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**PAPER**

# Synthesis of novel *N*-hydroxy heterocycles *via* intramolecular reductive cyclization of diketoximes by $NaBH_3CN$†

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A simple and efficient protocol for the construction of substituted piperazines, piperidines, thiomorpholines, decahydroquinolines, perhydrocyclopenta[*b*]pyridine, and pyrrolidines bearing *N*-hydroxy substituents through intramolecular reductive cyclization of diketoximes using sodium cyanoborohydride is described.

## Introduction

Piperazine, piperidine, thiomorpholine, decahydroquinoline, and pyrrolidine are important classes of nitrogen heterocycles having outstanding biological properties and a wide range of applications to pharmaceutical and synthetic intermediates. One of the privileged scaffolds in medicinal chemistry is the piperazine unit, which is found in many important drugs on the market. An examination of 1000 orally administered drugs disclosed that 7% of them contain a piperazine scaffold.[1] Piperazine nuclei are found in a range of biologically active compounds.[2] The significant hurdle in using piperazines as biological scaffolds is the difficulty in introducing substituents on their carbon backbone, which restricts SAR studies to substitution at the nitrogens.[3] Syntheses of the piperazine entity have been achieved by organometallic catalysis,[4] reductive cyclization,[5] and condensation reactions.[6] Recently *N*-Boc and *N*-OH protected piperazines have been prepared from pyrazine *N*-oxides.[7] Hulme's UDC (Ugi/de-Boc/cyclize) sequence leads to unsymmetrical diketopiperazines which can be reduced to the corresponding piperazines.[8] Recently chiral piperazine scaffolds were obtained by ring opening of aziridines with amino acids, followed by Fukuyama–Mitsunobu cyclization.[9]

The substituted piperidines are core structures of many naturally occurring alkaloids[10] and have attractive pharmacological activities.[11] Thus, the synthesis of highly substituted piperidines has gained considerable attention.[12] Previously, *N*-hydroxypiperidine and pyrrolidine[13] were obtained by Michael addition of bis α,β-unsaturated diesters with hydroxylamine. *N*-Alkylhydroxylamine can be oxidized[14] to furnish the corresponding nitrones which are useful for 1,3-dipolar cycloaddition.[15] The *N*-hydroxyl group could be deprotected by zinc dust in methanol and synthetic modifications can be achieved on the nitrogen.[16] The thiomorpholine chemistry has been developed extensively and thiomorpholine analogs are associated with a variety of pharmacological activities including antimycobacterial, antimalarial, analgesic, and anti-inflammatory activities.[17] Thiomorpholines serve as precursors for sulfur ylides useful in the asymmetric epoxidation of aldehydes.[18]

About forty decahydroquinoline alkaloids have been isolated from frog skin extracts. Decahydroquinolines were initially believed to be unique to amphibians until recently when two isomers of this class were isolated in extracts of myrmicine ants.[19] Recently diverse synthetic strategies and methods have been developed to access such motifs, and a variety of general, broadly applicable approaches have emerged. Strategies that involve intramolecular Diels–Alder reaction[20] NIS promoted aminocyclization[21] Beckmann rearrangements of tetrahydroindanones,[22] [3,3]-sigmatropic rearrangements,[23] and biomimetic approaches [24] have also been put forward.

Cyanoborohydride[25] is a versatile reducing agent for a variety of organic functional groups, like carbonyls, oximes, enamines, in addition to effecting reductive amination.[26] $NaBH_3CN$ in conjugation with $Bu_3SnCl$ effects radical reductive cyclisation *via* demethoxylation,[27] whilst the combination of $NaBH_3CN$ and $BF_3$ etherate reduces indole and acridine to their dihydro derivatives.[28] Very recently, primary amines have been synthesised from aldehydes through reductive amination.[29]

## Results and discussion

A facile general synthetic protocol for the above mentioned heterocycles bearing *N*-hydroxyl groups has been developed and the results are described here. When substituted *N*-aryl-*N*,*N*-diphenacylamine dioximes **1** were subjected to sodium cyanoborohydride in the expectation of generating bis-*N*-alkylhydroxylamines **2**, interestingly, the reaction resulted in

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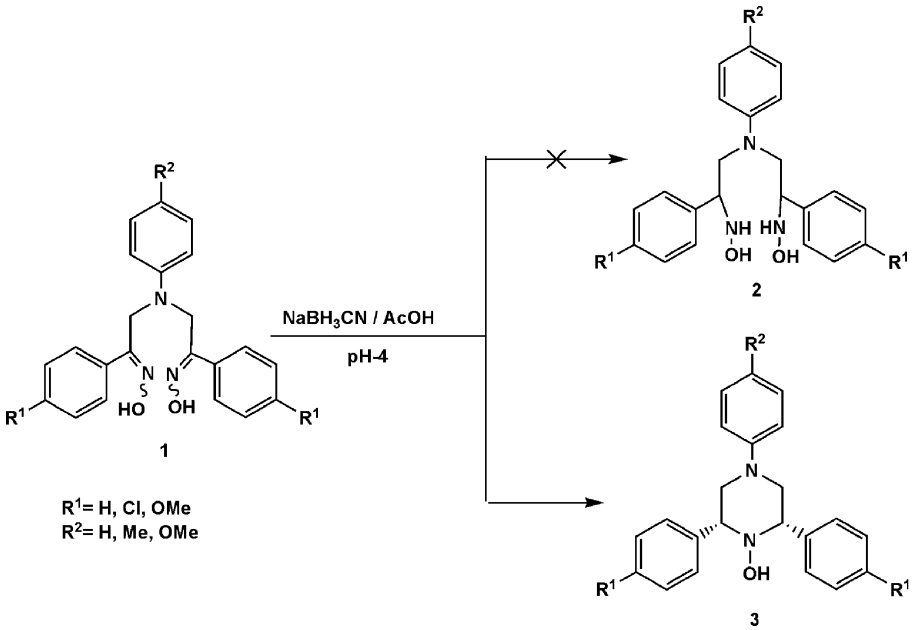



**Scheme 1** Synthesis of 1-hydroxy-2,4,6-triarylpiperazine.

**Table 1** Isolated yield and reaction time of **3** and **5**

| Entry | Product | $R^1$ | $R^2$ | Yield (%) | Time (min) |
|---|---|---|---|---|---|
| 1 | **3a** | H | H | 86 | 20 |
| 2 | **3b** | H | OMe | 82 | 15 |
| 3 | **3c** | H | $CH_3$ | 87 | 20 |
| 4 | **3d** | OMe | OMe | 86 | 25 |
| 5 | **3e** | Cl | OMe | 81 | 30 |
| 6 | **5** | — | — | 78 | 25 |

intramolecular reductive cyclization furnishing a series of 1-hydroxy-2,4,6-triarylpiperazines **3** (Scheme 1, Table 1) in excellent yields (above 80%) and the reaction was completed within 15–30 min. This reaction proceeds stereoselectively giving a single isomer with all substituents oriented equatorially[30] (Fig. 1). It is pertinent to note that none of the existing strategies offers immediate access to *cis*-2,6-disubstituted N-hydroxy-*N′*-arylpiperazine.

Elsewhere, aldoximes were reduced under these conditions to give dialkylhydroxylamine with primary alkyl substitution adjacent to nitrogen, and normal ketoximes were reduced to *N*-alkylhydroxylamines, as the major products.[26a] In the present case, ketoximes yielded cyclic dialkylhydroxlamines with secondary alkyl substitution adjacent to nitrogen, and these were given exclusively. A plausible mechanism for the formation of **3** is shown in Scheme 2, as proposed for the similar intermolecular reaction.[26a]

The scope of the above reaction was also investigated with a tetraoxime of the type **4** (Scheme 3), which was obtained as a single isomer by a reported procedure.[31] The reaction of **4** with cyanoborohydride affords an interesting molecule with two piperazyl units linked by a phenyl ring, **5**. The $^1$H and $^{13}$C NMR spectra of **5** confirm that the molecule is symmetrical (Scheme 3, Table 1).

In an attempt to synthesise an *ortho* analogue of **5**, we tried to prepare the tetraoxime from *o*-phenylenediamine and 4-methoxy-$\alpha$-bromoacetophenone oxime. This, however, resulted in the formation of 2-(2-aminophenylamino)-1-(4-methoxyphenyl) ethanone oxime **6**. Further alkylation of **6** under these conditions might have been blocked due to the monosubstituted derivative preferring to exist in a cyclic form.

