The ^{1}H NMR spectra of **19** and **20** were very similar but not identical with those of **13** and **14**. As expected, the most noticeable differences appeared in the olefin absorption region.

From the data described above we must conclude that the structure proposed by Pace-Asciak and Wolfe for their biosynthetic metabolite is incorrect. Further aspects of this research regarding the origin of this unknown arachidonic acid metabolite are under investigation in our laboratory.

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(10) All new compounds gave spectral data consistent with the assigned structures as well as satisfactory analytical figures via combustion analysis or high-resolution spectrometry. Complete spectral data are available upon request.
(11) With either reagent we obtained a 45–50% isolation yield of **9**. The remaining material (30–35%) consisted of Δ^8-olefins resulting from mesylation at C-9 followed by elimination. The rationale for the stereoselective outcome of this cyclization is under investigation.
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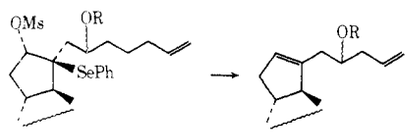
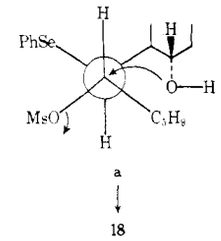
(14) The authors thank Dr. N. A. Nelson and Dr. R. A. Johnson for supplying authentic samples of (6*R*)- and (6*S*)-13,14-dihydro-PGI$_1$ methyl esters. For assignment of stereoconfiguration of 5,6-dihydroprostacyclins (PGI$_1$'s) see N. A. Nelson, *J. Am. Chem. Soc.*, **99**, 7362 (1977).
(15) The low resolution spectra of **13** and **14** were recorded on the same derivatives and under the identical conditions as reported by Pace-Asciak and Wolfe in ref 1.
(16) Grignard addition to lactol **16**, in contrast to lactol **7**, was seriously hampered by reductive cleavage of the 7-phenylselenenyl group which gave after isolation the unsubstituted lactol in equal amount.



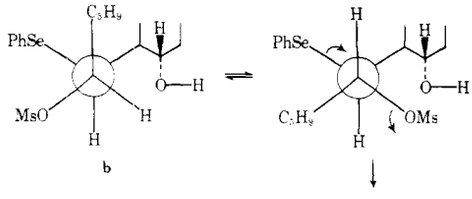
R = H, OSO_2CH_3

(17) J. F. King and J. R. duManoir, *J. Am. Chem. Soc.*, **97**, 2566 (1975).
(18) Use of mesyl chloride–Et_3N produced **18** in poorer yield (27%) and increased amounts of Δ^6-olefin derived products. The formation of a single (6*R*)-6,9-cyclized isomer (**18**) can be rationalized if one considers the preferred conformers available for an internal S_N2 displacement of the (6*R*)- and (6*S*)-mesylate isomers. The preferred conformer a leading to the formation of **18** would place the phenylselenenyl and pentenyl groups in a favored, sterically less crowded anti relationship. In contrast the required (6*R*)-mesylate conformer b forces the pentenyl group into a less favored gauche relationship with the phenylselenenyl group. In this instance 6,9-ether formation is diverted and elimination to olefin is the major pathway. However, as in the case of **8** one cannot exclude the possibility that Grignard addition to lactols **7** and **16** proceeded in a stereoselective manner to generate a single C-6 isomer.



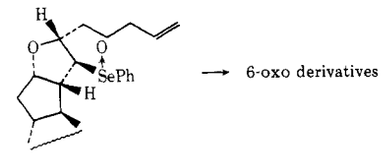
a

18



Δ^6-olefin derivatives

(19) Under the same conditions which affected selenoxide elimination from **4** and **10**, one is able to isolate selenoxide a. The desired Δ^7-olefin was obtained in 30% yield after warming a in CH_2Cl_2 at 45 °C. The low yield



a

can be attributed in part to the nonselective elimination of selenoxide a. After aqueous workup and chromatography, we inevitably always isolated some 6-oxo derived products.

