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Tetrahedron
Tetrahedron 63 (2007) 2865–2874

(L)-Proline-catalysed novel tandem reactions of 1-substituted piperidin-4-ones with (*E*)-4-arylbut-3-en-2-ones: *N*-substituent mediated product selectivity and synthesis of novel nitrogen heterocycles

Murugesan Srinivasan and Subbu Perumal*

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, Tamil Nadu, India

Received 30 October 2006; revised 5 January 2007; accepted 18 January 2007
Available online 21 January 2007

Abstract—(L)-Proline-catalysed reaction of 1-alkyl/aralkylpiperidin-4-ones with (*E*)-4-arylbut-3-en-2-ones furnishes novel isoquinoline derivatives, with two or three rings, in good yields via tandem Robinson annulation–Michael addition(s) sequences, while the reaction of 1-arylpiperidin-4-ones with (*E*)-4-arylbut-3-en-2-ones affords 3-azabicyclo[3.3.1]nonan-9-ones via a tandem Michael addition–aldol reaction sequence.

1. Introduction

Nitrogen heterocycles like isoquinolines and azabicyclo-[3.3.1]nonanes assume great importance, as several substituted isoquinolines display important biological activities like cytotoxic,[1] antimalarial,[2] antileishmanial,[3] trypanosomal,[4] antiestrogenic,[5] antiproliferative[5] and antitumour.[6] Azabicyclo[3.3.1]nonanes are found to possess useful biological activities such as antiarrhythmic,[7] analgesic,[8] antitussive,[9] anti-inflammatory,[10] local anaesthetic[11] and neuroleptic.[12] Several 3-azabicyclo[3.3.1]nonanes are found to be useful as sedative,[13] analgesic,[13] antipyretic,[14] psycholaleptic[14] and hypoglycemic[15] agents.

Tandem reactions are one-pot multi-step processes and hence very powerful for the rapid construction of complex organic molecules efficiently and elegantly in a convergent and eco-friendly manner with minimum waste generation.[16] The biological importance of the above nitrogen heterocycles and our continued interest in the synthesis of novel organic molecules employing tandem sequences[17] prompted us to investigate the reactions of several 1-substituted piperidin-4-ones with (*E*)-4-arylbut-3-en-2-ones furnishing hitherto unreported complex nitrogen heterocycles, important from a synthetic perspective. (L)-Proline, known as the smallest enzyme[18] was chosen for catalysing these reactions, as it is known to be efficient in several reactions, such as Michael addition,[19] Robinson annulation,[20] Mannich reaction, [21] aldol reaction,[22] etc.

2. Results and discussion

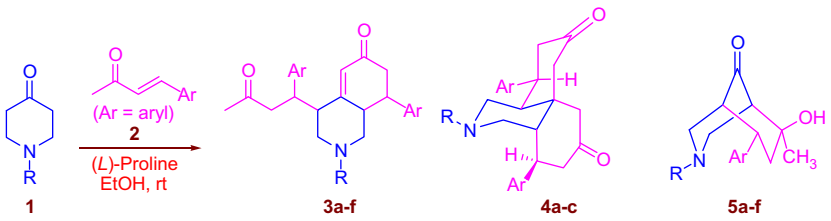
2.1. Tandem reactions of 1-alkyl- and 1-aralkyl-piperidin-4-ones with (*E*)-4-arylbut-3-en-2-ones

The 1-substituted piperidin-4-ones **1a–i** were prepared following a literature method[23] from the reaction of the appropriate amine with *N*,*N*-dimethyl-4-oxopiperidinium sulfate. The reaction of 1-*R*-piperidin-4-ones **1a–d** [R=CH_3, $CH_2C_6H_5$, $(CH_2)_3CH_3$ or $C(CH_3)_3$] with (*E*)-4-arylbut-3-en-2-ones **2** in a 1:2 molar ratio in presence of 25 mol % of (L)-proline at ambient temperature affords novel bicyclic compounds, 2-alkyl-4-(3-oxo-1-arylbutyl)-8-aryl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolinones **3a–f**, while the reaction of (*R*)-1-phenylethylpiperidin-4-one **1e** with **2** affords novel tricyclic compounds, 4,8-diaryl-6-[(*R*)-1-phenylethyl]octahydro-1*H*-benzo[*d*]isoquinoline-2,10(3*H*,11*H*)-diones **4a–c** (Scheme 1). The products, **3** and **4** were isolated in a pure form by flash chromatography in 58–76% yield.

The products, **3a–f** were found to exist as a single diastereomer in each case, as evident from one set of signals found in the NMR spectra. They show no optical rotation and are also resolved into two peaks of equal intensity in chiral HPLC and hence are racemic. The structure of **3a–f** was determined from one- and two-dimensional NMR spectroscopic studies. The H,H-COSY and HMBC correlations (Fig. 1) and the ^{1}H

Keywords: (L)-Proline; 1-Substituted piperidin-4-ones; (*E*)-4-Arylbut-3-en-2-ones; Isoquinolines; Azabicyclo[3.3.1]nonan-9-ones; Tandem Robinson annulation; Michael addition; Aldol reaction.
* Corresponding author. Tel./fax: +91 0452 2459845; e-mail: subbu.perum@gmail.com

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.01.038



1 and 3-5		R	Ar
1a	3a	CH_3	C_6H_5
1a	3b	CH_3	4-ClC_6H_4
1a	3c	CH_3	4-$CH_3C_6H_4$
1b	3d	$C_6H_5CH_2$	C_6H_5
1c	3e	$(CH_3)_3C$	C_6H_5
1d	3f	$CH_3(CH_2)_3$	C_6H_5
1e	4a	$C_6H_5(CH_3)CH$	C_6H_5
1e	4b	$C_6H_5(CH_3)CH$	4-ClC_6H_4
1e	4c	$C_6H_5(CH_3)CH$	4-$CH_3C_6H_4$
1f	5a	C_6H_5	C_6H_5
1f	5b	C_6H_5	4-ClC_6H_4
1f	5c	C_6H_5	4-$CH_3C_6H_4$
1g	5d	4-ClC_6H_4	C_6H_5
1h	5e	3-ClC_6H_4	C_6H_5
1i	5f	3-$O_2NC_6H_4$	C_6H_5

Scheme 1.

and ^{13}C chemical shifts of **3a** assigned from one- and two-dimensional NMR spectroscopic data (Fig. 2) are given as an example. As it proved difficult to obtain crystals of **3** suitable for single crystal X-ray study, the stereochemistry of **3** was deduced from NMR spectroscopic data and mechanistic considerations as described below.

(i) The *J* values of the doublet of doublets of doublets at 3.95 ppm due to H-8 (11.1, 7.8 and 4.5 Hz) show that this proton, oriented axially, is having diaxial coupling with both H-8a (11.1 Hz) and H-7ax (7.8 Hz) and an axial–equatorial coupling with H-7eq (4.5 Hz). This, in turn, shows that the phenyl at C-8 is oriented equatorially. The axial orientation of H-8 is also supported by the fact that H-8 and H-7eq have a NOESY correlation, while H-8 and H-7ax do not (Fig. 3). From the above, it follows that C-8a–H-8a and C-8a–C-8 bonds are oriented, respectively, pseudoaxially and equatorially from the piperidine ring.

