CHAPTER 1
SYNTHEtic ELABORATIONS ON CHALcone AND ITS DERIVATIVES

1.1 Introduction

Chalcone (benzylidene acetophenone or 1,3-diphenyl-2-propen-1-one) and its derivatives constitute a distinct class of secondary metabolites. In addition, they are the biosynthetic precursors to a variety of natural products such as flavones, isoflavanones, flavanols, aurones, etc. Chalcones also show impressive biological activity. All these facts make them desired synthetic targets and more importantly they have been extensively employed as intermediates in the synthesis of heterocyclic and carbocyclic systems.

The term chalcone was first coined by Kostanecki, a pioneer in the field of natural pigments. Synthesis of this versatile molecule can be carried out easily and conveniently by Claisen-Schmidt reaction in which acetophenone and benzaldehyde and their derivative are reacted in the presence of aqueous alkali (Scheme 1.1). Chalcones can also be synthesised by other methods such as debromination of corresponding α,β-dibromides, from Schiff’s bases, and from organometallic compounds.

Reagent and conditions: i. base, rt.

Scheme 1.1
Chalcone 3 can be viewed as bifunctional molecule imbibed with a keto group and a conjugated double bond. Reactions can be performed with nucleophiles either in 1,2 fashion or 1,4-fashion. The basic skeleton of chalcone also has two aromatic rings in 1,3-relationship. Thus, the parent molecule can be viewed as a source of 15 carbon atoms which can be assembled in a single step. Not surprisingly, chalcone and its derivatives have been employed extensively for the synthesis of heterocyclic targets having nitrogen, oxygen and sulfur.\textsuperscript{10}

A detailed monograph on chalcones covering literature up to 1981 was written by Dhar.\textsuperscript{11} Since most of the work described in the present thesis involve synthetic elaborations on chalcone and related compounds, it is appropriate to present an overview of literature on this topic. We have scanned the literature from 1982-1998 and selected some references. The selection of references, focussed on most recent ones, reflects our interest and is not exhaustive.

1.1.1 Synthesis of Heterocyclic Compounds from Chalcone and its Derivatives

![Scheme 1.2](image)

*Reagents and conditions:* i. urea-H\textsubscript{2}O\textsubscript{2}, THF, polyleucine catalyst, DBU, rt; ii. MCPBA, CH\textsubscript{2}Cl\textsubscript{2}, reflux, rt; iii. (±)-2-methylamino-1-phenylethanol, CH\textsubscript{2}Cl\textsubscript{2}, 0°C – rt; iv. aq. LiOH, Et\textsubscript{2}O, THF, rt; v. NaBH\textsubscript{4}, MeOH, 0°C→rt.

*Scheme 1.2*
A three step enantioselective synthesis of five membered nitrogen heterocyclic natural product, (+)-clausenamide 5, from chalcone 3 has been reported (Scheme 1.2). Asymmetric epoxidation under Julia-Colonna conditions was the key step in this reaction sequence.

Pyrrolidine, pyrrolizidine and oxindole alkaloids constitute a class of compounds with significant biological activity. Spiro [pyrrolidineoxindole] system is common to most oxindole alkaloids. Solid phase synthesis of pyrrolidine libraries by the azomethine ylide dipolar cycloaddition strategy has been achieved. An azomethine ylide, generated by the decarboxylative condensation of an isatin 6 with α-amino acid 7 was trapped by chalcone 3 to afford 8 (Scheme 1.3).

\[ \begin{align*} 
6 & \quad + \quad 7 \quad + \quad \text{3} \quad \rightarrow \quad \text{8} \\
\text{Reagents and conditions:} & \quad \text{i. dioxane-H}_2\text{O, 80-90°C.} \\
\text{Scheme 1.3}
\end{align*} \]

Condensation of chalcone with semicarbazide or hydroxylamine hydrochloride has become an extremely popular method for making pyrazoline or isooxazole derivatives (9 or 10; Scheme 1.4). A wide array of these compounds have been synthesised with a view to test their biological activity.

Several pyrazoline derivatives were synthesised from the reaction of chalcone 3 with phenyl hydrazine hydrochloride 11 or with hydrazine hydrate 12 (Scheme 1.5) to test their ability as chemotherapeutic agents against gram positive and
gram negative bacteria.

Reagents and conditions: i. H$_2$NNCONH$_2$, NaOH, EtOH; ii. NH$_2$OH.HCl, NaOH, EtOH.

Scheme 1.4

Reagents and conditions: i. gl. acetic acid, 110-120°C; ii. EtOH, 70-80°C.

Scheme 1.5

Oligopyridines attract considerable attention in supramolecular chemistry and have been incorporated into helicates, catenanes, dendrimers and knots. A methodology for preparing terpyridines, which have the potential for undergoing regioselective reaction was established starting from chalcone 17. Reaction of diacetyl pyridine derivative 15 with p-tolualdehyde 16 furnished the chalcone 17,
which on reaction with N-(methylacetyl)pyridinium chloride furnished protected terpyridines. Deprotection yielded the desired terpyridine 18 (Scheme 1.6).

Reagents and conditions: i. EtOH, 0°C; ii. N-(methylacetyl) pyridinium chloride; iii. p-formaldehyde, (CH$_3$)$_2$NH, DMF; iv. N-methylacetylpyridinium chloride; v. Pyridine, HCl, reflux.

Scheme 1.6

The synthesis of substituted pyridine derivatives 20, which have the potential to get converted to NADPH analogs, was carried out by starting from the N-silyl-1-azaallyl anion 19 and chalcone 3 (Scheme 1.7).$^{27}$

Similarly, condensation of chalcone and guanidine nitrate$^{28,29}$ or urea$^{30}$ resulted in pyrimidine derivatives which show impressive antimicrobial activity. For example the extra nucleo heterosteroids with pyrimidine fused in different position of steroidal ring systems possess significant antibiotic activities. Heterosteroid 23 in
which C-16, C-17 of steroids are fused to a pyrimidine ring system has been synthesized from ketone 21 via chalcone derivative 22 (Scheme 1.8).\textsuperscript{30}

\begin{center}
\includegraphics{structure1.png}
\end{center}

Reagents and conditions: i. \textit{p}-RC\textsubscript{6}H\textsubscript{4}CHO, alc. KOH, EtOH, 10\textdegree{}C-rt; ii. urea, aq. NaOH, EtOH, reflux.

Scheme 1.8

Derivatives of 1,4-diazepines\textsuperscript{31,32} and 1,5-benzothiazepine,\textsuperscript{33} are found to have anticoagulant, antiarterosclerotic, antihypertensive and antidepressant properties. The reaction of aromatic and heterocyclic 1,2-diamines with chalcones is a very convenient and versatile method for preparation of condensed 1,4-diazepine systems with high regioselectivity. For example, triamines 24 reacted with equimolar amounts of chalcone 3 to generate the desired 1,4-diazepine 25 (Scheme 1.9).

\begin{center}
\includegraphics{structure2.png}
\end{center}

Reagents and conditions: i. CH\textsubscript{3}COOH, reflux.

Scheme 1.9

Chalcones have been used as starting materials for the synthesis of a variety of
Reagents and conditions: i. Tl(NO₃)₃·3H₂O, CH(OCH₃)₃, MeOH; ii. MeOH-acetone, H₂, Pd-C; iii. MeOH, Conc. HCl, reflux; iv. Ag₂O, pyridine; v. α-acetobromoglucose; vi. CH₃COOH, NaOMe, reflux.

Scheme 1.10

natural products. 4',7-dihydroxy-6-methoxy isoflavone (glycitein) 28 and its 7-O-β-D-glucopyranoside (glycitin) 30 were isolated from soybeans. Glycitein 28 was synthesized by oxidative rearrangement of the protected chalcone 26 to yield the hydroxy acetal 27, followed by deprotection and ring closure. Glycosylation of 28 with α-acetobromoglucose and subsequent saponification resulted in glycitin 30 via 29 (Scheme 1.10).³⁴

Synthesis of (R,S)-dioelein 33, a bioactive flavanone, isolated from the root bark of *Dioclea grandiflora* Mart.ex.Benth. has been achieved starting from chalcone 31.³⁵ Treatment of 31 with KF yielded the flavanone 32, which on deprotection gave 33 (Scheme 1.11).

Biflavanoids, lophirone B 37 and lophirone C 36 have been isolated from an African medicinal plant *Lophira lanceolata* (Ochnaceae). The biogenetic synthesis
of 36 and 37 was achieved on the basis of oxidative dimerisation of chalcone 34 with

![Chemical structures and reaction schemes](image)

**Reagents and conditions:** i. KF, MeOH, reflux; ii. BCl₃, CH₂Cl₂, -60°C-rt.

**Scheme 1.11**

**Reagents and conditions:** i. horseradish peroxidase, acetone-water, 20°C-rt; ii. TMSBr, CH₂Cl₂, -30°C-0°C; iii. Conc. HCl, MeOH, 60°C.

