DOI: 10.1002/ejoc.201100700

One-Pot Regioselective Double-Mannich Annulations Affording Azabicyclononanones as a Key Step in the Synthesis of Natural Products

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Keywords: 2-Acetylcyclohexanone / Azabicyclic systems / Annulation / Green chemistry / Indazoles / Nitrogen heterocycles

The first regioselective one-pot syntheses of a number of azabicyclic ring systems (compounds **3**) in very good yields, under green-chemistry conditions in the presence of water without use of organic solvents, through acid-catalysed double-Mannich reactions from 2-acetylcyclohexanone, ring-substituted anilines and formaldehyde have been developed. In addition, treatment of the acetylazabicyclononanones **3** with hydrazine, methylhydrazine and hydroxylamine was thoroughly investigated, leading in the case of hydrazine to the formation of the pyrazole-fused azatricyclic derivatives **6** as the main reaction products. In the cases of methylhydrazine and hydroxylamine, though, the tetrahydroindazoles **8** and **9** and the tetrahydrobenzisoxazoles **10**, respectively, were obtained, through subsequent ring opening of the initially formed pyrazole- and oxazole-fused azatricyclic ring systems. Plausible mechanistic schemes for the formation of compounds **8**, **9** and **10** are proposed. Structure elucidation of the products and full assignment of all ^{1}H and ^{13}C NMR chemical shifts was accomplished by 1D and 2D NMR experiments. COSY H–H and COLOC C–H correlations as well as H–H coupling constants were analysed in detail in combination with conformational analysis to determine the final stereochemistries of products **3**.

Introduction

The pharmaceutical industry's ability to produce new medicines is directly tied to its success in identifying drug-like molecules that target clinically relevant pathways. Fragment-based drug design is another tool for drug discovery that has emerged in the past decade[1] and appeared to require even more demanding and novel diverse building blocks than high-throughput screening. As a result, fragment-based strategies represented an ongoing challenge to synthetic chemists. Moreover, in the design of drug candidates the conformationally restricted and rigid building blocks exhibit some advantages over flexible analogues, mainly due to the decreases in entropy of binding of the potential candidate drugs with their biological targets.[2] The fragment-based drug-design concept is embodied in aza-substituted bicyclic scaffolds, which are frequently encountered both in natural products[3] (e.g., atropine, cocaine, cyclazocine) and in synthetic drugs (e.g., the anti-HIV agent maraviroc[4] or the serotonin 5-HT3 receptor antagonist granisetron[5]). Moreover, aza-substituted bicyclic scaffolds are also involved as specific ligands or bases in organic transformations.[6] Double-Mannich-based annulations are an attractive prospect for one-pot syntheses of azabicyclic ring systems as key steps in syntheses of alkaloids.[7] Unfortunately, these direct syntheses of azabicycles under standard Mannich conditions are limited in scope, low-yielding,[8] and in many cases fail to afford the desired azabicyclic ring systems.[9] In some instances, these targets have been obtained by more lengthy indirect syntheses.[8,10] It has also been shown that the use of *N*,*N*-bis(alkoxymethyl)alkylamine reagents, developed as preformed Mannich reagents,[11] can improve the yields of azabicyclic ring systems obtained through double-Mannich reactions with cyclic β-oxo esters.[12] More recently, an extension of this methodology to cyclic ketone substrates has also been described.[13,14]

In a contribution to syntheses of azabicyclononane frameworks[15,16] through double-Mannich annulations we explored the potential for the use of the underexploited 1,3-dicarbonyl compounds under green-chemistry conditions. Moreover, the preferred conformations of the expected compounds are anticipated to be advantageous for the formation of additional fused oxazole or pyrazole rings through reactions between the two carbonyl groups and hydroxylamine or hydrazines, thus leading to new heterocyclic rigid scaffolds, most probably with additional biological properties.

Results and Discussion

Initial studies of double-Mannich annulations were conducted with 2-acetylcyclohexanone (**1**, Table 1), formalde-

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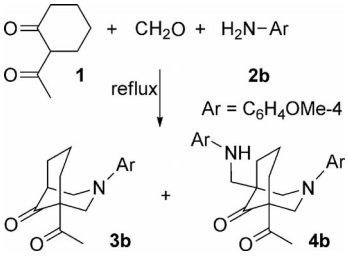
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100700.

hyde and *p*-anisidine (**2b**) as follows: mixing of 2-acetylcyclohexanone (2 equiv.) with an ethanolic solution of *p*-anisidine (1 equiv.) and with formaldehyde (9 equiv. in 36% aqueous solution) resulted, after heating at reflux for 2 min, in the formation of two azabicyclic products, which – after separation by column chromatography – were identified as the double-Mannich derivative **3b** (73% yield) and the triple-Mannich derivative **4b** (22% yield). The yield ratios of the two products were found to be highly dependent on the reflux times (Table 1), becoming 42% for **3b** and 55% for **4b** after 5 min at reflux, and 5% for **3b** and 81% for **4b** after 20 min at reflux. The yield of **3b** was optimized (91%) when hydrochloric acid (two drops) or a catalytic amount of a Lewis acid ($BF_3{\cdot}Et_2O$) was added to the reaction mixture.

Table 1. Investigation of the double-Mannich reaction conditions.



Entry	Catalyst	Solvent	*T* [min]	**3b** [%]	**4b** [%]
1	none	ethanol	2	73	22
2	none	ethanol	5	42	55
3	none	ethanol	20	5	81
3	HCl	ethanol	5	91	–
4	HCl	water	5	89	–
5	$BF_3{\cdot}Et_2O$	ethanol	5	91	–

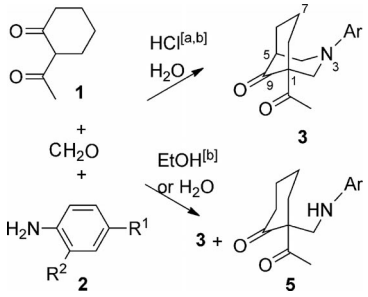
The reaction proceeded analogously (**3b** in 89% yield, HCl catalysis) when ethanol was replaced by water. In contrast, no reaction was observed in aprotic solvents (DMSO, MeCN). In addition, no substantial difference was observed on increasing the reflux time up to 20 min.

