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INTRAMOLECULAR TRAPPING BY EPOXIDES OF INTERMEDIATES GENERATED BY ORGANOCUPRATE ADDITIONS TO PROPIOLATE ESTERS.

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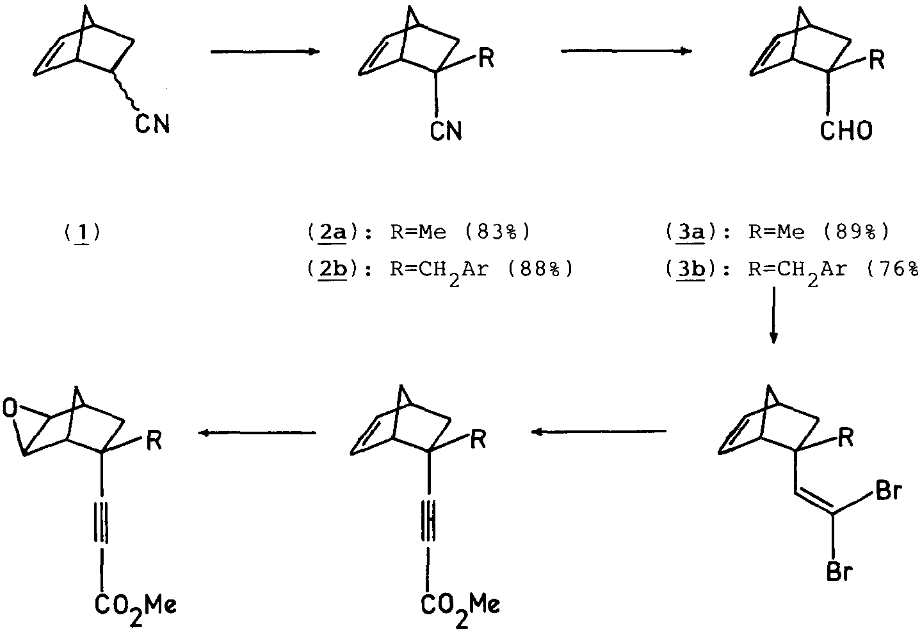
Summary: The facility with which intramolecular trapping of the intermediates generated by conjugate addition of organocopper nucleophiles to propiolate esters may be effected by internal epoxides is critically dependent on the nature of the nucleophile.

As the key step of a synthesis in these laboratories, we found it necessary to effect a Michael-initiated ring closure by intramolecular trapping of the intermediate formed by conjugate addition of an organocuprate reagent to a propiolate ester, with an internal epoxide functioning as the intramolecular electrophile. While such trapping reactions have been shown to proceed with an ester as the intramolecular electrophile,[1] the only report of trapping of these intermediates by epoxides, to our knowledge, is that of Marino and Linderman,[2] who report that the intermolecular reaction is successful only when the epoxides of terminal, acyclic olefins are used. Herein, we report that the course of intramolecular trapping of such intermediates by internal epoxides is critically dependent on the nature of the organocuprate used to effect the Michael addition, and that such reactions are extremely rapid when higher order mixed cuprates (Lipshutz reagents)[3] are used.

The compounds chosen for this study were the epoxyesters (**6**), which, because of the rigidity of the norbornane ring system, possess the advantages of a well defined geometry and enforced proximity of the groups participating in the trapping reaction. Nonetheless, it was recognized that some of the advantages inherent in the trapping reaction because of its intramolecular nature might well be offset by the stereoelectronic requirements of the intramolecular S_N2 ring opening of the epoxide, which would require that the nucleophile enter the endo cavity of the norbornane.

The synthesis of the required epoxyesters was effected in five steps from the known nitrile (**1**) (Scheme 1).[4] Thus, alkylation of (**1**) [LDA, THF, -78°C; RX, -78 to 0°C] afforded the corresponding nitriles (**2**) as single diastereoisomers. Reduction of the nitriles [DIBAL-H, hexane-Et_2O, 0°C] gave the aldehydes (3), which were converted to the corresponding vinylidene dibromides (4) by the method of Corey and Fuchs[5] [Ph_3P (2.2 eq.), CBr_4 (1.1 eq.), CH_2Cl_2, 0°C]. Further elaboration to the propiolate esters (5) was straightforward[5] [n-BuLi (2 eq.), THF, -78°C; $ClCO_2Me$]. As anticipated, the epoxidation of the norbornenes (5) [m-CPBA (2 eq.), CH_2Cl_2, 0°C to R.T., 18 h] afforded the exo epoxides free of regio- and stereoisomers.



