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DIASTEREOSELECTIVE METHYLATION OF 2,3-DIALKYLCYCLOPENTANONE ENOLATES

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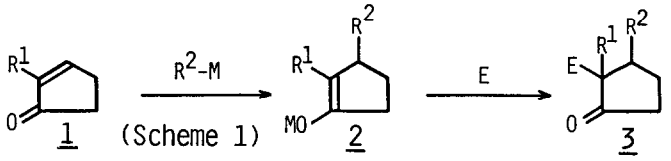
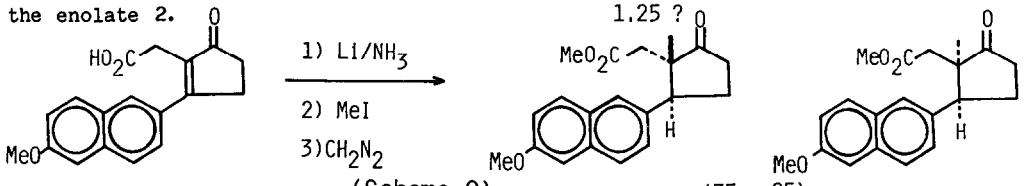
Summary: Diastereoselective methylation of the enolates derived by the Michael addition to 2-alkylcyclopentenones **4**, **7** gave the unexpected products **5**, **8**, and **10** formed by the cis attack of electrophiles from a hindered side as the major isomers.

Regio- and stereoselective carbon-carbon bond formation at α- and β-positions in cyclopentenones is an important operation in natural product syntheses. As a typical example, Michael addition to the enone 1 and subsequent trapping of the resulting enolate 2 with various electrophiles (alkyl halides[1-4], α-silylvinyl ketone[5]) are well documented(Scheme 1). The stereochemical consequences of alkylation of 2,3-dialkylcyclopentanone enolate 2 have been explained by two factors[3a] ; steric approach control (early transition state) and product development control (late transition state). Most experimental results [2,3]suggest that the stereochemistry of enolate alkylation is controlled by the steric approach factor (less hindered side attack[6]).



(Scheme 1)

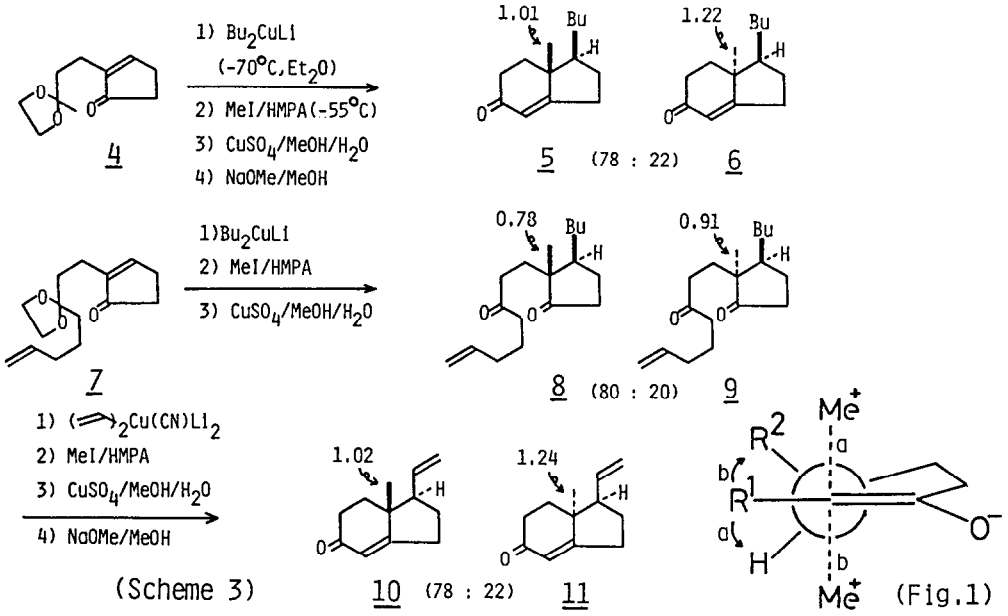
The single example (Scheme 2) reported by Birch[7] supports the product development control. But Evans questioned in his comprehensive review[6] that the stereochemical assignment appeared to be ambiguous and should probably be reversed[8]. Thus none of stereochemical studies on alkylation of 2 supports positively the product development control. In this paper, we wish to report the first solid evidence of the product developement control in the methylation of the enolate 2.



(Scheme 2) (75 : 25)

A typical procedure for the conjugate addition-enolate trapping with methyl iodide is as follows (Scheme 3): Treatment of the enone **4** with dibutylcuprate (formed from 2 equiv. of n-BuLi and 1 equiv. CuI) in ether at -70°C gave the Cu-enolate which was transformed to the Li-enolate at -30°C. Addition of an excess of HMPA to the Li- enolate, followed by addition of MeI at -55°C afforded a mixture of methylated diastereoisomers that was inseparable by HPLC and gas chromatography. This mixture was treated with $CuSO_4$/MeOH/ H_2O at reflux, and basic

treatment (NaOMe/MeOH at reflux) gave the enones **5** and **6** in a ratio of 78 : 22 (70% overall yield) as determined by ^{1}H-NMR spectrum[9] and HPLC analysis. The major product in the methylation was formed by the **cis** addition of the methyl to butyl group. Similarly a 80 : 20 mixture of the diketones **8** and **9**[10] was obtained in 72% overall yield from the enone **7** . The addition of higher order cuprate $(vinyl)_2Cu(CN)Li_2$ to the enone **4** gave the enones **10** and **11** in a ratio of 78 : 22 (60% overall yield). Our tentative explanation for preferential formations of cis-isomers **5**, **8** and **10** in the above reactions is that the transition state developed from the less hindered side attack (path b in Fig. 1) suffers from the eclipsing interaction between two bulkier groups (R^1 and R^2), while the transition state from the hindered side attack (path a) does not experience this unfavorable interaction. Therefore, the methylation proceeds in such a way as to make two adjacent larger groups becoming trans to each other[11] (Product development control). Previous results[2,3] can also be explained by the same factor.



(Scheme 3) (Fig.1)

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