These encouraging results prompted us to use other substituted anilines (Table 2), and in all cases compounds **3** were isolated as the only reaction products (Scheme 1) in very good yields (88–93%). Remarkably, when amines other than *p*-anisidine were used without acid catalysis, the azabicyclic compounds **3** were furnished only in minor amounts, and the triple-Mannich products **4** were not even detectable, whereas the main reaction products were the aminomethylation derivatives **5**, their yields increasing at the expense of those of compounds **3**. This result can readily be explained: with use of anilines with electron-withdrawing substituents the double-Mannich reaction is not favoured, due to the decrease in the electron density on the aniline nitrogen atom.

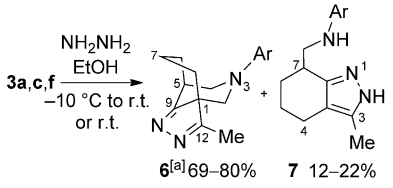
Next, the formation of additional fused pyrazole or oxazole rings by treatment of the aza-substituted bicyclic scaffolds **3** with hydrazines or hydroxylamine was attempted. Initial studies were conducted with the azabicyclononanone **3f** and hydrazine in ethanol at room temperature, whereupon – after stirring for 2 h – two products were formed. After separation by column chromatography, the major product was shown to be the target fused derivative **6f** (Scheme 2), obtained in 73% yield, whereas the minor product (22%) was characterized as the tetrahydro-2*H*-indazole **7f**. Analogous results were obtained when the reaction was repeated at –10 °C and even at –78 °C (Table 3). Treatment with hydrazine proved to be insensitive to the aryl substituents on **3**, always resulting in the target tricyclic pyrazoles **6** (69–80%) along with indazoles **7**, isolated as the minor components (12–22%).

Table 2. Comparison of the acid-catalysed syntheses of compounds **3** in water and in ethanol.

Amine	Ar	Solvent	Product	Yield (%)
2a	C_6H_5	water	**3a**	90
2a	C_6H_5	ethanol	**3a**	93
2b	C_6H_4OMe-4	water	**3b**	89
2b	C_6H_4OMe-4	ethanol	**3b**	91
2c	C_6H_4Me-4	water	**3c**	88
2c	C_6H_4Me-4	ethanol	**3c**	91
2d	$C_6H_3Me_2$-3,4	water	**3d**	89
2d	$C_6H_3Me_2$-3,4	ethanol	**3d**	91
2e	C_6H_4Cl-4	water	**3e**	90
2e	C_6H_4Cl-4	ethanol	**3e**	92
2f	C_6H_4Br-4	water	**3f**	89
2f	C_6H_4Br-4	ethanol	**3f**	91



Scheme 1. Synthesis of the 8-azabicyclo[3.3.1]nonan-9-ones **3** under green-chemistry conditions. [a] Concd. HCl (2 drops). [b] Reflux for 5 min, then room temp. overnight.



Scheme 2. Treatment of compounds **3** with hydrazine. [a] The numbering of compounds **6** follows that of **3** for comparison of the two systems.

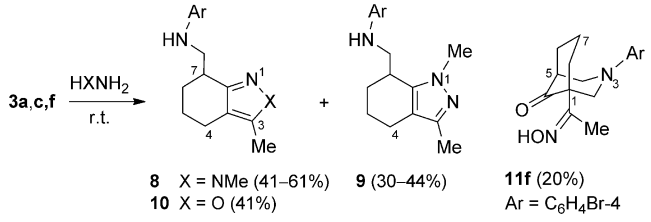
Encouraged by the results with hydrazine, we then repeated the reaction with methylhydrazine, whereupon separable mixtures of the 2*H*- and 1*H*-indazoles **8** and **9** were formed in approximately 90% total yields in all cases, even at –10 °C (Table 3, Scheme 3), most probably through the intermediates **12**–**14** and **18**–**20** (Scheme 4). Treatment with

Table 3. Treatment of 8-azabicyclo[3.3.1]nonan-9-ones (**3**) with hydrazines and with hydroxylamine.

Compd. **3**	Amine	*T* [°C]	Time	Product (yield [%])				
				6	**7**	**8**	**9**	**10**
3a	hydrazine	room temp.	1 h	**6a** (80)	**7a** (12)			
3c	hydrazine	room temp.	1 h	**6c** (75)	**7c** (21)			
3f	hydrazine	room temp.	1 h	**6f** (73)	**7f** (22)			
3f	hydrazine	–10 to room temp.	2 h	**6f** (71)	**7f** (19)			
3f	hydrazine	–78 to room temp.	3 h	**6f** (69)	**7f** (18)			
3a	methylhydrazine	room temp.	5 h			**8a** (47)	**9a** (44)	
3c	methylhydrazine	room temp.	5 h			**8c** (41)	**9c** (42)	
3f	methylhydrazine	room temp.	5 h			**8f** (63)	**9f** (32)	
3f	methylhydrazine	–4 to room temp.	12 d			**8f** (60)	**9f** (33)	
3f	methylhydrazine	–10 to room temp.	12 d			**8f** (61)	**9f** (30)	
3f	hydroxylamine	room temp.	24 h					**10f** (41)[a]

[a] Along with the oxime **11f** (20% yield).

hydroxylamine proceeded in an analogous manner, leading from **3f** to a mixture of the tetrahydrobenzisoxazole **10f** (41%) and the oxime **11f** (20%).