(ii) The *J* values of the triplet of doublets of doublets at 3.27 ppm due to H-4 (10.6, 5.7 and 1.8 Hz) are in accord with the predominance of the rotamer, **3a**′ (Fig. 4). The proton H-4 has a diaxial coupling with H-3ax (10.6 Hz) and an equal coupling (10.6 Hz) with the side chain proton, H-1′, an axial–equatorial coupling with H-3eq (5.7 Hz), and a long range coupling with H-5 (1.8 Hz). This discloses an axial orientation for H-4 and an equatorial orientation for the side chain at C-4. This conclusion is also supported by the existence of a NOESY correlation of H-4 with H-3eq, but not with H-3ax. Presumably, the rotamer **3a**′ is more stable than **3a** (Fig. 3), as evident from the large *J* value

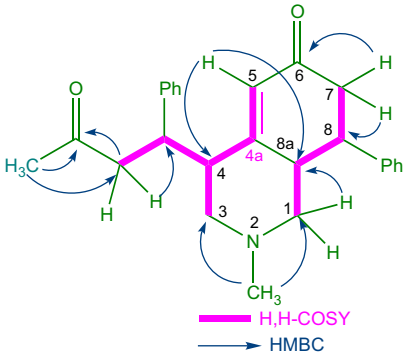


Figure 1. Selected two-dimensional NMR correlations for **3a**.

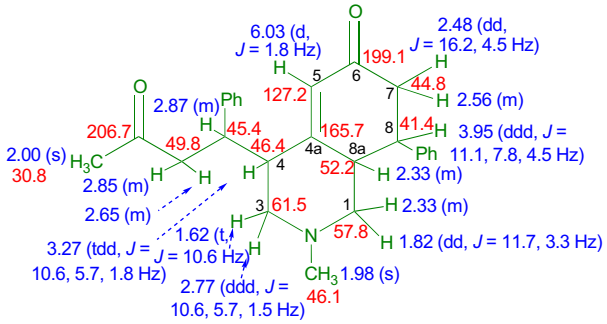


Figure 2. ^1H and ^{13}C chemical shifts of **3a**.

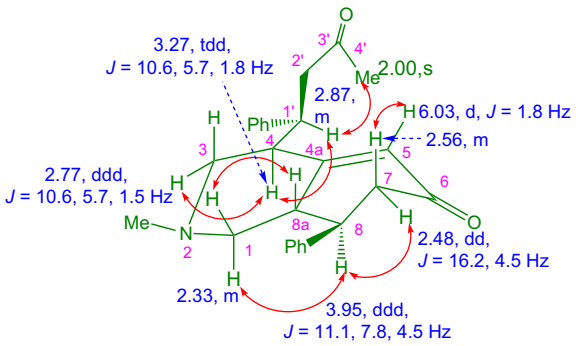


Figure 3. NOESY correlations of **3a**.

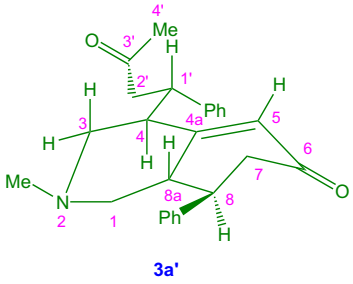


Figure 4. Predominant rotamer, **3a**′.

(10.6 Hz) for the coupling of H-1′ and H-4, as in the latter, the CH_2–CO–CH_3 could interact sterically with H-3ax.

(iii) The relative arrangements of the enone and enamine in the Michael addition step (Fig. 5) is likely to be favoured by the hydrogen bonding between the carboxyl group of the proline of the enamine and the enone, which could facilitate the Michael addition. This would result in the relative

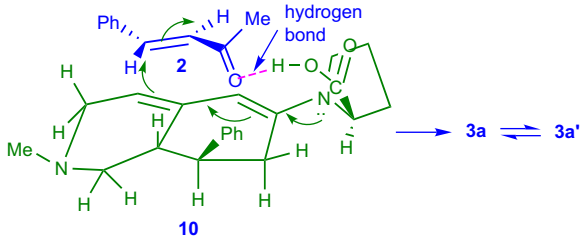


Figure 5. Stereochemistry of Michael addition of **10** to **2**.

configuration of C-1′ for **3** as depicted in Figures 3 and 4. It is pertinent to note that stereoselectivity of (L)-proline-catalysed Michael additions has been ascribed to the hydrogen bonding between the carboxyl group of proline in the enamines and the Michael acceptors.[19a,b,24]

The heterocycle, **4** was obtained as a 1:1 mixture of diastereomers, as evident from: (i) the equal intensities of the ^{1}H NMR signals (doublets) of the methyl of the phenylethyl group of the diastereomers, and (ii) GC–MS analysis, which gives two peaks of equal intensity in the gas chromatogram, while both the diastereomers underwent decomposition in the mass spectrometer of the GC–MS instrument. The heterocycle **4**, comprising of a 1:1 mixture of two diastereomers: (i) shows optical activity implying that the diastereomers have an unequal optical rotation, and (ii) are characterised by sharp melting points like any pure single compound. The diastereomers of **4** could not be separated as they differ little in their R_f values. Hence, **4** affords a large number of proton and carbon signals with close chemical shift values for the diastereomers, whose individual assignments and structure extraction from NMR spectroscopic data proved difficult. Hence, the structure of **4** was elucidated completely by an X-ray crystallographic study of a single crystal of **4a** (Fig. 6), which also shows that the diastereomers are in a 1:1 ratio, four molecules each, in the unit cell. The absolute configuration of the stereocentres of the diastereomers, viz. (4*S*,4a*R*,7a*R*,8*R*) and (4*S*,4a*S*,7a*S*,8*R*) available from an X-ray study, is shown in the structures in Figure 6.

The 1:1 ratio of mixture of diastereomers of **4** shows that the (*R*)-1-phenylethyl group in **1e** fails to favour the formation of any one diastereomer of **4**. As the configuration of the α-phenylethyl group in **4** is fixed as (*R*), as only (*R*)-**1e** is subjected to the reaction, formation of a pair of enantiomers for each diastereomer (and enantioselectivity) of **4** does not arise for this reaction.

The reaction of 1-alkyl/aralkylpiperidin-4-ones **1a–e** with **2** was investigated in the presence of pyrrolidine and DBU also with a view to (i) unearthing the role of the catalyst and (ii) optimising the yield of **3**. The data furnished in Table 1 reveal that the yield of **3a** remains almost constant, when (L)-proline employed in this reaction is varied from 15–100 mol % (entries 1–4). The reaction of 1-methylpiperidin-4-one with (*E*)-4-phenylbut-3-en-2-one in a 1:2 molar

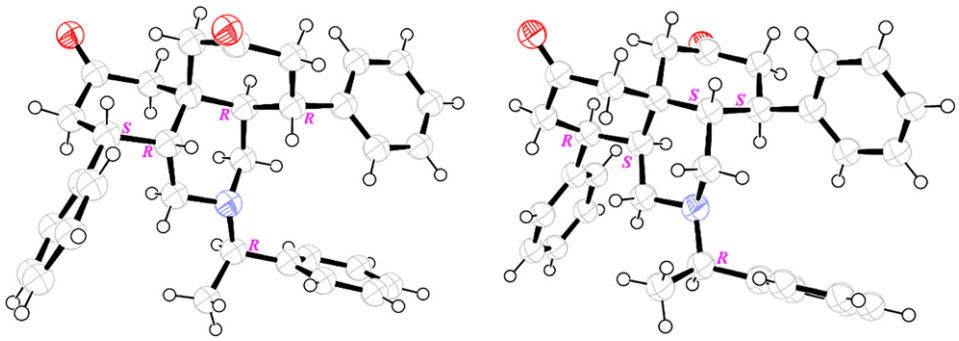


Figure 6. X-ray structure of 4,8-diphenyl-6-(1-phenylethyl)octahydro-1*H*-benzo[*d*]isoquinoline-2,10(3*H*,11*H*)-dione **4a** [two diastereomeric molecules, (4*S*,4a*R*,7a*R*,8*R*) and (4*S*,4a*S*,7a*S*,8*R*), picked out from the lattice reoriented appropriately and shown].