**Scheme 1.12**
enzyme horseradish peroxidase to give 35 and recyclisation of dihydrofuran ring to a chromanone ring (Scheme 1.12).^{36}

trans-3-Hydroxyflavanones and their 3-O-substituted derivatives are important intermediates in the synthesis of a wide variety of flavanoid compounds and also play a significant role in the biogenesis of naturally occurring flavanoid type derivatives. Epoxidation of 2’-hydroxy chalcones 38 by dimethyl dioxirane (DMD) followed by either acid or base catalysed ring closure provides a novel, general and efficient method for the synthesis of trans-3-hydroxyflavanones 40 (Scheme 1.13).^{37}

Synthesis of polyoxygenated chalcone epoxides 42, from chalcone 41, has been carried out for use as chirons in the enantiomerically enriched dihydroflavanol synthesis.^{38} These efforts resulted in a general synthesis of oligomeric anthocyanidin precursors with 2,3-trans and 2,3-cis flavanoid chain extender units 43 and 44 (Scheme 1.14).
Reagents and conditions: i. H₂O₂, NaOH, poly-L-alanine, CCl₄; ii. BuSH/SnCl₄, -20-0°C; iii. AgBF₄, CH₂Cl₂, 0°C.

Scheme 1.14

Reagents and conditions: i. PTC, Na₂S, rt.

Scheme 1.15

The reactions of chalcones with sulfur nucleophiles have also been reported³⁹. The major product with sodium sulfide is the heterocycle 45 (Scheme 1.15).

1.1.2 Synthesis of Carbocycles from Chalcone and its Derivatives

Conjugate addition to α, β-unsaturated ketone with the α-carbanion of a ketone and subsequent aldol condensation and dehydration (Robinson annulation) is a popular method for generation of six membered carbocycles.⁴⁰ For example,
condensation of acetyl acetone 46 with chalcone 3 under basic conditions resulted in Robinson annulated product 47 (Scheme 1.16).\(^1\)

![Reaction Scheme 1.16](image)

**Reagents and conditions:** i. NaOH, 120\(^\circ\)C.

**Scheme 1.16**

Similar condensation of ethylacetoacetate 48 resulted in cyclic \(\beta\)-ketoester 49 (Scheme 1.17).\(^2\)

![Reaction Scheme 1.17](image)

**Reagents and conditions:** i. Piperidine, BuOH.

**Scheme 1.17**

On the other hand, condensation of diethylmalonate (DEM) with chalcone appeared to depend upon reaction conditions. For example, treatment of two moles of chalcone with sodium salt of DEM 50 in ether resulted in cyclohexene 51, while conducting the above reaction with DEM 50 in the presence of sodium in ethanol resulted in cyclohexanone 52 (Scheme 1.18).\(^3\)
Reagents and conditions: i. Et₂O; ii. Na, EtOH, Et₂O, 48h.

Scheme 1.18

Condensation of ethylcyanoacetate 53 with chalcone in the presence of NaOEt in ether resulted in the formation of a cyclohexanol derivative 54. Formation of 54 involves two consecutive Michael additions followed by aldol condensation (Scheme 1.19).\(^{44}\) Formation of cyclohexene 51, cyclohexanone 52 and cyclohexanol 54 are relevant to the present work as these simple reaction sequences results in densely functionalised products in a single-pot operation.

Reagents and conditions: i. NaOEt, Et₂O, rt.

Scheme 1.19

Normally base-mediated condensation of acetophenone 1 and benzaldehyde 2 is expected to yield only chalcones. However, when the reaction was conducted in biphasic medium in the presence of catalytic benzyltriethylammonium chloride (phase transfer catalyst), 2,4-dibenzoyl-1,3,5-triphenylcyclohexanol 55 has formed.\(^{45}\) It has been suggested that under the reaction conditions, the intermediate carbanions are stable and survive unquenched until two moles of benzaldehyde are condensed with three moles of acetophenone (Scheme 1.20).
Chalcones 3 undergo cyclodimerisation to furnish cyclopentanols 56 or stereoisomers 57a, 57b in the presence of Yb metal or YbCl₃-Zn. When the reaction of chalcone was conducted in the presence of benzaldehyde, the intermediate dianion got trapped to form interesting cyclopentanol derivative 58 along with the dimer 57a (Scheme 1.21).

Thus it is clear from the above discussion that chalcone is a unique molecule. It undergoes reaction with carbanions to generate diverse and interesting
heterocycles and carbocycles. Driven by our interest towards the synthesis of

![Chemical structure](image)

Reagents and conditions: i. Ba(OH)_2, EtOH, rt.

Scheme 1.22

azasteroids we explored the reaction of chalcones with cyclopentanone and
cyclohexanone. In our laboratory, it was found previously that chalcone 3 and
cyclopentanone 59 reacts to give densely substituted bicyclic alcohol 61 having six
stereogenic centres along with 1,5-diketone 60 (Scheme 1.22).^{48}

In the present chapter, results obtained with the reaction of substituted
chalcones with cyclopentanone to generate bicyclic alcohol of the type 61 and (or)
any other interesting products, has been presented. Purpose of the study is to
understand the mechanistic aspect of the reaction and also to explore the electronic
fine tuning required for the formation of unique and unusual carbocycles.

1.2 Results and Discussions

The substituted chalcones 62-66 having electron withdrawing (chloro, bromo
and nitro) and electron donating (methyl, methoxy) substituents in the *para* position of
the acetophenone portion were prepared employing the Claisen-Schmidt reaction.^{49}
The chalcones were subjected to conjugate addition (Michael addition) with the anion
generated from cyclopentanone in the presence of barium hydroxide as base and
ethanol as solvent^{50}(Scheme 1.23). From the column purification of the mixture of
products formed in the reaction, we could isolate a few interesting and unexpected
products in addition to the diastereomeric mixture of 1,5-diketones 67-71. Characterization of the products is given in the following.

\[
\begin{align*}
62: X = \text{Cl} & & 67: X = \text{Cl} & & 72: X = \text{Cl} & & 73: X = \text{Cl} \\
63: X = \text{Br} & & 68: X = \text{Br} & & 74: X = \text{Br} \\
64: X = \text{NO}_2 & & 69: X = \text{NO}_2 & & 70: X = \text{Me} & & 71: X = \text{OMe} \\
65: X = \text{Me} & & & & 73-74
\end{align*}
\]

Reagents and conditions i. Ba(OH)$_2$, EtOH, rt, 12h.

**Scheme 1.23**

When p-chlorochalcone 62 was subjected to the Michael addition reaction, three products, 1,5-diketone 67, bicyclic alcohol 72 and spiroketodiol 73 were obtained. When this reaction was extended to other chalcones having substituents like p-bromo 63, p-nitro 64, p-methyl 65 and p-methoxy 66, the results were found to be varying. The p-bromo chalcone 63 furnished only the spiroketodiol 74, in addition to the 1,5-diketone 68. In the case of p-nitro, p-methoxy and p-methyl chalcones 64, 65 and 66, neither the bicyclic alcohol nor the spiroketodiol were isolated.

1.3 Isolation and Characterization of a Bicyclic Alcohol from the Reaction of p-Chloroalchone with Cyclopentanone.

Base-mediated reaction of cyclopentanone with p-chlorochalcone 62 furnished three products 67, 72 and 73, which were isolated by the column purification of the reaction mixture (Scheme 1.24). Fraction with the highest R$_f$ value on TLC was found to be a mixture of diastereomers of 1,5-diketones 67. One of the two diastereomers
Reagents and conditions: i. Ba(OH)$_2$, EtOH, rt, 12h.

Scheme 1.24

crystallised out from column fractions as colourless crystals (mp. 108 °C). Its molecular formula was deduced as C$_{20}$H$_{19}$ClO$_2$ based on analytical and mass spectroscopic data. The IR spectrum of 67 showed two carbonyl absorptions at 1730 and 1680 cm$^{-1}$ assignable to cyclopentanone and aromatic carbonyl stretching frequencies. The $^1$H NMR spectrum (Fig. 1.1) revealed the presence of aromatic and aliphatic protons in the ratio 1:1.1. The aromatic region of the spectrum revealed AA'-BB' quartet at δ 7.4 and 7.9 ppm for p-chloroacetophenone portion of the molecule. The downfield signals at δ 3.6 and 3.9 ppm in the aliphatic region could be assigned to two protons on C$_2$. As expected from the structure of 67, the $^{13}$C NMR spectrum (Fig. 1.2) showed sixteen signals in which six were located in the aliphatic region (~0-80 ppm), eight in the aromatic region (~120-160 ppm).
Fig. 1.1 $^1$H NMR spectrum of 1-(4-chlorophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (67)
Fig. 1.2 $^{13}$C NMR spectrum of 1-(4-chlorophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (67)
Fig. 1.3 Minimum energy structure (MMX) for cis- and trans-\(1-(4\text{-chlorophenyl})-3-(2\text{-oxocyclopentyl})-3\text{-phenyl-1-propanone}\) (67)
Fig. 1.4 $^1$H NMR spectrum of (3aS,5S,6S,7S,4R)-6-(4-chlorobenzoyl)-3a-hydroxy-5,7-diphenylperhydro-4-indenyl-4-chlorophenylmethanone (72)
Molecular mechanics calculations\textsuperscript{51} revealed the preferred conformation of like and unlike diastereomers of the diketone 68 (Fig. 1.3). Calculations reveal that the R,R (or S,S) configuration is stable (MMXE = 37.42) over the R,S (or S,R) configuration (MMXE = 37.89).