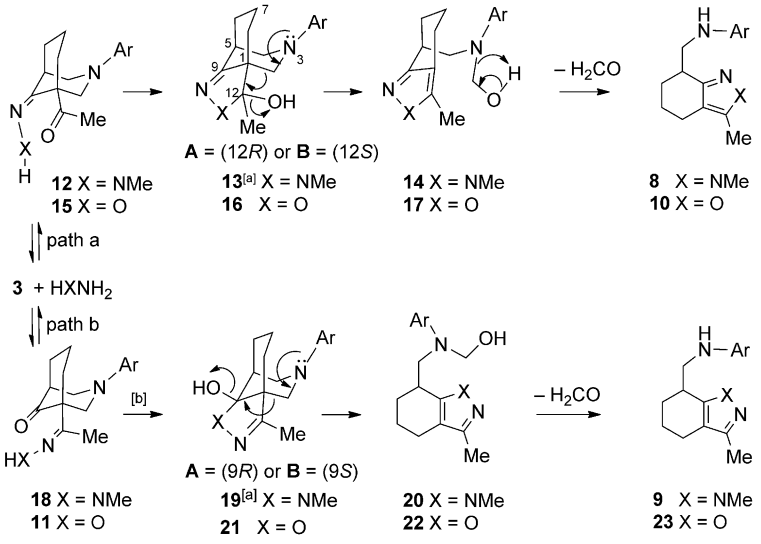


Scheme 3. Treatment of compounds **3** with methylhydrazine and with hydroxylamine.

A mechanistic interpretation of the reactions between the azabicyclononanones **3** and methylhydrazine or hydroxylamine is illustrated in Scheme 4. For the formation of the indazoles **8** or **9** it is conceivable that initially the amino group of the ambident nucleophile methylhydrazine reacts either with the carbonyl group at the 9-position (path a) or with the 1-acetyl carbonyl group (path b), forming the intermediate hydrazones **12** or **18**, respectively, which subsequently cyclize to the intermediates **13** or **19**. The intermediates **13** and **19** can each exist as two stereoisomers: namely as **13A** (12*R*) or **13B** (12*S*) and as **19A** (9*R*) or **19B** (9*S*). The (*R*),(*S*) configurations were used for the calculations presented in Table 4. Subsequent C1–C2 bond fission, assisted by the adjacent nitrogen atom and accompanied by hydroxy group migration and formation of **14**, leads finally – with loss of formaldehyde – to the isolated products **8**. Analogously, the indazoles **9** can be formed by path b.

The reactions with hydroxylamine proceeded analogously, as far as path a is concerned, affording the benzisoxazoles **10**, whereas when path b was followed – after initial reaction with the acetyl carbonyl group of **3** – the reaction did not proceed any further, and finally the oximes **11** were isolated along with the benzisoxazoles **10**.

To provide support for the proposals discussed above, some theoretical calculations were carried out (AM1). The heats of formation for the intermediates included in the



Scheme 4. Mechanistic interpretation of the reactions between the diketones **3** and methylhydrazine or hydroxylamine. [a] The numbering of the tricyclic skeleton is arbitrary, following that of **3**. [b] The intermediates **21** and **22** and the product **23** are imaginary for comparison of their calculated ΔH_f values with their counterparts in path a.

Table 4. Calculated energies of formation (ΔH_f, AM1) for the intermediates and products of the reactions between compounds **3a** and **3f** and NH_2NHMe or NH_2OH (Scheme 4).

Interm.	ΔH_f	$\Delta\Delta H_f$	Interm.	ΔH_f	$\Delta\Delta H_f$	Interm.	ΔH_f	$\Delta\Delta H_f$	Interm.	ΔH_f	$\Delta\Delta H_f$
12a	29.93	0.00	**15a**	–6.38	0.00	**12f**	34.33	0.00	**15f**	–1.92	0.00
13a (A)	38.27	8.34[a]	**16a (B)**	–5.01	1.37[a]	**13f (A)**	42.58	8.25[a]	**16f (B)**	–0.53	1.39[a]
13a (B)	38.85	8.92[a]	**16a (A)**	–5.30	1.08[a]	**13f (B)**	43.17	8.84[a]	**16f (A)**	–0.58	1.34[a]
14a	32.55	–5.72[b]	**17a**	5.28	10.58[b]	**14f**	36.59	–5.99[b]	**17f**	9.02	9.60[b]
8a[c]	41.60	9.05[a]	**10a**[c]	13.24	7.96[a]	**8f**[c]	43.73	7.14[a]	**10f**[c]	16.86	7.84[a]
18a	29.99	0.00	**11a**	–5.55	0.00	**18f**	34.51	0.00	**11f**	–1.07	0.00
19a (B)	46.88	16.89[a]	**21a (A)**	7.10	12.65[a]	**19f (B)**	50.97	16.46[a]	**21f (A)**	11.57	12.64[a]
19a (A)	48.03	18.04[a]	**21a (B)**	8.50	14.05[a]	**19f (A)**	52.08	17.57.[a]	**21f (B)**	12.63	13.70[a]
20a	35.60	–11.28[b]	**22a**	7.78	0.68[b]	**20f**	40.07	–10.90[b]	**22f**	12.17	0.60[b]
9a[c]	41.94	6.34[a]	**23a**[c]	14.31	6.53[a]	**9f**[c]	44.83	4.76[a]	**23f**[c]	18.57	6.40[a]

[a] Energy differences relative to previous intermediates. [b] Energy differences relative to the most stable previous (*R*) or (*S*) isomers (AM1, in kcal mol^{-1} at 298 K, in vacuo). [c] The calculations also include the formaldehyde molecules.

plausible mechanism shown in Scheme 4 were calculated and are presented in Table 4. Because all calculations were performed under the assumption that the various species were in vacuo, whereas the experimental results were obtained in ethanol, only the relative values of $\Delta\Delta H_f$ are meaningful and will be discussed.

