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 ^{1}H 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.

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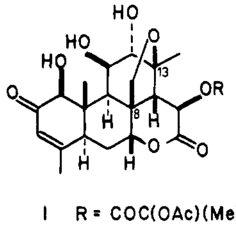
Synthetic Studies on Quassinoids: A Novel, General Method for the Elaboration of the C(8),C(13) Epoxymethano Bridge of Quassimarin

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**)].

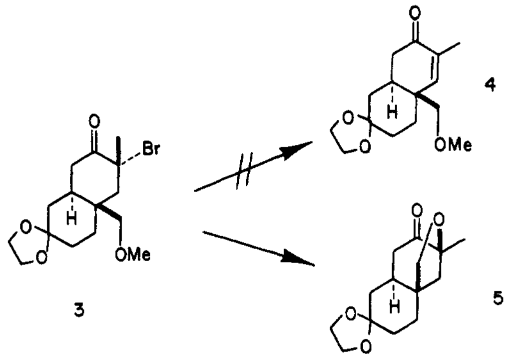


1 R = COC(OAc)(Me)Et

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%



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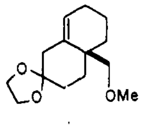
(1) For previous work on quassinoids from our laboratory, see: Grieco, P. A.; Ferriño, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601. Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C.; Williams, E. *Tetrahedron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

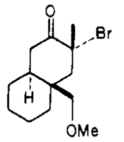
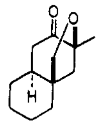
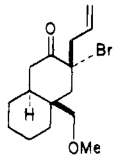
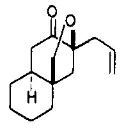
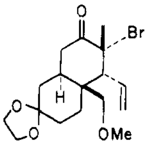
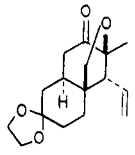
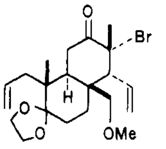
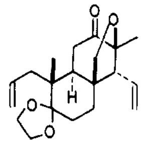
(4) Bromo ketone **3** was prepared (50% overall) from the known octalin **i**[5] via a five-step sequence [(1) $CrO_3 \cdot 2Py$, CH_2Cl_2; (2) LDA, THF, HMPA, −78 °C; MeI, 0 °C; (3) Li, NH_3, *t*-BuOH, −78 °C; (4) HMDS, Me_3SiI,[6] C_5H_{12}, −23 °C → 0 °C; (5) NBS, THF, −78 °C → 0 °C].



i

0022-3263/84/1949-3867$01.50/0

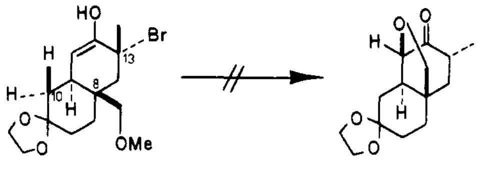
Table I. Epoxymethano Bridge Formation[a]

substrate	product	yield
 8[8]	 9	93%
 10[8]	 11	88%
 12[9]	 13	91%
 14[11]	 15	90%

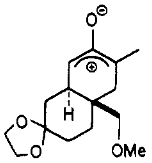
[a] All reactions were carried out at 140 °C for 20 min in DMF.

of octalone 4 was obtained. Much to our surprise, there was isolated in 79% yield a single crystalline compound, mp 97.5–98.5 °C, to which we have assigned structure 5. The structure of 5 follows from its IR [1720 cm^{-1}] and ^{1}H NMR spectra. Examination of the ^{1}H NMR (360 MHz) spectrum reveals, in addition to the lack of a methyl ether, the presence of a three-proton singlet at δ 1.18 and an AB quartet [J = 8.2 Hz, $\Delta\nu_{AB}$ = 193.8 Hz] centered at δ 3.87. The formation of the epoxymethano bridged decalone 5 does not require the presence of lithium bromide and lithium carbonate. The reaction proceeds in 95% yield when conducted in dimethylformamide for 20 min at 140 °C.

In the conversion of 3 into 5 which presumably proceeds via either 6 or the oxallyl cation 6a, the isomeric epoxymethano bridged compound 7 could not be detected. The formation of 7 from 6 sets up a 1,3-interaction between the incoming methoxy group and the β-oriented axial hydrogen at C(10). The transformation of 3 into 5 is most likely a solvolytic-like process in which the oxygen of the methoxymethyl group interacts with the incipient charge generated at the tertiary carbon bearing the bromine atom. It is unlikely that the reaction proceeds via direct backside displacement of bromide by the oxygen of the methoxymethyl group.[7]



6 7



6a

In order to probe the generality of the epoxymethano bridging reaction, we prepared the bromo ketones illustrated in Table I. All reactions were performed in DMF at 140 °C (20 min). Examination of the table reveals that yields range from 88% to 93%. Particularly noteworthy is the transformation of bromo ketone 14[11] into ketone 15, mp 176–177 °C, which proceeds in 90% yield. Ketone 15, which embodies the BCE ring system of quassimarin, constitutes a viable intermediate for conversion into quassimarin. Studies along these lines are currently in progress.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (CA28865) from the National Cancer Institute. The 360-MHz NMR instrument (Nicolet) used in the above studies was purchased in part through funds provided by the National Science Foundation (Grant No. CHE-81-05004).

Registry No. 1, 59938-97-5; 3, 91949-61-0; 4, 91949-62-1; 5, 91949-63-2; 8, 91949-64-3; 9, 91949-65-4; 10, 91949-66-5; 11, 91949-67-6; 12, 91949-68-7; 13, 91949-69-8; 14, 91949-70-1; 15, 91949-71-2.

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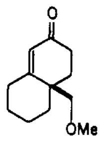
(5) Grieco, P. A.; Noguez, J. A.; Masaki, Y. *J. Org. Chem.* **1977**, *42*, 495.

(6) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, *8*, 730.

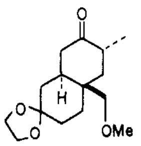
(7) Tetrahydrofuran ring formation via an intramolecular oxygen alkylation of a MOM-type ether by a tertiary alkyl halide has been observed: Ronald R. C.; Gewali, M. B.; Ronald, B. P. *J. Org. Chem.* **1980**, *45*, 2229.

(8) Substrates 8 and 10 were prepared from the known octalone ii[5] by employing the standard sequence described in ref. 4 above.

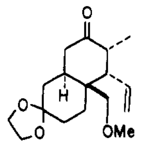


ii

(9) The synthesis of bromo ketone 12 commenced with octalone 4, mp 63.5–64.5 °C, which was made available in 94% yield from decalone iii[4] by employing standard organoselenium chemistry. Conjugate addition of vinyllithium to enone 4 using Noyori's procedure[10] provided access (95% yield) to iv which was transformed (80%) into 12 via a two-step sequence [(1) Me$_3$Si,[6] HMDS, C_5H_{12}; (2) NBS, THF, −20 °C].



iii



iv

(10) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1247.

(11) The synthesis of 14 which employs the chemistry described above will be reported in due course.

(12) Lubrizol Graduate Research Fellow, 1983–1984.

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