3. SYNTHESIS OF SUBSTRATE MOLECULES (Schemes)

The substrates, chosen for our study were a decalone based $\beta$-keto esters (Scheme 3.1). Depending on the nature of the C-8a group, the substrates were denoted as substrate $81$ $R = $H; $85$ $R = $ Me; $92$ $R = $ COOEt where the groups were hydrogen, methyl carbethoxy respectively; the NMR evidence shows that all the 3 substrates exist predominantly in enol forms in the equilibrium mixture.

\[
\text{Scheme 3.1}
\]

3.1 SYNTHESIS OF SUBSTRATE $81$ $R = $H (methyl (4aR,8aR)-3-oxoperhydro-2-naphthalenecarboxylate)

The $\beta$-ketoester $81$ was synthesized according to the Scheme 3.2. Cyclohexanone enamine was treated with methyl vinyl ketone (MVK) at pH 5, to furnish Robinson annulation product $79$. Reduction of $79$ with Li / NH$_3$ followed by PCC oxidation of the reduced product mixture provided ketone $80$. Regioslective methoxycarbonylation under thermodynamic control yielded $81$ (75%).

3.2 SYNTHESIS OF SUBSTRATE $85$ $R = $Me (methyl (4aR,8aR)-8a-methyl-3-oxoperhydro-2-naphthalenecarboxylate)

The ketoester $85$ was synthesized according to the scheme 3.3. Methyl cyclohexanone $82$ was treated with MVK in the presence of catalytic amount of concentrated H$_2$SO$_4$ to furnish Robinson annulation product $83$. Reduction of $83$ with Li / NH$_3$ followed by PCC oxidation of the reduced product mixture provided ketone $84$. Regioslective methoxycarbonylation under thermodynamic control yielded $85$ (74%).

3.3 SYNTHESIS OF SUBSTRATE $92$ $R = $ COOEt (8a-ethyl 2-methyl (4aR,8aS,)-3-oxoperhydro-2,8a-naphthalenedicarboxylate)

The ketoester $92$ was synthesized according to the Scheme 3.4. 2-Carbethoxycyclohexanone $87$ was prepared by jlylalio of the enamine of cyclohexanone using ethyl chloroformate. The $\beta$-keto ester $87$ was transformed to decalone via diketone $88$ using Robinson annulation with Ni(acac)$_2$ catalyst.$^{89}$ The reduction of enone $89$ to the ketone $90$ having trans ring junction was achieved by using PtO$_2$ / H$_2$.$^{90}$ Carboxymethylation under thermodynamic control resulted in $\beta$-keto ester $92$. The NMR spectra of ($^1$H NMR and $^{13}$C
NMR) of 95 revealed the predominance of enol tautomer to the extent of more than 90% in the equilibrium mixture.

Reagents, conditions and yields: i. a. pyrrolidine, MVK, benzene, reflux, 24 h, b. AcOH, H2O / AcONa (2:2:1) buffer, reflux, 4 h, 71%; ii. a. Li / NH3, Et2O, t-BuOH, b. NH4Cl, c. PCC, CH2Cl2, 0.5h, 60%; iii. DMC, NaH, benzene, reflux, 6h, 75%.

Scheme 3.2

Reagents, conditions and yields: i. MVK, H2SO4 (cat), benzene, reflux, 6 h, 50%; ii. a. Li / NH3, Et2O, t-BuOH, b. NH4Cl, c. PCC, CH2Cl2, 0.5h, 74%; iii. DMC, NaH, benzene, reflux, 6h, 75%.

Scheme 3.3
Reagents, conditions and yields: i. morpholine, ethylchloroformate, benzene, reflux, 10 h, 62; ii. MVK, 1 mol% Ni (acac)$_2$, 1, 4 dioxan, $85^\circ$C, 18 h, 92%; iii. pyrrolidine, benzene, AcOH, H$_2$O / AcONa (2:2:1) buffer, reflux, 7 h, 92%; iv. PtO$_2$ / H$_2$, EtOAc, rt, 4 h, 98% iv. DMC, NaH, benzene, reflux, 10 h, 89%.

Scheme 3.4

4. EXPERIMENTAL TECHNIQUES

As our objective of this experimental probe is to bring out a possible demonstration of the influence of remote substituent in alkylation of a ketone enolates, in this study, we have conducted benzylolation of keto esters 81, 85 and 92 with electronically finely tuned benzyl bromide. We have selectively chosen the substrates, alkylating agent, base and solvent to meet our objective.

The substrates chosen for present study 81, 85 and 92 were trans decalone based $\beta$-keto esters. The trans decalones have the inherent advantage in the sense that they are conformationally immobile and therefore, effects due to flipping (dynamic effects) in the rings are avoided. It appeared to us that if the stereoselectivity of alkylation on a system 92 having C-8a-COOR functionality lies in between those systems with hydrogen 81 at C-8a-position and methyl group 85 at C-8a-position, the result would indicate a lesser degree of steric hindrance offered by an ester group. However, a more profound change would advocate stereoelectronic effects due to syn-axial ester group. Previously in our laboratory, Rao and Reddy studied methylation and benzylolation reactions on 81, 85 and 92. However their results