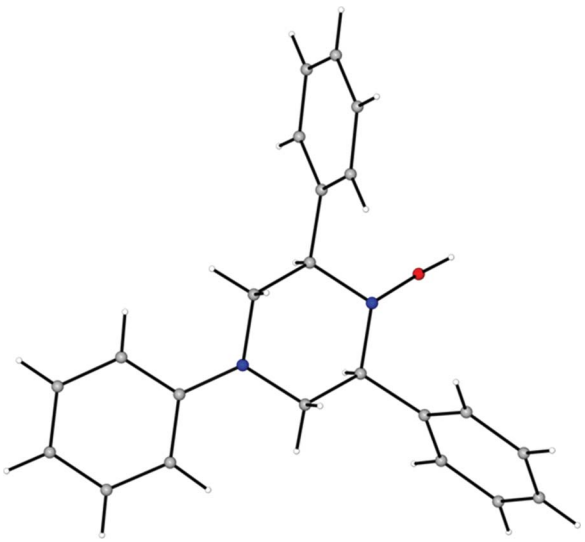
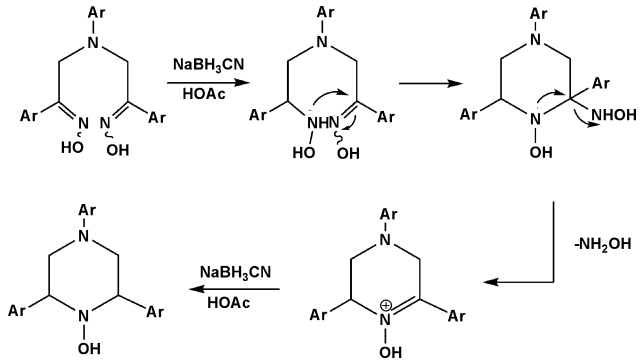


**Fig. 1** Structure of **3a** from X-ray analysis.

### *N*-Hydroxypiperidine

After the generation of piperazine units, our attention turned to the construction of 1-hydroxy-2,4,6-triarylpiperidine derivatives from 1,3,5-triphenylpentane-1,5-dione. These ketones, incidentally, were prepared by a modified literature method [32] from acetophenone and aryl aldehyde with a catalytic amount of tetrabutylammonium bromide and potassium hydroxide under solvent free conditions. The oximes of these ketones **7**, when treated with cyanoborohydride, gave two diastereomers, **8** and **9** in a 1 : 1 ratio (Scheme 4, Table 2). The H-4 appears as a broadened




**Scheme 2** Mechanism for the formation of **3**.

**Table 2** Isolated yield and reaction time of **8**, **9** and **11**

| Entry | Product | *R* | Yield (%) | Time (min) |
|---|---|---|---|---|
| 1 | **8a** : **9a** | Phenyl | 40 : 42 | 20 |
| 2 | **8b** : **9b** | 2-Pyridyl | 41 : 43 | 25 |
| 3 | **8c** : **9c** | 4-Chloro-phenyl | 38 : 40 | 30 |
| 4 | **8d** : **9d** | 1-Naphthyl | 38 : 36[a] | 30 |
| 5 | **11a** | H | 87 | 15 |
| 6 | **11b** | Cl | 86 | 10 |
| 7 | **11c** | Br | 86 | 10 |
| 8 | **11d** | Me | 85 | 15 |
| 9 | **11e** | OMe | 84 | 20 |

[a] Inseparable diastereoisomers.

singlet at 3.20 ppm in **8a**, while it appears as a triplet of triplets ($J$ = 12.0 Hz, 3.0 Hz) at 3.01 ppm in **9a**. The structure of **8b** has also been confirmed by single crystal analysis (Fig. 2).[33]

### *N*-Hydroxythiomorpholine

This strategy was then extended to the synthesis of thiomorpholines by employing dioximes of substituted diphenacyl sulfides **10**. This afforded 4-hydroxy-3e,5e-diaryl thiomorpholines **11** diastereoselectively (Scheme 5). The ring closure is relatively quicker in these cases (Table 2).

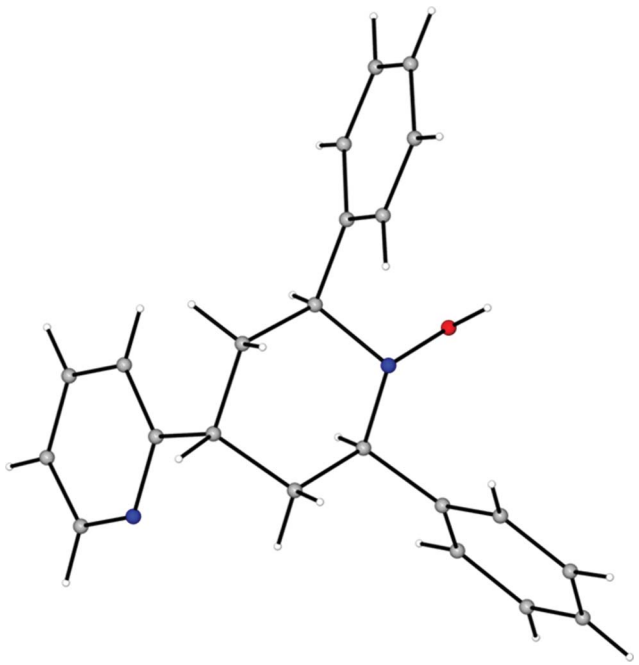
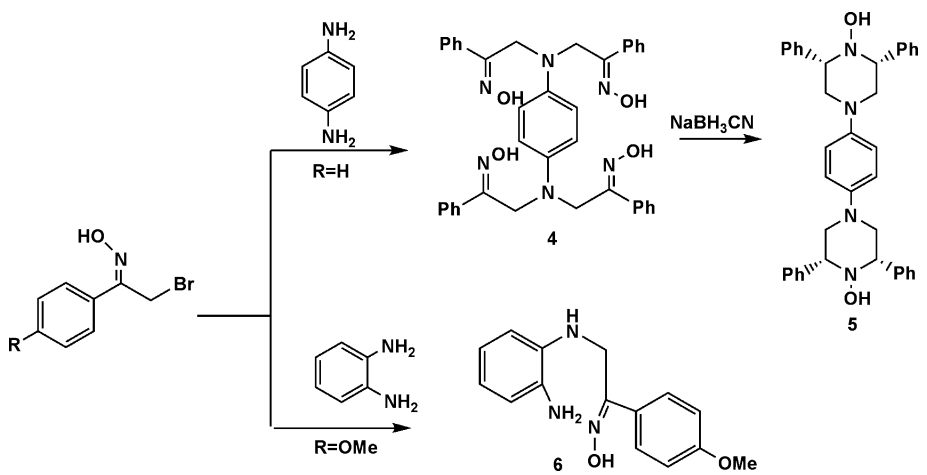


**Fig. 2** Structure of **8b** from X-ray analysis.

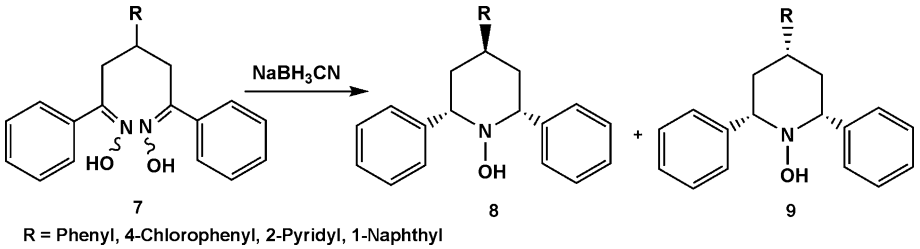
### *N*-Hydroxydecahydroquinoline

In a similar manner, *N*-hydroxy 2,4,6-trisubstituted decahydroquinolines have also been prepared from the oximes of 2-(3-oxo-1,3-diarylpropyl)cyclohexanone **12** (Scheme 6). This ketone is diastereomerically almost pure with a trace of another isomer as evidenced from the NMR spectrum. Upon oximation, however, more geometrical isomers were obtained, the mixture of which was subjected to reductive cyclisation. Though 2,4,6-trisubstituted decahydroquinoline derivatives possess five stereogenic centers, only four diastereoisomers, **13**, **14**, **15** and **16**, were obtained. Among them, *cis*-decahydroquinolines (**13**, **14** and **15**) were obtained predominantly, even though *trans*-decahydroquinoline is expected to be thermodynamically more stable (Table 3). This can be explained by the facts that (i) the cyclic oxime is reduced preferentially due to internal strain relief and (ii) the attack of hydride is favoured from the less hindered side of the ring.

