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STEREOSELECTIVE SYNTHESIS OF HOMOALLYLIC ALCOHOLS CONTAINING TRISUBSTITUTED OLEFINIC DOUBLE BONDS

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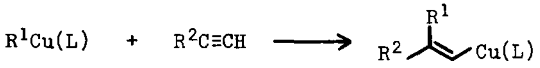
Homoallylic alcohols and their derivatives such as the corresponding halides and sulfonates are very useful compounds for the synthesis of natural products, especially various terpenoids. Among the applications of these homoallylic systems have been syntheses of Cecropia juvenile hormone[1] and steroids.[2] Several methods have previously been reported for the preparation of homoallylic alcohols and derivatives.[3] Among the more recent methods are the use of vinyllithium reagents,[4] vinylaluminum compounds,[5] π-allylnickel complexes,[6] organoselenium compounds,[7] 2-thiazolines,[8] and rearrangements of cyclopropylcarbinols.[9] Many of the natural products that are derivable from homoallylic compounds contain trisubstituted olefinic units. Therefore, especially important are those methods which permit the stereoselective synthesis of homoallylic systems in which the olefinic portions exist as trisubstituted alkenes. Unfortunately, many of the methods above do not permit the synthesis of these types of systems with high stereoselectivity.

A reaction which is quite useful for the synthesis of olefins is the addition of alkylcopper complexes to acetylenes (equation 1) as was originally reported by Normant[10] and further investigated by Westmijze.[11] In at least some cases, the addition reaction

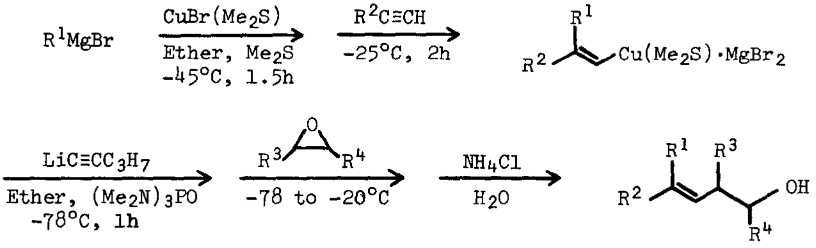


1

(1)

may be improved through use of the dimethylsulfide complex of cuprous bromide[12] to generate the initial alkylcopper species.[13] On the basis of the known reactions of various organocopper complexes with epoxides,[14] the alkylation of the vinylcopper species (1) with epoxides would conceivably provide a route to homoallylic alcohols containing stereospecifically trisubstituted olefinic units.[15] However, the vinylcopper complexes (1) obtained from the addition reaction (equation 1) exhibit low reactivity in alkylation reactions.[4] Indeed, we have found that the reaction of 1 with epoxides proceeds rather sluggishly.

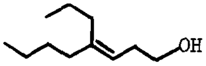
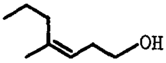
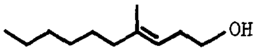
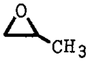
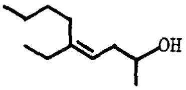
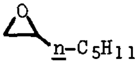
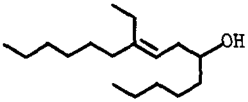
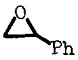
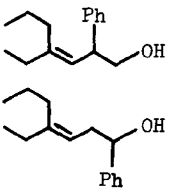
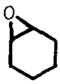
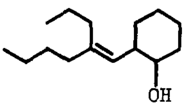
Based upon our earlier work,[13a] we have investigated the possibility of increasing the reactivity of the vinylcopper intermediates (1) toward epoxides by adding a 1-lithioacetylene to the reaction mixture for the purpose of perhaps generating a more reactive mixed cuprate.[16] This approach, as outlined in equation 2, has been quite successful.[17,18]



2 (2)

The results summarized in Table I demonstrate that this one-flask reaction sequence is a very efficient method for the synthesis of the desired homoallylic alcohols. High regioselectivity is observed in the case of monoalkylated epoxides (runs 4 and 5); the only products that are detected are those resulting from reaction at the less substituted position. Styrene oxide (run 6), however, gives a mixture of two products. Cyclohexene

Table I. Synthesis of Homoallylic Alcohols (2)