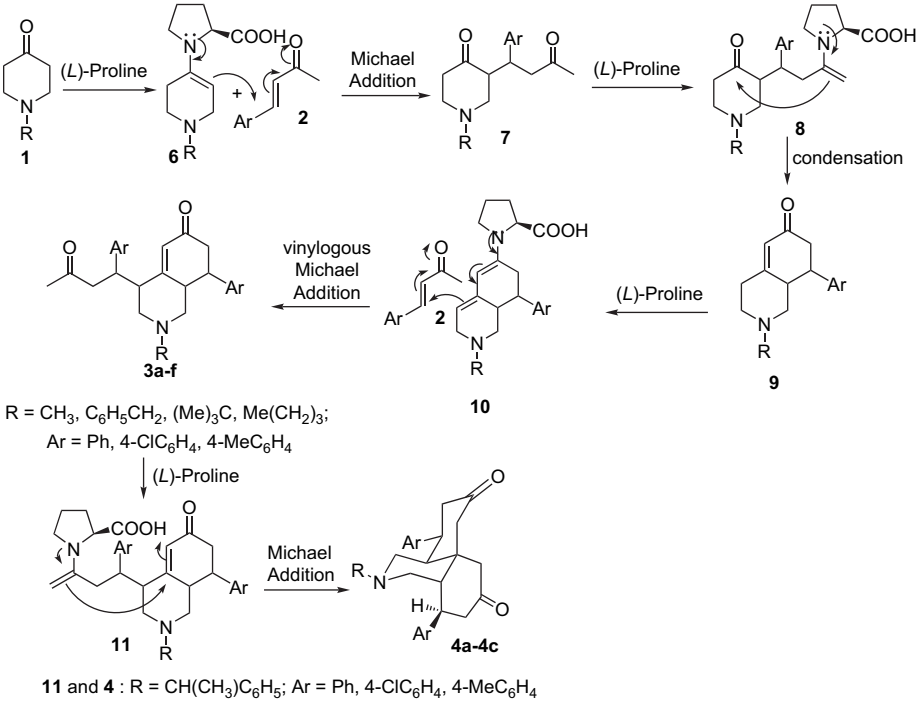
Table 1. Tandem reactions of 1-substituted piperidin-4-ones with (*E*)-4-arylbut-3-en-2-ones affording **3–5**

Entry	R	Ar	Reagent (mol %)	Product	Yield	Reaction time (days)
1	CH_3	C_6H_5	(L)-Proline (15)	**3a**	71	2
2	CH_3	C_6H_5	(L)-Proline (25)	**3a**	73	2
3	CH_3	C_6H_5	(L)-Proline (50)	**3a**	73	2
4	CH_3	C_6H_5	(L)-Proline (100)	**3a**	73	2
5	CH_3	C_6H_5	Pyrrolidine (25)	**3a**	36	4
6	CH_3	4-ClC_6H_4	(L)-Proline (25)	**3b**	68	2
7	CH_3	4-$CH_3C_6H_4$	(L)-Proline (25)	**3c**	64	2
8	$PhCH_2$	C_6H_5	(L)-Proline (25)	**3d**	72	3
9	$(CH_3)_3C$	C_6H_5	(L)-Proline (25)	**3e**	62	1
10	$CH_3(CH_2)_3$	C_6H_5	(L)-Proline (25)	**3f**	58	2
11	$Ph(CH_3)CH$	C_6H_5	(L)-Proline (25)	**4a**	76	2
12	$Ph(CH_3)CH$	C_6H_5	Pyrrolidine (25)	**4a**	42	4
13	$Ph(CH_3)CH$	4-ClC_6H_4	(L)-Proline (25)	**4b**	71	2
14	$Ph(CH_3)CH$	4-$CH_3C_6H_4$	(L)-Proline (25)	**4c**	66	2
15	C_6H_5	C_6H_5	(L)-Proline (25)	**5a**	81	2
16	C_6H_5	C_6H_5	Pyrrolidine (25)	**5a**	58	3
17	C_6H_5	4-ClC_6H_4	(L)-Proline (25)	**5b**	77	2
18	C_6H_5	4-$CH_3C_6H_4$	(L)-Proline (25)	**5c**	73	2
19	4-ClC_6H_4	C_6H_5	(L)-Proline (25)	**5d**	76	2
20	3-ClC_6H_4	C_6H_5	(L)-Proline (25)	**5e**	79	2
21	3-$O_2NC_6H_4$	C_6H_5	(L)-Proline (25)	**5f**	71	2

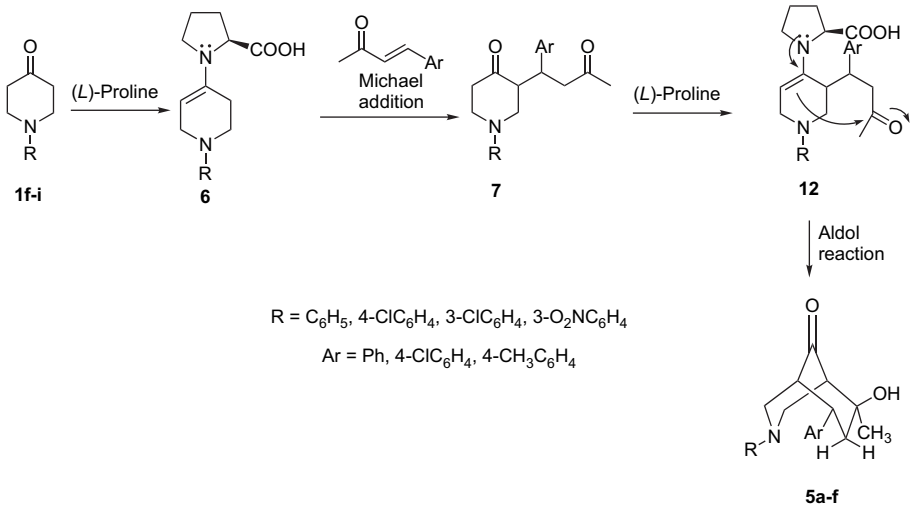
ratio using 25 mol % of pyrrolidine in ethanol took 4 days for completion affording **3a** in 36% yield (entry 5). In presence of (L)-proline, this reaction is completed within 2 days furnishing an enhanced yield of **3a** (71%; entry 1). This reaction in the presence of DBU failed to afford **3–5**, which suggests that catalyses by (L)-proline and pyrrolidine probably involve the intermediacy of enamines. The greater efficacy of (L)-proline than pyrrolidine may probably be ascribed to the concerted nucleophilic and acidic catalyses by (L)-proline, wherein the secondary amino functionality presumably forms enamine and enhances the nucleophilicity of the carbon α- to the carbonyl towards Michael addition, while the carboxyl group increases the electrophilicity of the carbonyl of the Michael acceptor towards aldol formation by hydrogen bonding.

The influence of solvent on the reaction of **1** with **2** was studied with a view to examine whether enantioselectivity can be achieved in some solvents. In the present study, the reaction between **1** and **2** does not occur in chloroform, while in DMF this reaction proceeds very slowly and in poor yield. The reaction in DMSO affords a lower yield (35%) of **3a** along with other products, which could not be characterised. Analysis of the product **3a** obtained from the reaction in DMSO using chiral HPLC shows that it is racemic and hence the reaction occurs non-enantioselectively. Hence all the reactions of the present investigation were investigated in detail in ethanol.

The reaction sequence leading to either **3** or **4** is envisaged to occur via an initial Michael addition of the enamine **6** with (*E*)-4-arylbut-3-en-2-ones affording **7** (Scheme 2).



Scheme 2. Mechanism for the proline-catalysed formation of **3a–f** and **4a–c**.



Scheme 3. Mechanism for the proline-catalysed formation of **5a–f**.

