confirm that, under the mild conditions used, allylic reversal is occurring and that this reversal *requires* a homoallylic species.

In earlier,[7] but related, work, some alkali metal salts of highly branched tertiary alcohols were cleaved thermally, but temperatures in the range of 200–300 °C were required. Significantly in none of these cases did the tertiary alcoholates contain an alkenyl group as in our examples. It is also noteworthy that the rate of *addition* of allylic-type organometallics to ketones is rapid[8] compared with that of other alkyl groups. Since it is now obvious that such additions are reversible, it is not surprising that in the reverse step it is the allylic group which is cleanly removed. Implications of these and related findings will be published later.

Acknowledgment. We wish to thank the National Science Foundation for its financial support of this work.

Supplementary Materials Available. The procedure for the preparation of all starting materials and the experimental details of the crossover study (total, 3 pages). Ordering information is given on any current masthead page.

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(1) R. A. Benkeser and W. E. Broxterman, *J. Am. Chem. Soc.*, **91**, 5162 (1969).
(2) P. Miginiac, *Bull. Soc. Chim. Fr.*, 1077 (1970).
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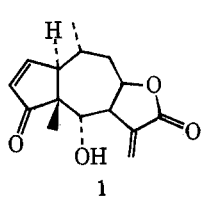
The Stereospecific Synthesis of α-Methylene-γ-butyrolactones of *trans*-1,3-Dihydroxycycloalkanes

Summary: The reactions of 1,1-diethoxy-2-propenyl cuprates with 3,4-epoxycycloalkenes have been found to be largely regiospecific and stereospecific; the product from 1,2 opening of 1,3-cycloheptadiene monoepoxide has been converted to the *trans*-hydroxy-*cis*-butyrolactone of cycloheptane.

Sir: Despite the plurality of synthetic methods[1] for the preparation of α-methylene-γ-butyrolactones fused to cycloalkanes, there is a scarcity of regiospecific and stereospecific methods for construction of α-methylene lactones of 1,3-diols.[2] We wish to report an efficient synthetic scheme for the conversion of cyclic allylic epoxides into the *trans*-hydroxy-*cis*-α-methylene-γ-butyrolactone system found in the antitumor natural product, helenalin (1). The related *cis*-hydroxy-*trans*-α-methylene-γ-butyrolactone found in euparotin (2) is also potentially accessible from the reactions described herein.



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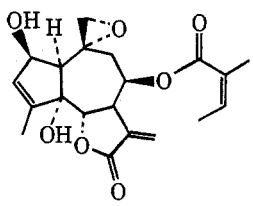
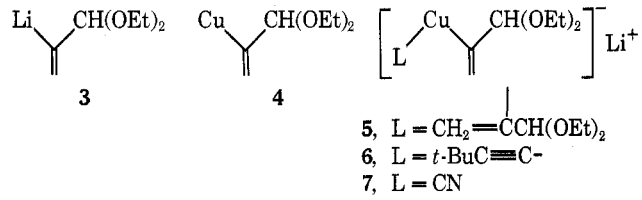


2

As part of our general interest in the synthesis of naturally occurring antitumor agents possessing the α-methylene lactone unit, we have investigated the reactions of various epoxides with organometallic synthons of an acrylate unit. In this paper we report the reactivity of several organocopper reagents (**4–7**)[3] and the corresponding lithio species (**3**),[4] de-



3 **4**

5, L = $CH_2{=}C(CH(OEt)_2)$–
6, L = *t*-Bu$C{\equiv}C$–
7, L = CN

rived from 2-bromo-3,3-diethoxypropene, with several simple epoxides and three activated epoxycycloalkenes.

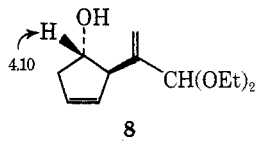
All of the organocopper reagents listed above were prepared from the isopropenyllithium derivative **3**. Copper reagents **5** and **6** have been previously described;[3] the reagent **4** was prepared from the reaction of **3** with 1 equiv of cuprous iodide in THF at −55 °C, while reagent **7** (L = CN) was prepared from cuprous cyanide and **3** in THF at −40 °C.[5]