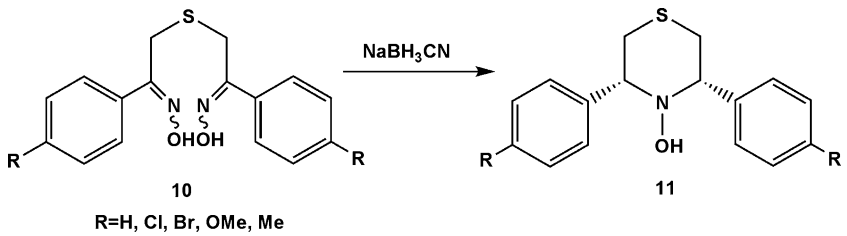



**Scheme 3** Synthesis of 4,4′-(1,4-phenylene)bis(2,6-diphenylpiperazin-1-ol).

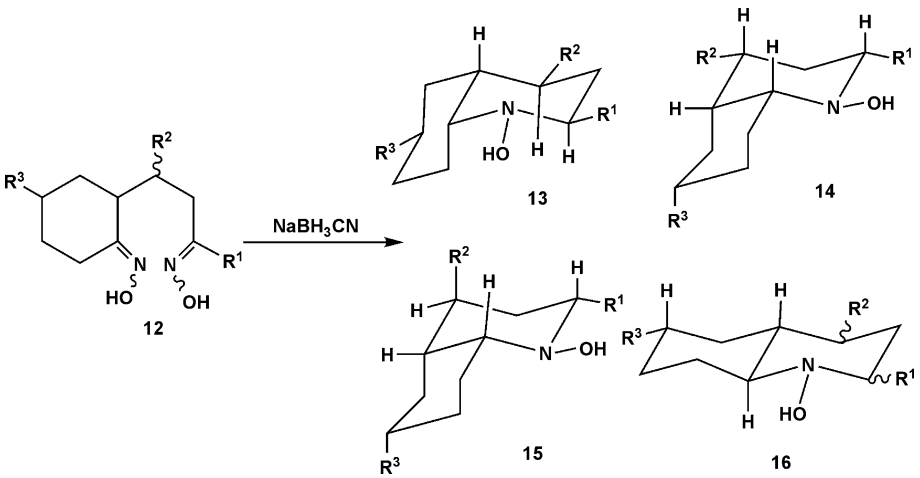
 




**Scheme 4** Synthesis of 1-hydroxy-2,4,6-triarylpiperidine.




**Scheme 5** Synthesis of 4-hydroxy-3,5-diarylthiomorpholine.




**Scheme 6** Synthesis of 2,4,6-trisubstituted decahydroquinoline.

**Table 3** Isolated yield of decahydroquinoline derivatives

| Entry | $R^1$ | $R^2$ | $R^3$ | **13** | **14** | **15** | **16** |
|---|---|---|---|---|---|---|---|
| **a** | Ph | Ph | H | 35 | 26 | 5 | 15 |
| **b** | Ph | 4-Cl-Ph | H | 35 | 30 | — | 12 |
| **c** | Ph | 4-Cl-Ph | t-Bu | — | trace | 35 | 21 |
| **d** | 4-Me-Ph | Ph | t-Bu | 9 | — | 36 | 22 |

The conformations of **13–16** have been assigned readily as it is possible to identify the hydrogens at the ring junctions, those adjacent to nitrogen and the benzylic hydrogens from one and two dimensional NMR spectra in all these cases.

The signal of H-4 of **13** has two diaxial and one axial–equatorial couplings (ddd, 12.6, 12.6 and 4.5 Hz) suggesting that H-4 and H-4a are likely to be *trans* to each other. H-4a occurs as a broadened doublet implying a *cis* relationship between H-4a and H-8a. Similarly, H-8a also appeared as a broadened doublet. The structure of **13a** has been confirmed by X-ray crystallographic study of a single crystal (Fig. 3).[34]

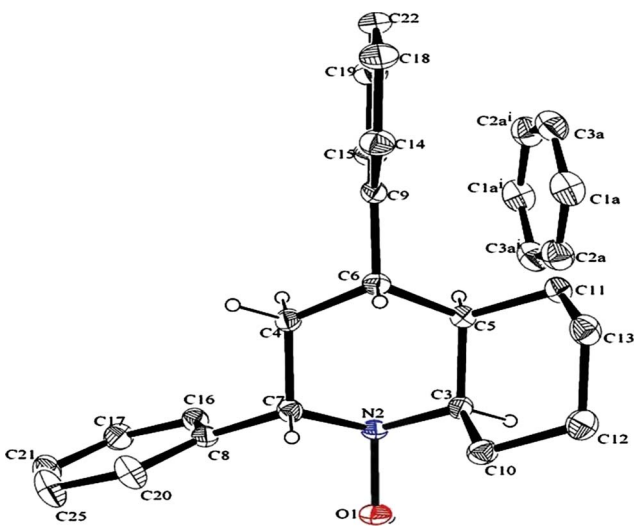
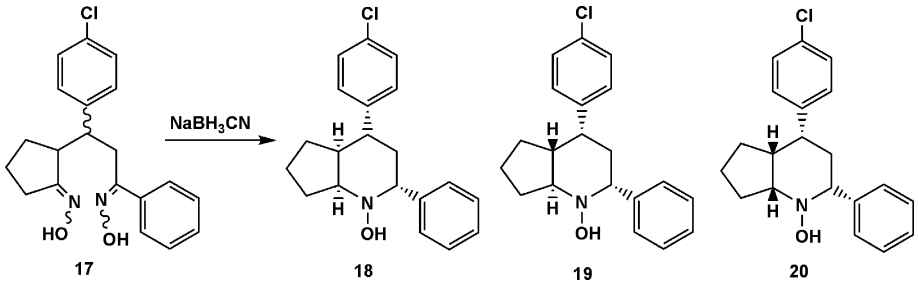



**Fig. 3** Structure of **13a** from X-ray analysis.




**Scheme 7** Synthesis of 4-(4-chlorophenyl)-2-phenyloctahydro-1*H*-cyclopenta[*b*]pyridin-1-ol.

In **14**, H-4 has one diaxial and two axial–equatorial couplings (ddd, 13.2, 3.9 and 3.9 Hz) which reveals that C4–H and C4a–H are *cis* to each other. C4a–H appears as a multiplet, while C8a–H appears as an apparent quartet with negligible coupling, revealing that C4a–H and C8a–H are *cis* to each other. The structure **14b** has been confirmed by X-ray crystallographic study of a single crystal (Fig. 4).[35]

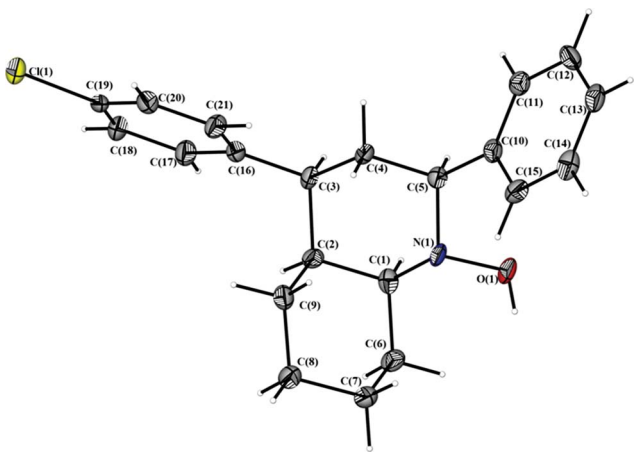



**Fig. 4** Structure of **14b** from X-ray analysis.

It is interesting to find that the presence of a *tert*-butyl group at the 6th position leads to the formation of **15** as the major product. The C4–H has only one weak coupling in **15**, pointing to the axial orientation of the aryl at C-4. As C4a–H has only one diaxial type coupling, it is inferred to be *cis* to C8a–H, which occurs as an apparent quartet with a very small coupling. As C8a–H is not found to have any axial–axial relationship with any of its neighbouring hydrogens, the ring fusion is deduced to be *cis* as in **14**.

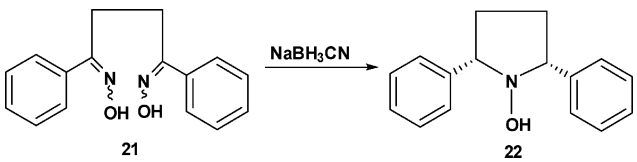
The remaining isomer **16** needs to be necessarily a *trans*-decahydroquinoline system. Relief of steric strain in isomer **16**, compared to the situation in isomers **13–15**, has led to deshielding of the carbon nuclei and shielding of the protons at the ring junction and at the benzylic center. However, the relative stereochemistry at C2 and C4, with reference to the ring junctions, could not be deduced unequivocally.

### *N*-Hydroxyperhydrocyclopenta[*b*]pyridine

Another bicyclic system comprising a cyclopentyl system fused to a piperidine moiety has also been synthesised using this protocol. The dioxime **17** of the ketone prepared by Michael addition of cyclopentanone to chalcone, was treated with cyanoborohydride to yield three isomers (**18**, **19** and **20**) in almost equal amounts. The three diastereoisomers were successfully separated by column chromatography. The nature of the ring fusion and the stereochemistry around C2 and C4 (Scheme 7) could be established by one and two dimensional NMR experiments. Related compounds have been recently reported *via* reductive cyclization of mono oximes using $NaBH_4$.[36]

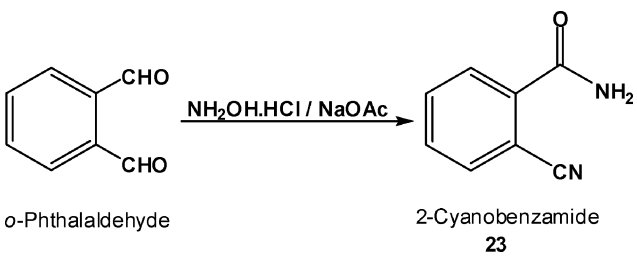
### *N*-Hydroxypyrrolidine

The above reactions employ 1,5-diketones as the precursors. Next, we were prompted to extend the application of this methodology for the creation of heterocycles using 1,4-diketones. Thus, the 1,4-dioxime **21** of dibenzoyl ethane was subjected to sodium cyanoborohydride treatment. As expected, the reductive cyclisation of **21** afforded an excellent yield of 2,5-diphenyl-*N*-hydroxypyrrolidine **22** (Scheme 8), with the two aryl groups *cis* to each other, as evidenced by their chemical equivalence in the NMR spectrum.