While continuing the column purification, the second compound with lower R\textsubscript{f} value, compared to the 1,5-diketone 67, began to crystallise out as colourless crystals from the column fractions (yield 7\%). This product, mp. 221 °C, was found to have molecular formula of C\textsubscript{35}H\textsubscript{30}Cl\textsubscript{2}O\textsubscript{3} based on analytical and spectroscopic data. The IR spectrum of 72 revealed the presence of a hydrogen bonded hydroxy group (ν = 3430 cm\textsuperscript{-1}) and two aromatic ketones (ν = 1680, 1660 cm\textsuperscript{-1}), out of which one was involved in hydrogen bonding (ν =1660 cm\textsuperscript{-1}). The \textsuperscript{1}H NMR spectrum (Fig. 1.4) revealed the presence of aromatic protons and aliphatic protons in the ratio of 1.5:1, indicating that two chalcones and one cyclopentanone molecule were involved in the formation of 72. The cyclopentanone protons were observed as multiplet from δ 0.94-1.8 ppm. The spectrum was remarkably similar to the bicyclic alcohol 61 derived from two units of unsubstituted chalcone and cyclopentanone, which was previously isolated from our laboratory.\textsuperscript{48b} Careful analysis of the spectra also revealed that the stereochemistry of the substituents was also the same as the compound 61 previously isolated (Scheme 1.22). The spectral assignments of the characteristic protons is given in Fig 1.5. The \textsuperscript{13}C NMR (Fig.1.6) of 72 also matched well with 61 (Scheme1.22). The assignments for the \textsuperscript{13}C signals is given in Fig. 1.7. Thus the new compound isolated was assigned as (3aS,5S,6S,7S,4R)-6-(4-chlorobenzoyl)-3a-hydroxy-5,7-diphenylperhydro-4-indenyl-4-chlorophenylmethanone (72).
Fig. 1.6 $^{13}$C NMR spectrum of
(3aS,5S,6S,7S,AR)-6-(4-chlorobenzoyl)-3a-hydroxy-5,7-diphenylhydro-4-indenyl-4-chlorophenylmethanone (72)
7.14 - 7.2 ppm, m
7.3 ppm, d, $J = 9$ Hz

Fig. 1.5 $^1$H NMR assignments for characteristic protons of 72

2.9 ppm, dd, $J = 18.6, 6$ Hz
4.14 ppm, d, $J = 4.88$ Hz
3.35 ppm, dd, $J = 13.5, 5.9$
4.6 ppm, s
4.04 ppm, dd, $J = 12, 5$ Hz

Fig. 1.7 $^{13}$C NMR assignments for characteristic carbons of 72

Support for the proposed bicyclic alcohol 72 also came from theoretical calculations using PC model program. The minimum energy conformation was generated using molecular mechanics calculation in MMXE mode. These calculations revealed that the trans bicyclic alcohol is more stable ($\text{MMXE} = 79.72$) (Fig.1.8) compared to the corresponding cis compound.
M06: Energy = 79.726
Str   = 2.710
Bnd   = 8.381
StrBnd= 0.358
Tor   = 48.926
VDW   = 17.95°
QQ     = 1.345
Dip Moment = 2.490
Hf = -31.57 SE = 71.2

Dielec: 1.500
Const: Std
Print: Min

Fig. 1.8 Minimum energy structure for trans-(3aS,5S,6S,7S,4R)-6-(4-chlorobenzoyl)-3a-hydroxy-5,7-diphenylperhydro-4-indeny1-4-chlorophenylmethanone (72)
1.3.1 Mechanism for the Formation of Bicyclic Alcohol

The proposed mechanism for the formation of the bicyclic alcohol 72 is given in the Scheme 1.25. A series of domino reactions are expected to take place to result in the formation of product. The initial step is the Michael addition of the anion generated from cyclopentanone to chalcone 62 to form the intermediate enolate anion 67. This intermediate 67 reacts with one more molecule of chalcone 62 in a Michael fashion resulting in the C_{35} intermediate enolate anion 75. Intramolecular aldol condensation of 75 results in the bicyclic alcohol 72 via 76.

![Scheme 1.25](image)

Formation of bicyclic alcohol 72 meets several desirable features of an organic reaction, such as, efficiency of formation of a single diastereomer out of possible 32 isomers through three domino reactions taking place in a single pot and finally assembling thirty five carbons from extremely simple starting materials. It is also interesting to note that C_{4} benzoyl group is axially oriented instead of the anticipated equatorial orientation. This arrangement of the aroyl group in the equatorial conformation avoids severe steric congestion during the second step of the sequence.
Mechanism for the formation of bicyclic alcohol indicates that the 1,5-diketone 67 is an intermediate in the reaction sequence. To confirm this, the 1,5-diketone 67 was independently subjected to reaction with chalcone 62 under similar conditions (Scheme 1.26). The bicyclic alcohol 72 could be isolated in over 20% yield. Thus this experiment not only supported the intermediacy of the diketone 67 in the reaction, but also helped to increase the yield of the desired bicyclic alcohol. However attempts to increase the yield even further under different basic conditions such as NaOEt/ether, NaOEt/ethanol and KOH/ethanol proved to be futile.

\[
\begin{array}{c}
\text{Reagents and conditions: i. Ba(OH)\textsubscript{2}, EtOH, rt, 12h.} \\
\text{Scheme 1.26}
\end{array}
\]

1.4 Isolation and Characterization of a Spirodiol from the Reaction of \textit{p}-Chlorochalcone with Cyclopentanone

Further elution of the product mixture, obtained from the reaction of \textit{p}-chlorochalcone and cyclopentanone, by column chromatography, resulted in another novel crystalline product 73 (Scheme 1.24). This product, a colourless crystalline solid, mp. 225 °C, obtained in 3% yield, was found to have molecular formula C\textsubscript{25}H\textsubscript{27}ClO\textsubscript{3} from analytical and mass spectral data. The IR spectrum revealed the presence of a hydrogen bonded hydroxy group (\(\nu = 3192 \text{ cm}^{-1}\)) and a carbonyl group (\(\nu = 1716 \text{ cm}^{-1}\)). The \(^1\text{H} \text{NMR} \) (Fig. 1.9) spectrum revealed the presence of aromatic and aliphatic protons in the ratio 1:2, which indicated that the product was formed from two units of
Fig. 1.9 ¹H NMR spectrum of (1'S,3'S,aS,7'aS,5'R)-7'-(4-chlorophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73)
cyclopentanone and one unit of chalcone. The two hydroxy groups (washable with D₂O) were observed as broad singlets at δ 3.3 and 3.98 ppm. The absence of signal in the IR spectrum for aromatic carbonyl group (~1660 cm⁻¹) and signals in the ¹H NMR between δ 3.5-4.5 ppm suggested the involvement of the aromatic carbonyl group of chalcone in the bond formation. The ¹H NMR revealed a double doublet at δ 3.43 ppm (J = 13.5, 4 Hz, 1H) indicating the presence of C₆-H, tertiary benzylic hydrogen next to methylene group. At δ 3 ppm a double doublet for C₆-Hax with J = 14, 13.5 Hz was observed. The ¹H-¹H COSY spectrum (Fig. 1.10) revealed the connectivity between the double doublet at δ 3.43 and 3 ppm. COSY also revealed the connectivity between the peak at δ 3 ppm and the double doublet located at δ 1.76 ppm assignable to C₆-Heq. Generally axially oriented hydrogen in cyclohexane appear upfield compared to the equatorial one due to shielding effect. In the present case, the appearance of axial hydrogen downfield, maybe due to anisotropic effect of the sterically closer carbonyl molecule.

The ¹H NMR revealed a double doublet at δ 2.95 ppm (J = 13, 7.5 Hz) attributable to axially oriented C₇-H.

The ¹³C NMR (Fig. 1.11) showed the presence of 12 aliphatic type carbons, 8 aromatic carbons and 1 carbonyl carbon. The carbonyl carbon was observed at δ 223.37 ppm indicating it to be a cyclopentanone type. The two carbons attached to hydroxy group are observed at δ 76.5 and 83.94 ppm. The DEPT spectrum (Fig. 1.12) revealed the number of protons attached to each carbon atom. There were seven methylene carbons, two methine carbons and three quaternary carbons in addition to one carbonyl carbon. Hetero COSY spectrum (Fig. 1.13) revealed the connectivity between the carbon and the hydrogens attached to it. NOESY spectrum (Fig. 1.14) revealed the steric proximity of various hydrogens. Based upon the spectral data, the structure of the novel product 73 formed in the reaction was proposed as (1'S,3'aS,7'aS,5'R)-7'-(4-
Fig. 1.10 $^1$H-$^1$H HOMOCOSY spectrum of (1'S,3'aS,7''aS,5'R)-7''-(4-Chlorophenyl)-3a',7''-dihydroxy-5''-phenylspiro[cyclopentane-1,4''-perhydroindene]-2-one (73)
Fig. 1.11 $^{13}$C NMR spectrum of $(1'S,3'aS,7'aS,5'R)-7'-(4$-Chlorophenyl)$-3a',7'$-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73)
Fig. 1.12 DEPT-135 NMR spectrum of (1'S,3'S,7'S,5'R)-7'-((4-Chlorophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73)
Fig. 1.13 $^1$H-$^{13}$C HETEROCOSY spectrum of (1'S,3'S,7'S,5'R)-7'-((4-Chlorophenyl)-3a',7''-dihydroxy-5''-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73)
Fig. 1.14 NOESY spectrum of (1'5'S,3'S,7'S,5'R)-7'-{(4-Chlorophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73)
Assignment of spectral values to various hydrogens and carbons is given in Fig. 1.15.