Condensation of **7** via enamine **8** furnishes α,β-unsaturated ketone **9**. Presumably, **9** reacts with (L)-proline forming enamine **10**, which subsequently undergoes Michael addition over **2** giving **3a–f**. In the case of (*R*)-1-phenylethylpiperidin-4-one, the tricyclic compound **4** is formed from an intramolecular Michael addition of the enamine **11**, formed from the reaction of the side chain carbonyl of **3a–f** with (L)-proline, over the β-carbon of the α,β-unsaturated carbonyl functionality as shown in Scheme 2. Probably, the steric interactions arising from the *N*-α-phenylethyl group cause some flattening of the piperidin-4-one ring in **1e**, which could facilitate the approach of the side chain enamine functionality towards intramolecular Michael addition over the β-carbon of the α,β-unsaturated carbonyl of **11** resulting in **4a–c**.

It was found that even when 1-methylpiperidin-4-one **1a** and **2** are taken in a 1:1 molar ratio in presence of (L)-proline with a view to statistically direct the reaction to afford **9**, only **3a** is obtained as the major product. This suggests that the second Michael addition occurs more rapidly than the Robinson annulation so that as soon as **9** is formed, it is converted into **10** and subsequently to **3**. This may arise from the greater stability of the enamine, with extended conjugation **9** requiring less free energy of activation for its formation, as well **6** that leads to the Michael addition.

2.2. Tandem reactions of 1-arylpiperidin-4-ones with (*E*)-4-arylbut-3-en-2-ones

The reaction of 1-arylpiperidin-4-ones **1f–i** with **2** in a 1:1 molar ratio in the presence of (L)-proline at ambient temperature affords 6-hydroxy-6-methyl-3,8-diaryl-3-azabicyclo[3.3.1]nonan-9-ones, **5** (Scheme 3) stereoselectively. The products, **5a–f**, isolated in a pure state by flash chromatography in 71–81% yields were found to be racemic by chiral HPLC analysis and they also show no optical rotation. This shows that (L)-proline functions as a non-enantioselective catalyst in reactions leading to **3** and **5**. It is found that the reaction of 1-arylpiperidin-4-ones **1f–i** and **2** in a 1:2 molar ratio in the presence of (L)-proline also affords **5a–f** only. Under these conditions, the isoquinolinones **3a–f** and **4a–c** could not be detected even in traces. Further Michael addition of **5a–f** with **2** is also not observed, in contrast to the two or three Michael additions observed in the case of 1-alkylpiperidin-4-ones. This is ascribable to the fact that the carbons α to the carbonyl of **5a–f** are at bridgehead positions, which is likely to preclude the formation of enamines.

The structure of azabicyclo[3.3.1]nonanones **5a–f** has also been deduced from NMR spectroscopic data. The HMBC correlations (Fig. 7) and complete assignment of the ^{1}H and ^{13}C chemical shifts of **5a** (Fig. 8) made from one- and two-dimensional NMR spectroscopic data are given as an example. That the nonanones **5** adopt a twin-chair conformation is evident from the fact that H-7ax of **5a** occurs far downfield at 3.19 ppm than H-7eq at 1.88 ppm due van

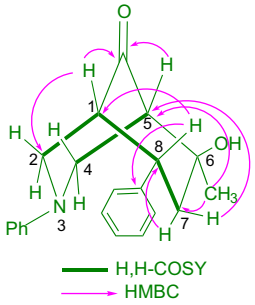


Figure 7. Selected two-dimensional NMR correlations for **5a**.

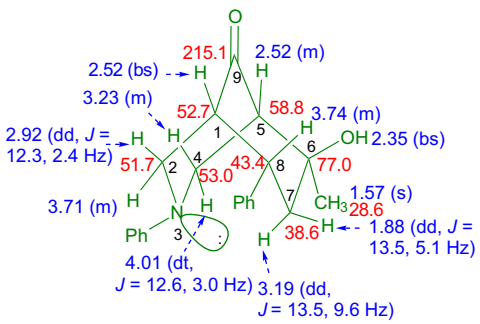


Figure 8. ^{1}H and ^{13}C chemical shifts of **5a**.

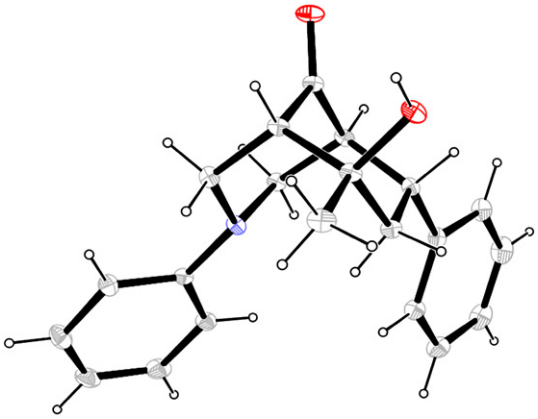
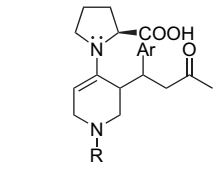


Figure 9. X-ray structure of 6-hydroxy-6-methyl-3,8-diphenyl-3-azabicyclo[3.3.1]nonan-9-one **5a**.

der Waals interaction between the nitrogen lone pair and H-7ax. The structure of **5a** determined by a single crystal X-ray study (Fig. 9) is in good agreement with that deduced from NMR spectroscopic studies.

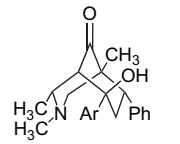
This reaction leading to **5** presumably proceeds through a tandem Michael addition–aldol reaction sequence (Scheme 3). The aryl ring attached to the nitrogen of **1f–j** is likely to flatten the piperidone ring of **2** by N–Ar conjugation facilitating the formation of enamine **12**, which could add over the side chain carbonyl affording azabicyclo[3.3.1]nonanones, **5**. On the other hand, the Michael adduct **7** with *N*-alkyl substituent, without much ring flattening (Scheme 2) might probably find it difficult (i) to form enamine **13** relative to the enamine **8** and/or (ii) to react with **2** through the enamine **13** (Fig. 10).

It is pertinent to note that the heterocycles **3** and **5** are new and, to the best of the knowledge of the authors, even compounds having structures closely resembling **3** and **5** are not available in the literature, while two compounds **6** (Fig. 11), having the same structure as **5**, but carrying different



R = alkyl
(difficult to form or react)
13

Figure 10.



Ar = 4-ClC$_6$H$_4$, C$_6$H$_5$
6a and **6b**

Figure 11.

substituents, viz., aryl instead of methyl at C-6, two more methyl groups in the piperidone ring and N–Me instead of N–Ar have been synthesised by Vatsadze et al.[25] from the reaction of 1,2,5-trimethylpiperidin-4-one to chalcones in presence of potassium hydroxide in low yields.

3. Conclusions

This work describes one-pot tandem sequences providing a rapid access to novel complex substituted isoquinolinones and azabicyclo[3.3.1]nonanones from 1-substituted piperidin-4-ones and (*E*)-4-arylbut-3-en-2-ones in presence of (L)-proline, at ambient temperature. Incidentally, this study discloses the subtle dependence of the product-selectivity of these reactions on the *N*-substituent of the piperidin-4-ones. These novel heterocycles with two or more functionalities can be useful building blocks for further synthetic manipulations. The versatility and the synthetic utility of these tandem reactions are being currently explored in our research group employing a host of carbo- and heterocyclic ketones and other Michael acceptors.

4. Experimental section

4.1. General methods

The mp of the isoquinolinones and azabicyclo[3.3.1]nonanones are uncorrected. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker (Avance) NMR spectrometer operating at 300 and 75 MHz, respectively and the chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. Two-dimensional NMR spectra were also measured in the same instrument employing standard Bruker software throughout. Elemental analyses of all the hitherto unreported isoquinolinones and azabicyclo[3.3.1]nonanones were performed on a Perkin Elmer 2400 Series II Elemental CHNS Analyser. Optical rotation values were measured using an autopol IV automatic polarimeter at sodium D line at 25 °C. HPLC analyses were carried out on a Shimadzu SPD-10ATvp model with CHIRALPAK AD-H column using *n*-hexane/isopropyl alcohol [90:10 (v/v)] eluent at a flow rate of 1 ml/min. The GC–MS analysis of **4** was performed on a Thermo-Finnigan GC–MS instrument.