**Scheme 8** Synthesis of 2,5-diphenylpyrrolidin-1-ol.

An attempted oximation of the aromatic dialdehyde *o*-phthalaldehyde by the treatment of hydroxylamine hydrochloride and anhydrous sodium acetate yielded only 2-cyanobenzamide **23** exclusively and not the dioxime (Scheme 9).

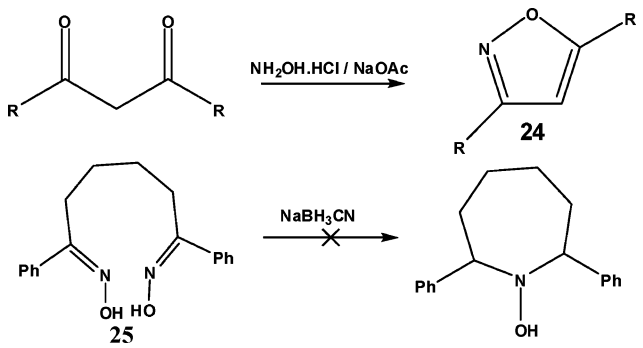



**Scheme 9** Reaction of *o*-phthalaldehyde with hydroxylamine.

Similarly, efforts to obtain the 1,3-dioxime also proved difficult, as this reaction always led to the formation of isoxazole **24**. It is pertinent to note that a typical 1,6-dioxime **25** of the ketone generated by Friedel–Crafts acylation of benzene with adipoyl

chloride failed to undergo reductive cyclisation even after 24 h (Scheme 10).




**Scheme 10** Other attempted reactions.

All the above reactions, when carried out with sodium borohydride instead of sodium cyanoborohydride, were found to be ineffective giving only poor yields of the cyclised products, despite prolonged reaction times. It should be mentioned that Pradhan *et al.* have reported unusual reactions of steroidal and non steroidal 1,5-dioximes with $NaBH_4$.[37] During the synthesis of polyhydroxylated aza-heterocycles by double reductive amination using $NaBH_3CN$, *in situ* formation of oxime and subsequent cyclization has been effected in a 1,4-dicarbonyl unit.[38]

## Conclusions

A simple methodology for the synthesising *N*-hydroxy heterocycles through intramolecular reductive cyclization of diketoximes using sodium cyanoborohydride has been developed. The proposed strategy of preparing heterocycles has advantages over other methods, through the readily availability of the reagents and their low cost, its progress under transition metal-free conditions, and its facile and expedient experimental procedure. Work is in progress in our research group in expanding the substrate range to obtain novel heterocycles with asymmetric induction.

## Experimental section

Nuclear Magnetic Resonance ($^1$H and $^{13}$C NMR) spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ using TMS as internal standard. Chemical shifts are reported in parts per million ($\delta$), coupling constants ($J$ values) are reported in hertz (Hz). $^{13}$C NMR spectra were routinely run with broadband decoupling. Infrared spectra were recorded on a Shimadzu FT-IR instrument (in KBr pellets). Band positions are reported in reciprocal centimetres ($cm^{-1}$). Melting points were determined on a melting point apparatus (Inlab Pvt Ltd, India) equipped with a thermometer and were uncorrected. Column chromatography was carried out on silica gel (60–120 mesh) using petroleum ether–ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 series II Elemental CHNS analyzer.

Substituted *N*-aryl-*N*,*N*-diphenacylamine dioximes **1a** and **4** have been synthesized by a reported procedure [31] while all other dioximes have been prepared by oximation of the corresponding ketones.[39]

**Typical experimental procedure for the reductive cyclization of diketoxime with sodium cyanoborohydride[26a]**

To a suspension of diketoxime (2.7 mmol) in 5 ml of methanol was added sodium cyanoborohydride (11.8 mmol) and glacial acetic acid (20 mL) in four portions with three minute intervals, each time adjusting the pH to 4 by adding glacial acetic acid with trace of bromocresol green as indicator. The reaction was monitored by TLC. After the completion of the reaction, the pH was brought to 9 by addition of 6 N potassium hydroxide solution. The reaction mixture was then extracted with chloroform. The combined extracts were dried (anhydrous sodium sulfate) and evaporated *in vacuo*. The individual compounds were isolated by column chromatography using 1% ethyl acetate and petroleum ether.

**2,4,6-Triphenylpiperazin-1-ol (3a)**

Colorless solid; mp 140–142 °C; IR (KBr) 3535, 3056, 3028, 2869, 2840, 1595, 1502, 1452, 1197, 743, 698 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.06 (dd, $J$ = 12.0 Hz, 11.4 Hz, 2H), 3.75 (dd, $J$ = 12.0 Hz, 3.0 Hz, 2H), 4.10 (dd, $J$ = 11.4 Hz, 3.0 Hz, 2H), 4.59 (s, 1H), 6.86 (t, $J$ = 7.2 Hz, 1H), 6.95 (d, $J$ = 7.2 Hz, 2H), 7.28 (t, $J$ = 7.2 Hz, 2H), 7.32 (bt, $J$ = 7.5 Hz, 2H), 7.38 (t, $J$ = 7.5 Hz, 4H), 7.56 (dd, $J$ = 7.5 Hz, 1.2 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 56.6, 70.1, 116.0, 119.9, 127.6, 127.7, 128.6, 129.2, 140.4, 149.5; Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.83; H, 6.63; N, 8.38%.

**4-(4-Methoxyphenyl)-2,6-diphenylpiperazin-1-ol (3b)**

Colourless solid; mp 123–125 °C; IR (KBr) 3235, 3056, 1495, 1482, 1412, 1386, 1232, 1192, 740, 672 $cm^{-1}$; Theoretical mass: 361.4; measured mass: 361.5 and 402.6 (acetonitrile adduct); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.96 (dd, $J$ = 12.1 Hz, 11.4 Hz, 2H), 3.56 (bd, $J$ = 12.1 Hz, 2H), 3.72 (s, 3H), 4.10 (dd, $J$ = 11.4 Hz, 3.0 Hz, 2H), 4.58 (s, 1H), 6.77 (d, $J$ = 9.0 Hz, 2H), 6.84 (d, $J$ = 9.0 Hz, 2H), 7.28 (t, $J$ = 7.2 Hz, 2H), 7.38 (t, $J$ = 7.2 Hz, 4H), 7.53 (d, $J$ = 7.2 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 55.5, 58.2, 70.33, 114.4, 118.2, 127.6, 127.7, 128.5, 140.5, 143.9, 153.9; Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.53; H, 6.68; N, 7.69%.

**2,6-Diphenyl-4-(4-methylphenyl)-piperazin-1-ol (3c)**

Viscous liquid; IR (KBr) 3432, 2869, 2840, 1502, 1238, 1197, 722, 678 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.25 (s, 3H), 2.96 (dd, $J$ = 12.3 Hz, 11.7 Hz, 2H), 3.64 (bd, $J$ = 12.3 Hz, 2H), 4.05 (dd, $J$ = 11.7 Hz, 2.8 Hz, 2H), 4.65 (bs, 1H), 6.78 (d, $J$ = 8.4 Hz, 2H), 7.02 (d, $J$ = 8.4 Hz, 2H), 7.21 (t, $J$ = 7.5 Hz, 2H), 7.30 (t, $J$ = 7.5 Hz, 4H), 7.51 (d, $J$ = 7.5 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 20.3, 57.1, 70.1, 116.3, 127.6, 128.1, 128.5, 129.4, 129.7, 140.5, 147.4; Anal. Calcd. for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.06; H, 7.14; N, 8.19%.

**2,4,6-Tris-(4-methoxyphenyl)piperazin-1-ol (3d)**

Viscous liquid; IR (KBr) 3325, 3056, 2869, 2840, 1585, 1495, 1238, 1197, 722, 681 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.94 (dd, $J$ = 12.0 Hz, 11.4 Hz, 2H), 3.54 (bd, $J$ = 12.0 Hz, 2H), 3.74 (s, 3H), 3.86 (s, 6H), 4.05 (dd, $J$ = 11.4 Hz, 2.4 Hz, 2H), 4.56 (s, 1H) 6.78

(d, $J$ = 9.0 Hz, 2H), 6.85 (d, $J$ = 9.0 Hz, 2H), 6.90 (d, $J$ = 8.4 Hz, 4H), 7.44 (d, $J$ = 8.4 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 159.2, 154.0, 144.1, 132.7, 128.7, 118.2, 114.5, 113.9, 69.8, 58.2, 55.5, 55.3; Anal. Calcd. for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.28; H, 6.59; N, 6.53%.

**2,6-Bis(4-chlorophenyl)-4-(4-methoxyphenyl)piperazin-1-ol (3e)**

Colorless solid; mp 154–156 °C; IR (KBr) 3335, 3056, 2859, 2820, 1498, 1228, 1187, 740, 698 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.91 (dd, $J$ = 12.3 Hz, 11.1 Hz, 2H), 3.53 (bd, $J$ = 12.3 Hz, 2H), 3.77 (s, 3H), 4.08 (dd, $J$ = 11.1 Hz, 2.7 Hz, 2H), 4.59 (bs, 1H), 6.78 (d, $J$ = 8.7 Hz, 2H), 6.86 (d, $J$ = 8.7 Hz, 2H), 7.38 (d, $J$ = 7.2 Hz, 4H), 7.50 (d, $J$ = 7.2 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 154.3, 143.7, 138.8, 133.4, 128.9, 128.7, 118.5, 114.6, 69.8, 58.1, 55.5; Anal. Calcd. for $C_{23}H_{22}Cl_2N_2O_2$: C, 64.34; H, 5.16; N, 6.52. Found: C, 64.19; H, 5.22; N, 6.48%.