When reagent **3** was treated with cyclohexene epoxide, propylene oxide, and styrene epoxide under a variety of reaction conditions, including the presence of salts such as anhydrous magnesium bromide, no detectable amounts of alcohol products were found. In the case of the reactive 1,3-cyclohexadiene monoepoxide and 1,3-cycloheptadiene monoepoxide, reagent **3** was once again ineffective, at temperatures up to −40 °C in THF or ether, in opening the epoxide ring.[6]

Previous studies involving the reactions of organocuprates with epoxides have largely focused on the reactions of dialkyl cuprates with simple epoxides and in some cases acyclic vinyl epoxides.[7] The most relevant work to this paper comes from investigations of Rickborn[8] and Weiland and Johnson[9] of 1,3-cyclohexadiene monoepoxide and dialkylcuprates. These workers found that both 1,2 and 1,4 additions of the cuprates occurred to about equal extent and that the stereochemistry of the products with dimethylcopper lithium was exclusively trans.

We have found that the organocopper reagents (**4–7**) undergo the expected 1,2 and 1,4 additions to the monoepoxides of cyclopentadiene, 1,3-cyclohexadiene, and 1,3-cycloheptadiene. More significantly from a synthetic standpoint, the regiospecificity of the addition can be altered to maximize the 1,2 product with trans stereochemistry. Maximum yields of total adducts from the cuprates (**5–7**) were obtained at −40 °C with 1.5–2 equiv of reagent. The effect of ether as the reaction solvent was significant in optimizing the ratio of 1,2 to 1,4 products. Furthermore, the mixed cyanocuprate **7** consistently gave the lowest yields of the adducts with the various unsaturated epoxides. The neutral copper(I) reagent **4** also seemed to be less reactive than reagents **5** and **6** and gave predominately the 1,4 regioisomer from 3,4-epoxycyclohexene. The yields and isomer ratios of the reaction products are summarized in Table I.

The structural assignments of the respective regioisomers were made on the basis of the diagnostic chemical shifts of the protons on carbons bearing the hydroxyl group in key compounds.[10] The regioisomers **8** and **9** from 3,4-epoxycyclo-



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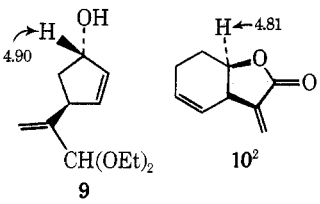
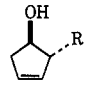
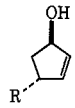
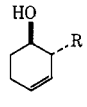
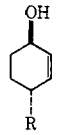
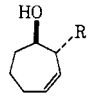
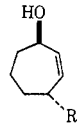


9 **10**[2]

Table I. Reactions of Organocopper Reagents (4–7) with 1,3-Cycloalkadiene Monoepoxides

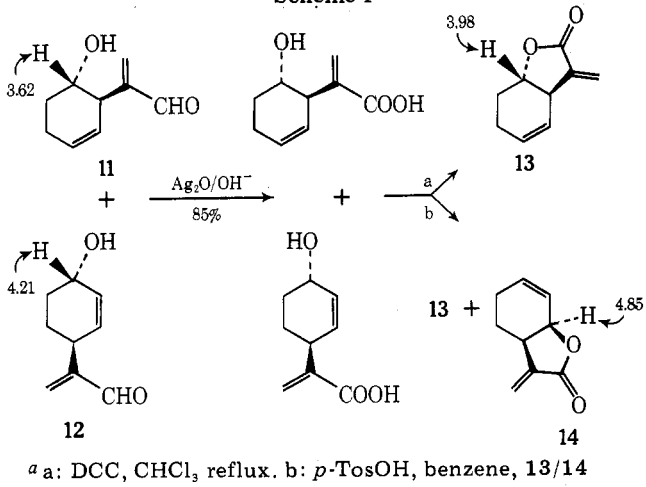
Epoxide	Products[a] [R = CH_2=$\overset{|}{C}$CH$(OEt)_2$]	Reagent[b]	% yield[c]	1,2/1,4 ratio[d] (solvent)
	 	5	87	2.5 (THF)
		6	80	2.0 (THF)
		7	43	1.0 (THF)
	 	4	71	0.6 (THF)
		5	94	1.5 (THF), 2.7 (Et_2O)
		6	72	1.5 (THF)
		7	50	0.7 (THF)
	 	4	58	2.7 (THF)
		5	98	2.9 (THF), 4.3 (Et_2O)
		6	70	2.3 (THF)
		7	0	