![Diagram of chemical structure]

- 2.32 ppm, dt, $J = 14, 8.5$ Hz
- 2.07 ppm, ddd, $J = 15, 7.5, 4.5$
- 2.95 ppm, dd, $J = 13, 7.5$ Hz
- 3.0 ppm, dd, $J = 14, 3.5$ Hz
- 3.98 ppm, s
- 1.76 ppm, dd, $J = 14, 4$ Hz
- 3.43 ppm, dd, $J = 13.5, 4$ Hz
- 3.3 ppm, s
- 7.51 ppm, dd, $J = 8, 1.5$ Hz
- 7.3 ppm, dd, $J = 8, 1.5$ Hz
- 35.4 ppm
- 20.9 ppm
- 47.4 ppm
- 32.7 ppm
- 44.3 ppm
- 223.4 ppm
- 18.6 ppm
- 58.9 ppm
- 42.5 ppm
- 19.4 ppm
- 45.3 ppm
- 83.9 ppm
- 76.5 ppm
- 141.2 ppm
- 128.5 ppm
- 128.9 ppm
- 137.6 ppm

**Fig. 1.15** $^1$H and $^{13}$C NMR assignments for characteristic protons and carbons of 73

The stereochemistry of the various substituents in 73 was fixed on the basis of coupling constants as revealed in high resolution $^1$H NMR spectrum. As expected from
the structure of 73 C₅ proton appeared as dd at δ 3.43 ppm with coupling constants of 13.5 and 4 Hz. The magnitude of the coupling constants indicated that C₅ proton is having axial-axial coupling with C₆-H axial and axial-equatorial coupling with C₆-H equatorial. Thus the C₅-phenyl group is equatorially oriented and the C₅-H is axially oriented. The two protons on C₆ appeared as double doublets at δ 3 and 1.76 ppm. As discussed earlier, hydrogen bonding interaction between the two OH groups at C₇ and C₉a was indicated by the IR spectrum. Hence, the C₉a OH and C₇ OH should be in axial position. Thus the C₇ chlorophenyl group is in equatorial position. The stereochemistry of the ring junction being trans is indicated by the coupling constants of C₇a-H (δ 2.95 ppm, dd, J = 13, 7.5 Hz). The cis ring junction would have revealed coupling constants of smaller magnitude.

Confirmation of the proposed structure of 73 was also obtained by X-ray analysis (done by Prof. E. Subramanian in Madras University) on a crystalline sample obtained by dissolving the compound in dichloromethane and adding few drops of hexane which is kept in freezer for 3 days after which very thin needle shaped crystals were obtained. The line diagram for 73 is given in Fig. 1.16 and the ORTEP diagram is shown in Fig. 1.17. Torsion angles around the cyclohexane ring indicate that the ring adopts a chair conformation. The torsion angles around the cyclopentane rings indicate that both the rings adopt envelope conformation. The atoms C9, C1, C3, C2 in ring A and C5, C10, C11, C13 in ring C forms the best plane. The bicyclic ring system consisting of ring A and B adopts a chair-envelope conformation which is energetically the most favored. The phenyl ring I is quite planar, with the C1 atom lying in the plane, however atom C8 of the cyclohexane ring deviates by 0.14 Å. Phenyl ring II is also planar with atom C6 lying in the plane. The two rings are oriented at an angle of 104 (1)° to each other. The phenyl rings I and II are in equatorial orientation, the
Fig. 1.16 Line diagram of (1'S,3'aS,7'aS,5'R)-7'-(4-chlorophenyl)-3a',7'-dihydroxy-5':phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73)
Fig. 1.17 ORTEP diagram of (1'S,3'a,7'S,7'aS,5'R)7-(4-chlorophenyl)-3a',7'-dihydroxy-5'-phenylaspiro[cyclopentane-1,4'-perhydropindene]-2-one (73)
corresponding torsion angles being respectively C4-C9-C8-C14 = -174 (3)° and C4-C5-C6-C20 = -177 (3)°. The angle between the best plane of the cyclohexane ring and the phenyl rings I and II are 111(2)° and 90 (2) respectively. The hydroxyl group O2 is in axial orientation. The hydroxyl group O1 at C4 is in staggered conformation with respect to C8 atom and eclipsed with respect to C10 atom as evidenced from the torsion angles C8-C9-C4-O1 = -62(4)° and C10-C5-C4-O1 = -172(3)°. The dihedral angles, which the best plane of the cyclohexane ring B makes with cyclopentane rings A and C respectively, are 27(3)° and 105(2)°. A short hydrogen bond of length 2.66 occurs between O1 and symmetry-related O2. The structure is stabilized mainly by VanderWalls interaction. The minimum energy conformation of this molecule was also generated using molecule mechanical calculation using MMXE mode (MMXE = 53.42)51 (Fig. 1.18)

1.4.1 Mechanism for the Formation of the Spiro-diol (73)

The proposed mechanism for the formation of the spiro-diol 73 is given in Scheme 1.27. The 1,5-diketone 67 formed via the Michael addition of anion generated from cyclopentanone reacts with one more unit of cyclopentanone in 1,2 fashion to furnish the diketone alcohol 78. Aldol condensation of 78 result in spiroketodiol 73. The involvement of two hydroxy groups in intramolecular hydrogen bonding may be the driving force for the formation of the final product.

Since the yield of spirodiol was very low, we attempted to increase the yield by various methods. According to the mechanism proposed, the formation of spirodiol is due to the addition of two cyclopentanone moieties to one chalcone moiety. Hence 1,5-diketone 67 and cyclopentanone 59 was allowed to react under similar reaction conditions (Scheme 1.28). But instead of the spirodiol 73, the bicyclic alcohol 72 and
Fig. 1.18 Minimum energy structure (MMX) for (1'S,3'aS,7'aS,5'R)-7'-(4-chlorophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73)
unreacted 1,5-diketone 67 was obtained as a mixture. This maybe due to the formation of chalcone 62 under the reaction conditions which then adds to the unreacted 1,5-diketone 67 to give the bicyclic alcohol 72.

Scheme 1.27

Reagents and conditions: i. Ba(OH)$_2$, EtOH, rt, 12h  

Scheme 1.28

Variations in the reaction conditions such as heating to reflux and prolonged stirring (36h) did not improve the yield of 73. Change of solvent from absolute alcohol
to acetonitrile, as well as sonication also did not increase the yield of the desired product.

1.5 Isolation and Characterization of Products obtained from Reaction of p-Bromochalcone with Cyclopentanone

The reaction of p-bromochalcone 63 with cyclopentanone 59 in the presence of barium hydroxide resulted in two products 68 and 74 (Scheme 1.29), out of which one with higher $R_f$ value was the expected diastereomeric mixture of 1,5-diketones 68 and the compound with lower $R_f$ value was the spiroketodiol 74. One of the diastereomeric 1,5-diketone was obtained in a pure form through fractional crystallisation. The IR spectrum revealed two carbonyl absorption at 1730 and 1680 cm$^{-1}$ assignable to cyclopentanone and aromatic ketone stretching frequencies. The $^1$H NMR spectrum (Fig. 1.19) showed the presence of aromatic and aliphatic protons in the expected ratio of 1:1:1. The $^1$H NMR was similar to that obtained for 67. The $^{13}$C spectrum (Fig. 1.20) showed the presence of two carbonyl groups at $\delta$ 198.1 and 220.6 ppm, 8 aromatic carbons and 6 aliphatic carbons.

Reagents and conditions: i. Ba(OH)$_2$, EtOH, rt, 12h.

Scheme 1.29

The compound having lower $R_f$ value was found to be the spirodiol 74 having spectral data similar to the spirodiol 73 obtained from the reaction of $p$-chlorochalcone.
Fig. 1.19 $^1$H NMR spectrum of 1-(4-bromophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (68)
Fig. 1.20 $^{13}$C NMR spectrum of 1-(4-bromophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (68)
The IR spectrum of 74 revealed the presence of hydroxy group ($\nu = 3300$ cm$^{-1}$) and carbonyl group ($\nu = 1720$ cm$^{-1}$). The $^1$H NMR spectrum (Fig. 1.21) revealed the presence of aromatic and aliphatic protons in the ratio 1:2 indicating one chalcone and two cyclopentanone moieties were involved in the formation of the spirodiol. The two OH protons were observed as broad singlets at $\delta$ 3.27 and 3.91 ppm. The $^{13}$C NMR
Fig. 1.21 $^1$H NMR spectrum of (1'S,3'aS,7'aS,5'R)-7'- (4-bromophenyl)-3a',7'-dihydroxy-5' -phenylspiro[cyclopentane-1,4'-perhydronene]-2- one (74)
Fig. 1.22 $^{13}$C NMR spectrum of (1'S,3'aS,7'aS,5'R)-7'-(4-bromophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (74)
spectrum (Fig. 1.22) showed the presence of twelve aliphatic carbons, eight aromatic carbons and one carbonyl carbon. The carbons attached to the two hydroxy groups were observed at δ 76.5 and 83.96 ppm. The ring junction carbon was observed at δ 47.29 ppm, while the spiro carbon was observed at δ 58.92 ppm. Thus by comparison of the spectral values obtained for 73, structure of the spiro diol 74 was assigned as (1'S,3'aS,7'aS,5'R)-7'-{(4-bromophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one. Assignment of spectral values to various hydrogens and carbons is given in Fig. 1.23.

