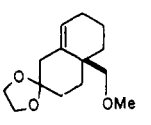
at 140 °C for 20 min in dimethylformamide containing lithium bromide and lithium carbonate. Under these standard conditions for dehydrobromination, less than 1%

(1) For previous work on quassinoids from our laboratory, see: Grieco, P. A.; Ferriño, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601. Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C.; Williams, E. *Tetrahedron Lett.* **1981**, *22*, 1071. Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 1022.

(2) For an excellent review on quassinoids, see: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

(3) Three other approaches for construction of the C(8),C(13) epoxymethano bridge of quassinoids have appeared in the literature: Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353.

(4) Bromo ketone **3** was prepared (50% overall) from the known octalin **i**[5] via a five-step sequence [(1) CrO_3·2Py, CH_2Cl_2; (2) LDA, THF, HMPA, −78 °C; MeI, 0 °C; (3) Li, NH_3, *t*-BuOH, −78 °C; (4) HMDS, Me_3SiI,[6] C_5H_{12}, −23 °C → 0 °C; (5) NBS, THF, −78 °C → 0 °C].



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