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ALKYLATION OF ENOLATE IONS GENERATED REGIOSPECIFICALLY VIA ORGANOCOPPER CONJUGATE ADDITION REACTIONS. SYNTHESIS OF DECALIN SESQUITERPENE VALERANE AND OF A PROSTAGLANDIN MODEL SYSTEM

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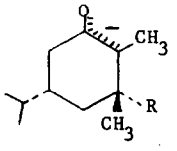
Regiospecific α-alkylation of unsymmetrical ketones is often difficult and yet highly desirable.[2] Various blocking and activating groups have been developed to direct α-alkylation of unsymmetrical ketones at the more or less highly substituted α-carbon atoms,[2a] and specific structural isomers of lithium enolates have been prepared from diverse types of enol derivatives and have been alkylated.[3] We have been studying alkylation reactions of several different structural types of cycloalkanone enolate ions which are generated regiospecifically via an organocopper reaction with an α,α'-dibromo ketone[4] or with a 2-cycloalkenone.[5] We present here our results on alkylation of cycloalkanone enolate ions 1 and 2 and on use of a new mixed cuprate(I) reagent; these results have led to a new total synthesis of the decalin sesquiterpene valerane and to a highly efficient method for construction of a model system for 11-deoxyprostaglandins E_2 and E_3.



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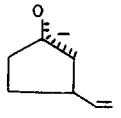
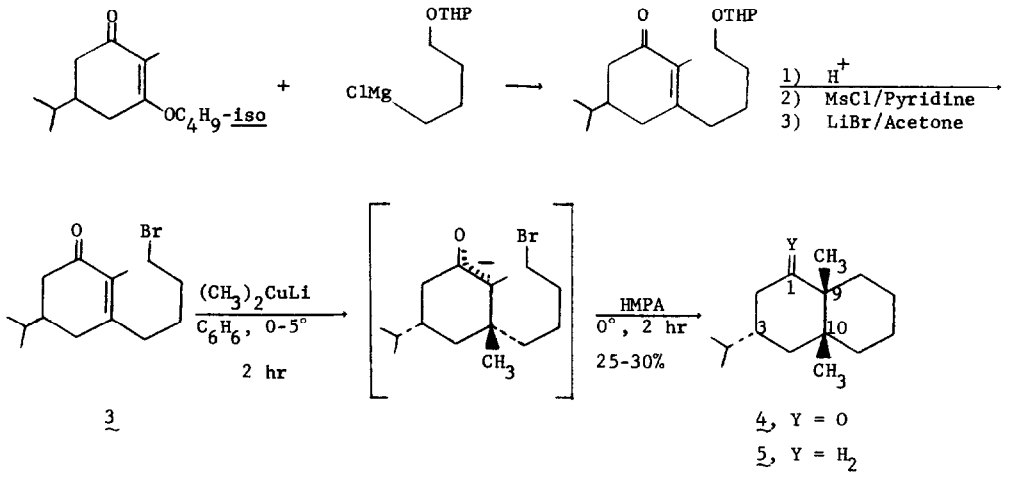


2

Conjugate addition of organocopper reagents to 2-cycloalkenones leads to specific enolate structural isomers some of which have been alkylated directly by reactive (e.g., methyl, allyl, and benzyl) halides,[6] and such conjugate additions have been used to prepare specific enol acetates and enol silyl ethers.[3] Conjugate addition of organocopper reagents to 5-alkyl-2-cyclohexenones stereoselectively introduces the newly attached group axially, trans to the 5-alkyl substituent.[7] We have now used a lithium dimethylcopper conjugate addition to a 5-isopropyl-2-cyclohexenone system not only to attach the transferred methyl group stereoselectively trans to the 5-isopropyl group but also to generate enolate ion 1 regiospecifically. If the R group in anion 1 were ω-bromobutyl, then intramolecular alkylation might be expected to occur. Indeed enolate ion 1 [R = $(CH_2)_4Br$] in benzene-HMPA solvent at 0° undergoes cycloalkylation to form cis-1-decalone 4 stereospecifically (scheme I, no trans-1-decalone is observed).[2c,8-10] The yield in this conjugate addition-cycloalkylation procedure (3→4) is about 30% by analytical glpc and about 25% after column chromatography; this yield has not yet been maximized, however. Reduction of decalone 4 produces d,l-valerane (5).[11] This two-step one-pot reaction of organocopper conjugate addition-cycloalkylation represents a novel, highly stereoselective entry into the valerane class of sesquiterpenes characterized by the

synthetically challenging angular cis-dimethyl substitution pattern.[12] Application of this method to efficient construction of other decalin (e.g., eudesmane, eremophilane) sesquiterpenes is in progress.