4.2. General procedure for the preparation of tandem products 3 and 4

To a mixture of (L)-proline (0.086 g, 0.75 mmol, 15 mol %), 1-methylpiperidin-4-one **1a** (0.6 mL, 5 mmol) and (*E*)-4-phenylbut-3-en-2-one **2** (1.46 g, 10 mmol) was added dry ethanol (5 mL) at room temperature. The mixture was stirred at room temperature until TLC analysis indicated completion of the reaction. The reaction mixture was treated with saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 (35 mL). The combined organic extracts were washed successively with water (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The

product was purified by column chromatography on silica gel using pet. ether/ethyl acetate [4:1 (v/v)] mixture as an eluent.

4.2.1. 2-Methyl-4-(3-oxo-1-phenylbutyl)-8-phenyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolinone 3a. Isolated as a white solid (71%), mp 137 °C [Found: C, 80.65; H, 7.49; N, 3.64. $C_{26}H_{29}NO_2$ requires C, 80.59; H, 7.54; N, 3.61%]; R_f (20% ethyl acetate/pet. ether) 0.35; ν_{max} (KBr) 1731, 1705, 1647 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.22–7.41 (10H, m, Ph), 6.03 (1H, d, *J* 1.8 Hz, COC*H*=C), 3.95 (1H, ddd, *J* 11.1, 7.8, 4.5 Hz, C*H*(Ph)CH_2), 3.27 (1H, tdd, *J* 10.6, 5.7, 1.8 Hz, C*H*C=CH), 2.87 (1H, m, C*H*(Ph)CH_2), 2.85 (1H, m, C$H_a$$H_b$CO), 2.77 (1H, ddd, *J* 10.6, 5.7, 1.5 Hz, $CH_a$$H_b$NMe), 2.65 (1H, m, $CH_a$$H_b$CO), 2.56 (1H, m, $CH_a$$H_b$CO), 2.48 (1H, dd, *J* 16.2, 4.5 Hz, C$H_a$$H_b$CO), 2.33 (1H, m, C*H*$CH_2$), 2.33 (1H, m, $CH_a$$H_b$NMe), 2.00 (3H, s, CO*Me*), 1.98 (3H, s, N*Me*), 1.82 (1H, dd, *J* 11.7, 3.3 Hz, C$H_a$$H_b$NMe), 1.62 (1H, t, *J* 10.6 Hz, C$H_a$$H_b$NMe); δ_C (75 MHz, $CDCl_3$) 206.7, 199.1, 165.7, 143.7, 142.2, 129.3, 129.1, 128.4, 127.9, 127.6, 127.2, 126.9, 61.5, 57.8, 52.2, 49.8, 46.4, 46.1, 45.4, 44.8, 41.4, 30.8.

4.2.2. 8-(4-Chlorophenyl)-4-[1-(4-chlorophenyl)-3-oxobutyl]-2-methyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolinone 3b. Isolated as a white solid (68%), mp 141 °C [Found: C, 68.39; H, 5.91; N, 3.11. $C_{26}H_{27}Cl_2NO_2$ requires C, 68.42; H, 5.96; N, 3.07%]; R_f (20% ethyl acetate/pet. ether) 0.28; ν_{max} (KBr) 1725, 1702, 1653 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.01–7.48 (8H, m, 4-ClC_6H_4), 6.06 (1H, d, *J* 1.8 Hz, COC*H*=C), 4.03 (1H, ddd, *J* 11.1, 7.8, 4.5 Hz, C*H*(Ph)CH_2), 3.41 (1H, tdd, *J* 10.6, 5.7, 2.1 Hz, C*H*C=CH), 2.92 (1H, m, C*H*(Ph)CH_2), 2.89 (1H, m, C$H_a$$H_b$CO), 2.80 (1H, ddd, *J* 10.6, 5.7, 1.5 Hz, $CH_a$$H_b$NMe), 2.69 (1H, m, $CH_a$$H_b$CO), 2.59 (1H, m, $CH_a$$H_b$CO), 2.51 (1H, dd, *J* 16.2, 4.5 Hz, C$H_a$$H_b$CO), 2.41 (1H, m, C*H*$CH_2$), 2.41 (1H, m, $CH_a$$H_b$NMe), 2.03 (3H, s, CO*Me*), 1.95 (3H, s, N*Me*), 1.81 (1H, dd, *J* 11.7, 3.3 Hz, C$H_a$$H_b$NMe), 1.66 (1H, t, *J* 10.6 Hz, C$H_a$$H_b$NMe); δ_C (75 MHz, $CDCl_3$) 207.3, 199.3, 165.4, 143.3, 142.1, 129.4, 129.0, 128.5, 128.0, 127.5, 127.1, 126.4, 61.2, 58.2, 52.5, 50.4, 46.5, 45.7, 44.9, 41.7, 40.7, 30.4.

4.2.3. 2-Methyl-8-(4-methylphenyl)-4-[1-(4-methylphenyl)-3-oxobutyl]-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolinone 3c. Isolated as a white solid (64%), mp 123 °C [Found: C, 80.88; H, 7.97; N, 3.41. $C_{28}H_{33}NO_2$ requires C, 80.93; H, 8.00; N, 3.37%]; R_f (20% ethyl acetate/pet. ether) 0.30; ν_{max} (KBr) 1728, 1707, 1652 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.17–7.45 (8H, m, 4-MeC_6H_4), 6.12 (1H, d, *J* 1.8 Hz, COC*H*=C), 3.97 (1H, ddd, *J* 11.1, 7.8, 4.5 Hz, C*H*(Ph)CH_2), 3.21 (1H, tdd, *J* 10.6, 5.7, 2.1 Hz, C*H*C=CH), 2.86 (1H, m, C*H*(Ph)CH_2), 2.86 (1H, m, C$H_a$$H_b$CO), 2.79 (1H, ddd, *J* 10.6, 5.7, 1.5 Hz, $CH_a$$H_b$NMe), 2.69 (1H, m, $CH_a$$H_b$CO), 2.59 (1H, m, $CH_a$$H_b$CO), 2.45 (1H, dd, *J* 16.2, 4.5 Hz, C$H_a$$H_b$CO), 2.26 (1H, m, C*H*$CH_2$), 2.26 (1H, m, $CH_a$$H_b$NMe), 2.23 (3H, s, 4-*Me*C_6H_4), 2.21 (3H, s, 4-*Me*C_6H_4), 1.99 (3H, s, CO*Me*), 1.91 (3H, s, N*Me*), 1.85 (1H, dd, *J* 11.7, 3.3 Hz, C$H_a$$H_b$NMe), 1.58 (1H, t, *J* 10.6 Hz, C$H_a$$H_b$NMe); δ_C (75 MHz, $CDCl_3$) 206.2, 199.0, 165.1, 143.4, 142.5, 129.5, 129.0, 128.7, 127.6, 127.3, 127.1, 126.5, 61.8, 57.5, 51.7, 49.9, 46.2, 45.5, 45.0, 41.3, 40.5, 31.3, 21.2, 21.1.

