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REGIOCONTROLLED SYNTHESIS OF BICYCLO[3.2.1]OCTANE DERIVATIVES BY CUPRATE ADDITION AND INTRAMOLECULAR ACYLATION

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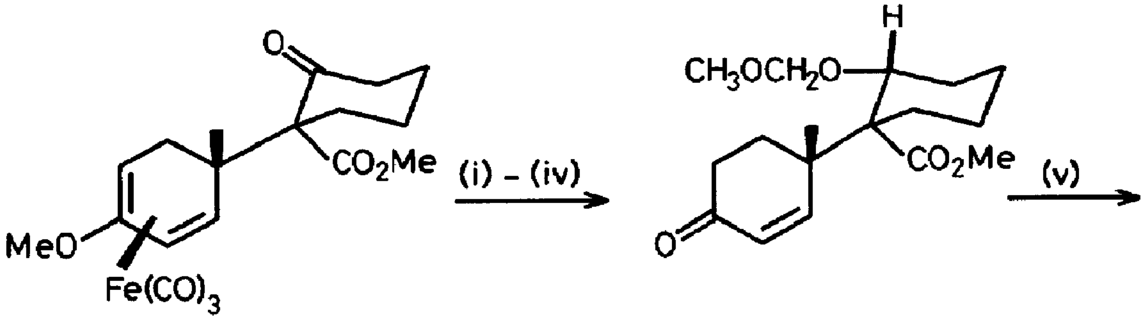
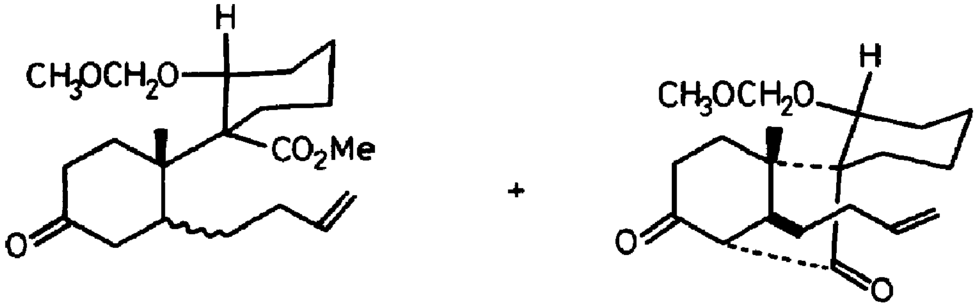
Summary: Copper-catalysed reaction of 4-butenylmagnesium bromide with cyclohexenones (2) and (5) occurs with intramolecular acylation of the intermediate enolate to give bicyclo[3.2.1]octane derivatives (4) and (6).

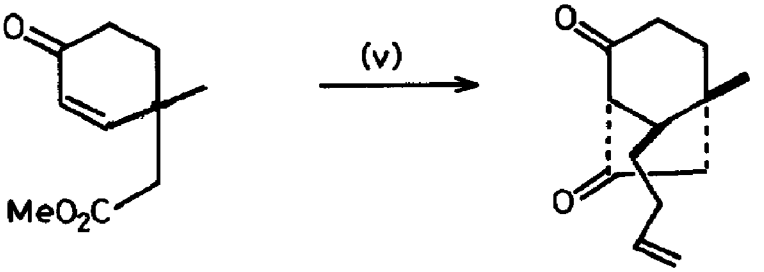
During the course of another investigation we required to study the reaction, with suitable functionalised cuprate reagents, of the 4,4-disubstituted cyclohexenone (2), readily obtained from the cyclohexadiene-Fe(CO)$_3$ complex (1)[1] by the steps indicated below.[2] We chose as a suitable reagent the cuprate derived from 4-butenylmagnesium bromide. At low temperatures (-35 to -40°C), reaction of the Grignard reagent (4-5 equiv.) with the enone (2), in the presence of cuprous bromide (25 mol %, THF, 4-5 h), followed by quenching with saturated aqueous NH$_4$Cl, gave the alkylation product (3)[3] (40-50% at 90% conversion), which was required as part of a model study towards aphidicolane and stemodinane syntheses, together with a smaller amount of a faster running component (t.l.c., silica gel, 10% EtOAc-C$_6$H$_6$; 15-20%). When this reaction was conducted at slightly higher temperature (-20 to -23°C) the latter compound became the major product, as a single stereoisomer (n.m.r.) (60% at 80% conversion). Spectroscopic data were in accord with structure (4) for this new compound,[2] the result of intramolecular reaction of the enolate, formed during conjugate addition, with the ester group. Although this behaviour has been observed for halides[4] and aldehydes or ketones,[5] so far as we are aware there are no recorded examples of this type of acylation. The stereochemistry of (4) follows from the known mode of cuprate addition where attack occurs preferentially at the less hindered face of the cyclohexenone.[6]