Scheme I



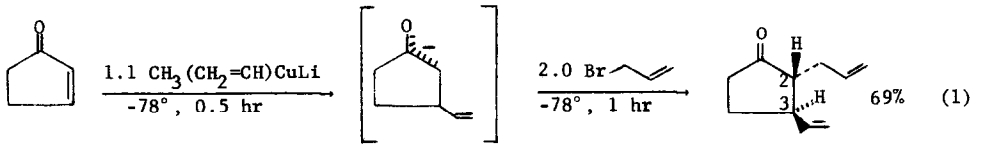
3

4, Y = O

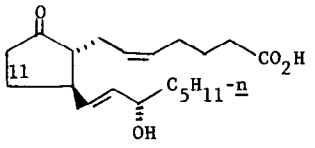
5, Y = H_2

Regiospecific alkylation of unsymmetrical cyclopentanones is notoriously difficult because cyclopentanones tend to self-condense in basic media and because cyclopentanone enolate ions equilibrate relatively rapidly.[2b,2c,13] Nevertheless, we have prepared specific enolate structural isomer 2 by a vinylcuprate conjugate addition to 2-cyclopentenone; anion 2 reacts with 2 equiv of allyl bromide at -78° for 1 hr to afford 2-allyl-3-vinylcyclopentanone (6) in 69% isolated yield after pruification (eq. 1).[14] Glpc analysis of the crude product of reaction 1 indicates the presence of only one stereoisomer of 6, trans-2-allyl-3-vinylcyclopentanone, and of two minor as yet unidentified side products (8% of each). Hydrogenation of the major product gave trans-3-ethyl-2-n-propylcyclopentanone,[14] the trans stereochemistry of which was unambiguously determined by nmr decoupling experiments using a europium shift reagent to separate α-methylene from α-methine absorptions; the C_2-H—C_3-H coupling constant[15] is 11 Hz.[16] A new mixed cuprate(I) reagent was developed for this vinyl conjugate addition-allylation procedure; lithium methyl(vinyl)cuprate is prepared conveniently and rapidly by adding 1 equiv of vinyllithium and then 1 equiv of methyllithium to 1 equiv of cuprous iodide in THF at -35°. The stoichiometry of the vinyl group transfer is good since only 1.1 equiv of the mixed cuprate is required to consume 1.0 equiv of 2-cyclopentenone.[17-20] Furthermore reaction of enolate ion 2 with allyl bromide is unaffected by the presence of methyl valerate, which is recovered in 75% yield. Treating anion 2 with n-butyl iodide in HMPA under various reaction conditions produces a mixture of 2-n-butyl-3-vinylcyclopentanone (40%) and

polyalkylated cyclopentanones (20%); nmr decoupling experiments using a europium shift reagent indicate unambiguously that the 2-n-butyl-3-vinylcyclopentanone is not contaminated by any 2-n-butyl-4-vinylcyclopentanone. Reaction 1 is the first published conjugate addition-direct alkylation of a cyclopentenone,[21] and it represents a highly efficient new method for conversion of cyclopentenones into cyclopentanones having the α,β-disubstitution pattern found in prostaglandins E_2 and E_3. Details of these transformations will be reported in a full paper.



2 6



11-Deoxy-PGE_2

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References

1. (a) NDEA Fellow, 1969 - 1972; taken in part from the Ph.D. thesis of Charles E. Whitten, The Johns Hopkins University, February, 1974;
   (b) Sonneborn Foundation Fellow, 1972 - present;
   (c) NSF Trainee, 1970 - present.

2. (a) For a good discussion with leading references on the difficulties in controlling α-alkylation of ketones, see H. O. House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, New York, N. Y., 1972, chapter 9; see also
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9. A mesyloxy group in place of the primary bromine atom causes organocopper direct displacement to compete effectively against conjugate addition.

10. Choice of benzene as solvent is critical; neither diethyl ether nor tetrahydrofuran produce as good results.

11. The spectral properties of d,l-valerane (5) prepared via scheme 1 are identical with those of 5 prepared independently and are distinctly different from those of d,l-isovalerane (having the angular methyl groups and the isopropyl group all cis): (a) P. N. Rao, J. Org. Chem., 36, 2426 (1971); (b) see also D. J. Dawson and R. E. Ireland, Tetrahedron Lett., 1899 (1968).

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19. Lithium methyl(vinyl)cuprate undergoes preferential transfer of the methyl group in coupling reactions with acid chlorides and epoxides, and transfer of both the methyl and the vinyl groups to the β-carbon atom of cyclopentenone occurs when diethyl ether is used as solvent instead of THF.

20. The near ideal stoichiometry in vinyl group transfer via eq. 1 will be of utmost importance for attachment of the optically active C_{13}-C_{20} vinyl side chains common to the prostaglandins; successful syntheses of prostaglandins already involve conjugate addition of optically active C_{13}-C_{20} vinylcuprates to 2-alkylcyclopentenones in which the 2-alkyl group contains the C_1-C_7 atoms found in natural prostaglandins: see J. B. Heather, R. Sood, P. Price, G. P. Peruzzotti, S. S. Lee, L-F. H. Lee and C. J. Sih, Tetrahedron Lett., 2313 (1973), and references cited therein.

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