

A New Synthesis of Olefins and Dienes: Steroids

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LITHIUM DIMETHYLCOPPER(I) is a versatile reagent effective for the methylation of organic bromide and iodides¹ and for the synthesis of allenes from prop-2-ynyl acetates.²

We report a stereoselective synthesis of olefins and the synthesis of a substituted diene, with organo-copper(I) reagents. Addition of the olefin (I) to a 50% excess of LiMe₂Cu in ether at -10° and storage of the reaction mixture at room temperature overnight gave (II)† [33% after work up and chromatography (Florosil), m.p. 40—41°‡ (MeOH); [α]_D + 67°; λ_{max} 278 (ε 1900) and 287 nm. (1820); n.m.r.: 0.76 (s, 18-H), 0.94 (t, CH₂-CH₃, J 9 Hz), 1.92 (br q, -CH₂-CH₃, J 7 Hz), 5.0 (br s, =CH)]. In addition starting material (34%) and (III) (23%, m.p. and mixed m.p. with an authentic sample 108°), were obtained on further elution of the column.¹ The configuration of the 17-(*exo*) double bond was assigned, with the ethyl substituent *trans* to the 18-methyl group, on the basis of the 18-H chemical shift.³

Reaction of (I) with the organocopper(I) reagents, LiBu₂Cu and LiPh₂Cu, gave the corresponding olefin (IV) as an oil [40%; [α]_D + 57°; λ_{max} 278 (1900), 287 nm. (1820) n.m.r.: 0.76 (s, 18-H), 5.0 (br m, =CH); *m/e* 352 (*M*⁺)] and (V) [m.p. 99—101° (MeOH); [α]_D + 50°; λ_{max} 270 (1550), 278 (2090), 287 nm. (1860); n.m.r.: 0.83 (s, 18-H), 3.33 (d, -CH₂-Ph, J 7 Hz), 5.26 (broad s, =CH); *m/e* 372 (*M*⁺)] in 29% yield. Both (IV) and (V) were accompanied by starting material and the by-product (III). The *trans*-configuration was assigned to the 17-double bond in (IV) and (V) by analogy with (II). No evidence indicating the presence of the geometric isomer at C-17 could be obtained on examination of various fractions from column chromatography, by t.l.c., or by high resolution n.m.r.

A similar reaction of the *gem*-difluorocyclopropene steroid (VI)⁴ with a ten-fold molar excess of LiMe₂Cu gave a single product (VIII) [74%; m.p. 90—91°; [α]_D + 93°; λ_{max} 230 (18,670), 278 (1900), and 287 nm. (1740)]. Compound (VII),⁵ under identical conditions, gave (IX) in low yield, [m.p. 45—47°; λ_{max} 240 nm. (14,130)].

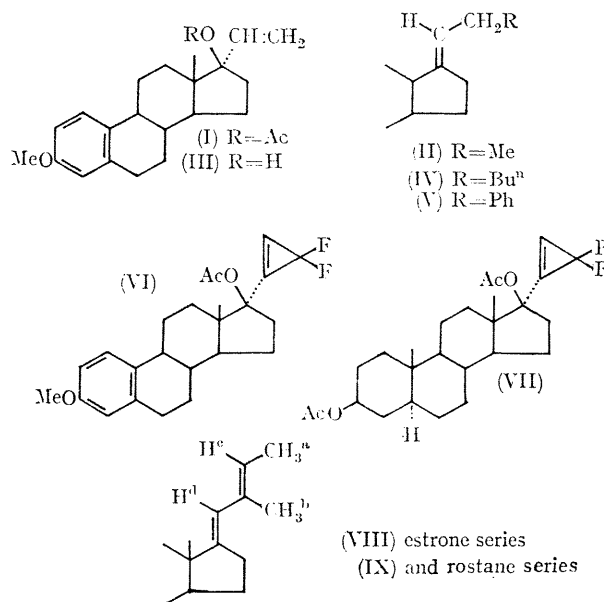
† Satisfactory elementary analyses were obtained for all new compounds.

‡ M.p.'s were taken on a Fisher-Johns apparatus. Optical rotations were measured at 27° in CHCl₃. U.v. spectra were measured in EtOH on a Beckman DU spectrometer. N.m.r. spectra, unless otherwise stated, were recorded on Varian A60 or T-60 spectrometers, in CDCl₃. Chemical shifts δ (p.p.m.) downfield from internal tetramethylsilane standard.

§ The u.v. absorption maximum of (IX) is in agreement with the predicted value (R. B. Woodward, *J. Amer. Chem. Soc.*, 1942, 64, 72) of 242 nm., while a long range interaction with the benzene chromophore may be responsible for the 12 nm. shift to lower wave length in the absorption maximum of (VIII).

The structure of compounds (VIII) and (IX) is based mainly on the u.v.,§ n.m.r. and mass spectral data. The mass spectrum of (VIII) exhibited a molecular ion at *m/e* 336, indicating replacement of the two fluorine atoms and the acetyl group by two methyl groups and a hydrogen in the side chain. The relevant features of the n.m.r. spectra (100 MHz) are summarized in the Table.

Assignment	(VIII)	(IX)	Appearance
18-H	0.83	0.79	s
a	1.62	1.59	Br d, J 7.5 Hz
b	1.85	1.82	Unresolved quartet
c	5.25	5.20	Br m
d	5.81	5.74	Br s



The chemical shifts and coupling constants are in good agreement with values reported for similar systems.⁶

Irradiation of (VIII) at the frequency of group a decoupled the protons of b and c, the resultant signals being a slight broadened singlet for b and broad singlet for c. These broadenings are the result of long-range coupling between protons b and c. Irradiation at the frequency of group b exposed a 1:4:4:1 quartet for proton c (J_{ac} 6 Hz), but the broad signal of proton d was not affected. The broadening of the signal of proton d, results from allylic coupling with the C-16 proton (J 1 Hz).

The configuration of the C-17 double bond is not established but on the basis of the observed 18-H chemical shift,³ the side chain is probably *trans* to C-18.

The transformations reported here, together with the reaction of organocopper(I) compounds with prop-2-ynyl acetates,² establish the further usefulness of organocopper reagents for the synthesis of olefins and possibly for substituted butadienes.

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¹ E. J. Corey and G. H. Posner, (a) *J. Amer. Chem. Soc.*, 1967, **89**, 3911; (b) 1968, **90**, 5616.

² P. Rona and P. Crabbé, *J. Amer. Chem. Soc.*, 1968, **90**, 4733.

³ A. M. Krubiner, N. Gottfried, and E. P. Oliveto, *J. Org. Chem.*, 1968, **33**, 1715, reported the synthesis of the corresponding *cis*-isomer. The 18-H signal in the n.m.r. spectrum of this compound appears at 0.90 p.p.m. The value reported for the *trans*-methyl analogue (0.77 p.p.m.) is in good agreement with our results.

⁴ P. Anderson, P. Crabbé, A. D. Cross, J. H. Fried, L. H. Knox, and E. Velarde, *J. Amer. Chem. Soc.*, 1968, **90**, 3888.

⁵ E. Velarde and P. Crabbé, unpublished result.

⁶ (a) M. G. Barber, A. Hardisson, L. M. Jackman, and B. C. L. Weedon, *J. Chem. Soc.*, 1961, 1625; (b) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Varian NMR Catalog, Varian Associates, Palo Alto, California 1962.