It is accepted that *N*-methylhydrazine initially reacts with its free amino group as the more strongly nucleophilic centre, because the net charge on this nitrogen atom is calculated to be q_{net} = –0.461 electrons, whereas the methyl nitrogen atom is calculated to have q_{net} = –0.400 electrons. The reaction could follow paths a and/or b, beginning with carbonyl condensation at the 9-position or at the 1-acetyl group, respectively, and after the experimental time the thermodynamically stable final products would be formed. The transformations of **12** into **13** were calculated to be favoured over those of **18** into **19** by ca. 8 kcal mol^{-1}. On the whole, the increases in ΔH_f (Table 4) can be attributed to increases in strain energy due to the formation of five-membered rings. The next step, aromatization of the heterocyclic rings followed by fission of the piperidine rings and relief of van der Waals interactions, was calculated to be favoured in all transformations, especially in those of **13** to **14** and of **19** to **20**, consistent with the experimental results. However, it should be mentioned that in the case of **3f** there is a preference for the formation of **8f** over **9f** (Table 3). For the reactions with hydroxylamine no preferences between the two carbonyl groups are calculated, but in the next step the transformations of **15** to **16** were calculated to be highly favoured (almost spontaneous), leading to the final products **10**, whereas those of **11** were inhibited due to much greater energy demands, again consistent with experimental results.

The structural characterization of the products was based on rigorous spectroscopic analysis [IR, NMR including ^{1}H, ^{13}C, DEPT, COSY H-H, NOESY H-H, HETCOR (or HMQC) and COLOC (or HMBC)] and on mass spectra and elemental analysis data. Some multiplicities in the ^{1}H spectra were confirmed by simulation.[17]

With regard to the structures of the isolated azabicycles **3**, the assignment of **3b** is described analytically, because – to the best of our knowledge – no complete analysis of analogous systems based on 2D NMR spectroscopy has yet been reported in the literature. In the saturated region, there are many multiplets, and their COSY H–H correlations reveal their proximity, whereas by C–H COSY the carbon–proton pairs are defined revealing a saturated carbon chain, as depicted in Figure 1. The methylene protons are diastereotopic because of the molecular rigidity of the carbon skeleton. The more downfield signals at δ = 3.81 (dd, J = 12.2, 2.2 Hz) and 3.48 ppm (dd, J = 12.2, 1.7 Hz) and at δ = 3.75 (ddd, J = 11.5, 3.0, 2.2 Hz) and 3.30 ppm (ddd, J = 11.5, 3.0, 1.2 Hz) with their carbon atoms resonating at δ = 59.1 and 58.0 ppm, respectively, belong to the 2- and 4-methylene group protons adjacent to the nitrogen atom. Furthermore, the multiplet signal at δ = 2.57–2.65 ppm was assigned to the 5-position methine proton (its carbon atom resonating at δ = 47.5 ppm), because it showed COSY correlations both with the 4-CH_2 protons and with the multiplet at δ = 2.15–2.35 ppm, corresponding to the 6-CH_2 protons (carbon signal at δ = 34.0 ppm). In addition, two more methylene group signals at δ = 20.1 and 36.4 ppm showed multiplets for their protons at δ = 1.58–1.70 and 2.68 ppm (ddddd, J = 13.1, 11.6, 11.1, 6.0, 5.1 Hz) and at δ = 2.44 (ddd, J = 13.7, 11.6, 6.1, 1.7 Hz) and 2.25 ppm (masked under a broad multiplet), respectively. The pattern of multiplets at δ = 2.68 ppm and at δ = 2.44 ppm with two and three coupling constants of about 12 Hz reveals their vicinal antiaxial configuration. Fortunately, from the spectrum of **3a** it was possible to identify a low-intensity COSY correlation of the 2-CH_2 protons at δ = 3.52 ppm with the corresponding multiplet of the proton signal at δ =

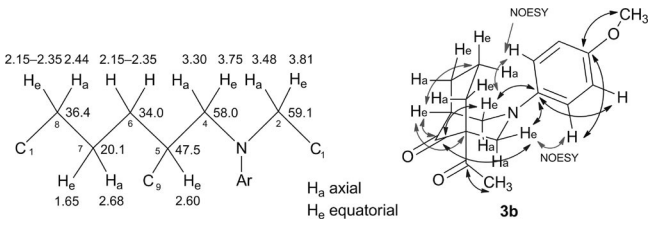


Figure 1. Saturated carbon chain of compound **3b** with proton and carbon signal assignments together with critical COLOC and NOESY correlations.

2.42 ppm. This long-range coupling is due to the "W" relative configuration of these protons. This methylene group (carbon signal at δ = 36.4 ppm) was therefore assigned to the 8-position.

With regard to the structure of **3b**, the more downfield proton signals of each of the 2-CH_2 and 4-CH_2 groups, namely at δ = 3.81 and 3.75 ppm, show COLOC correlations with the carbonyl carbon signal at δ = 214.4 ppm (C-9) and with the *N*-aryl *ipso*-carbon signal at δ = 143.8 ppm. As a result, the signal at δ = 3.81 ppm was assigned to 2-H_{eq} and the one at δ = 3.75 ppm to 4-H_{eq}. The 2-H_{ax} and 4-H_{ax} protons, in favoured configurations, gave COLOC correlations with carbon atoms C-8 and C-6, respectively. The 5-CH proton shows a COLOC correlation with the quaternary carbon signal at δ = 62.7 ppm (C-1) and with the carbonyl carbon signal at δ = 214.4 ppm (C-9). The 7-H_{eq} proton gave COLOC correlations with C-1, revealing its favoured configuration. Finally, the acetyl methyl group protons gave COLOC correlations with the carbonyl signal at δ = 207.2 ppm. Characteristic COLOC correlations for the phenyl ring were also observed. Figure 1 also shows some critical COLOC $^2J_{C,H}$ and $^3J_{C,H}$ correlations between protons and carbon atoms observed for compound **3b**, which confirm the presented conformation and the proximity of the 3-N and 7-CH_2 moieties, along with some NOESY correlations.