1.6 Characterization of Products from the Michael Addition of Cyclopentanone to p-Nitro, p-Methyl and p-Methoxy Chalcones

Reaction of p-nitrochalcone 64 with cyclopentanone resulted in the diastereomeric mixture of 1,5-diketones 69 (Scheme 1.30). Repeated recrystallisation resulted in a light yellow solid (m.p. 100-2°C) enriched in one isomer. IR spectrum revealed absorption due to two carbonyl groups at ν 1728 and 1685 cm⁻¹ assignable to

![Chemical structure](image)

Reagents and conditions: i. Ba(OH)₂, EtOH, rt, 12h

Scheme 1.30
cyclopentanone and aromatic ketone stretching frequency and aromatic nitro group at ν 1522 cm⁻¹. The ¹H NMR (Fig.1.24) spectrum showed the ratio of aromatic to aliphatic
Fig. 1.24 $^1$H NMR spectrum of 1-(4-nitrophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (69)
Fig. 1.25 $^{13}$C NMR spectrum of 1-(4-nitrophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (69)
protons to be 1:1:1. The $^{13}$C NMR (Fig.1.25) showed six signals in the aliphatic region, eight signals in the aromatic region and two carbonyl signals. From this reaction, we could not isolate any compound related to bicyclic alcohol 72 or spirodiol 73, 74.

The reaction of cyclopentanone with chalcones having electron donating substituents has been very sluggish. In the case of $p$-methyl chalcone 65, the diastereomeric mixture of the 1,5-diketone 70 was the only product isolated in about 43% yield (Scheme 1.31). The spectral values of this compound matched well with the other 1,5-diketones obtained previously.

![Chemical structure](image)

**Reagents and conditions:** i. Ba(OH)$_2$, EtOH, rt, 12h

**Scheme 1.31**

Reaction of $p$-methoxychalcone 66 was also sluggish, but in addition to the expected diastereomeric mixture of 1,5-diketones 71, a minor product 79 (5% yield) was also obtained from the column fractions (Scheme 1.32).

![Chemical structure](image)

**Reagents and conditions:** i. Ba(OH)$_2$, EtOH, rt, 12h

**Scheme 1.32**
IR spectrum of 79 showed the presence of two keto groups at $\nu$ 1729 and 1670 cm$^{-1}$. The $^1$H NMR (Fig. 1.26) revealed the ratio of aromatic to aliphatic protons to be 1.2:1 indicating that one unit each of chalcone, cyclopentanone and benzaldehyde condensed together to form this product. The $^1$H NMR revealed a singlet for methoxy group at $\delta$ 3.82 ppm. The olefinic hydrogen appeared as a singlet at $\delta$ 5.8 ppm. $^{13}$C NMR (Fig. 1.27) of this compound revealed the presence of three aromatic rings. The analysis of off-resonance decoupled spectrum and proton decoupled spectrum indicated the structure of 79 to be 1-(4-methoxyphenyl)-3-{2-oxo-3-[(E)-1-phenylmethylidene]cyclopentyl}-3-phenyl-1-propanone. Further spectral studies such as 2D NMR of this compound is required to confirm the structure unambiguously. The mechanism for the formation of 79 is given in Scheme 1.33.

Scheme 1.33
Fig. 1.26 $^1$H NMR spectrum of $1$-(4-methoxyphenyl)-3-[(E)-1-phenylmethylidene]cyclopentyl]-3-phenyl-1-propanone (79)
Fig. 1.27 $^{13}$C NMR spectrum of 1-(4-methoxyphenyl)-3-{2-oxo-3-[(E)-1-phenylmethylidene]cyclopentyl}-3-phenyl-1-propanone (79)
The olefinic dione 79 may have been generated via aldol condensation of diketone 66 and benzaldehyde 2 to furnish 80 followed by dehydration from chalcone 66. The benzaldehyde required for reaction may have been generated from chalcone 66 through retro pathways.

1.7 Attempts to Synthesise a Chiral Auxiliary from 1,5-diketones Derived from Chalcone and Cyclopentanone

Recent years has seen the explosion in the field of asymmetric synthesis in synthetic organic chemistry. Several naturally occurring chiral auxillaries based upon terpenes (α-pinenes), alkaloids (quinine), amino acid (proline) and diesters (tartaric acid) have been developed for asymmetric induction. In this connection we have envisaged an easy access to chiral auxiliary such as 83 for chiral induction in hydroboration reactions.

\[
\begin{align*}
\text{Reagents and conditions:} & \quad \text{i. dry } \text{C}_6\text{H}_6, \text{ reflux, } 12\text{h; ii. NaBH}_4, 0^\circ\text{C-rt, } 4\text{h.} \\
\text{Scheme 1.34} & \\
\text{connection we have envisaged an easy access to chiral auxillary such as 83 for chiral} \\
\text{induction in hydroboration reactions.}
\end{align*}
\]
With plenty of 1,5-diketone 81 in hand, we attempted to synthesize chiral ligand 83, which can be utilized for further reactions. The 1,5-diketone 81 was condensed with phenyl alaninol 82, obtained from a one step reduction of phenylalanine. A product obtained, in 30% yield, was tentatively assigned the structure 84 and the expected chiral alcohol 83 could not be realized (Scheme 1.34). The $^1$H NMR spectrum was complex indicating that the product was a mixture of diastereomers. $^{13}$C NMR showed signals around $\delta$ 95 ppm (s) indicating the presence of quarternary carbon having two oxygen atoms attached to it. Absence of signals around $\delta$ 200 ppm indicated that the carbonyl groups of the starting materials have been utilised in the bond formation.

![Chemical Structure](image1)

**Reagents and conditions:** i. Dry C$_6$H$_6$, reflux, 12h; ii. NaBH$_4$, 0°C-rt, 4h.

**Scheme 1.35**

Similar attempts towards the realization of the chiral auxillaries 86 and 87 were made on the 1,5-diketones 85 and 60 generated from chalcone and phenyl vinyl ketone
with cyclopentanone. But only uninteractable products were obtained from these reactions (Scheme 1.35).

1.8 Attempts to Synthesize Oxaazasteroidal system:

Steroids play an important role in biochemical processes particularly as hormones. Several steroids such as estrone, progesterone and testosterone are commercially important. Many steroids incorporating heteroatom in the carbon skeleton have been synthesised with the intention of evaluating their biological activity. When nitrogen is the heteroatom, such molecules are called as azasteroids. Previously we tried to use readily available 1,5-diketones such as 81 and 60, as convenient starting materials for 8-azasteroidal molecules. However, this goal is yet to be realized. But in the process, several substituted perhydroquinolines were prepared and characterized. As a part of the present work, we attempted the synthesis of oxaazasteroidal system 88 through a simple route. Retrosynthesis for achieving this objective is given in Scheme 1.36.

![Scheme 1.36](image)

Initially, methoxy methyl (MOM) chloride was used to install the protecting group for o-hydroxyl portion of 92, since the deprotection of MOM group can be achieved readily under mild acidic conditions. Thus the chalcone 95 was prepared from protected o-hydroxyacetophenone 94 and benzaldehyde. But further reaction with cyclopentanone resulted in deprotected chalcone only and the 1,5-diketone 96 could not
be realized (Scheme 1.37). Thus, under reaction conditions deprotection of MOM group was taking place preferentially.

Reagents and conditions: i. NaOH, PTC, CH₂Cl₂, rt, 45min; ii. NaOH, EtOH, rt, 12h; iii. Ba(OH)₂, EtOH, rt, 12h.

Scheme 1.37

Alternatively, the benzylated chalcone 99 was prepared from benzaldehyde 2 and o-benzyloloxycetophenone 98, which was obtained from o-hydroxyacetophenone 92 and benzyl chloride 97. The chalcone 99 was subjected to Michael addition with cyclopentanone 59 to furnish diastereomeric mixture of 1,5-diketones 100, out of which one was a major isomer (Scheme 1.38). The IR spectrum of 100 showed the presence of two carbonyl stretching frequencies at ν 1732 and 1672 cm⁻¹ assignable to cyclopentanone and aromatic ketone stretching frequencies. The ¹H NMR spectrum (Fig. 1.28) revealed the presence of aromatic and aliphatic protons in the ratio of 1.2:1 indicating the condensation of one mole each of chalcone 99 and cyclopentanone 59.
The methylene protons were observed at δ 5.14 ppm and 4.7 ppm. The $^{13}$C NMR spectrum revealed the presence of aliphatic carbons, carbonyl signals and aromatic carbons expected for diastereomeric mixture of 100.

\[
\begin{align*}
\text{92} & \quad \text{COCH}_3 \quad + \quad \text{97} \quad \text{CH}_3\text{Cl} \quad \xrightarrow{i} \quad \text{98} \quad \text{COCH}_3 \quad + \quad \text{CHO} \\
\text{100} & \quad \text{OCH}_2\text{Ph} \quad \xrightarrow{ii} \quad \text{101} \quad \text{OCH}_2\text{Ph} \\
\text{59} & \quad \xrightarrow{iii} \quad \text{99}
\end{align*}
\]

Reagents and conditions: i. 15% NaOH, reflux, 2h; ii. NaOH, EtOH, rt, 12h; iii. Ba(OH)$_2$, EtOH, rt, 12h.