[a] All products listed in this table and their derivatives gave satisfactory (±0.2%) combustion analyses. Products were either isolated by preparative GLC (5% SE-30 on Chrom P; 5 ft × 0.25 in., vacuum distillation, HPLC, or preparative TLC. [b] With THF as the solvent, the reagents were formed at −40 °C and the reaction mixtures were kept at −40 °C for 5–6 h. When the reactions were carried out in anhydrous ether, the reagent **3** was formed with *tert*-butyllithium at −70 °C. [c] Yields were determined by NMR integration of key absorbances using an internal standard. In all cases, product mixtures after workup were shown to be >95% pure adduct by VPC analysis. [d] The isomer ratios of the cyclopentene epoxide and cyclohexene epoxide were based on NMR analysis of the corresponding aldehydes. The isomer ratio of the cycloheptene epoxide was obtained from NMR analysis of the 1,2 cyclic hemiacetal and 1,4-aldehyde derived from hydrolysis of the initial adducts.

pentene were easily distinguished by the large difference (0.8 ppm) in chemical shifts for the carbinol hydrogens and by decoupling experiments. The trans stereochemistry for **8** and **9** was assumed after both isomers failed to cyclize to the corresponding cyclic acetals or methylene lactones.

The trans stereochemistry was assigned to the initial adducts for 3,4-epoxycyclohexene and their respective hydrolysis products **11** and **12** on the basis of literature precedence for cuprate additions,[8,9] correlation of key NMR chemical shifts, and the chemical transformations outlined in Scheme I. Oxidation of a 1.5:1 mixture of **11** and **12** with silver(I) oxide in base produced the corresponding acrylic acid isomers in 85% yield. Treatment of the mixture of carboxylic acids with dicyclohexylcarbodiimide (DCC) in refluxing chloroform produced the *trans*-1,2-butyrolactone[11] **13** (mp 89–90 °C) which was spectroscopically different from the previously reported[2] cis isomer **10**. When the mixture of carboxylic acids was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene, the *trans*-lactone **13** was again isolated along with a new unsaturated *cis*-butyrolactone[12] **14**.

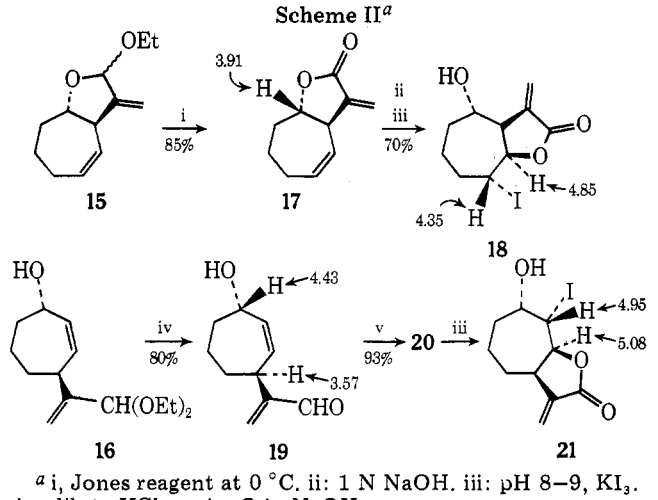
Scheme I[a]



[a] a: DCC, $CHCl_3$ reflux. b: *p*-TosOH, benzene, **13**/**14** ≅ 1.5.

Upon vacuum distillation of the product mixture from the reaction of 3,4-epoxycycloheptene, the 1,2 adduct cyclizes to the acetal **15** and is easily separated from the 1,4 adduct **16** by distillation.[13] Oxidation of the cyclic acetal **15** with Jones reagent under standard conditions resulted in a 75% yield[14] of crystalline *trans*-lactone[15] **17** (mp 74–75 °C). Conversion of **17** into the hydroxy-*cis*-lactone[15] **18** (mp 137.5–138.5 °C) was achieved in an overall yield of 70% as indicated in Scheme II.

Scheme II[a]



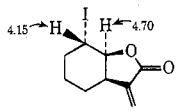
[a] i, Jones reagent at 0 °C. ii: 1 N NaOH. iii: pH 8–9, KI_3. iv: dilute HCl. v: Ag_2O in NaOH.