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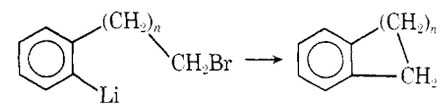
A New Anionic Cyclization of the Parham Type. Selective Ring Opening of Epoxides

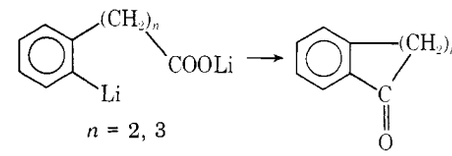
Summary: Epoxides derived from *o*-bromophenyl allyl ethers undergo bromine–lithium exchange with butyllithium at −100 °C. The resulting lithium reagents undergo cyclization by exo attack on the epoxide linkage as predicted by the Baldwin rules.

Sir: Of the synthetic possibilities opened up by Parham's development of functionalized aryllithium reagents,[1] the most important involve novel cyclization reactions which can be effected when the functional group is ortho to the lithium atom. While the majority of these ring closures involved the addition of an external electrophile, examples were provided of two novel reactions in which the electrophile is in the side chain, but remains passive until the halogen–metal exchange on the aryl nucleus is complete. These two reactions, the Parham cyclialkylation[2] (eq 1) and cycliacylation[3,4] (eq 2), have both found immediate application to important synthetic problems.[5-7]



(1)

n = 1, 2



(2)

n = 2, 3

It seemed likely that there should be other electrophilic groups which at −100 °C would remain passive long enough to permit halogen–metal exchange to occur. Of these the epoxide linkage appeared particularly interesting, for in theory rings of two different sizes might be produced. Reaction of monosubstituted epoxides with Grignard[8] and organolithium[9] reagents has been demonstrated to take place with anionic attack preferentially at the unsubstituted end. On the other

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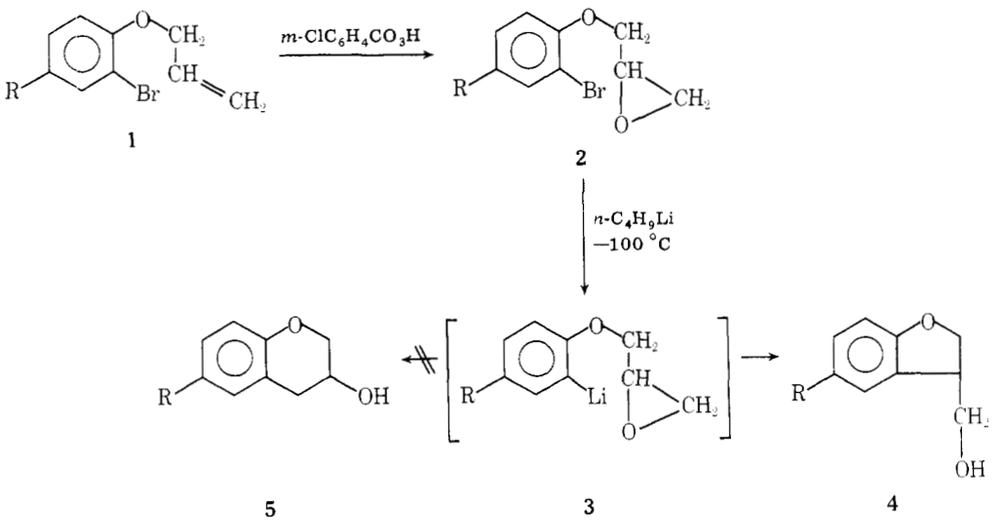

hand, Stork et al.,[10] in a further study of their closely related epoxynitrile cyclization,[11] concluded that "the epoxynitrile cyclization always yields the smaller ring, when both ends of the epoxide are equally substituted."[12] Baldwin, in his "rules for ring closure",[13] did not consider the effect of substitution, but stated simply that "the rules for opening three-membered rings to form cyclic structures seem to lie between those for tetrahedral and trigonal systems, generally preferring exo modes."