Scheme 1.38

The diketone 100 was then subjected to Leuckart reaction using ammonium formate/polyethylene glycol reflux. Two products were obtained from this reaction (TLC). The product with higher R$_f$ was the perhydrocyclopenta[b]pyridine derivative 101 obtained as a mixture of stereoisomers and the product with the lower R$_f$ was the cyclopenta[b]pyridine derivative 102 (Scheme 1.39). The $^1$H NMR (Fig. 1.29) spectrum of 102 showed characteristic triplet for benzylic methylenes at 3.08 ppm and a singlet for α-benzyl methylene at δ 5.02 ppm. The $^{13}$C NMR showed aliphatic signals and aromatic signals expected for 102 in addition to some impurities such as polyethylene glycol.
Fig. 1.28 $^1$H NMR spectrum of 1-(2-benzyloxyphenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (100)
Fig. 1.29 $^1$H NMR spectrum of 2-(2-benzylxyphenyl)-4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (102)
Fig. 130: 1H NMR spectrum of 2-(4-phenyl)-6,7-dihydro-5H-cyclo[1]pyridin-2-yl)phenol (103)
Reagents and conditions: i. HCOONH₄, PEG 200, reflux, 4h.

Scheme 1.39

Attempts were made to deprotect the benzyl group from perhydrocyclopenta[b]pyridine derivative 101 with ammonium formate/palladium-carbon. This reaction furnished a product whose Rₓ was higher than that of starting material. The IR spectrum of 103 showed the presence phenolic hydroxy group with a broad band at ν = 3020 cm⁻¹. The ¹H NMR spectrum (Fig. 1.30) revealed the presence of aromatic and aliphatic protons in the ratio 1.7:1. The cyclopentane ring protons appeared as two triplets at δ 2.97 and 3.04 ppm and a multiplet at δ 2.05 ppm. The ¹³C NMR (Fig. 1.31) revealed the presence of 3 types of aliphatic protons as expected for a

Reagents and conditions: i. HCOONH₄, 10% Pd/C, MeOH, reflux, 4h.

Scheme 1.40

cyclopenta[b]pyridine derivative. Thus under the reaction conditions of deprotection, aromatisation of the piperidine ring was taking place to give 103 (Scheme 1.40).
Fig. 1.31. $^{13}$C NMR spectrum of 2-(4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)phenol (103)
Deprotection in the presence of hydrogen gas/Pd-C resulted in an uninteractable mixture of products. Thus, our attempts to synthesise oxaazasteroids resulted in cyclopenta[b]pyridine derivatives only.

1.9 Experimental section

General

Progress of all the reactions were monitored by TLC (TLC silica gel, Qualigens or TLC alumina, SRL, India) using hexane/ethyl acetate solutions as eluant. After completion of the reaction workup was done in which the reaction mixture was diluted with dichloromethane and washed with water and brine and the organic extract were collected. It was dried with anhydrous Na₂SO₄ and the solvent was distilled under reduced pressure. Column chromatography was done using silica gel (100-200 mesh, Acme synthetic chemicals) with hexane/ethylacetate solutions as eluant. Melting points were noted using a Gallenkamp melting point apparatus. IR spectra were recorded as KBr pellets or 'neat' or using nujol mull using JASCO FT IR and Perkin-Elmer spectrophotometer. The frequencies at which the ¹H NMR and ¹³C NMR were recorded in CDCl₃ with Bruker 500 MHz, JEOL 400 MHz, Varian 300 MHz and Bruker 200 MHz are also noted in the spectral data. 2D NMR spectra were recorded on Bruker 500 MHz instrument. X-ray spectra were recorded on Enraf-Nonius CAD4 and SMART (Siemens) diffractometer.

Representative procedure for the Michael addition of 4-chlorochalcone 62 with cyclopentanone 59:

To a stirred suspension of freshly activated Ba(OH)₂ (heated at 100°C for 2 h and cooled in a desiccator, 0.171g, 1mmol) in 5mL of absolute alcohol, cyclopentanone (0.5mL, 5.5mmol) was added dropwise at room temperature and stirring continued for 10 minutes. The 4-chlorochalcone 62 (5mmol) was then added portion-wise to the
reaction mixture and stirring was continued at room temperature for 12 h by which time the reaction mixture turned reddish brown. TLC of the reaction mixture indicated the presence of three products which were separated after normal workup by column chromatography using silica gel (100-200) mesh with hexane/ethyl acetate solutions as eluent (98:2 to 80:20).

1-(4-Chlorophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (67). Single diastereomer was obtained by fractional recrystallisation. \( R_f = 0.6 \). Yield = 49%. \( mp = 108^\circ C \). IR (KBr) \( \nu = 2961, 1730, 1589, 1450, 1400, 1215, 1093, 993, 815, 698, 526 \) cm\(^{-1} \). \(^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta = 7.90 \) (dd, \( J = 15.5 \) Hz, 2H), 7.30-7.50 (m, 2H), 7.10-7.30 (m, 5H, aro H), 3.90 (dd, \( J = 17.5, 7.5 \) Hz, 1H), 3.50-3.70 (m, 1H), 3.30 (ddd, \( J = 20, 15, 5 \) Hz, 1H), 2.30-2.50 (m, 1H), 2.00-2.30 (m, 2H), 1.60-2.00 (m, 4H). \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \( \delta = 221.0(C_2), 197.9(C_1-), 142.1(C_1-), 139.4(C_4-), 135.4(C_1-), 129.6(C_2-), 128.9(C_2-), 128.5(C_3-), 128.4(C_3-), 126.8(C_4-), 53.0(C_1), 41.2(C_3), 40.9(C_2), 39.7(C_3), 27.1(C_5), 20.6(C_4).

(3aS,5S,6S,7S,7aS,4R)-6-(4-chlorobenzoyl)-3a-bydroxy-5,7-diphenylperhydro-4-indenylchlorophenylmethanone (72). \( R_f = 0.45 \). Yield = 7%. \( mp = 221^\circ C \). IR (KBr) \( \nu = 3500, 3000, 1660, 1590, 1400, 1090, 700 \) cm\(^{-1} \). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.60 \) (d, \( J = 8 \) Hz, 2H), 7.30 (d, \( J = 9 \) Hz, 2H), 7.20-7.60 (m, 2H), 7.14-7.20 (m, 2H), 7.10-7.12 (m, 5H), 7.00-7.05 (m, 5H), 4.60 (s, 1H), 4.21 (t, 4.88 Hz, 1H), 4.14 (d, \( J = 4.88 \) Hz, 1H), 4.04 (dd, \( J = 12 \), 5 Hz, 1H), 3.35 (dd, \( J = 13.5 \), 5.86 Hz, 1H), 2.9 (broad dd, 1H), 1.94-2.06 (m, 1H), 1.70-1.80 (m, 1H), 1.60-1.70 (m, 1H), 1.45-1.60 (m, 1H), 1.38-1.45 (m, 1H), 0.94-1.10 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 203.8(C_8), 201.4(C_8), 144.3(C_1-), 139.73(C_1-), 139.2(C_4), 139.1(C_4), 137.9(C_1-), 136.2(C_1-), 129.5(C_2), 129.2(C_2), 128.9(C_2), 128.7(C_2), 128.5(C_3), 128.4(C_3), 128.2(C_3), 127.3(C_3), 127.0(C_4), 126.1(C_4), 80.9(C_3), 55.3(C_4), 55.2(C_8), 48.6(C_5), 48.2(C_7), 43.4(C_7a),
42.4(C₃), 33.5(C₁), 24.0(C₂). HRMS (M⁺) m/z calcd. for C₃₅H₃₀Cl₂O₃ 569.525 obsd. 569.521.

(1'S,3'a,7'S,7'aS,5'R)7'-(4-chlorophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73). Rᵣ = 0.26. Yield = 3%. mp = 225°C. IR (KBr) v 3192, 2961, 1716, 1493, 1452, 1404, 1323, 1252, 1186, 1157, 1093, 1057, 1012, 960, 883, 812, 763, 704, 574, 547, 497 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 7.51 (dd, J = 8, 1.5 Hz, 2H), 7.30 (dd, J = 8, 1.5 Hz, 2H), 7.20 (m, 3H), 7.18 (dm, J = 8, 1.5 Hz, 2H), 3.98 (s, 1H), 3.43 (dd, J = 13.5, 4, 1H), 3.30 (br, s, 1H), 3.0 (dd, J = 14, 13.5 Hz, 1H), 2.95 (dd, J = 13, 7.5 Hz, 1H), 2.32 (dt, J = 14, 8.5, Hz, 1H), 2.07 (ddd, J = 15, 7.5, 4.5 Hz, 1H), 1.98 (ddd, J = 17.5, 8.5, 5 Hz, 2H), 1.76 (dd, J = 14.4 Hz, 1H), 1.70-1.75 (m, 2H), 1.50-1.60 (m, 2H), 1.22-1.30 (m, 2H), 0.62-0.72 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 223.4(C₂), 145.6(C₁⁻), 141.2(C₁⁻), 132.6(C₄⁻), 128.9(C₃⁻), 128.5(C₂⁻), 128.4(C₃⁻), 127.2(C₂⁻), 126.0(C₄⁻), 83.9(C₃ₐ), 76.5(C₇), 58.9 (C₄), 47.4(C₇ₐ), 45.3(C₅), 44.3(C₃), 42.5(C₅), 35.4(C₁⁻), 32.7(C₃), 20.9(C₂'), 19.4(C₆'), 18.9(C₄). HRMS (M⁺) m/z calcd. for C₂₅H₂₇ClO₃ 410.938 obsd. 410.933.