For the structure elucidation of the pyrazole tricyclic derivatives **6**, the assignment of **6f** is described. The new skeleton is more rigid than its predecessor, as a result of which the proximity of N-3 to the 7-methylene group has been changed. This change was also concluded from the chemical shifts and confirmed by COSY H–H and HMQC results. The 7-methylene protons showed a multiplet of 47.6 Hz width for H_{ax} at δ = 1.63 ppm and a multiplet of 30.0 Hz width for H_{eq} at δ = 2.05 ppm (Figure 2). From a comparison with the chemical shifts of the parent compound (H_{eq} signal at δ = 1.65 ppm and H_{ax} signal at δ = 2.48 ppm) it is obvious that H_{ax} is directed away from N-3.

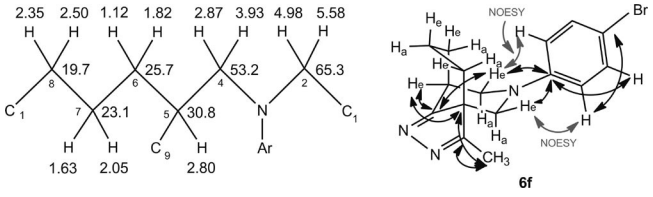


Figure 2. Saturated carbon chain of compound **6f** with proton and carbon signal assignments together with some critical HMBC and NOESY correlations.

For the structure of the indazole **8c** the combination of COSY H–H and HMQC spectra revealed a saturated carbon chain, as depicted in Figure 3. The assignment of the methyl group on N-2 and not on N-1, established by COLOC correlations of the methyl protons, confirmed the structure **8c** and ruled out that of **9c**.

Finally, with regard to the structures of the indazoles **9**, in **9f** the combination of COSY H–H and HMQC spectra revealed an analogous saturated carbon chain, as depicted

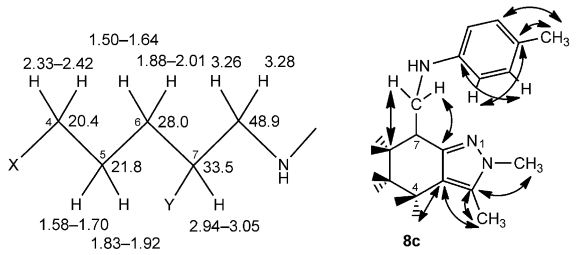


Figure 3. Saturated carbon chain of compound **8c** with proton and carbon signal assignments together with some critical COLOC correlations.

in Figure 4. The methyl group on N-1 shows COLOC correlations with the quaternary carbon signal at δ = 139.4 ppm, whereas the 3-methyl protons have COLOC correlations with the quaternary carbon signals at δ = 144.9 and 114.7 ppm, confirming the structure of **9f**.

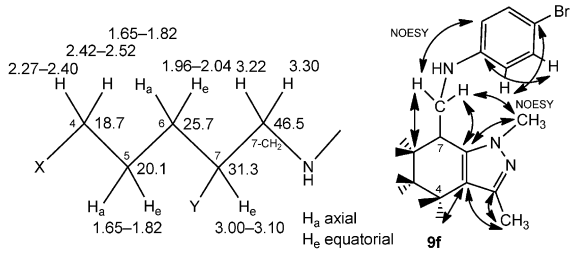


Figure 4. Saturated carbon chain of compound **9f** with proton and carbon signal assignments together with some critical COLOC and NOESY correlations.

Conformation Analysis of Compounds 3

With regard to the relative stabilities of the various conformers of compound **3a**, depicted in Figure 5, the calculated (AM1 and DFT) heats of formation (ΔH_f) predict that the chair-chair conformer **A** should be the most stable and

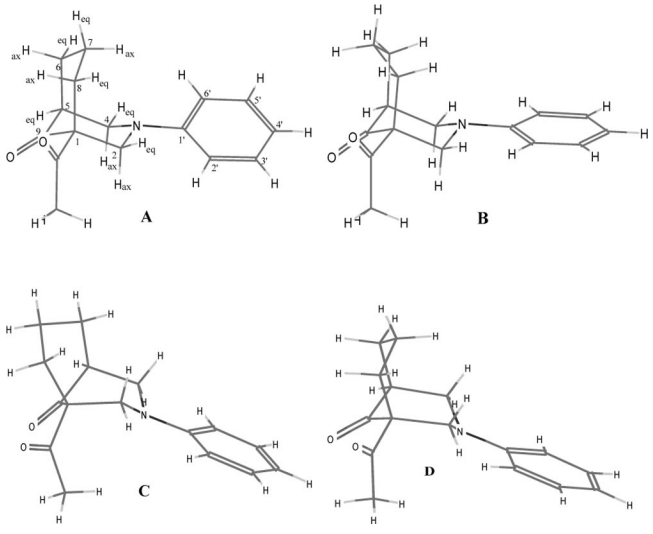


Figure 5. Four low-energy conformations for **3a**: chair-chair (**A**), boat-chair (**B**), boat-boat (**C**), chair-boat (**D**).

the boat-boat **C** the least stable. The interconversion of **A** to **B** is not favoured, because the required transition energy is calculated to be ca. 4.2 kcal mol^{-1}, whereas that of **A** to **D** is the preferred one. On the other hand, only the interconversion of **C** to **B** is favoured, as it is obvious from Table 5. The chemical shift of the 7-H_{ax} proton signal at a position much more downfield (δ =2.68 ppm) than that of its 7-H_{eq} counterpart (δ =1.65 ppm) can be explained only on the basis of the preferred conformation **A**, because it is deshielded from the magnetic anisotropy effects both of the aromatic ring and of the nitrogen lone pair.[15,18]

Table 5. Calculated enthalpies of formation (ΔH_f, AM1) and total energies (E_{total}, DFT) for the conformations **A**–**D** of **3a**.