(1) (2)



(3) (4)



(5) (6)

Reagents:

(i) $NaBH_4$, DME-MeOH, 80%.

(ii) CH_3OCH_2Cl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, reflux, 100%.

(iii) Me_3NO, C_6H_6, reflux, 93%.

(iv) Oxalic acid, $MeOH$-H_2O, 70%.

(v) $CH_2{:}CH(CH_2)_2MgBr$, CuBr, THF, temperature as in text.

The simpler enone (5), which was available from our earlier studies,[7] was also examined in this reaction. Subjection of this compound to similar conditions (C_4H_7MgBr, CuBr, THF, -28 to -12°C, 3.5 h) gave as the major product (60%) the bicyclo[3.2.1]octane derivative (6). The observation of a doublet (4.5 Hz) for angular proton H_z establishes that the structural integrity of the enolate intermediate is maintained during this reaction. However, the coupling constant is that expected for either the equatorial/equatorial protons in (6), or the axial/equatorial protons in helminthosporal derivatives (3.6-4.8 Hz)[8] which have the alternative stereochemistry. Consequently, our assignment is tentative and is based on the literature precedent for cuprate additions.[6]

This reaction is interesting in view of the widespread occurence of this ring system in natural products related to gibberellic acid and helminthosporal.

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References and Notes

1. A.J. Pearson, E. Mincione, M. Chandler and P.R. Raithby, J.C.S. Perkin I, in press.
2. All new compounds were obtained as racemates and gave satisfactory analytical and spectroscopic data, as follows:

   Compound (2): m.p. 48-49°C; ν_{max} ($CHCl_3$) 1728, 1673 cm^{-1}; $\delta(CDCl_3)$ 7.27 (1H, dd, J 11, 2.5 Hz), 5.75 (1H, d, J 11 Hz), 4.55 (2H, ABq, J 7 Hz, $C\underline{H}_2OMe$), 3.73 (3H, s), 3,6 (1H, m), 3.32 (3H, s), 2.6-1.1 (12 H), 1.21 (3H, s). M 310. Found: C 65.91, H 8.34; $C_{17}H_{26}O_5$ requires: C 65.78, H 8.44%.

   (4): m.p. 78-79°C; ν_{max} (CCl_4) 3080, 1745, 1715, 1645, 920 cm^{-1}; $\delta(CDCl_3)$ 5.7 (1H, m), 5.05 (1H, d, br, J 8 Hz), 4.88 (1H, s, br), 4.63 (2H, s, C$\underline{H}_2$O), 3.53 (1H, dd, J 11, 6 Hz), 3.30 (3H, s), 3.0-1.1 (18 H), 1.07 (3H, s). M 334.2111, $C_{20}H_{30}O_4$ requires 334.2144. Found: C 72.02, H 9.12. Requires C 71.82, H 9.04%. (6): colourless oil, ν_{max} (CCl_4) 3082, 1757, 1720, 1645, 997, 920 cm^{-1}; δ($CDCl_3$) 5.7 (1H, m), 5.03 (1H, d, br, 6 Hz), 4.85 (1H, s, br), 3.21 (1H, d, 4.5 Hz), 2.5-1.1 (10 H), 1.19 (3H, s, Me). M 206.1297, $C_{13}H_{18}O_2$ requires 206.1298.

3. Approx. 2:1 mixture of stereoisomers. Further details will be published elsewhere.
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5. F. Näf, R. Decorzant and W. Thommen, Helv. Chim. Acta., 1975, 58, 1808.
6. G.H. Posner, Org. Reactions, 1972, 19, 1, and references cited therein.
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