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ON THE STEREOCHEMICAL COURSE OF CUPRATE-MEDIATED HOMOCONJUGATE ADDITION TO AN ACTIVATED CYCLOPROPANE

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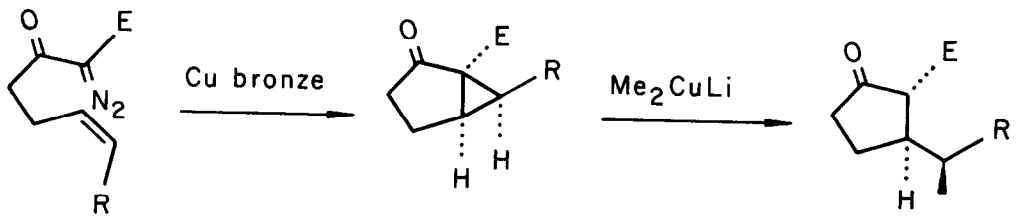
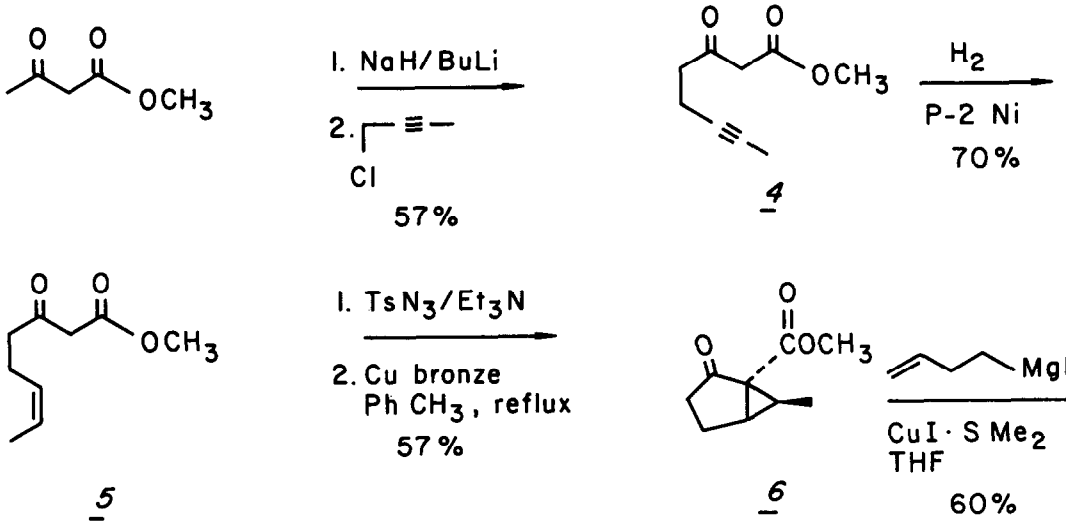
SUMMARY: Cuprate-mediated homoconjugate addition to activated cyclopropane 6 is shown to proceed with inversion of absolute configuration at the apical carbon of the cyclopropane.

A variety of natural products (e.g. vitamin D, ophiobolin, juvabione, the pseudoguaianolides) have both ring and side-chain chiral centers. The sequence cyclopropanation-homoconjugate addition [2] (1→2→3) is one of the few strategies for ring formation that allow direct control of side-chain stereochemistry [3]. Although it has been commonly accepted [2a-c] that cuprate-mediated homoconjugate addition proceeds with inversion of absolute stereochemistry at the apical center (2→3), this point has never been demonstrated in a sterically unconstrained system. The best evidence to date has been that of Casey [4], who showed that such a process with a monoactivated cyclopropane proceeded to give a stereochemically homogeneous product. As side-chain stereochemistry is critical to a synthetic project we currently have in hand, we have investigated this point. We now report that homoconjugate addition of an alkyl cuprate to an activated cyclopropane does indeed proceed with inversion of absolute configuration.