4.2.4. 2-Benzyl-4-(3-oxo-1-phenylbutyl)-8-phenyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolinone 3d. Isolated as a white solid (72%), mp 124 °C [Found: C, 82.85; H, 7.21; N, 3.07. $C_{32}H_{33}NO_2$ requires C, 82.90; H, 7.17; N, 3.02%]; R_f (20% ethyl acetate/pet. ether) 0.27; ν_{max} (KBr) 1718, 1679, 1641 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.88–7.46 (15H, m, Ph), 5.95 (1H, d, *J* 1.5 Hz, COC*H*=C), 3.98 (1H, m, C*H*(Ph)CH_2), 3.62 (1H, d, *J* 12.9 Hz, C$H_a$$H_b$Ph), 3.36 (1H, m, C*H*C=CH), 3.01 (1H, d, *J* 12.9 Hz, $CH_a$$H_b$Ph), 2.91 (1H, m, C*H*(Ph)CH_2), 2.87 (1H, m, C$H_a$$H_b$CO), 2.81 (1H, m, $CH_a$$H_b$NMe), 2.68 (1H, m, $CH_a$$H_b$CO), 2.58 (1H, m, $CH_a$$H_b$CO), 2.44 (1H, dd, *J* 16.2, 4.5 Hz, C$H_a$$H_b$CO), 2.35 (1H, m, C*H*$CH_2$), 2.35 (1H, m, $CH_a$$H_b$NMe), 1.95 (1H, dd, *J* 11.7, 3.3 Hz, C$H_a$$H_b$NMe), 1.89 (1H, t, *J* 10.8 Hz, C$H_a$$H_b$NMe), 1.76 (3H, s, CO*Me*); δ_C (75 MHz, $CDCl_3$) 207.4, 198.6, 163.1, 142.3, 142.2, 138.8, 129.5, 129.3, 128.9, 128.7, 128.3, 127.8, 127.7, 127.4, 127.2, 62.5, 60.9, 53.6, 50.0, 47.6, 45.2, 44.4, 42.6, 41.8, 30.8.

4.2.5. 2-(*tert*-Butyl)-4-(3-oxo-1-phenylbutyl)-8-phenyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolinone 3e. Isolated as a yellow solid (62%), mp 117 °C [Found: C, 81.12; H, 8.16; N, 3.30. $C_{29}H_{35}NO_2$ requires C, 81.08; H, 8.21; N, 3.26%]; R_f (20% ethyl acetate/pet. ether) 0.35; ν_{max} (KBr) 1722, 1701, 1642 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.11–7.46 (10H, m, Ph), 5.89 (1H, d, *J* 1.8 Hz, COC*H*=C), 3.86 (1H, m, C*H*(Ph)CH_2), 3.21 (1H, tdd, *J* 10.6, 5.7, 2.1 Hz, C*H*C=CH), 2.89 (1H, m, C*H*(Ph)CH_2), 2.86 (1H, m, C$H_a$$H_b$CO), 2.71 (1H, m, $CH_a$$H_b$NMe), 2.61 (1H, m, $CH_a$$H_b$CO), 2.59 (1H, m, $CH_a$$H_b$CO), 2.51 (1H, m, C$H_a$$H_b$CO), 2.35 (1H, m, C*H*$CH_2$), 2.35 (1H, m, $CH_a$$H_b$NMe), 1.95 (3H, s, CO*Me*), 1.88 (1H, dd, *J* 11.7, 3.3 Hz, C$H_a$$H_b$NMe), 1.78 (1H, t, *J* 10.6 Hz, C$H_a$$H_b$NMe), 0.99 (3H, s, C*Me*$_3$), 0.98 (6H, s, C*Me*$_3$); δ_C (75 MHz, $CDCl_3$) 206.6, 198.7, 165.1, 143.5, 142.0, 129.5, 128.9, 128.6, 128.2, 127.8, 127.5, 127.2, 62.3, 61.7, 58.2, 52.6, 49.2, 45.7, 44.3, 41.6, 40.7, 30.6, 18.5, 18.4, 18.3.

4.2.6. 2-Butyl-4-(3-oxo-1-phenylbutyl)-8-phenyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolinone 3f. Isolated as a yellow solid (58%), mp 132 °C [Found: C, 81.03; H, 8.25; N, 3.21. $C_{29}H_{35}NO_2$ requires C, 81.08; H, 8.21; N, 3.26%]; R_f (20% ethyl acetate/pet. ether) 0.34; ν_{max} (KBr) 1713, 1702, 1640 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.14–7.46 (10H, m, Ph), 6.12 (1H, d, *J* 1.8 Hz, COC*H*=C), 3.89 (1H, m, C*H*(Ph)CH_2), 3.21 (1H, tdd, *J* 10.6, 5.7, 2.1 Hz, C*H*C=CH), 2.90 (1H, m, C*H*(Ph)CH_2), 2.87 (1H, m, C$H_a$$H_b$CO), 2.80 (1H, ddd, *J* 10.6, 5.7, 1.5 Hz, $CH_a$$H_b$NMe), 2.71 (1H, dd, *J* 17.4, 4.8 Hz, $CH_a$$H_b$CO), 2.62 (1H, m, $CH_a$$H_b$CO), 2.52 (1H, dd, *J* 16.2, 4.5 Hz, C$H_a$$H_b$CO), 2.36 (1H, m, C*H*$CH_2$), 2.36 (1H, m, $CH_a$$H_b$NMe), 2.12 (2H, m, N$CH_2$), 1.95 (3H, s, CO*Me*), 1.86 (1H, dd, *J* 11.7, 3.3 Hz, C$H_a$$H_b$NMe), 1.67 (1H, t, *J* 10.6 Hz, C$H_a$$H_b$NMe), 1.41 (4H, m, C$H_2CH_2$Me), 0.88 (3H, t, *J* 6.6 Hz, CH_2*Me*); δ_C (75 MHz, $CDCl_3$) 206.9, 198.6, 165.5, 143.5, 141.8, 129.1, 128.7, 128.1, 127.7, 127.5, 126.9, 126.1, 61.8, 57.9, 52.1, 49.4, 46.3, 45.6, 44.9, 41.5, 41.0, 30.7, 30.2, 20.8, 15.6.

4.2.7. (4*S*,4a*R*,7a*R*,8*R*)- and (4*S*,4a*S*,7a*S*,8*R*)-4,8-Diphenyl-6-[(*R*)-1-phenylethyl]octahydro-1*H*-benzo[*d*]-isoquinoline-2,10(3*H*,11*H*)-dione 4a (mixture of diastereoisomers in the ratio of 1:1).[26] Isolated as yellow needles (76%), mp 118 °C [Found: C, 82.93; H, 7.33; N,

2.97. $C_{66}H_{70}N_2O_4$ requires C, 82.98; H, 7.39; N, 2.93%]; R_f (20% ethyl acetate/pet. ether) 0.33; $[\alpha]_D^{25}$ −20.1 (*c* 0.1, MeOH); ν_{max} (KBr) 1720, 1712, 1704, 1695, 1648 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.89–7.34 (30H, m, Ph), 3.84 (2H, m), 3.53 (3H, m), 3.26 (1H, q, *J* 7 Hz, C*H*Me), 3.09 (3H, m), 2.49 (14H, m), 2.05 (11H, m), 0.99 (3H, d, *J* 7 Hz, CH*Me*), 0.95 (3H, d, *J* 7 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 209.7, 209.6, 208.6, 208.4, 143.2, 140.7, 140.5, 140.2, 129.3, 128.9, 128.8, 128.7, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.0, 126.9, 126.8, 126.6, 64.3, 63.9, 51.3, 50.1, 49.6, 49.1, 48.7, 47.4, 47.1, 46.7, 45.6, 45.9, 44.4, 44.3, 43.8, 43.6, 42.8, 41.2, 39.8, 39.5, 39.4, 18.2, 17.4.

