

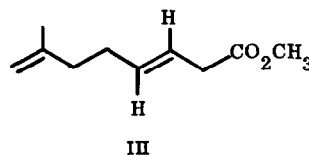
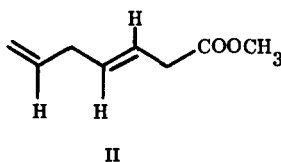
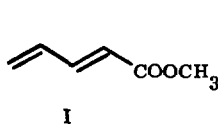
ADDITION OF ORGANOCOPPER REAGENTS TO $\Delta^{2,4}$ -DIENOIC ESTERS.
A HIGHLY STEREOSELECTIVE ROUTE TO TRI- AND TETRASUBSTITUTED OLEFINS

E. J. Corey and R. H. K. Chen

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

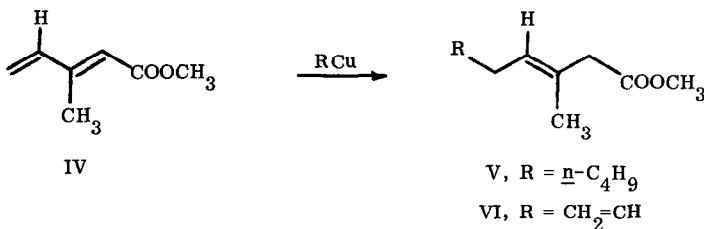
(Received in USA 23 February 1973; received in UK for publication 26 March 1973)

A stereospecific synthesis of $\Delta^{2,4}$ -dienoic esters by reaction of vinylic copper reagents with propargylic esters has recently been reported.¹ In the simplest cast, for example, methyl trans-2,4-pentadienoate (I) was obtained in 85% yield from vinyl copper and methyl propynoate (ether or tetrahydrofuran solution at -78° , followed by quenching with methanol at -78°). It was also noted that the reaction of I with vinylicopper and 2-methylcopper at -78° under these same conditions afforded with >98% stereospecificity the trans- Δ^3 esters II and III, respectively. This communication reports our further work on



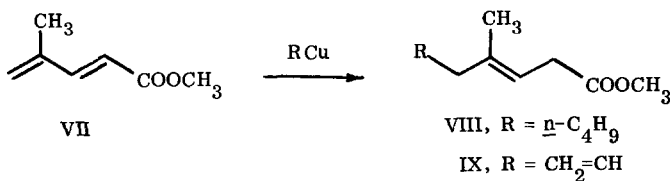
this extraordinary "overall 1,4-addition" reaction and its adaptation as a new method for the stereoselective synthesis of tri- and tetrasubstituted olefins.

Reaction of methyl trans-3-methyl-2,4-dienoate (IV) with ca. 2.2 equiv. of n-butylcopper or vinylcopper² in ether at -20° (initial temperature -78°) for ca. 2.5 hr. followed by quenching with cold (-20°) methanol produced the E olefins V (75% yield) and VI (55% yield), respectively, in >95% stereochemical purity as determined by vapor phase chromatographic (v. p. c.) analysis.^{3,4} In contrast, treatment of IV with the n-butyl or vinyl cuprate reagents R_2CuLi at -78° in ether for 10 min. followed by quenching with methanol at -78° resulted in nonstereoselective addition to give in each case a mixture of Z and E isomers

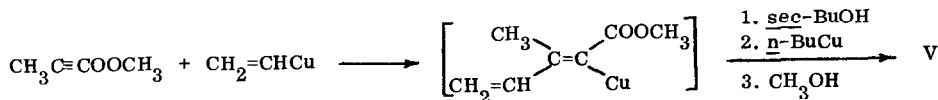


($\underline{Z}/\underline{E}$ ratio of 55:45 for V and 45:55 for VI). The assignment of stereochemistry to the \underline{E} and \underline{Z} isomers of V and VI was made by the observation of relative p. m. r. chemical shifts for the two stereoisomers of the groups attached to C(4) relative to one another and to shifts for groups attached to C(3) and COOCH_3 protons using the "shift reagent" $\text{Eu}(\text{fod})_3$.⁵ For example, the magnitude of the shift for the 3-methyl substituent relative to COOCH_3 was the same for the \underline{E} and \underline{Z} isomers, but the olefinic proton at C(4) underwent a 50% larger shift relative to 3-methyl or COOCH_3 in the isomer designated as \underline{E} (V) than in the isomer designated as \underline{Z} .⁶

The reaction of methyl *trans*-4-methyl-2,4-dienoate (VII) with *n*-butylcopper or vinylcopper² at -20 to -30° in ether was somewhat slower than with IV as substrate, but was still stereoselective to give in each case the \underline{E} isomer VIII (70% yield, $>96:4 \underline{E}/\underline{Z}$ ⁴) and IX (35% yield, $93:7 \underline{E}/\underline{Z}$ ⁴), respectively. Again, as was the case with substrate IV, the reaction of the conjugated ester VII with cuprate reagents R_2CuLi was fast at -78° but relatively nonselective, the formation of \underline{E} isomer being somewhat favored.



The stereoselective synthesis of V in a very convenient, direct operation from methyl 2-butyrate could also be accomplished according to the following outline:

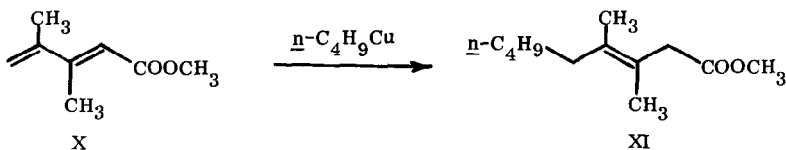


The procedures given immediately below are illustrative.