Hydrolysis of the 1,4 adduct **16** with dilute hydrochloric acid produced the aldehyde **19**, whose NMR spectrum most easily confirmed the 1,4-isomer assignment. Oxidation of **19** to the corresponding acid **20** proceeded in 93% yield, and acid **20** was converted to the iodolactone[16] **21** (mp 133–136 °C), in order to relate the stereochemistry of the free hydroxyl group to the lactone.

The high yield of the initial reaction of **5** with 3,4-epoxycycloheptene and the preponderence of the 1,2 regioisomer (80:20 mixture in ether) render this synthetic approach superior to any existing methodology for construction of α-methylene-γ-butyrolactones of trans 1,3 cyclic diols.

References and Notes

(1) P. A. Grieco, *Synthesis*, 67 (1975), and references therein.
(2) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. Studt, *Tetrahedron Lett.*, 2035 (1974).
(3) J. P. Marino and J. S. Farina, *Tetrahedron Lett.*, 3901 (1975).
(4) J. Ficini and J. C. Depezay, *Tetrahedron Lett.*, 4795 (1969).
(5) The upper limit for the thermal stability of reagents **3–6** has been estimated by us and others[4] to be approximately −40 °C. Reaction mixtures kept above −40 °C for any period of time darkened and the yields of products were diminished.
(6) The 3,4-epoxycyclohexene reaction with reagent **3** at −40 °C yielded about 7% 1,2 adduct. The reaction of **3** with 3,4-epoxycycloheptene failed to yield any adducts at −40 °C for 6–8 h.
(7) G. H. Posner, *Org. React.*, **22**, 253 (1975).
(8) B. Rickborn and J. Starosick, *J. Am. Chem. Soc.*, **93**, 3046 (1971).
(9) D. M. Wieland and C. R. Johnson, *J. Am. Chem. Soc.*, **93**, 3047 (1971).
(10) All of the chemical shifts cited here are given in ppm downfield from internal tetramethylsilane (60 MHz). The specific protons cited as well as the particular compounds were chosen because they were the most informative and definitive in making structural assignments. The multiplicities of the protons cited are not easily described without an actual spectrum but they are consistent with the assigned structures.
(11) The chemical shifts of the methine protons on carbons bearing the lactone oxygen in *cis*-α-methylene butyrolactone of cyclohexane and the corresponding trans isomer are δ 4.46 and 3.65 respectively [J. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965)]. Also see ref 2 for spectral data for compound **10.**
(12) Lactone **14** was independently prepared by dehydrohalogenation of iodolactone i with DBN in benzene at room temperature. The preparation of i has been previously reported by us [J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, **96**, 7138 (1974)].



i

(13) Acetal **15** distilled between 95 and 100 °C (0.05 mmHg).
(14) Yields reported are isolated yields but they have not necessarily been maximized.
(15) The literature (see reference cited in 11) value for the chemical shifts of the lactone methines for *cis*- and *trans*-α-methylene-γ-butyrolactones of the cycloheptane series are δ 4.72 and 4.10, respectively. The absorptions that we have observed for the *trans*-lactone **17** (3.91) and the *cis*-lactone **18** (4.85) are most consistent for the assignments made.
(16) The 60-MHz NMR spectrum of **21** clearly showed coupling constants and chemical shifts for all of the methine hydrogens which were most consistent for the stereochemistry shown. Iodolactone **21** also failed to give an epoxide when treated under basic conditions. The preparation of **21** and analysis of its NMR spectrum were carried out by D. M. Floyd in this laboratory and full details will be published in a full paper.

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Allylic Substitutions with Retention of Stereochemistry

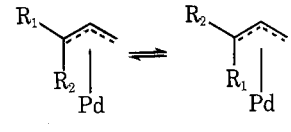
Summary: The "net SN2 displacements" of allylic acetates catalyzed by palladium proceed with complete retention of configuration at the carbon undergoing displacement and without loss of olefin geometry in a trisubstituted double bond.