It seemed desirable to test the new cyclization with an epoxide having no substituents on the more remote carbon atom, hence more likely to contravene the Baldwin rules. For convenience in the preparation of the requisite *o*-bromo compounds this preliminary study was carried out using epoxides (**2**) derived from *o*-bromophenyl allyl ethers (**1**). If a 2.5 M solution of *n*-butyllithium was added to the epoxides (**2**), approximately 0.12 M, in a 80:20 (v/v) mixture of tetrahydrofuran and hexane at such a rate that the temperature did not exceed −95 °C, complete halogen–metal exchange occurred in 15 min as evidenced by ^{1}H NMR of samples withdrawn from the reaction mixture and quenched in 5% sodium bicarbonate solution. After 2 h at −100 °C the anion (**3**) was still unchanged, but if the temperature was raised to −78 °C, ^{1}H NMR indicated that cyclization occurred to the extent of 40–65% after 2 h. In preparative experiments the mixture was stirred for 30 min at −100 °C, allowed to warm to room temperature (~2 h), and then allowed to remain at room temperature for an additional 3 h before workup. The results are summarized in Table I. Although the yields of cyclized product ranged from 90 to 53%, in no case was more than one cyclization product detectable by gas chromatography. The (2,3-dihydro-3-benzofuran)methanol (**4a**) expected from exo cyclization of **3a** was unknown, but what would be the product of endo cyclization, 3-chromanol (**5a**, mp 79 °C), obtained by reduction of 3-chromanone is reported[14] to show a three-proton multiplet in the δ 2.71 region of the ^{1}H NMR. This resonance was absent from the spectrum of each of our cyclization products. Interpretation of the 100-MHz ^{1}H NMR for **4a** [($CDCl_3$, Me_4Si internal standard) δ 1.90 (bs, 1, OH), 3.7 (m, 3, CH_2O, $CHCH_2O$), 4.6 (m, 2, $ArOCH_2$), 6.80–7.35 (m, 4, ArH)] was assisted by addition of 2.61 mol % of Eu(fod)$_3$-d_{27} [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-octanedione-d_3)europium(III)]. The shifted spectrum showed: δ 3.82 (m, 1, $CHCH_2O$), 4.24 (d, 2, J = 6 Hz, CH_2OH), 4.66 (d, 2, J = 7 Hz, $ArOCH_2$), 5.46 (bs, 1, OH), 6.68–7.32 (m, 4, ArH). In decoupling experiments using the solution of **4a** containing shift reagent, irradiation of the resonance at δ 5.46 resulted in sharpening the doublet at δ 4.24. A similar result was observed when D_2O was added. Irradiation of the δ 3.82 multiplet gave a broad singlet at δ 4.24 (sharpened by addition of D_2O) and a singlet at δ 4.66.

Table I

R	% yield,[a] 4	bp, °C (mm)
a H	64 (90)	69–72 (0.05)
b CH_3	59 (84)	89–91 (0.08)
c C_6H_5	53	95.5–97.5[b]
d OCH_3	53	110–112 (0.10)
e Cl	63	99–102 (0.10)

[a] Yields in parentheses are by use of gas chromatography 10% SE-30 on 50/60 Chromosorb W, AW, DMCS, 6 ft × ¼ in. stainless steel column at 130 °C. [b] Mp of sample recrystallized from chloroform–hexane.

Further evidence for the assigned structure of **4a** was afforded by the mass spectrum: *m/e* (rel intensity) 150 (39), 132 (47), 131 (68), 119 (100), 94 (26), 91 (79). The peak of *m/e* 119 corresponds to the loss of CH_2OH from the molecular ion (*m/e* 150). The ^{1}H NMR spectrum of each of the substituted epoxides (**4b–e**) showed the expected similarity to that of **4a**, evidence that each had been formed by exo cyclization. Endo cyclization has been achieved in the Stork epoxynitrile cyclization when the oxirane ring has fewer substituents at the more remote than at the near carbon.[11] That our system gives only exo products is probably due to the decreased flexibility resulting from incorporation of an aromatic ring into the chain. This stiffness evidently inhibits the achievement of the collinearity of the anion[10] with that C–O bond of the oxirane which must be broken if a six-membered ring is to be formed.

The new cyclization not only offers a convenient route to (2,3-dihydro-3-benzofuran)methanols (**4**), but also promises to provide homocyclic as well as heterocyclic analogues having rings of various size. Further work in this direction is in progress. All new allyl ethers, epoxides, and cyclization products gave satisfactory elemental analyses (C, H ± 0.36%).

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