Crystal data and structure refinement of (1'S,3'a,7'S,7'aS,5'R)7'-(4-chlorophenyl)-3a',7'-dihydroxy-5'-phenylspiro[cyclopentane-1,4'-perhydroindene]-2-one (73).

Single crystals were obtained by dissolving the compound in dichloromethane and adding few drops of hexane which is kept in freezer for 3 days after which very thin needle shaped crystals were obtained. These were filtered and dried. A reasonably good crystal of dimensions of 0.05X0.10X0.3 mm was mounted on a glass fiber for X-ray analysis. Accurate unit-cell parameters was obtained by a least-squares fit of the 2θ values for several high angle reflections measured using CuKα radiation on an in-house Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator. The crystal data are summarized in Table I. The complete 3-D intensity data for all
Table I: Crystal data and structure refinement for C_{25}H_{27}ClO_{3}

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<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
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<td>Compound Name</td>
<td>1-8-phenyl-3-8-phenyl-4-[spiro-1'-oxo-cyclopentano]-trans-hydrindane-1α,9α-diol</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C_{25}H_{27}ClO_{3}</td>
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<td>c</td>
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<td>Computer programs used</td>
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Table II: Atomic co-ord. ($x \times 10^4$) and equivalent isotropic displacement parameters

(A$^2 \times 10^3$) for non-hydrogen atoms (e.s.d's are in parantheses)

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$U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor
reflections with $\theta < 140^\circ$ ($\sin \theta / \lambda \leq 0.61 \text{A}^{-1}$) were collected at 293K by the $\omega/2\theta$ scan mode using CuK$\alpha$ radiation on the diffractometer. The scan widths were calculated using the expression $(1.00 + 0.14 \tan \theta)^\circ$. The maximum time spent on any reflection was 60 sec. Background measurements were made for 30 sec at the beginning and at the end of each scan. The crystal orientation was checked once every 200 reflections. Three standard reflections were monitored every 2 hours for crystal deterioration or damage and these showed no systematic drift in their intensities during the course of the data collection. The structure was solved by direct methods using the computer program SHELX86. An E-map which had the combined figure of merit 0.0543 revealed all non-hydrogen atoms. The reliability index (R-factor) for this solution was 0.243. The refinement converged to a final R-index of 0.0447. The final atomic co-ordination and their equivalent isotropic thermal displacement parameters for all the non-hydrogen atoms are listed in Table II.

Reaction of 4-bromochalcone 63 with cyclopentanone 59.

The general procedure was followed to yield two products 68 and 74.

1-(4-Bromophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (68). $R_f = 0.55$. Yield = 48%. mp = 124°C. IR (KBr) v 2961, 1730, 1680, 1583, 1493, 1448, 1398, 1259, 1215, 1151, 1070, 993, 812, 727, 698, 561 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.80 (dd, $J = 17.5$, 7.5 Hz, 2H), 7.60 (d, $J = 7.5$ Hz, 2H), 7.10-7.40 (m, 5H, aro H), 3.90 (dd, $J = 15$, 5 Hz, 1H), 3.60-3.75 (m, 1H), 3.20-3.50 (dd, $J = 15$, s Hz, 1H), 2.40-2.60 (m, 1H), 2.00-2.30 (m, 2H), 1.60-2.00 (m, 4H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 220.6(C$_2$), 198.1(C$_1$), 142.0(C$_{-}$), 135.7(C$_{1-}$), 131.8(C$_{3-}$), 129.7(C$_{2-}$), 128.5(C$_{2-}$), 128.4(C$_{3-}$), 128.2(C$_{4-}$), 126.8(C$_4$), 52.9(C$_1$), 41.1(C$_{3-}$), 40.8(C$_2$), 39.7(C$_3$), 27.1(C$_5$), 20.5(C$_4$).

(1'S,3'a,7'S,7'aS,5'R)-7'-(4-Bromophenyl)-3a',7'-dihydroxy-5'-phenylspirop[cycloentane-1,4'-perhydroindene]-2-one (74). $R_f = 0.28$. Yield = 2%. mp = 202°C. IR
(KBr) ν 3300, 2900, 1800, 1720, 1500, 1400, 1100, 960, 900, 840, 780, 710, 550 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.43-7.49 (m, 4H), 7.17-7.26 (m, 5H), 3.91 (s, 1H), 3.43 (dd, J = 13, 3 Hz, 1H), 3.27 (s, 1H), 2.7 (dt, J = 12, 7 Hz, 1H), 2.30 (dt, J = 14, 8, Hz, 1H), 2.09 (ddd, J = 20, 12, 6 Hz, 1H), 1.93 (ddd, J = 18, 9, 5, Hz, 2H), 1.75-1.80 (m, 2H), 1.69-1.74 (m, 2H), 1.51-1.61 (m, 2H), 1.21-1.27 (m, 2H), 0.63-0.70 (m, 2H).

¹³C NMR (50 MHz, CDCl₃) δ 223.4 (C~), 146.1 (C₁⁻), 141.2 (C₁⁻), 131.2 (C₃⁻), 128.9 (C₂⁻), 128.5 (C₃⁻), 127.2 (C₂⁻), 126.4 (C₄⁻), 120.7 (C₄⁻), 83.9 (C₃⁻), 76.5 (C₇⁻), 58.9 (C₄⁻), 47.3 (C₇⁻), 45.3 (C₅⁻), 44.2 (C₃), 42.5 (C₅), 35.4 (C₁⁻), 32.7 (C₃⁻), 20.8 (C₂⁻), 19.4 (C₆⁻), 18.6 (C₄). HRMS (M⁺) m/z calcd. for C_{25}H_{27}BrO₃ 455.389 obsd. 455.386.

**Reaction of 4-nitrochalcone 64 with cyclopentanone 59.**

The general procedure was followed to yield 1,5-diketone 69.

1-(4-Nitrophenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (69). Rᵣ = 0.45. Yield = 66%. mp = 100-102°C IR (KBr) ν 3113, 2932, 1728, 1685, 1602, 1521, 1402, 1346, 1201, 1153, 995, 854, 746, 702, 513 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ 8.15 (dd, J = 16, 5 Hz, 2H), 7.40-7.60 (m, 2H), 7.10-7.40 (m, 5H, aro H), 4.00 (dd, J = 12, 6 Hz, 1H), 3.50-3.70 (m, 1H), 3.35 (ddd, J = 20, 16, 6 Hz, 1H), 2.40-2.60 (m, 1H), 2.10-2.30 (m, 2H), 1.50-2.00 (m, 4H). ¹³C NMR (50 MHz, CDCl₃) δ 219.9 (C₂), 197.2 (C₁⁻), 150.2 (C₄⁻), 142.4 (C₁⁻), 141.7 (C₁⁻), 129.4 (C₂⁻), 129.0 (C₂⁻), 128.6 (C₃⁻), 126.9 (C₄⁻), 123.8 (C₃⁻), 52.7 (C₁), 43.9 (C₂), 41.3 (C₃), 38.8 (C₃⁻), 28.6 (C₅), 20.2 (C₄).

**Reaction of 4-methylchalcone 65 with cyclopentanone 59.**

The general procedure was followed to yield 1-(4-Methylphenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (70) in 53% yield whose Rᵣ (0.53) was found to be comparable to the Rᵣ of other substituted 1,5-diketones.

**Reaction of 4-methoxychalcone 66 with cyclopentanone 59.**
The general procedure was followed to yield two products 71 and 79. The 1,5-diketone 1-(4-Methoxyphenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (71) was found to have Rf (0.55) comparable to the Rf of other substituted 1,5-diketones.

1-(4-Methoxyphenyl)-3-{2-oxo-3-[(4-phenylmethylidene)cyclopentyl]-3-phenyl-1-propanone (79). \( R_f = 0.25 \). Yield = 15%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.79-7.82 (m, 2H), 7.64-7.72 (m, 5H), 6.83-6.98 (m, 2H), 5.8 (s, 1H), 4.48 (d, \( J = 12.2 \) Hz, 1H), 4.32-4.36 (m, 1H), 3.82 (s, 3H), 3.38 (dd, \( J = 16.6, 5.3 \) Hz, 1H), 3.23 (dd, \( J = 16.6, 6.8 \) Hz, 1H), 2.50-2.64 (m, 1H), 2.24-2.27 (m, 2H), 1.64 (m, 2H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 196.7(C\(_6\)), 163.4(C\(_4\)), 142.7(C\(_1\)), 139.4(C\(_1\)), 130.9(C\(_2\)), 129.9(C\(_2\)), 128.7(C\(_3\)), 128.2(C\(_3\)), 126.6(C\(_2\)), 126.2(C\(_4\)), 113.6(C\(_3\)), 50.9(C\(_4\)), 43.9(C\(_7\)), 42.9(C\(_4\)), 31.7(C\(_5\)), 22.9(C\(_6\)). HRMS (M\(^+\)) m/z calcd. for C\(_{28}\)H\(_{26}\)O\(_3\) 410.510 obsd. 410.507.

o-Benzylxyacetophenone (98). o-hydroxyacetophenone (0.68g, 5 mmol), 15% NaOH (5.1 mL) and benzyl chloride (0.85g, 6.775 mmol) was taken in a 50 mL round bottomed flask fitted with a condensor and allowed to reflux for 2 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (25mL), washed with water (2 x 10 mL), brine (2 x 5 mL), dried (Na\(_2\)SO\(_4\)) and concentrated to give 98 (\( R_f = 0.46; \) Yield = 88%). The product was characterised on the basis of the mp of the 2,4-dinitrophenylhydrazone derivative (obs. 206\(^\circ\)C; lit 206-8\(^\circ\)C).\(^5\)