Conformation	ΔH_f	$\Delta\Delta H_f$[a]	E_{total}	$\Delta\Delta E$[b]
A	–41.61	0.00	–826.007834	0.00
B	–40.72	0.89	–826.005503	1.46
C	–38.68	2.93	–825.997723	6.34
D	–41.07	0.54	–826.004869	1.86
TS **A** to **B**	–37.43	4.18		
TS **A** to **D**	–40.35	1.26		
TS **B** to **C**	–37.52	3.20		

[a] Energy difference relative to the most stable conformation **A** (AM1, kcal mol^{-1}). [b] Energy difference relative to the most stable conformation **A** [B3LYP/6-31G(d), kcal mol^{-1}] including the zero-energy correction (298 K, in vacuo).

For compound **10f**, 2D NMR spectroscopic data (COSY and NOESY) predicted a conformation folded at C-5. The lower energy conformation after DFT calculations is depicted in Figure 6.

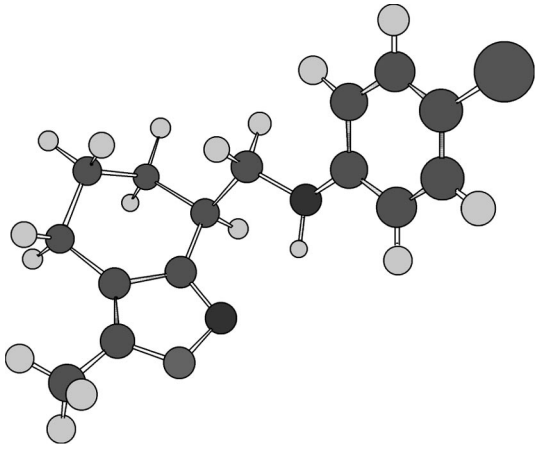


Figure 6. Low-energy conformation (DFT) for **10f**.

Conclusions

We have developed a catalytic direct method for the synthesis of a series of azabicyclic ring systems **3** in very high yields (88–93%), through double-Mannich reactions with cheap and common reagents as raw materials. To the best of our knowledge, these are the first examples of double-Mannich reactions taking place in water without the use of organic solvents. The first example of a triple-Mannich reaction product is also reported. In addition, our initial goal, the formation of the rigid pyrazole-fused azatricyclic derivatives **6**, was accomplished by treatment of the acetylazabicyclononanones **3** with hydrazine, whereas the tetrahydroindazoles **8** and **9** isolated on treatment of compounds **3** with methylhydrazine constitute unknown derivatives belonging to a class of pharmacologically interesting compounds.[19] Moreover, the structure elucidation of all products was accomplished by 1D and 2D NMR experiments. In addition, the final stereochemistry of products **3** in solution was determined by analysis of COSY H–H, NOESY H–H and COLOC C–H correlations together with H–H coupling constants in combination with conformational analysis.

Experimental Section

General Information: Melting points were measured with a Kofler hot-stage. Column chromatography was carried out with Merck silica gel. TLC was performed with precoated silica gel glass plates (0.25 mm) containing fluorescent indicator UV254 purchased from Macherey–Nagel with use of a 3:1 mixture of petroleum ether/ethyl acetate. Petroleum ether (PE) refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature with a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, with $CDCl_3$ as solvent. Chemical shifts are expressed as δ values in ppm relative to TMS as internal standard for ^{1}H and relative to TMS (δ = 0.00 ppm) or to $CDCl_3$ (δ =77.05 ppm) for ^{13}C NMR spectra. Coupling constants (^nJ) are reported in Hz. Second-order ^{1}H NMR spectra were analysed by simulation.[17] IR spectra were recorded with a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm^{-1}). LC-MS (ESI, 1.65 eV) spectra were recorded with an LCMS-2010 EV system (Shimadzu). Elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their IR, MS and NMR spectra (^{1}H, ^{13}C, DEPT, COSY, NOESY, HMQC or HETCOR and HMBC or COLOC). The MO calculations for minimum-energy conformations of compounds were computed with the AM1 method as implemented in the MOPAC package[20] and DFT calculations with use of the B3LYP level with the 6-31G(d) basis set as implemented in the Gaussian 03W package.[21]

General Procedure for Acid-Catalysed Reactions of Anilines, Formaldehyde and 2-Acetylcyclohexanone. Preparation of the 1-Acetyl-3-aryl-3-azabicyclo[3.3.1]nonan-9-ones 3a–3f: A formaldehyde solution (37%, 9 mmol) and concd. hydrochloric acid (2 drops) were added to a suspension of the amine **2** (1.0 mmol) in water (15 mL), and the mixture was warmed gently for 5 min to dissolve all the reactants. 2-Acetylcyclohexanone (2.0 mmol) was added, and the reaction mixture was initially heated at reflux for 5 min and was then stirred at room temperature overnight. The organic material was extracted with dichloromethane and dried with anhydrous Na_2SO_4, the solvent was distilled off, and the resulting residue was subjected to column chromatography on silica gel with PE/EtOAc (10:1). The reaction proceeded analogously with slightly better yields (Table 2) when the water was replaced by ethanol, possibly due to better solubility of the reactants. Finally, replacement of the hydrochloric acid by $BF_3{\cdot}Et_2O$ did not produce any substantial change in the product yield.