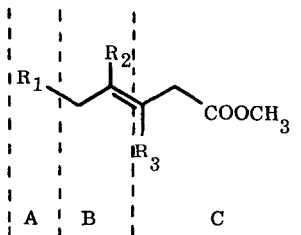
A. Methyl E-4-methyl-3 nonenoate (VIII). To 5 ml. of an isopropyl sulfide solution² of cuprous iodide (10 mmol.) and 30 ml. of ether, 7 ml. (1.4 M, 9.8 mmol.) of n-butyllithium in hexane was added at -78° under argon. The yellow colored reagent was formed almost instantly. Methyl trans-4-methyl-2,4-pentadienoate (VII) (550 mg., 4.4 mmol.) in 2 ml. of ether was added at -78°, and the reaction mixture was well stirred at -20° (dry ice--CCl₄ bath) for 2.5 hr., then quenched with cold (-20°) methanol. The crude product was isolated by adding saturated aqueous ammonium chloride solution and ether, extracting with ether, drying over magnesium sulfate, and concentrating under reduced pressure below 30°. V. p. c. analysis⁴ of this crude yellow product showed E and Z isomers of VIII in a ratio of 96:4. The ester VIII was isolated by bulb to bulb distillation at 105° (22 mm.) which gave 554 mg. (70%) of VIII³ having 99% purity by v. p. c. analysis;⁴ found: molecular ion at m/e 184.1463 (calcd. 184.1463), carbonyl absorption at 1742 cm.⁻¹

B. Methyl E-3-methyl-3-nonenoate (V) Directly from Methyl Butynoate. To 2.5 ml. of isopropyl sulfide solution² of cuprous iodide (5 mmol.) and 25 ml. of ether was added 1.8 ml. of 2.7 M vinyl lithium reagent in THF at -78° under argon, and stirring was continued at this temperature for 30 min. To this reagent, 210 mg. (2.35 mmol.) of methyl-2-butynoate in 1 ml. of ether was added. The mixture was stirred for 25 min. at -78°, quenched with 370 mg. (5 mmol.) of sec-butyl alcohol in 0.5 ml. of ether at -78°, and then allowed to warm to 0° (a black precipitate was formed). The total reaction mixture was then transferred by syringe to a prepared solution of 5 mmol. of n-BuCu in 15 ml. of ether at -78°. The mixture was warmed to -20° (dry ice--CCl₄) and stirred at this temperature for 3 hr., then quenched with cold (-20°) methanol. The crude product was isolated as described above for VIII. A concentrated pentane solution of the crude product was placed on a column of 1.5 g. of silica gel which was washed with an additional 10 ml. of pentane to remove nonpolar hydrocarbon materials which were present in the commercial vinyl lithium reagent which was used. Elution of the product V was effected by washing the column with 50 ml. of ether. Removal of ether and distillation at a bath temperature of 110° (24 mm.) gave 210 mg. (50%) of the desired E ester V,³ infrared max at 1741 cm.⁻¹, molecular ion at m/e 184.1466.

The stereoselective formation of the trisubstituted olefins V and VI from IV and VIII and IX from VII can be associated with a transition state structure in which the groups attached to C(3) and C(4) of the diene unit are trans and coplanar with the C(3)-C(4) bond, a structure which in turn can be related to an s-trans conformation of the 1,3-diene unit.⁷ This geometric preference was also observed for the reaction of n-butylcopper with the substrate methyl trans-3,4-dimethyl-2,4-dienoate (X) which afforded in 76% yield methyl E-3,4-dimethyl-3-nonenoate (XI) with >99% stereoselectivity.^{3,4} To our knowledge there is no previously described method which is comparably effective for the stereoselective synthesis of tetrasubstituted olefins such as XI.



In summary, the above described processes open up practical and highly stereoselective routes to β,γ -unsaturated esters of type XII. Parts A, B, and C of structure XII originate from the reagents R_1Cu , $H_2C=C(R_2)Cu$, and $R_3C\equiv CCOOCH_3$, respectively.⁸



XII

References

1. E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *J. Amer. Chem. Soc.*, **94**, 4395 (1972). See also E. J. Corey and J. A. Katzenellenbogen, *ibid.*, **91**, 1851 (1969); J. B. Siddall, M. Biskup, and J. H. Fried, *ibid.*, **91**, 1853 (1969); and F. Näf and P. Degen, *Helv. Chim. Acta*, **54**, 1939 (1971), *idem*, *ibid.*, **55**, 82 (1972), for other examples of stereoselective *cis*-1,2-addition of organocopper reagents to propargylic esters.
2. The organocopper reagents were prepared by reaction of a slight excess (2% over 1 equiv.) of cuprous iodide in isopropyl sulfide (0.5 ml./mmol. of CuI) and ether with commercial solutions of *n*-butyllithium (in hexane) or vinylolithium (in tetrahydrofuran). All reactions and manipulations involving organometallic reagents were performed under an inert atmosphere (N_2 or argon).
3. Satisfactory infrared, proton magnetic resonance (p.m.r.), and high resolution mass spectral data were obtained for each new substance reported herein.
4. Analysis performed at 100° using a 6-ft. x 0.12-in. column with 5% of silicone (SE 30) as liquid phase.
5. See R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971); J. W. de Haan and W. J. M. van de Ven, *Tetrahedron Lett.*, 2703 (1971), K. Tsukida, M. Ito, and F. Ikeda, *Experientia*, **28**, 721 (1972).
6. In general, the assignments made herein follow the rule that the group at C(4) which showed the greater sensitivity to shift by the reagent $Eu(fod)_3$ is that which is *cis* to the CH_2COOCH_3 unit.⁵
7. An alternative explanation based on a thermodynamic preference for formation of the organocopper intermediate of \underline{Z} configuration cannot now be excluded.
8. This work was assisted financially by grants from the National Institutes of Health and the National Science Foundation.