Run	R^1	R^2	Epoxide	Product(s)		Yield (%)[a]
1	$\underline{n}$-C_3H_7	$\underline{n}$-C_4H_9				95
2	$\underline{n}$-C_3H_7	CH_3				95
3	CH_3 [b]	$\underline{n}$-C_6H_{13}				75 [c]
4	$\underline{n}$-C_4H_9	C_2H_5				82
5	C_2H_5	$\underline{n}$-C_6H_{13}				94
6	$\underline{n}$-C_3H_7	C_2H_5			(63:37)	75
7	$\underline{n}$-C_3H_7	$\underline{n}$-C_4H_9				26

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[a] Unless otherwise noted, the yields were determined by glpc with the use of an internal standard. [b] The addition of the methylcopper complex required 65h at -23°C (see ref 13c) whereas the other alkylcopper complexes required only 2 h. [c] Isolated yield.

oxide (run 7), an epoxide of relatively low reactivity, gives a low yield of product under our conditions. Our assignment of olefin stereochemistry is based, first of all, upon the earlier studies by Normant who reported that alkylcopper reagents undergo *cis*-addition to acetylenes.[19] Further evidence is provided by ^{1}H-nmr spectra of the products of runs 2 and 3. In these compounds the proton resonances of the vinyl-CH_3 groups appear at δ 1.64 and 1.58, respectively, which is consistent with the assigned stereochemistry.[20] According to glpc analyses, the products are formed with a stereoselectivity of at least 99%. A typical procedure is given below.

(E)-4-Methyl-3-decen-1-ol. To a solution of CuBr(Me_2S) (0.82 g, 4.0 mmol), anhydrous ether (5 ml), and dimethyl sulfide (4 ml) at -45°C under a nitrogen atmosphere was added a 2.90 *M* solution (1.38 ml, 4.0 mmol) of methylmagnesium bromide in ether over a 2-min period. After 2 h, 1-octyne (0.52 ml, 3.5 mmol) was added over 1 min to the yellow-orange suspension. The mixture was stirred at -23°C for 65 h,[21] and then the resulting dark green solution was cooled to -78°C. A solution of 1-lithiopentyne (prepared from 4.0 mmol of *n*-butyllithium and 4.0 mmol of 1-pentyne) and ether (5 ml) to which hexamethylphosphoric triamide (1.4 ml, 8 mmol) had been added was transferred to the green solution. After 1 h, ethylene oxide (0.21 ml, 4.0 mmol) was added with a chilled syringe over a 15-min period. The resulting mixture was stirred at -78°C for 2 h, allowed to stand at -25°C for 24 h, quenched at 0°C by addition of an aq. solution (5 ml) of ammonium chloride (adjusted to pH 8 with ammonia), and then partitioned between ether and water. The crude product (90% pure by glpc) was purified by column chromatography (CH_2Cl_2/silica gel) to give 0.44 g (75%) of **2** (R^1=CH_3, R^2=*n*-C_6H_{13}, R^3=R^4=H) as a colorless liquid: ir (neat film) 3300, 1669, and 874 cm^{-1}; H-nmr ($CDCl_3$) δ 5.05 (t, J = 7 Hz, 1 H, $C{=}C{-}\underline{H}$, 3.55 (t, J = 7 Hz, 2 H, $C\underline{H}_2{-}OH$), and 1.58 (s, 3 H, $C{=}C{-}C\underline{H}_3$) overlapping a series of multiplets at 0.65 - 2.40 (15 H); ms (70 eV) m/e 170.1691 (M^+, calculated for $C_{11}H_{22}O$, 170.1667).

In summary, we have developed a very direct and efficient route to homoallylic alcohols bearing trisubstituted olefinic moieties. This method should be conveniently applicable to the synthesis of many naturally occurring compounds. For example, the product of run 2 contains a key portion of the carbon skeleton of a codling moth constituent,[22] and the product of run 3 contains a type of methyl-substituted olefinic unit commonly found in terpenoids. We are presently exploring some of the synthetic applications of our method.

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FOOTNOTES AND REFERENCES

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17. We do not intend to imply specific structures for any of the organometallic intermediates involved in this work.

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