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METALATION OF 2,2-DIMETHYL-5-METHYLENE-1,3-DIOXANE---A FUNCTIONALIZED ALLYLOXY CARBANION.

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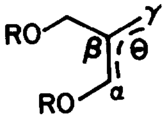
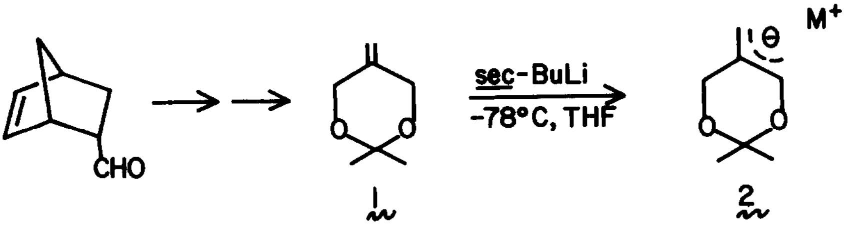
In the course of our studies directed toward the total synthesis of the ergot alkaloids,[1] the need arose to have access to an allyloxy carbanion I possessing a hydroxymethyl substituent at the β-position. This desire led us



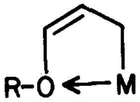
I

to examine the metalation of the dioxane 1 a compound conveniently prepared as previously described from the commercially available 5-norbornene-2-carboxaldehyde by a three step sequence involving a Cannizzaro reaction with formaldehyde, a retro Diels-Alder reaction (quartz chips, 520°C), and acetonide formation (2,2-dimethoxypropane, p-toluenesulfonic acid).[2]



The metalation of 1 was readily effected by reaction with sec-butyllithium at -78°C in tetrahydrofuran (THF). A pale yellow colored solution of 2 (M=Li) resulted after stirring for 30 min at this temperature. Upon addition of an electrophile (El), the solution rapidly lost its original color. After 30 min at -78°C, and an additional 10 min at room temperature, the reaction mixture was quenched with water and extracted with ether. The isolated crude product was generally purified by silica gel chromatography. In the cases where a carbonyl compound served as the electrophile, purification and analysis of the product mixture was best performed by prior conversion of the alcohol to its acetate (acetic anhydride,pyridine).

The results of the reactions of **2** with a variety of electrophilic agents are displayed in the accompanying *Table*. Although **2** **is incapable of forming an internally coordinated metallocycle II**, as is possible for the allyl ethers studied by other workers,[3] we were



II

pleased to find that the general trends of reactivity as previously recorded were fairly well adhered to, although with some minor variations.[4] As has been discussed by Still,[3d] allylic anions possessing a destabilizing group generally undergo alkylation at the γ-position, the site of highest electron density. Carbonyl compounds, in contrast, generally react at the α-position via a mechanism involving rearrangement through a cyclic transition state (alternatively, an antarafacial S_E2 attack or a one electron transfer process may be involved).[5]

With benzaldehyde as the electrophile, there was little preference for α- or γ- attack of **2** when lithium was the counterion (entry 1). The allylzinc reagent did, however, provide predominantly the compound of α-attack, a product dependency factor previously noted by Evans and co-workers.[3a] The cadmium reagent was found to be less effective in controlling reaction site selectivity (entry 3). The use of THF-HMPA mixtures led surprisingly to a preponderance of the product of γ-attack.[3d] With cyclohexanone as the carbonyl substrate, predominate attack at the α-position was observed, in contrast to entry 1, with lithium as the counterion.

While allyl bromide showed only a slight preference for formation of the enol ether product, *t*-butyldimethylchlorosilane reacted with high regioselectivity at the γ-position.[6]

The combined isolated yields (α + γ) for the reactions of **2** with both halides and carbonyl compounds were generally good. Entry 9, in which *cis*-2,3-epoxybutane[7] served as the electrophile, was the only case studied for which the isolated yield was unsatisfactory.[8]

Applications of **2** in natural product synthesis will be reported in due course.

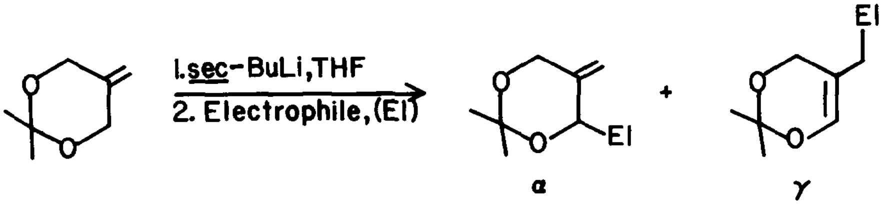


Table. Reactions of **2** with Electrophiles

Entry	Electrophile	Solvent-additive	Ratio $\alpha:\gamma$	Isolated Yield (%) ($\alpha + \gamma$)
1	benzaldehyde	THF	1.2:1[a]	83
2	"	THF-HMPA	1:4[b]	95
3	"	THF-CdCl$_2$	3.4:1[a]	95
4	"	THF-ZnCl$_2$[c]	>19:1[b]	100
5	cyclohexanone	THF	7.5:1[a]	95
6	*t*-butyldimethylchlorosilane	THF	<1:19[b]	99
7	allyl bromide	THF	1:1.5[b]	100
8	iodomethane	THF	1:3.5[b]	98
9	*cis*-2,3-epoxybutane	THF	1:2.8[a]	36

(a) $\alpha:\gamma$ ratio determined by ^{1}H NMR integration of the olefinic proton resonances of the acetates derived from the initially formed alcohols by acetic anhydride/pyridine treatment.

(b) $\alpha:\gamma$ ratio determined by ^{1}H NMR integration of the olefinic proton resonances.

(c) The zinc chloride was freshly fused.

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References and Notes

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2. F. Weiss, A. Isard and R. Bensa, *Bull. Soc. Chim. Fr.*, 1355 (1965); E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 3775 (1975).
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4. It is also of interest to note that while arylthioallyllithium reagents react with halides to furnish α-alkylation products, the related alkylthioallylcopper reagents undergo alkylation exclusively γ to sulfur. See, J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 5629 (1968) and K. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 7926 (1973).
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6. Satisfactory spectral data was obtained for all new compounds.
7. D. J. Pasto and C. C. Cumbo, *J. Org. Chem.*, **30**, 1271 (1965).
8. The Biellmann anion has been found to react with 1,2-epoxybutane exclusively α to sulfur: H. Ishida, work in progress. For an intramolecular example of this process, see M. Kodama, Y. Matsuki, and S. Itô, *Tetrahedron Lett.*, 3065 (1975). The behavior of metalated dihydrothiopyrans toward expoxides has also been examined, see P. L. Stotter and R. E. Hornish, *J. Am. Chem. Soc.*, **95**, 4444 (1973) and K. Kondo, A. Negishi, K. Matsui, D. Tunetomo, and S. Masamune, *J. Chem. Soc., Chem. Commun.*, 1311 (1972).

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