**2-((4-(Bis(2-(hydroxyimino)-2-phenylethyl)amino)phenyl)(2-(hydroxyimino)-2-phenylethyl)amino)-1-phenylethanone oxime (4)**

Colorless solid; mp 162 °C; IR (KBr) 3335, 3215, 2859, 2820, 1625, 1567, 1366, 1228, 1187, 740, 698 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 4.09 (s, 4H), 4.40 (s, 4H), 6.58 (s, 4H), 7.19 (d, $J$ = 7.5 Hz, 4H), 7.31 (m, 16H), 10.71 (s, 2H), 11.32 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 156.9; 153.3, 141.3, 140.6, 136.0, 133.6, 128.6, 128.4, 128.1,* 127.3 115.4, 55.4, 46.6; Anal. Calcd. for $C_{38}H_{36}N_6O_4$: C, 71.23; H, 5.66; N, 13.12; Found: C, 71.09; H, 5.78; N, 13.03%. *Two carbons merged here.

**4,4′-(1,4-Phenylene)bis(2,6-diphenylpiperazin-1-ol) (5)**

Colorless solid; mp 190–192 °C; IR (KBr) 3525, 3026, 3018, 2861, 2838, 1590, 1498, 1452, 1376, 1231, 1192, 741, 690 cm$^{-1}$; Theoretical mass: 583.3; measured mass: 583.2; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.95 (dd, $J$ = 11.7 Hz, 11.4 Hz, 4H), 3.56 (bd, $J$ = 11.7 Hz, 4H), 4.08 (dd, $J$ = 11.4 Hz, 3.0 Hz, 4H), 4.53 (s, 2H), 6.81 (s, 4H), 7.28 (t, $J$ = 7.2 Hz, 4H), 7.38 (t, $J$ = 7.2 Hz, 8H), 7.53 (d, $J$ = 7.2 Hz, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 57.7, 70.3, 117.7, 127.6, 127.7, 128.6, 140.6, 143.8; Anal. Calcd. for $C_{38}H_{38}N_4O_2$: C, 78.32; H, 6.57; N, 9.61. Found: C, 78.18; H, 6.46; N, 9.57%.

**2-(2-Aminophenylamino)-1-(4-methoxyphenyl)ethanone oxime (6)**

To a solution of *o*-phenylenediamine (0.37 g, 3.4 mmol) in 20 mL of 50% aqueous ethanol, $\alpha$-bromo-4-methoxyacetophenone oxime (1.12 g, 4.6 mmol) was added in portions within 5 min. The reaction mixture was stirred at room temperature for an hour. The precipitate formed was filtered and recrystallized from ethanol. Yellow solid; yield = 72%; mp 76–78 °C; IR (KBr) 3535, 3356, 2059, 2820, 1625, 1516, 1366, 1228, 1187, 740, 698 cm$^{-1}$;$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.83 (s, 3H), 4.06 (s, 2H), 4.41 (s, 2H), 6.52 (d, $J$ = 7.5 Hz, 1H), 6.76 (t, $J$ = 7.5 Hz, 1H), 6.92 (d, $J$ = 8.7 Hz, 2H), 7.69 (t, $J$ = 7.5 Hz, 1H), 7.31 (d, $J$ = 7.5 Hz, 1H), 7.85 (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 41.7, 55.3, 113.1, 113.8, 119.0, 127.7, 127.8, 128.0, 129.5, 133.6, 137.0, 156.9, 161.5; Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49; Found: C, 66.35; H, 6.29; N, 15.44%.

**2e,4a,6e-Triphenylpiperidin-1-ol (8a)**

Colorless solid; mp 183–185 °C; IR (KBr) 3221, 1498, 1427, 1089, 1047, 762, 701, 587 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.28 (td, $J$ = 12.0 Hz, 4.8 Hz, 2H), 2.42 (bd, $J$ = 12.0 Hz, 2H), 3.20 (bs, 1H), 3.92 (bd, $J$ = 12.0 Hz, 2H), 4.43 (s, 1H), 7.25 (d, $J$ = 7.5 Hz, 2H), 7.33–7.40 (m, 9H), 7.46 (d, $J$ = 6.9 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 34.8, 39.3, 67.2, 126.9, 127.2, 128.5, 128.7, 128.9, 131.8, 140.8, 143.7; Anal. Calcd. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.71; H, 7.11; N, 4.12%.

**2e,4e,6e-Triphenylpiperidin-1-ol (9a)**

Colorless solid; mp 162–164 °C; IR (KBr) 3201, 1547, 1463, 1095, 756, 721, 621 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.96 (q, $J$ = 12.0 Hz, 2H), 2.13 (dd, $J$ = 12.0 Hz, 3.0 Hz, 2H), 3.01 (tt, $J$ = 12.0 Hz, 3.0 Hz, 1H), 3.93 (dd, $J$ = 12.0 Hz, 3.0 Hz, 2H), 4.63 (s, 1H), 7.22 (dd, $J$ = 7.2 Hz, 2.4 Hz, 2H), 7.26–7.28 (m, 5H), 7.36 (t, $J$ = 8.1 Hz, 4H), 7.52 (dd, $J$ = 8.1 Hz, 1.5 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 41.9, 43.0, 72.1, 126.3, 126.6, 127.0, 127.1, 128.4, 128.5, 143.6, 144.2; Anal. Calcd. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.71; H, 7.12; N, 4.14%.

**2e,6e-Diphenyl-4a-(pyridin-2-yl)piperidin-1-ol (8b)**

Colorless solid; mp 171–173 °C; IR (KBr) 3191, 1581, 1463, 1081, 1037, 763, 700, 549 cm$^{-1}$; Theoretical mass: 331.4; measured mass: 331.25; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.24 (td, $J$ = 12.6 Hz, 3.0 Hz, 2H), 2.61 (bd, $J$ = 12.6 Hz, 2H), 3.25 (bs, 1H), 4.01 (dd, $J$ = 12.6 Hz, 3.0 Hz, 2H), 4.48 (s, 1H), 7.24 (td, $J$ = 7.5 Hz, 2.4 Hz, 1H), 7.26 (bt, $J$ = 8.4 Hz, 2H), 7.34 (t, $J$ = 8.4 Hz, 4H), 7.41 (d, $J$ = 7.5 Hz, 1H), 7.47 (dd, $J$ = 8.4 Hz, 1.2 Hz, 4H), 7.70 (td, $J$ = 7.5 Hz, 1.8 Hz, 1H), 8.65 (d, $J$ = 7.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 38.1, 38.7, 67.5, 120.9, 121.8, 126.9, 127.1, 128.4, 136.2, 144.3, 149.3, 162.4; Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.84; H, 6.59; N, 8.35%.

**2e,6e-Diphenyl-4e-(pyridin-2-yl)piperidin-1-ol (9b)**

Colorless solid; mp 168–170 °C; IR (KBr) 3255, 1557, 1425, 1092, 758, 703, 563 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.10 (q, $J$ = 12.0 Hz, 2H), 2.21 (bd, $J$ = 12.0 Hz, 2H), 3.15 (tt, $J$ = 12.0 Hz, 3.0 Hz, 1H), 3.93 (dd, $J$ = 12.0 Hz, 3.0 Hz, 2H), 4.56 (s, 1H), 7.16 (td, $J$ = 7.2 Hz, 2.4 Hz, 1H), 7.13 (d, $J$ = 7.2 Hz, 1H), 7.23 (bt, $J$ = 7.5 Hz, 2H), 7.33 (t, $J$ = 7.5 Hz, 4H), 7.52 (dd, $J$ = 7.5 Hz, 1.2 Hz, 4H), 7.63 (td, $J$ = 7.2 Hz, 1.8 Hz, 1H), 8.45 (dd, $J$ = 7.2 Hz, 1.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 41.5, 43.9, 71.9, 120.9, 121.5, 127.0, 127.1, 128.4, 136.5, 143.6, 149.2, 163.1; Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.89; H, 6.62; N, 8.40%.

**4a-(4-Chlorophenyl)-2e,6e-diphenylpiperidin-1-ol (8c)**

Colorless solid; mp 153–155 °C; IR (KBr) 3232, 1581, 1463, 1087, 1039, 786, 725, 624 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.25 (td, $J$ = 12.0 Hz, 4.8 Hz, 2H), 2.40 (bd, $J$ = 12.0 Hz, 2H), 3.19 (bs, 1H), 3.96 (bd, $J$ = 12.0 Hz, 2H), 4.40 (s, 1H) 7.24–7.47 (m, 10H), 7.68 (d, $J$ = 7.5 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 34.8, 39.3, 67.3, 126.9, 127.1, 128.2, 128.4, 128.7, 131.8, 140.1, 143.7; Anal. Calcd. for $C_{23}H_{22}ClNO$: C, 75.92; H, 6.09; N, 3.85. Found: C, 75.83; H, 6.01; N, 3.78%.