(1)

(2a): R=Me (83%)
(2b): R=CH_2Ar (88%)

(3a): R=Me (89%)
(3b): R=CH_2Ar (76%)

(6a): R=Me (51%)
(6b): R=CH_2Ar (59%)

(5a): R=Me (>98%)
(5b): R=CH_2Ar (70%)

(4a): R=Me (58%)
(4b): R=CH_2Ar (50%)

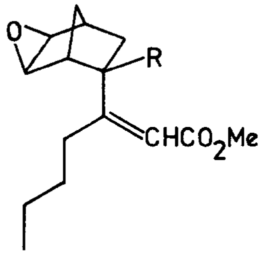
Ar=m-C_6H_4OMe

SCHEME 1

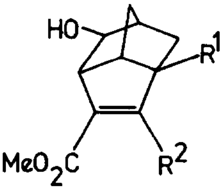
The progress of the conjugate addition reaction was conveniently monitored by gc-ms, since norbornene oxides exhibit an intense fragment ion at m/z 81 in the mass spectrum. In a typical reaction, a THF solution of the epoxyester was cannulated rapidly into a stirred solution of the freshly prepared organocopper reagent (2 eq.) in THF at 0°C, and aliquots withdrawn, quenched with methanol, and analyzed by gc-ms.

The conjugate addition of lithium di-*n*-butylcuprate to the propiolate (5a) was rapid at 0°C, and afforded the acrylate (7) as a mixture of geometric isomers. Further intramolecular reaction of the organometallic intermediate was not observed, however, and the epoxide proved to be resistant to attack by the intramolecular nucleophile even after 24 hours at room temperature; heating the reaction mixture served only to initiate decomposition. Although it has been reported[6] that the addition of $BF_3.Et_2O$ to organocuprates enhances the nucleophilic activity of such species, such catalysis was not attempted in this study due to the potential for Lewis acid-catalyzed rearrangement of the norbornene oxide *via* the norbornyl cation.

Due to the failure of the simple Gilman reagent to effect the desired ring closure, we chose to investigate the use of higher order mixed cuprates developed by Lipshutz,[3] since these reagents have been shown to react with electrophiles towards which simple Gilman reagents are inert. Under conditions identical to those above, the addition of lithium di-*n*-butylcyanocuprate to the epoxyester (6a) afforded, **within one minute at 0°C**, the homoallylic alcohol (8a); no intermediates corresponding to (7) were detected, and low-temperature studies of this reaction are under way in an attempt to intercept the intermediate organometallic species. To our knowledge, this represents the most rapid reaction of its type, and the first example in which an internal epoxide functions as the electrophile. Similar results (the rapid formation of (8b) and (8c) at 0°C) were obtained when the reaction of lithium dimethylcyanocuprate with (6a) and (6b) was carried out, although the course of this reaction is complicated by further reaction of the tricyclic products by 1,2-addition to afford methyl ketones and dimethylcarbinols.[7]



(7)

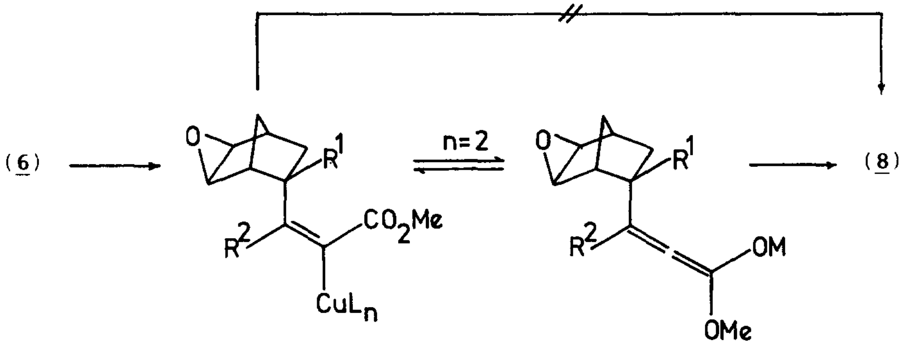


(8a): R^1=Me; R^2=*n*-Bu (66%)

(8b): R^1=R^2=Me (15% + 60% other tricyclic products)

(8c): R^1=*m*-$CH_2C_6H_4OCH_3$; R^2=Me (12% + 65% other tricyclic products)

To explain the remarkable differences in reactivity of the organometallic intermediates formed by conjugate addition of the lower order and higher order cuprates to (**6**), we favor arguments similar to those advanced by Marino and Linderman[2] to explain the stereochemical outcome of their trapping study. Thus, we propose that whereas the vinylcopper intermediate formed by addition of the simple Gilman reagent to (**6**) is stable as the carbon metalate, that formed by addition of the higher order cuprate to (**6**) is in equilibrium with a metal (lithium or copper) allenolate, which is the effective nucleophile in the trapping reaction (Scheme 2).



SCHEME 2

Further studies to determine the scope of this synthesis of homoallylic cycloalkenylcarbinols are in progress.

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