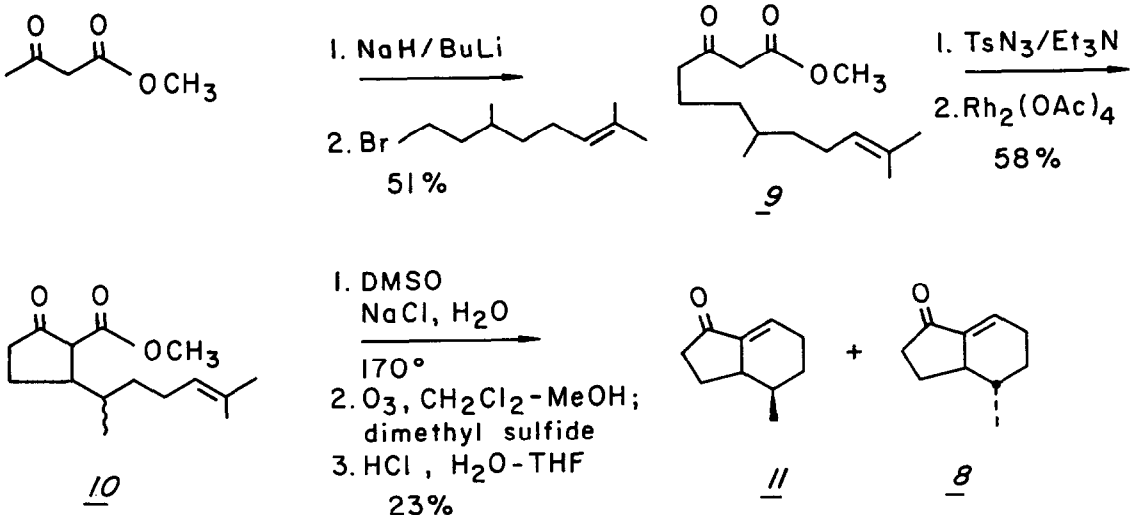


1 2 3

SCHEME I



SCHEME II



We chose to examine homoconjugate cuprate addition to cyclopropyl ketone 6. This substrate was readily prepared (Scheme I) by alkylation [5] of the dianion of methyl acetoacetate with 1-chloro-2-butyne [6]. To avoid ketone reduction during hydrogenation of 4 to 5, acetone (to quench any excess hydride) was added to P-2 nickel catalyst prepared by the method of Brown [7]. Diazo transfer [8] and copper-mediated cyclopropanation [9] then proceeded smoothly to give 6 [10].

Cuprous iodide-mediated homoconjugate addition of the Grignard reagent derived from 4-bromo-1-butene to 6 proceeded smoothly in THF. Decarbomethoxylation [11], ozonolysis and aldol condensation [12] then gave enone 8 as a single diastereomer (^{1}H NMR = 1.05, d, 3H). As this chemical shift is consistent with that of the exo diastereomer of a closely-related enone prepared by Evans (structure 14b in ref. 3a, ^{1}H NMR = 1.16, d, 3H), we concluded that homoconjugate addition to 6 does indeed proceed with inversion of absolute configuration at the apical carbon of the cyclopropane.

This strucutral assignment was further supported by deliberately preparing a mixture of 8 and its diastereomer 11 (Scheme II). Thus, alkylation [5] of the dianion of methyl acetoacetate with citronellyl bromide followed by diazo transfer [8] and intramolecular C-H insertion [13] led to 10 as a mixture of diastereomers. Decarbomethoxylation [11], ozonolysis and aldol condensation [12] as above then provided a mixture of 8 and 11 (^{1}H NMR = 1.05, d, 3H; 0.78, d, 3H; 43:57). Again, chemical shift of the methyl group of 11 correlated well with that for the endo isomer (structure 14a in ref. 3a, ^{1}H NMR = 0.85, d, 3H) in the Evans series. The enone mixture prepared from 6 (Scheme I) was > 95:5 8:11.

These assignments, while reasonable, are circumstantial. To eliminate any uncertainty, an X-ray structure [14] was obtained on the crystalline thiosemicarbazone of 7, fully confirming the relative stereochemistry shown.

Having established the steroechemical course of cuprate-mediated homoconjugate addition to an activated cyclopropane, we are now investigating the possibility of diastereofacial discrimination in the cyclopropanation step. Early results from these studies have been encouraging.

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10. 6: TLC R_f (20:80 EtOAc/hexane) = 0.15, IR: 2905, 1730, 1705, 1410, 1280, 1235, 1175, 1010 cm^{-1}; ^1H NMR: 1.18, d, J = 7, 3H; 1.84-2.7, m, 6H; 3.75, s, 3H; ^{13}C NMR: 7.9 (q), 16.7 (t), 27.9 (d), 37.0 (d), 38.5 (t), 41.6 (s), 51.5 (q), 167.9 (s), 205.2 (s); MS: 168 (100), 140 (65), 137 (67), 136 (98), 126 (88), 108 (82). Exact mass calculated for $C_9H_{12}O_3$ 168.078; observed 168.076.

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14. (a) The atomic co-ordinates for this work are available on request from the Cambridge Crystallographic Data Centre, University of Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW, UK. Any request should be accompanied by the full literature citation for this communication.

    (b) Supplementary data available: ORTEP plot of the thiosemicarbazone of 7, as well as derived crystal data, atom coordinates, isotropic and anisotropic temperature factors, bond lengths, bond angles, and observed and calculated structure factors. See Announcement to Authors, Tetrahedron Letters 47, 5154 (1983).

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