**4e-(4-Chlorophenyl)-2e,6e-diphenylpiperidin-1-ol (9c)**

Colorless solid; mp 171–173 °C; IR (KBr) 3191, 1621, 1463, 1095, 1042, 772, 731, 641 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.95 (q, $J$ = 12.0 Hz, 2H), 2.17 (bd, $J$ = 12.0 Hz, 2H), 2.96 (tt, $J$ = 12.0 Hz, 3.3 Hz, 1H), 3.90 (bd, $J$ = 12.0 Hz, 2H), 4.44 (s, 1H), 7.12–7.28 (m, 6H), 7.34 (t, $J$ = 8.4 Hz, 4H), 7.48 (dd, $J$ = 8.4 Hz, 1.5 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 41.4, 42.9, 72.0, 127.0, 127.2, 128.0, 128.5,* 132.0, 142.7, 143.4; Anal. Calcd. for $C_{23}H_{22}ClNO$: C, 75.92; H, 6.09; N, 3.85. Found: C, 75.84; H, 6.01; N, 3.78. * One carbon merged here%.

**4-(Naphthalen-1-yl)-2,6-diphenylpiperidin-1-ol (mixture of diastereoisomers, 8d and 9d)**

It is difficult to separate the diastereomers by column chromatography as they have close $R_f$ values. The spectrum of the crude reaction mixture reveals the presence of both isomers in nearly equal amounts.

**Preparation of 3, 5-disustituted 1-hydroxythiomorpholine**

All the diketo sulfide precursors were prepared from phenacyl bromide and sodium sulfide in ethanol at 25–30 C°. Oximation followed by ring closure was carried out as described above.

***cis*-3e,5e-Diphenylthiomorpholin-4-ol (11a)**

Colorless solid; mp 182–184 °C; IR (KBr) 3525, 2935, 2851, 1469, 1421, 1358, 1311, 1091, 1063, 1011, 821, 789, 746, 557, 513 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.65 (bd, $J$ = 13.8 Hz, 2H), 3.04 (dd, $J$ = 13.8 Hz, 11.1 Hz, 2H), 4.04 (bd, $J$ = 11.1 Hz, 2H), 4.50 (s, 1H) 7.25–7.30 (m, 6H), 7.45 (d, $J$ = 8.1 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 36.4, 73.2, 126.8, 127.4, 128.5, 142.5; Anal. Calcd. for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16; S, 11.82. Found: C, 70.75; H, 6.27; N, 5.11; S, 11.77%.

***cis*-3e,5e-Bis(4-chlorophenyl)thiomorpholin-4-ol (11b)**

Colorless solid; mp 128–130 °C; IR (KBr) 3552, 2935, 2877, 1488, 1411, 1367, 1311, 1098, 1066, 1006, 825, 792, 748, 569, 523 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.62 (bd, $J$ = 14.1 Hz, 2H), 2.99 (dd, $J$ = 14.1 Hz, 11.1 Hz, 2H), 3.99 (dd, $J$ = 11.1 Hz, 2.1 Hz, 2H), 4.46 (s, 1H), 7.32 (d, $J$ = 8.4 Hz, 4H), 7.37 (d, $J$ = 8.4 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 36.3, 72.7, 128.2, 128.9, 133.2, 140.8; Anal. Calcd. for $C_{16}H_{15}Cl_2NOS$: C, 56.48; H, 4.44; N, 4.12; S, 9.42. Found: C, 56.43; H, 4.48; N, 4.18; S, 9.38%.

***cis*-3e,5e-Bis(4-bromophenyl)thiomorpholin-4-ol (11c)**

Colorless solid; mp 168–170 °C; IR (KBr) 3544, 2925, 2867, 1481, 1419, 1363, 1309, 1093, 1066, 1006, 825, 792, 748, 557, 503 $cm^{-1}$; Theoretical mass: 428.2; measured mass: 487.3, 488.3, 489.2, and 502.2 (acetate adduct); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.62 (bd, $J$ = 14.1 Hz, 2H), 2.97 (dd, $J$ = 14.1 Hz, 11.1 Hz, 2H), 3.95 (dd, $J$ = 11.1 Hz, 1.8 Hz, 2H), 4.48 (s, 1H), 7.29 (d, $J$ = 8.4 Hz, 4H), 7.46 (d, $J$ = 8.4 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 36.2, 72.6, 121.3 128.5, 131.8, 141.3; Anal. Calcd. for $C_{16}H_{15}Br_2NOS$: C, 44.78; H, 3.52; N, 3.26; S, 7.47. Found: C, 44.73; H, 3.58; N, 3.23; S, 7.42%.

***cis*-3e,5e-Bis(4-methylphenyl)thiomorpholin-4-ol (11d)**

Colorless solid; mp 138–140 °C; IR (KBr) 3517, 2835, 2751, 1489, 1411, 1358, 1311, 1091, 1063, 1031, 831, 769, 746, 557, 523 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.34 (s, 6H), 2.64 (dd, $J$ = 13.2 Hz, 2.1 Hz, 2H), 3.04 (dd, $J$ = 13.2 Hz, 11.1 Hz, 2H), 4.00 (dd, $J$ = 11.1 Hz, 2.1 Hz, 2H), 4.40 (s, 1H), 7.16 (d, $J$ = 8.1 Hz, 4H), 7.34 (d, $J$ = 8.1 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 21.1, 36.5, 73.0, 126.7, 129.3, 137.2, 139.7; Anal. Calcd. for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68; S, 10.71. Found: C, 72.15; H, 7.11; N, 4.73; S, 10.68%.

***cis*-3e,5e-bis(4-methoxyphenyl)thiomorpholin-4-ol (11e)**

Colorless solid; mp 183 °C; IR (KBr) 3516, 2939, 2851, 1469, 1421, 1358, 1311, 1091, 1063, 1011, 821, 789, 746, 567, 543 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.61 (bd, $J$ = 13.8 Hz, 2H), 3.03 (dd, $J$ = 13.8 Hz, 11.1 Hz, 2H), 3.78 (s, 6H), 3.98 (dd, $J$ = 11.1 Hz, 1.8 Hz, 2H), 4.44 (s, 1H), 6.86 (d, $J$ = 8.1 Hz, 4H), 7.36 (d, $J$ = 8.1 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 36.5, 55.2, 72.8, 113.9 127.9, 134.8, 158.8; Anal. Calcd. for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; S, 9.67. Found: C, 65.18; H, 6.31; N, 4.19; S, 9.61%.

**Preparation of substituted *N*-hydroxy decahydroquinoline (13–16; a–d)**

The required ketones were prepared from the respective chalcone and cyclohexanone in ethanol medium with a catalytic amount of potassium hydroxide. Oximation of **12** and the subsequent cyanoborohydride treatment were carried out as described above. The diastereoisomers were isolated by column chromatography with petroleum ether : ethyl acetate (99 : 1).

**2e,4e-Diphenyl-*cis*-decahydroquinoline-1-ol (aryls *cis* to ring junction hydrogens) (13a)**

Colorless solid; mp 196–198 °C; IR (KBr) 3207, 1596, 1497, 1447, 718, 651, 567, 509 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.09–1.42 (m, 5H), 1.70–1.92 (m, 4H), 2.22 (bd, $J$ = 12.0 Hz, 1H), 2.27 (bd, $J$ = 11.1 Hz, 1H), 3.06 (ddd, $J$ = 12.0 Hz, 12.0 Hz, 4.5 Hz, 1H), 3.14 (bd, $J$ = 12.0 Hz, 1H), 4.06 (dd, $J$ = 11.4 Hz, 2.0 Hz, 1H), 6.0 (bs, 1H), 7.15–7.42 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 18.2, 21.0, 25.3, 27.8, 39.0, 41.2, 43.4, 64.5, 65.2, 126.6, 127.1, 127.4, 127.6, 128.3, 128.4, 143.0, 143.7; Anal. calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56; Found: C, 82.11; H, 8.09; N, 4.45%.

**4e-(4-Chlorophenyl)-2e-phenyl-*cis*-decahydroquinoline-1-ol (aryls *cis* to ring junction hydrogens) (13b)**

Colorless solid; mp 173–175 °C; IR (KBr) 3207, 1596, 1497, 1447, 718, 651, 567, 509 $cm^{-1}$; Theoretical mass: 342.8; measured mass: 342.5; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.30–1.35 (m, 6H), 1.72–1.90 (m, 3H), 2.14 (d, $J$ = 12.6 Hz, 1H), 2.25 (bd, $J$ = 12.3 Hz, 1H), 3.06 (ddd, $J$ = 12.6 Hz, 12.6 Hz, 4.5 Hz, 1H), 3.40 (bd, $J$ = 12.0 Hz, 1H), 4.06 (dd, $J$ = 11.7 Hz, 2.1 Hz, 1H), 4.98 (bs, 1H), 7.11 (d, $J$ = 8.1 Hz, 2H), 7.25 (dd, $J$ = 7.5 Hz, 1.8 Hz, 2H), 7.32 (t, $J$ = 7.5 Hz, 3H), 7.40 (d, $J$ = 8.1 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 18.2, 20.9, 25.2, 27.7, 38.6, 41.3, 43.5, 64.5, 65.2, 127.2, 128.4, 128.6, 128.7, 129.1, 131.9, 142.2, 143.1. Anal. calcd. for $C_{21}H_{24}ClNO$: C, 73.78; H, 7.08; N, 4.10; Found: C, 73.64; H, 7.01; N, 4.18%.