Sir: The ability to perform displacements with inversion of configuration constitutes one of the most fundamental synthetic reactions in organic chemistry. Alkylations utilizing allylic halides, allylic sulfonate esters, etc., suffer from their high reactivity and consequently make stereochemical control difficult. With cyclohexenyl derivatives, the problems are further confounded by a tendency toward elimination reactions competing with the desired substitution reaction. The use of palladium-catalyzed allylic alkylations,[1,2] which allows use of the configurationally stable and easily handled allylic acetates, overcomes these limitations. Furthermore, these processes proceed with a net retention of configuration in contrast to the usual inversion which is observed in normal alkylations. Surprisingly, even though these reactions presumably involve π-allylpalladium intermediates[3] the stereochemistry of a trisubstituted double bond is retained in the alkylations.

In a previous paper, we suggested that the "net SN2 displacement" catalyzed by palladium(0) complexes proceeded with retention of configuration.[2] In order to establish this point unambiguously, we examined the alkylations of the cis (**1**) and trans (**2**) isomers of 3-acetoxy-5-carbomethoxycyclohexene[4] (see Scheme I). The cis isomer **1** is available by the methanolysis and acetylation of lactone **3**,[5] whereas the trans isomer **2** is available by acetylation of the hydroxy ester which, in turn, was isolated from a cis-trans mixture[6] by selective lactonization of the cis isomer. Whereas **1** was isomerically pure, VPC analysis[7a] of **2** indicated contamination to the extent of 7% by **1.**

Alkylation of **1** with the sodium salt of dimethyl malonate [catalytic amount of $(Ph_3P)_4Pd$, Ph_3P, THF; reflux; 92% yield] gave a single product **4**[4] which was assigned the cis stereochemistry.[8] At 270 MHz, the requisite coupling constants could be determined—$J_{AD} = J_{BD} = J_{CD} = 12.5$ Hz, $J_{BC} = 6.0$, $J_{AC} \sim 5$ Hz—which clearly indicate that both H_A and H_B are pseudoaxial. Alkylation of **2** under identical conditions gave **5**[4] (80% yield) which VPC analysis[7b] indicated was contaminated by **4** to the same extent (7%) that **2** was contaminated by **1.** The trans stereochemistry was indicated by the coupling constants obtainable at 270 MHz—$J_{AC} = 5.7$, $J_{AD} = 4$, $J_{BC} = 10$, $J_{BD} = 4$, $J_{CD} = 13.5$ Hz—which clearly suggest that H_A is pseudoequatorial and H_B is pseudoaxial. The assignment is further confirmed by the base-catalyzed isomerization [$KOC(CH_3)_3$, CH_3OH, reflux] of the less stable trans isomer **5** to the more stable cis isomer **4.** Both isomers were decarbomethoxylated[4] [$(CH_3)_4NOAc$, HMPA, 100 °C, 75% yield] without loss of configurational purity. Compounds of this type have been utilized as intermediates to ibogamine.[9] *Thus, within experimental error, these "net SN2 displacements" of allylic acetates proceed with complete retention of configuration at the carbon undergoing displacement.* Furthermore, no evidence for elimination competing with substitution is seen.

The question of the stereochemical integrity of the double bond in these reactions is crucial for their applications in synthesis. The well-known isomerization of π-allylpalladium complexes[10] makes interconversions of olefin isomers highly



likely. Thus, to probe this question, alkylation of geranyl and neryl acetate was examined (see Scheme II). Alkylation of geranyl acetate with the sodium salt of either dimethyl malonate or methyl phenylsulfonylacetate under conditions identical with the above led to the product of substitution at the primary carbon, i.e., **6a**[4] and **6b**,[4] with complete retention of olefin geometry (VPC[7c] and NMR analysis) in 84–92% isolated yield. The *E* stereochemistry was confirmed by the ^{13}C NMR spectrum which showed a high field absorption for C_a compared (**6a**, δ_{C_a} 15.97, δ_{C_b} 17.63, δ_{C_c} 25.52; **6b**, δ_{C_a} 15.84, δ_{C_b} 17.40, δ_{C_c} 25.39) with the absorption for this methyl carbon in the *Z* isomer (vide infra). Unlike π-allylpalladium complexes from methylenecyclohexanes,[11] this alkylation reaction was insensitive to the nature of the phosphine present. On the other hand, it did show a sensitivity to the nature of the anion in which the sulfonyl anion led to attack only at the primary carbon atom.

Neryl acetate showed an even greater sensitivity to the nature of the anion. Alkylation under the usual conditions