\((E)-1-(2-Benzylxyphenyl)-3-phenyl-2-propen-1-one (99). NaOH (0.306g, 7.65 mmol) dissolved in 3mL of water and 1.8 mL of ethanol was maintained at 0-10 \(^\circ\)C. To this freshly distilled benzaldehyde (0.636g, 6 mmol) and o-benzylxyacetophenone 98 (1.356g, 6 mmol) were added while maintaining the temperature of the reaction mixture at 10-15\(^\circ\)C. The rm was stirred vigorously for 4-5 h after which the mixture turned so thick that stirring was no longer effective. The stirred mixture was kept inside the freezer for 12 h. The solid formed was filtered under suction, washed with cold water
until the washings were neutral to litmus and then with 3 mL of ice cold 50% ethanol. The crude chalcone was dried in air and recrystallised from ethanol to give 99 (Rf = 0.48; Yield = 87%). mp = 67°C. IR (KBr) v 3024, 2943, 1651, 1604, 1481, 1448, 1377, 1331, 1232, 1161, 1111, 1022, 974 858, 752, 696 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ 7.50-7.80 (m, 4H), 7.30-7.50 (m, 10H), 7.00-7.10 (m, 2H), 5.15 (s, 2H). ¹³C NMR (50 MHz, CDCl₃) δ 192.1(C₁), 157.6(C₂·), 142.8(C₁·), 136.3(C₁·), 135.3(C₂), 133.1(C₁·), 130.9(C₄·), 130.0(C₂·), 128.8(C₃·), 128.6(C₅·), 128.4(C₃·), 128.1(C₄), 127.5(C₂·), 126.9(C₄·), 121.2(C₃), 113.1 (C₃·), 70.9(C₁·).

1-(2-benzylloxyphenyl)-3-(2-oxocyclopentyl)-3-phenyl-1-propanone (100). To a stirred suspension of freshly activated Ba(OH)₂ (heated to 100°C for 2h and cooled in a dessicator, 0.068g, 0.4 mmol) in 5mL of absolute alcohol, cyclopentanone (0.1848g, 2.2 mmol) was added dropwise at room temperature and stirring continued for 10 min. Chalcone 99 (0.628g, 2mmol) was added to the reaction mixture stirring continued for 12 h at room temperature. The reaction was subjected to the usual workup to give the product which was purified by column chromatography using silica gel (100-200 mesh) with hexane/ethyl acetate solutions (90:10) as eluent to give 100 (Rf = 0.35; Yield = 71%). IR (neat) v 3447, 3030, 2961, 2878, 1732, 1672, 1597, 1494, 1450, 1286, 1236, 1161, 1005, 756, 700 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ 6.90-7.70 (m, 14H), 5.14 (s, 2H), 3.60-3.90 (m, 2H), 3.30-3.50 (m, 1H), 2.20-2.40 (m, 1H), 2.10-2.20 (m, 2H), 1.40-2.00 (m, 4H). ¹³C NMR (50 MHz, CDCl₃) δ 221.6(C₂), 200.6(C₁), 157.6(C₂·), 143.2(C₁·), 142.3(C₁·), 136.2(C₁·), 133.3(C₂·), 130.8(C₄·), 128.7(C₃·), 128.6(C₃·), 128.2(C₆·), 127.6(C₂·), 126.9(C₄·), 126.3(C₄·), 120.9(C₅·), 112.7(C₃·), 70.8(C₁·), 53.1(C₁), 40.9(C₃), 40.1(C₃), 38.8(C₂·), 26.6(C₃), 20.5(C₄). HRMS (M⁺) m/z calcd. for C₂₇H₂₆O₃ 398.499 obsd. 398.494.
Reaction of 1,5-diketone 100 with ammonium formate

To a stirred mixture of the 1,5-diketone (1.194g, 3mmol) in 10mL of polyethylene glycol 200, ammonium formate (0.756g, 12 mmol) was added and allowed to reflux in oil bath for 5 h. The reaction mixture was then allowed to cool to room temperature, diluted with CHCl₃ (15 mL), washed with saturated NaHCO₃ solution (2 x 15 mL), brine (2 x 10 mL), dried (Na₂SO₄) and concentrated to give a mixture of two products. This was separated by column chromatography using silica gel (100-200 mesh) with hexane/ethylacetate solutions (85:15) as eluent.

2-(2-benzyloxyphenyl)-4-phenylperhydrocyclopenta[b]pyridine 103. \( R_f = 0.35 \). Yield = 24%. IR (neat) \( \nu \) 3000, 2880, 2800, 1580, 1540, 1480, 1360, 1220, 1140, 1000, 740, 690 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 6.90-7.80 (m, 14H), 5.06 (s, 2H), 3.80-4.00 (m, 2H), 3.20 (m, 1H), 2.90 (m, 1H), 2.40-2.60 (m, 1H), 2.00-2.30 (m, 1H), 1.80-2.00 (m, 2H), 1.50 (br s, 1H), 0.80-1.30 (m, 4H). \(^13\)C NMR (100 MHz, CDCl₃) \( \delta \) 160.9(C₂⁻), 145.5 (C₁⁻), 141.7(C₁⁻), 136.7(C₁⁻), 133.3(C₂⁻), 130.5(C₄⁻), 128.9(C₃⁻), 128.5(C₃⁻), 128.3(C₆⁻), 127.4(C₂⁻), 126.6(C₄⁻), 126.1(C₄⁻), 120.8(C₅⁻), 112.6(C₃⁻), 75.58(C₇a), 70.61(C₂), 70.54(C₁⁻), 45.42(C₄), 36.07(C₇), 35.74(C₃), 29.06(C₅), 28.16(C₄), 27.24(C₆). HRMS (M⁺) m/z calcd. for C₂₁H₂₉NO 383.532 obsd. 383.525.

2-(2-benzyloxyphenyl)-4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine 102. \( R_f = 0.29 \). Yield = 40%. IR (neat) \( \nu \) 3020, 3000, 2880, 2820, 1700, 1570, 1480, 1440, 1360, 1220, 1000, 740, 680 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.68 (s, 1H), 6.98-7.33 (m, 13H), 5.02 (s, 2H), 3.08 (t, \( J = 7.33 \) Hz, 2H), 2.99 (t, \( J = 7.33 \) Hz, 2H), 2.04-2.08(m, 2H). \(^13\)C NMR (100 MHz, CDCl₃) \( \delta \) 165.2(C₂⁻), 155.9(C₁⁻), 144.0(C₁⁻), 141.3(C₄), 138.8(C₁⁻), 133.9(C₄), 131.1(C₆⁻), 129.5(C₄⁻), 129.3(C₂⁻), 128.6(C₃⁻), 128.5(C₃⁻), 128.2(C₂⁻), 127.6(C₄⁻), 127.2(C₅⁻), 126.7(C₃), 125.8(C₄⁻), 121.2(C₇a), 112.5(C₃⁻),
70.3(C₁⁻), 34.3(C₇), 30.5(C₅), 23.2(C₆). HRMS (M⁺) m/z calcd. for C₂₇H₂₉NO
377.484 obsd. 377.480.

2-(4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)phenol (103). To a stirred mixture of 101 (0.383 g, 1 mmol) and ammonium formate (0.3783 g, 6 mmol) in 10 mL of methanol, 10% Pd/C (20 mg, 5% by weight of starting material) was added and allowed to reflux for 4 h. The reaction mixture was then allowed to cool to room temperature, filtered through a pad of celite and methanol was removed in vacuo. The rm was then diluted with dichloromethane (25 mL), washed with water (2 x 10 mL), brine (2 x 10 mL), dried (Na₂SO₄) and concentrated. Purification of the product was done by column chromatography (silica 100-200 mesh) with hexane/ethylacetate solutions (90:10) as eluent to give 103. Rᵣ = 0.52. Yield = 73%. IR (neat) ν 3020, 2920, 1720, 1570, 1460, 1400, 1340, 1230, 1120, 960, 920, 800, 760, 650, 590, 520 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, J = 8.3, 1.46 Hz, 1H), 7.65 (s, 1H), 7.40-7.50 (m, 5H), 7.24 (dt, J = 6.83, 1.46 Hz, 1H), 7.01 (dd, J = 8.3, 1 Hz, 1H), 6.86 (dt, J = 8.3, 1.46 Hz, 1H), 3.06(t, J = 8.8 Hz, 2H), 2.99 (t, J = 7.3 Hz, 2H), 2.05-2.15 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 162.8(C₂⁻), 159.6(C₂), 156.1(C₁⁻), 147.0(C₁⁻), 138.5(C₄), 133.1(C₆), 130.6(C₅), 128.5(C₃⁻), 128.0(C₃⁻), 126.3(C₂⁻), 126.0(C₃), 125.8(C₄⁻), 119.2(C₇⁺), 118.5(C₄⁺), 116.1(C₆⁺), 34.0(C₇), 30.5(C₅), 23.2(C₆). HRMS (M⁺) m/z calcd. for C₂₀H₁₇NO 287.360 obsd. 287.353.
1.10 References:


51. Global energy minimizations were performed with PCModel version for Windows (Serena software) in the MMX mode.