**6e-*tert*-Butyl-4e-phenyl-2e-(4-methylphenyl)-*cis*-decahydroquinoline-1-ol (aryls *cis* to ring junction hydrogens) (13d)**

Viscous liquid; IR (KBr) 3207, 1596, 1497, 1447, 718, 651, 567, 509 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 0.71$ (s, 9H), 0.86–1.04 (m, 2H), 1.20–1.41 (m, 3H), 1.70–1.92 (m, 3H), 2.14–2.27 (m, 2H), 2.30 (s, 3H), 2.98 (ddd, $J$ = 12.0 Hz, 12.0 Hz, 3.6 Hz, 1H), 3.14 (bd, $J$ = 7.2 Hz, 1H), 4.03 (dd, $J$ = 11.4 Hz, 2.0 Hz, 1H), 5.28 (bs, 1H), 7.04 (m, 3H), 7.23 (d, $J$ = 7.5 Hz, 2H), 7.30 (t, $J$ = 7.2 Hz, 2H), 7.40 (d, $J$ = 7.5 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 18.5, 20.9, 26.1, 27.4, 28.8, 32.2, 39.2, 41.8, 43.3, 43.0, 64.6, 65.4, 127.1, 127.3, 127.5, 128.4, 129.0, 135.7, 140.4, 143.2. Anal. Calcd. for $C_{26}H_{35}NO$: C, 82.71; H, 9.34; N, 3.71. Found: C, 82.61; H, 9.39; N, 3.77%.

**2e,4e-Diphenyl-*cis*-decahydroquinoline-1-ol (aryls *trans* to ring junction hydrogens) (14a)**

Colorless solid; mp 201–203 °C; IR (KBr) 3207, 1596, 1497, 1447, 718, 651, 567, 509 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.90–0.94 (m, 1H), 1.15 (qt, $J$ = 9.3 Hz, 3.6 Hz, 1H), 1.28–1.46 (m, 2H), 1.66–1.79 (m, 3H), 1.84 (dp, $J$ = 10.7 Hz, 3.0 Hz, 1H), 2.04–2.10 (m, 1H), 2.23 (q, $J$ = 11.7 Hz, 1H), 2.33 (bd, $J$ = 12.6 Hz, 1H), 3.04–3.05 (m, 1H), 3.11 (ddd, $J$ = 12.6 Hz, 3.0 Hz, 3.0 Hz, 1H), 3.73 (dd, $J$ = 11.7 Hz, 3.6 Hz, 1H), 4.44 (s, 1H), 7.05 (dd, $J$ = 7.5 Hz, 1.2 Hz, 2H), 7.23 (t, $J$ = 7.2 Hz, 2H), 7.24–7.32 (m, 4H), 7.40 (d, $J$ = 7.2 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.6, 21.3, 26.5, 29.4, 35.2, 44.6, 45.3, 65.6, 73.3, 126.7, 127.3, 128.2, 128.5, 128.7, 131.7, 142.5, 143.6. Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56; Found: C, 81.95; H, 8.26; N, 4.64%.

**4e-(4-Chlorophenyl)-2e-phenyl *cis*-decahydroquinoline-1-ol (aryls *trans* to ring junction hydrogens) (14b)**

Colorless solid; mp 201–203 °C; IR (KBr) 3207, 1596, 1497, 1447, 718, 651, 567, 509 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.92–0.97 (m, 1H), 1.13 (qt, $J$ = 9.3 Hz, 3.6 Hz, 1H), 1.28–1.39 (m, 2H), 1.63–1.84 (m, 3H), 1.84 (dp, $J$ = 11.7 Hz, 3.3 Hz, 1H), 1.89–2.08 (m, 1H), 2.25 (q, $J$ = 12.3 Hz, 1H), 2.42 (bd, $J$ = 12.3 Hz, 1H), 3.01 (m, 1H), 3.09 (ddd, $J$ = 13.2 Hz, 3.9 Hz, 3.9 Hz, 1H), 3.71 (dd, $J$ = 12.6 Hz, 3.6 Hz, 1H), 4.44 (s, 1H), 7.05 (d, $J$ = 8.1 Hz, 2H), 7.21 (d, $J$ = 6.9 Hz, 2H), 7.24 (d, $J$ = 8.1 Hz, 2H), 7.32–7.40 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.5, 21.2, 26.5, 29.3, 35.4, 44.6, 44.7, 65.7, 73.0, 126.9, 127.1, 128.1, 128.5, 128.7, 131.7, 141.3, 144.4. Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.78; H, 7.08; N, 4.10; Found: C, 73.69; H, 7.13; N, 4.03%.

**6e-*tert*-Butyl-4e-(4-chlorophenyl)-2e-*cis*-decahydroquinoline-1-ol (aryls *trans* to ring junction hydrogens) (14c)**

Trace. $^1H$ NMR splitting pattern is similar to isomer **14a** and **14b**.

**2e,4a-Diphenyl-*cis*-decahydroquinoline-1-ol (15a)**

Obtained in traces contaminated with **14a**. $^1H$ and $^{13}C$ NMR spectral patterns are similar to **15c** and **15d**.

**6e-*tert*-Butyl-4e-(4-chlorophenyl)-2a-phenyl *cis*-decahydroquinoline-1-ol (15c)**

Viscous liquid; IR (KBr): 3365, 2854, 1527, 1415, 1193, 756, 722, 565 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.92 (s, 9H), 1.22–1.25 (m, 2H), 1.40–1.42 (m, 1H), 1.51–1.53 (m, 2H), 1.91 (q, $J$ = 12.3 Hz, 1H), 2.10 (bd, $J$ = 12.6 Hz, 1H), 2.29–2.30 (m, 1H), 2.35 (td, $J$ = 7.2 Hz, 1.5 Hz, 1H), 2.38–2.40 (m, 1H), 2.74 (bd, $J$ = 5.1 Hz, 1H), 2.86 (bd, $J$ = 2.7 Hz, 1H), 3.74 (dd, $J$ = 12.6 Hz, 3.0 Hz, 1H), 4.40 (s, 1H), 7.21–7.39 (m, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.9, 27.6, 29.0, 30.1, 32.6, 36.1, 41.8, 43.7, 48.0, 59.6, 68.8, 126.9, 127.0, 128.3, 128.5, 129.0, 131.4, 142.6, 144.5. Anal. Calcd. for $C_{25}H_{32}ClNO$: C, 75.45; H, 8.10; N, 3.52. Found: C, 75.37; H, 8.02; N, 3.56%.

**6-*tert*-Butyl-4a-phenyl-2e-(4-methylphenyl)-*cis*-decahydroquinoline-1-ol (15d)**

Viscous liquid; IR (KBr): 3343, 2842, 1521, 1435, 1186, 751, 731, 595 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.91 (s, 9H), 1.22–1.33 (m, 3H), 1.42–1.59 (m, 3H), 1.93 (q, $J$ = 12.3 Hz, 1H), 2.18–2.29 (m, 2H), 2.35 (s, 3H), 2.41 (m, 1H), 2.75 (d, $J$ = 5.7 Hz, 1H), 2.91 (bd, $J$ = 3.0 Hz, 1H), 3.82 (dd, $J$ = 12.3 Hz, 3.6 Hz, 1H), 4.31 (s, 1H), 7.16 (d, $J$ = 7.5 Hz, 2H), 7.22–7.37 (m, 5H), 7.41 (d, $J$ = 7.5 Hz, 2H), $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.8, 21.0, 27.6, 29.1, 30.2, 32.6, 36.3, 41.9, 43.9, 48.8, 59.7, 69.0, 126.9, 127.0, 127.5, 128.5, 129.0, 135.1, 141.1, 144.9. Anal. Calcd. for $C_{26}H_{35}NO$: C, 82.71; H, 9.34; N, 3.71. Found: C, 82.62; H, 9.28; N, 3.65%.

**2,4-Diphenyl-*trans*-decahydroquinoline-1-ol (16a)**

Viscous liquid; IR (KBr) 3255, 1557, 1425, 1092, 758, 703, 563 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.91 (qd, $J$ = 12.3 Hz, 3.3 Hz, 1H), 1.13 (qt, $J$ = 12.0 Hz, 4.5 Hz, 1H)1.26–1.29 (m, 2H), 1.43 (dt, $J$ = 12.9 Hz, 1.8 Hz, 1H), 1.59–1.84 (m, 3H), 1.93 (td, $J$ = 9.3 Hz, 2.1 Hz, 2H), 2.37–2.57 (m, 3H), 3.66–3.69 (m, 1H), 4.53 (s, 1H), 7.13 (dd, $J$ = 8.4 Hz, 1.5 Hz, 2H), 7.25–7.32 (m, 6H), 7.40 (d, $J$ = 7.5 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 24.7, 25.5, 30.3, 30.5, 43.0, 46.2, 48.6, 71.2, 72.7, 126.1, 127.2, 127.1, 127.3, 128.2, 128.3, 141.5, 142.8. Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56; Found: C, 82.11; H, 8.14; N, 4.48%.