4.2.8. (4*S*,4a*R*,7a*R*,8*R*)- and (4*S*,4a*S*,7a*S*,8*R*)-4,8-Bis(4-chlorophenyl)-6-[(*R*)-1-phenylethyl]octahydro-1*H*-benzo-[*d*]isoquinoline-2,10(3*H*,11*H*)-dione 4b (mixture of diastereoisomers in the ratio of 1:1).[26] Isolated as yellow solid (71%), mp 124 °C [Found: C, 72.48; H, 6.14; N, 2.52. $C_{66}H_{66}$ $Cl_4N_2O_4$ requires C, 72.52; H, 6.09; N, 2.56%]; R_f (20% ethyl acetate/pet. ether) 0.38; $[\alpha]_D^{25}$ −22.6 (*c* 0.1, MeOH); ν_{max} (KBr) 1725, 1711, 1699, 1692, 1650 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.80–7.48 (26H, m, Ph), 3.91 (2H, m), 3.67 (3H, m), 3.34 (1H, q, *J* 7 Hz, C*H*Me), 3.17 (3H, m), 2.42 (14H, m), 2.11 (11H, m), 1.02 (3H, d, *J* 7 Hz, CH*Me*), 0.96 (3H, d, *J* 7 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 209.9, 209.5, 209.2, 208.9, 143.4, 140.6, 140.2, 139.7, 129.6, 129.3, 129.1, 128.9, 128.7, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 127.4, 127.3, 127.1, 126.9, 126.8, 126.5, 126.1, 64.5, 63.7, 51.4, 50.2, 49.4, 49.0, 48.5, 47.7, 47.3, 46.4, 45.9, 45.7, 44.5, 44.2, 43.9, 43.2, 42.5, 41.8, 39.9, 39.6, 39.2, 18.6, 17.1.

4.2.9. (4*S*,4a*R*,7a*R*,8*R*)- and (4*S*,4a*S*,7a*S*,8*R*)-4,8-Bis(4-methylphenyl)-6-[(*R*)-1-phenylethyl]octahydro-1*H*-benzo-[*d*]isoquinoline-2,10(3*H*,11*H*)-dione 4c (mixture of diastereoisomers in the ratio of 1:1).[26] Isolated as yellow solid (66%), mp 109 °C [Found: C, 83.08; H, 7.80; N, 2.72. $C_{70}H_{78}N_2O_4$ requires C, 83.13; H, 7.77; N, 2.77%]; R_f (20% ethyl acetate/pet. ether) 0.35; $[\alpha]_D^{25}$ −18.8 (*c* 0.1, MeOH); ν_{max} (KBr) 1728, 1715, 1701, 1692, 1643 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.85–7.54 (26H, m, Ph), 3.85 (2H, m), 3.59 (3H, m), 3.29 (1H, q, *J* 7 Hz, C*H*Me), 3.17 (3H, m), 2.57 (14H, m), 2.22 (3H, s, 4-*Me*C_6H_4), 2.21 (6H, s, 4-*Me*C_6H_4), 2.20 (3H, s, 4-*Me*C_6H_4), 2.02 (11H, m), 1.08 (3H, d, *J* 7 Hz, CH*Me*), 0.98 (3H, d, *J* 7 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 209.6, 209.4, 208.8, 208.2, 142.7, 140.8, 140.7, 140.4, 129.4, 129.1, 128.9, 128.6, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 127.1, 127.0, 126.8, 126.5, 126.2, 64.6, 64.3, 51.7, 50.4, 49.8, 49.2, 48.5, 47.3, 47.0, 46.8, 45.8, 45.7, 44.7, 44.5, 43.9, 43.4, 42.5, 41.3, 40.2, 39.8, 39.6, 21.3, 21.2, 21.1, 21.0, 18.0, 17.6.

4.3. General procedure for the preparation of 5

To a mixture of (L)-proline (0.287 g, 2.5 mmol, 25 mol %), 1-phenylpiperidin-4-one **1f** (1.75 g, 10 mmol) and (*E*)-4-phenylbut-3-en-2-one **2** (1.46 g, 10 mmol) dry ethanol (5 ml) was added at room temperature and the mixture stirred until TLC analysis indicated the completion of the reaction. Work up of the reaction mixture, as done for **3** and **4**, afforded **5**.

4.3.1. 6-Hydroxy-6-methyl-3,8-diphenyl-3-azabicyclo-[3.3.1]nonan-9-one 5a. Isolated as yellow needles (81%), mp 148 °C [Found: C, 78.52; H, 7.18; N, 4.40. $C_{21}H_{23}NO_2$ requires C, 78.47; H, 7.21; N, 4.36%]; R_f (20% ethyl acetate/pet. ether) 0.39; ν_{max} (KBr) 3470, 1711 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.83–7.38 (10H, m, Ph), 4.01 (1H, dt, *J* 12.6, 3.0 Hz, CH_aH_bNPh), 3.74 (1H, m, C*H*(Ph)CH_2), 3.71 (1H, m, CH_aH_bNPh), 3.23 (1H, m, CH_aH_bNPh), 3.19 (1H, dd, *J* 13.5, 9.6 Hz, CH_aH_bCHPh), 2.92 (1H, dd, *J* 12.3, 2.4 Hz, CH_aH_bNPh), 2.52 (1H, m, C*H*CHPh), 2.52 (1H, m, C*H*CO), 2.35 (1H, s, O*H*), 1.88 (1H, dd, *J* 13.5, 5.1 Hz, CH_aH_bCHPh), 1.57 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 215.1, 149.2, 140.9, 129.3, 128.7, 128.1, 127.1, 119.9, 115.8, 77.0, 58.8, 53.0, 52.7, 51.7, 43.4, 38.6, 28.6.

4.3.2. 8-(4-Chlorophenyl)-6-hydroxy-6-methyl-3-phenyl-3-azabicyclo[3.3.1]nonan-9-one 5b. Isolated as a white solid (77%), mp 152 °C [Found: C, 70.92; H, 6.20; N, 3.98. $C_{21}H_{22}ClNO_2$ requires C, 70.88; H, 6.23; N, 3.94%]; R_f (20% ethyl acetate/pet. ether) 0.40; ν_{max} (KBr) 3476, 1702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.78–7.41 (9H, m, Ph), 4.13 (1H, dt, *J* 12.6, 3.0 Hz, CH_aH_bNPh), 3.77 (1H, m, C*H*(Ph)CH_2), 3.75 (1H, m, CH_aH_bNPh), 3.27 (1H, m, CH_aH_bNPh), 3.24 (1H, dd, *J* 13.5, 9.6 Hz, CH_aH_bCHPh), 2.98 (1H, dd, *J* 12.3, 2.4 Hz, CH_aH_bNPh), 2.64 (1H, m, C*H*CHPh), 2.64 (1H, m, C*H*CO), 2.41 (1H, s, O*H*), 1.76 (1H, dd, *J* 13.5, 5.1 Hz, CH_aH_bCHPh), 1.48 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 214.2, 149.6, 141.3, 129.3, 128.4, 127.7, 126.5, 120.2, 116.1, 76.6, 59.2, 53.4, 52.9, 52.3, 42.9, 38.2, 28.1.

4.3.3. 6-Hydroxy-6-methyl-8-(4-methylphenyl)-3-phenyl-3-azabicyclo[3.3.1]nonan-9-one 5c. Isolated as a white solid (73%), mp 136 °C [Found: C, 78.81; H, 7.48; N, 4.23. $C_{22}H_{25}NO_2$ requires C, 78.77; H, 7.51; N, 4.18%]; R_f (20% ethyl acetate/pet. ether) 0.44; ν_{max} (KBr) 3464, 1715 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.91–7.42 (9H, m, Ph), 3.99 (1H, dt, *J* 12.6, 3.0 Hz, CH_aH_bNPh), 3.75 (1H, m, C*H*(Ph)CH_2), 3.75 (1H, m, CH_aH_bNPh), 3.25 (1H, m, CH_aH_bNPh), 3.21 (1H, dd, *J* 13.5, 9.6 Hz, CH_aH_bCHPh), 2.91 (1H, dd, *J* 12.3, 2.4 Hz, CH_aH_bNPh), 2.55 (1H, m, C*H*CHPh), 2.55 (1H, m, C*H*CO), 2.32 (1H, s, O*H*), 2.21 (3H, s, 4-C$H_3C_6H_4$), 1.92 (1H, dd, *J* 13.5, 5.1 Hz, CH_aH_bCHPh), 1.61 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 214.2, 148.5, 140.5, 129.2, 128.9, 128.4, 127.5, 119.6, 115.2, 76.7, 59.2, 53.2, 52.5, 51.8, 43.1, 38.4, 28.7, 21.3.