1-Acetyl-3-phenyl-3-azabicyclo[3.3.1]nonan-9-one (3a): Yield: 0.231 g, 90% (93% in ethanol). R_f = 0.22 (PE/EtOAc, 10:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.62 (m, J = 13.1, 6.6, 5.8, 5.4, 2.8 Hz, 1 H, 7-H$_{eq}$), 2.15–2.32 (m, 3 H, 6-CH$_2$, 8-H$_{eq}$), 2.28 (s, 3 H, COMe), 2.43 (m, J = 13.6, 11.6, 5.8, 2.3 Hz, 1 H, 8-H$_{ax}$), 2.57 (m, J = 13.1, 11.6, 11.5, 5.5, 4.5 Hz, 1 H, 7-H$_{ax}$), 2.60 (m, J = 5.0, 4.2, 3.7, 2.5 Hz, 1 H, 5-H$_{eq}$), 3.32 (ddd, J = 11.9, 3.7, 1.9 Hz, 1 H, 4-H$_{ax}$), 3.52 (dd, J = 12.4, 2.0 Hz, 1 H, 2-H$_{ax}$), 3.90 (ddd, J = 11.9, 2.5, 2.3 Hz, 1 H, 4-H$_{eq}$), 3.96 (dd, J = 12.4, 2.3 Hz, 1 H, 2-H$_{eq}$), 6.86 (tt, J = 7.3, 1.1 Hz, 1 H, 4′-H), 6.94 (m, J = 8.3, 1.75, 1.1, 0.5 Hz, 2 H, 2′-H, 6′-H), 7.27 (m, J = 8.3, 7.3, 2.6, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9 (C-7), 28.0 (Me), 34.0 (C-6), 36.5 (C-8), 47.4 (C-5), 56.5 (C-4), 57.7 (C-2), 62.6 (C-1), 116.3 (C-2′, C-6′), 119.8 (C-4′), 129.2 (C-3′, C-5′), 149.5 (C-1′), 206.9 (1-CO), 213.9 (C-9) ppm. IR (neat): $\tilde{\nu}$ = 1712, 1718 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 312 (50) [M + MeOH + Na]$^{+\cdot}$, 280 (100) [M + Na]$^{+\cdot}$. $C_{16}H_{19}NO_2$ (257.33): calcd. C 74.68, H 7.44, N 5.44; found C 74.25, H 7.33, N 5.57.

1-Acetyl-3-(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (3b): Yield: 0.256 g, 89% (91% in ethanol). R_f = 0.24 (PE/EtOAc, 10:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.65 (m, J = 13.1, 6.1, 4.5, 3.0, 3.0 Hz, 1 H, 7-H$_{eq}$), 2.15–2.35 (m, 3 H, 6-CH$_2$, 8-H$_{eq}$), 2.29 (s, 3 H, COMe), 2.44 (m, J = 13.7, 11.6, 6.1, 1.7 Hz, 1 H, 8-H$_{ax}$), 2.60 (m, J = 4.5, 3.5, 3.0, 3.0 Hz, 1 H, 5-H$_{eq}$), 2.68 (m, J = 13.1, 11.6, 11.1, 6.0, 5.1 Hz, 1 H, 7-H$_{ax}$), 3.30 (ddd, J = 11.5, 3.0, 1.2 Hz, 1 H, 4-H$_{ax}$), 3.48 (dd, J = 12.2, 1.7 Hz, 1 H, 2-H$_{ax}$), 3.75 (ddd, J = 11.5, 3.0, 2.2 Hz, 1 H, 4-H$_{eq}$), 3.77 (s, 3 H, OMe), 3.81 (dd, J = 12.2, 2.2 Hz, 1 H, 2-H$_{eq}$), 6.86 (m, J = 8.8, 2.7, 2.4, 0.5 Hz, 2 H, 3′-H, 5′-H), 6.92 (m, J = 8.8, 2.7, 2.4, 0.5 Hz, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.1 (C-7), 28.1 (Me), 34.0 (C-6), 36.4 (C-8), 47.5 (C-5), 55.6 (OMe), 58.0 (C-4), 59.1 (C-2), 62.7 (C-1), 114.6 (C-3′, C-5′), 118.6 (C-2′, C-6′), 143.8 (C-1′), 154.0 (C-4′), 207.2 (1-CO), 214.4 (C-9) ppm. IR (neat): $\tilde{\nu}$ = 1717, 1704 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 342 (80) [M + Na + MeOH]$^{+\cdot}$, 310 (100) [M + Na]$^{+\cdot}$. $C_{17}H_{21}NO_3$ (287.35): calcd. C 71.06, H 7.37, N 4.87; found C 71.25, H 7.43, N 4.67.

1-Acetyl-3-(4-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one (3c): Yield: 0.239 g, 88% (91% in ethanol). R_f = 0.24 (PE/EtOAc, 9:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.58–1.72 (m, 1 H, 7-H$_{eq}$), 2.20–2.35 (m, 3 H, 6-CH$_2$, 8-H$_{eq}$), 2.28 (s, 3 H, Me), 2.30 (s, 3 H, Me), 2.39–2.52 (m, 1 H, 8-H$_{ax}$), 2.56–2.70 (m, 1 H, 7-H$_{ax}$), 2.58–2.63 (m, 1 H, 5-H$_{eq}$), 3.32 (dd, J = 11.8, 3.3 Hz, 1 H, 4-H$_{ax}$), 3.50 (dd, J = 12.2, 1.9 Hz, 1 H, 2-H$_{ax}$), 3.87 (ddd, J = 11.8, 2.3, 2.0 Hz, 1 H, 4-H$_{eq}$), 3.91 (dd, J = 12.2, 2.3 Hz, 1 H, 2-H$_{eq}$), 6.88 (m, J = 8.2, 2.4, 1.9, 0.5 Hz, 2 H, 2′-H, 6′-H), 7.11 (m, J = 8.2, 2.4, 1.9, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.0 (C-7), 20.4 (Me), 28.1 (Me), 34.1 (C-6), 36.5 (C-8), 47.5 (C-5), 57.0 (C-4), 58.1 (C-2), 62.7 (C-1), 116.6 (C-2′, C-6′), 129.5 (C-4′), 129.8 (C-3′, C-5′), 147.3 (C-1′), 207.3 (1-CO), 214.4 (C-9) ppm. IR (neat): $\tilde{\nu}$ = 1713, 1718 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 326 (60) [M + Na + MeOH]$^{+\cdot}$, 294 (100) [M + Na]$^{+\cdot}$. $C_{17}H_{21}NO_2$ (271.35): calcd. C 75.25, H 7.80, N 5.16; found C 75.06, H 7.93, N 5.29.