**4-(4-Chlorophenyl)-2-phenyl-*trans*-decahydroquinoline-1-ol (16b)**

Viscous liquid; IR (KBr) 3255, 1557, 1425, 1092, 758, 703, 563 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.92 (qd, $J$ = 12.6 Hz, 3.9 Hz, 1H), 1.13 (qt, $J$ = 12.6 Hz, 4.5 Hz, 1H), 1.22–1.25 (m, 2H), 1.41 (dt, $J$ = 13.2 Hz, 1.8 Hz, 1H), 1.59–1.86 (m, 3H), 1.94 (td, $J$ = 9.0 Hz, 2.4 Hz, 2H), 2.39–2.47 (m, 3H), 3.68–3.70 (m, 1H), 4.51 (s, 1H), 7.13 (dd, $J$ = 7.2 Hz, 1.5 Hz, 2H), 7.25 (d, $J$ = 7.5 Hz, 2H), 7.30–7.32 (m, 3H), 7.40 (d, $J$ = 7.5 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 24.9, 25.7, 30.1, 30.4, 43.1, 46.4, 48.8, 71.4, 72.8, 126.3, 127.0, 127.2, 127.5, 128.1, 128.4, 141.6, 143.8. Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.78; H, 7.08; N, 4.10; Found: C, 73.69; H, 7.01; N, 4.02%.

**6e-*tert*-Butyl-4-(4-chlorophenyl)-2-phenyl-*trans*-decahydroquinoline-1-ol (16c)**

Viscous liquid; IR (KBr) 3255, 1557, 1425, 1092, 758, 703, 563 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.77 (s, 9H),

0.88–1.45 (m, 5H), 1.63 (qt, $J$ = 9.0 Hz, 2.1 Hz, 1H), 1.86–1.94 (m, 3H), 2.31–2.50 (m, 3H), 3.65–3.68 (m, 1H), 4.62 (bs, 1H), 7.13 (dd, $J$ = 7.2 Hz, 1.5 Hz, 2H), 7.25 (d, $J$ = 7.8 Hz, 2H), 7.32 (t, $J$ = 7.2 Hz, 3H), 7.40 (d, $J$ = 7.8 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 25.5, 25.7, 27.4, 30.1, 30.4, 32.2, 46.0, 47.1, 48.2, 71.2, 72.7, 127.1, 127.2, 128.4, 128.5, 128.7, 131.8, 141.2, 143.2. Anal. Calcd. for $C_{25}H_{32}ClNO$: C, 75.45; H, 8.10; N, 3.52; Found: C, 75.38; H, 8.04; N, 3.46%.

**6e-*tert*-Butyl-4-phenyl-2-(4-methylphenyl)-*trans*-decahydroquinoline-1-ol (16d)**

Colorless solid; mp 162–164 °C; IR (KBr) 3255, 1557, 1425, 1092, 758, 703, 563 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.86 (s, 9H), 0.92–1.94 (m, 9H)2.33 (s, 3H), 2.36–2.55 (m, 3H), 3.64–3.68 (m, 1H), 4.63 (bs, 1H), 7.02–7.18 (m, 5H), 7.27 (t, $J$ = 6.9 Hz, 2H), 7.40 (d, $J$ = 7.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 24.9, 25.7, 26.8, 29.9, 30.1, 30.4, 33.5, 43.1, 46.4, 48.8, 71.4, 72.8, 126.9, 127.2, 128.0, 128.3, 129.0, 135.6, 140.7, 143.6. Anal. Calcd. for $C_{26}H_{35}NO$: C, 82.71; H, 9.34; N, 3.71. Found: C, 82.64; H, 9.23; N, 3.63%.

**Preparation of 2-(3-(4-chlorophenyl)-3-(hydroxyimino)-1-phenylpropyl) cyclopentanone oxime (17)**

The ketone for the preparation of **17** was obtained from the respective chalcone and cyclopentanone using catalytic amount of potassium hydroxide in ethanol. Oximation followed by cyanoborohydride treatment of **17** has yielded three diastereoisomers, which have been isolated by column chromatography with petroleum ether : ethyl acetate (99 : 1)

**4e-(4-Chlorophenyl)-2e-phenyloctahydro-1*H*-cyclopenta[b]pyridin-1-ol (Ring junction hydrogens and the aryl groups are all *cis* to each other) (18)**

Viscous liquid; yield 30%; IR (KBr) 3465, 2854, 2816, 1612, 1526, 1456, 1352, 1236, 1191, 1032, 826 cm$^{-1}$; Theoretical mass: 328.8; measured mass: 328.1; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.16 (qd, $J$ = 8.1 Hz, 3.0 Hz, 1H), 1.43–1.69 (m, 2H), 1.74–1.91 (m, 3H), 2.12–2.40 (m, 3H), 3.16 (t, $J$ = 4.5 Hz, 1H), 3.27 (dt, $J$ = 13.5 Hz, 4.5 Hz, 1H), 3.68 (dd, $J$ = 11.4 Hz, 2.4 Hz, 1H), 4.52 (bs, 1H), 7.09 (d, $J$ = 8.4 Hz, 2H), 7.24–7.35 (m, 5H), 7.44 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.6, 23.5, 30.5, 35.4, 40.8, 48.1, 70.3, 72.2, 127.1, 127.2, 128.3, 128.5, 128.6, 129.1, 142.7, 143.7. Anal. Calcd. For $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.14; H, 6.64; N, 4.15%.

**4e-(4-Chlorophenyl)-2e-phenyloctahydro-1*H*-cyclopenta[*b*]pyridin-1-ol (The ring fusion is *trans*) (19)**

Viscous liquid; yield 28%; IR (KBr) 3453, 2849, 2821, 1616, 1519, 1449, 1357, 1239, 1187, 1036, 820 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.23–1.25 (m, 1H), 1.43–1.71 (m, 4H), 1.80–1.91 (m, 2H), 2.01 (dt, $J$ = 13.8 Hz, 3.6 Hz, 1H), 2.12–2.15 (m, 1H), 2.54 (td, $J$ = 11.4 Hz, 3.6 Hz, 1H), 2.64–2.67 (m, 1H), 3.68 (dd, $J$ = 11.7 Hz, 2.7 Hz, 1H), 4.85 (bs, 1H), 7.09 (d, $J$ = 8.4 Hz, 2H), 7.23–7.32 (m, 5H), (t, $J$ = 7.41 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 20.1, 27.9, 29.8, 44.4, 47.2, 49.5, 73.8, 73.9, 127.2, 127.4, 128.3, 128.5, 128.6, 131.9, 142.3, 142.7. Anal. Calcd. for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.15; H, 6.64; N, 4.16%.

**4e-(4-Chlorophenyl)-2e-phenyloctahydro-1*H*-cyclopenta[b]pyridin-1-ol (The ring junction hydrogens are *trans* to the aryl groups) (20)**

Viscous liquid; yield 21%; IR (KBr) 3449, 2853, 2827, 1621, 1522, 1452, 1362, 1241, 1191, 1039, 824 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.83–0.97 (m, 1H), 1.25–1.37 (m, 2H), 1.60–1.71 (m, 2H), 1.81–2.07 (m, 3H), 2.32 (q, $J$ = 5.7 Hz, 1H), 2.54 (td, $J$ = 12.0 Hz, 3.6 Hz, 1H), 3.69–3.71 (m, 1H), 4.05 (dd, $J$ = 11.4 Hz, 2.7 Hz, 1H), 5.50 (bs, 1H), 7.11 (d, $J$ = 8.4 Hz, 2H), 7.23–7.32 (m, 5H), 7.41 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 19.6, 26.9, 27.0, 41.9,* 43.0, 64.2, 68.5, 127.3, 127.7, 128.4, 128.5, 129.0, 132.0, 142.3, 142.6. Anal. Calcd. for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.14; H, 6.64; N, 4.15%. *Two carbons merged here.

**Synthesis of 2,5 diphenyl-*N*-hydroxypyrrolidine (22)**

1,2-Dibenzoylethane, prepared through Friedel–Crafts acylation of benzene with succinoyl chloride, was converted to the corresponding oxime. After cyanoborohydride treatment, 2,5-diphenyl-*N*-hydroxypyrrolidine was obtained in excellent yield. Viscous liquid; yield 87%; IR (KBr) 3535, 3056, 3028, 2869, 2840, 1595, 1502, 1238, 1197, 743, 698 cm$^{-1}$; Theoretical mass: 240.3; measured mass: 240.1; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.83 (m, 2H), 2.26 (m, 2H), 3.98 (m, 2H), 4.59 (bs, 1H), 7.25–7.35 (m, 6H), 7.48 (d, $J$ = 7.8 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 29.8, 71.0, 127.2, 127.4, 128.4, 142.5; Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.17; H, 7.04; N, 5.73%.

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