4.3.4. 3-(4-Chlorophenyl)-6-hydroxy-6-methyl-8-phenyl-3-azabicyclo[3.3.1]nonan-9-one 5d. Isolated as a white solid (76%), mp 142 °C [Found: C, 70.84; H, 6.18; N, 3.98. $C_{21}H_{22}ClNO_2$ requires C, 70.88; H, 6.23; N, 3.94%]; R_f (20% ethyl acetate/pet. ether) 0.41; ν_{max} (KBr) 3513, 1714 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.81–7.40 (9H, m, Ph), 4.12 (1H, dt, *J* 12.6, 3.0 Hz, CH_aH_bNPh), 3.68 (1H, m, C*H*(Ph)CH_2), 3.68 (1H, m, CH_aH_bNPh), 3.26 (1H, m, CH_aH_bNPh), 3.26 (1H, m, CH_aH_bCHPh), 2.95 (1H, dd, *J* 12.3, 2.4 Hz, CH_aH_bNPh), 2.48 (1H, m, C*H*CHPh), 2.48 (1H, m, C*H*CO), 2.31 (1H, s, O*H*), 1.90 (1H, dd, *J* 13.5, 5.1 Hz, CH_aH_bCHPh), 1.55 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 214.7, 149.6, 141.3, 138.4, 129.1, 128.3, 127.4, 119.8, 115.2, 76.7, 59.2, 53.4, 52.6, 51.9, 43.3, 38.7, 28.8.

4.3.5. 3-(3-Chlorophenyl)-6-hydroxy-6-methyl-8-phenyl-3-azabicyclo[3.3.1]nonan-9-one 5e. Isolated as a white

solid (79%), mp 136 °C [Found: C, 70.91; H, 6.28; N, 3.90. $C_{21}H_{22}ClNO_2$ requires C, 70.88; H, 6.23; N, 3.94%]; R_f (20% ethyl acetate/pet. ether) 0.39; ν_{max} (KBr) 3432, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.80–7.42 (9H, m, Ph), 4.07 (1H, dt, *J* 12.6, 3.0 Hz, CH_aH_bNPh), 3.67 (1H, m, $CH(Ph)CH_2$), 3.67 (1H, m, CH_aH_bNPh), 3.22 (1H, m, CH_aH_bNPh), 3.22 (1H, m, CH_aH_bCHPh), 2.91 (1H, dd, *J* 12.3, 2.4 Hz, CH_aH_bNPh), 2.47 (1H, m, CHCHPh), 2.47 (1H, m, CHCO), 2.32 (1H, s, OH), 1.85 (1H, dd, *J* 13.5, 5.1 Hz, CH_aH_bCHPh), 1.61 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 215.2, 149.7, 141.0, 139.1, 129.0, 128.5, 128.4, 128.1, 127.0, 119.6, 115.7, 77.1, 59.0, 53.1, 52.7, 51.8, 43.5, 38.5, 28.5.

4.3.6. 3-(3-Nitrophenyl)-6-hydroxy-6-methyl-8-phenyl-3-azabicyclo[3.3.1]nonan-9-one 5f. Isolated as a white solid (71%), mp 151 °C [Found: C, 68.89; H, 6.01; N, 7.71. $C_{21}H_{22}N_2O_4$ requires C, 68.84; H, 6.05; N, 7.65%]; R_f (20% ethyl acetate/pet. ether) 0.40; ν_{max} (KBr) 3466, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.89–7.88 (9H, m, Ph), 4.11 (1H, dt, *J* 12.6, 3.0 Hz, CH_aH_bNPh), 3.69 (1H, m, $CH(Ph)CH_2$), 3.69 (1H, m, CH_aH_bNPh), 3.27 (1H, m, CH_aH_bNPh), 3.27 (1H, m, CH_aH_bCHPh), 2.96 (1H, dd, *J* 12.3, 2.4 Hz, CH_aH_bNPh), 2.55 (1H, m, CHCHPh), 2.55 (1H, m, CHCO), 2.34 (1H, s, OH), 1.91 (1H, dd, *J* 13.5, 5.1 Hz, CH_aH_bCHPh), 1.56 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 213.4, 149.3, 140.9, 139.4, 138.6, 128.9, 128.6, 128.3, 128.0, 127.5, 119.7, 115.6, 76.9, 58.8, 53.3, 52.4, 51.6, 43.4, 38.8, 28.9.

4.4. X-ray crystallographic determination of 4a and 5a

Data were collected at room temperature on an Enraf-Nonius MACH 3 four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å) for compounds **4a** and **5a**. The data collection, integration and data reduction for **4a** and **5a** were performed using CAD-4 EXPRESS[27] and XCAD4[28] programmes and an empirical absorption correction was applied using ψ scan method.[29] The unit cell parameters were determined by a least square fitting of 25 randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method. The structures were solved by direct methods (SHELXS 97)[30] and subsequent Fourier synthesis, and refined by full matrix least squares on SHELXL 97[31] for all non-hydrogen atoms in **4a** and **5a**. All hydrogen atoms were placed at calculated positions.

4.4.1. Compound 4a. $C_{33}H_{35}NO_2$, *M*=477.62, monoclinic, space group *C*2, *a*=30.051(8) Å, *b*=11.696(7) Å, *c*=20.899(9) Å, β=133.55°(6), *V*=5323.5(8) $Å^3$ *Z*=8, *f*(000)=1620, μ=0.059 mm^{-1}, D_c=0.946 mg/m^3. The reflections collected were 5356 of which 4924 unique [$R_{(int)}$=0.0359]; 2115 reflections $I>2\sigma(I)$, R_1=0.0432 and wR_2=0.0727 for 2115 [$I>2\sigma(I)$] and R_1=0.1730 and wR_2=0.1016 for all (4924) intensity data. Goodness of fit=1.003, residual electron density in the final Fourier map was 0.187 and −0.160 $eÅ^{-3}$. CCDC number is 616378.

4.4.2. Compound 5a. $C_{21}H_{23}NO_2$, *M*=321.40, monoclinic, space group *P*21/*a*, *a*=15.311(8) Å, *b*=8.322(3) Å, *c*=15.866(6) Å, β=116.91°(5), *V*=1802.9(8) $Å^3$, *Z*=4, *f*(000)=688, μ=0.076 mm^{-1}, D_c=01.184 mg/m^3. The reflections collected were 3793 of which 3168 unique [$R_{(int)}$=0.0894]; 2034 reflections $I>2\sigma(I)$, R_1=0.0907 and wR_2=0.2390 for 2034 [$I>2\sigma(I)$] and R_1=0.1304 and wR_2=0.2740 for all (3168) intensity data. Goodness of fit=1.008, residual electron density in the final Fourier map was 0.516 and −0.482 $eÅ^{-3}$. CCDC number is 616379.

Acknowledgements

S.P. thanks the Council of Scientific and Industrial Research, New Delhi for a major research project. S.P. also thanks Department of Science and Technology, New Delhi for funds under (i) IRHPA programme for the purchase of a high resolution NMR spectrometer and (ii) FIST programme and University Grants Commission, New Delhi for funds under the DRS and ASIST programmes. M.S. thanks CSIR for the award of a Senior Research Fellowship.

Supplementary data

Supplementary data (chiral HPLC chromatograms of **3a** and **5a**, and ^1H NMR, ^{13}C NMR, H,H–COSY, C,H–COSY and HMBC spectra of compounds **3a**, **4a** and **5a**) associated with this article are available online. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.038.

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