1-Acetyl-3-(2,4-dimethylphenyl)-3-azabicyclo[3.3.1]nonan-9-one (3d): Yield: 0.254 g, 89% (91% in ethanol). R_f = 0.30 (PE/EtOAc, 10:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.62–1.75 (m, 1 H, 7-H$_{eq}$), 2.08–2.17 (m, 1 H, 6-H), 2.17–2.25 (m, 2 H, 6-H, 8-H$_{eq}$), 2.27 (s, 3 H, Me), 2.28 (s, 3 H, Me), 2.41 (s, 3 H, 2′-Me), 2.33–2.45 (m, 1 H, 8-H$_{ax}$), 2.59–2.65 (m, 1 H, 5-H$_{eq}$), 2.85–3.05 (m, 1 H, 7-H$_{ax}$), 3.27 (ddd, J = 11.5, 3.8, 0.8 Hz, 1 H, 4-H$_{ax}$), 3.36 (ddd, J = 12.5, 2.4, 1.2 Hz, 1 H, 2-H$_{ax}$), 3.43 (dd, J = 11.5, 1.0 Hz, 1 H, 4-H$_{eq}$), 3.45 (dd, J = 12.5, 1.0 Hz, 1 H, 2-H$_{eq}$), 7.01 (dd, J = 9.0, 1.8 Hz, 1 H, 5′-H), 7.01 (d, J = 9.0 Hz, 1 H, 6′-H), 7.03 (d, J = 1.8 Hz, 1 H, 3′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.6 (Me), 20.2 (C-7), 20.7 (4′-Me), 28.0 (Me), 33.2 (C-6), 35.4 (C-8), 47.8 (C-5), 59.4 (C-4), 60.2 (C-2), 63.2 (C-1), 119.9 (C-6′), 127.3 (C-5′),* 132.2 (C-3′),* 132.6 (C-4′), 147.2 (C-1′), 207.2 (1-CO), 214.7 (C-9) ppm. * The assignments may be interchanged. IR (neat): $\tilde{\nu}$ = 1715, 1717 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 308 (100) [M + Na]$^{+\cdot}$. $C_{18}H_{23}NO_2$ (285.38): calcd. C 75.76, H 8.12, N 4.91; found C 75.92, H 8.00, N 4.80.

1-Acetyl-3-(4-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (3e): Yield: 0.263 g, 90% (92% in ethanol). R_f = 0.32 (PE/EtOAc, 10:1); yellow solid, m.p. 79–80 °C. ^{1}H NMR ($CDCl_3$): δ = 1.60–1.70 (m, 1 H, 7-H$_{eq}$), 2.15–2.35 (m, 3 H, 6-CH$_2$, 8-H$_{eq}$), 2.30 (s, 3 H, Me), 2.40–2.52 (m, 1 H, 8-H$_{ax}$), 2.50–2.63 (m, 1 H, 7-H$_{ax}$), 2.60–2.65 (m, 1 H, 5-H$_{eq}$), 3.33 (dd, J = 11.9, 3.3 Hz, 1 H, 4-H$_{ax}$), 3.52 (dd, J = 12.4, 1.9 Hz, 1 H, 2-H$_{ax}$), 3.87 (ddd, J = 11.9, 2.4, 2.2 Hz, 1 H, 4-H$_{eq}$), 3.92 (ddd, J = 12.4, 2.4, 2.0 Hz, 1 H, 2-H$_{eq}$), 6.87 (m, J = 8.60, 2.5, 2.0, 0.5 Hz, 2 H, 2′-H, 6′-H), 7.23 (m, J = 8.60, 2.5, 2.0, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9 (C-7), 28.1 (Me), 34.1 (C-6), 36.5 (C-8), 47.2 (C-5), 56.5 (C-4), 57.6 (C-2), 60.2 (C-1), 117.4 (C-2′, C-6′), 124.7 (C-4′), 129.1 (C-3′, C-5′), 148.0 (C-1′), 207.1 (C-1), 213.7 (C-9) ppm. IR (KBr): $\tilde{\nu}$ = 1710, 1716 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 314/316 (100) [M + Na]$^{+\cdot}$. $C_{16}H_{18}ClNO_2$ (291.77): calcd. C 65.86, H 6.22, N 4.80; found C 65.68, H 6.43, N 4.67.

1-Acetyl-3-(4-bromophenyl)-3-azabicyclo[3.3.1]nonan-9-one (3f): Yield: 0.303 g, 89% (91% in ethanol). R_f = 0.32 (PE/EtOAc, 10:1); white crystals; m.p. 76–78 °C (diethyl ether/PE). ^{1}H NMR ($CDCl_3$): δ = 1.60–1.70 (m, 1 H, 7-H$_{eq}$), 2.17–2.29 (m, 3 H, 6-CH$_2$, 8-H$_{eq}$), 2.30 (s, 3 H, COMe), 2.40–2.58 (m, 2 H, 7-H$_{ax}$, 8-H$_{ax}$), 2.59–2.65 (m, 1 H, 5-H$_{eq}$), 3.33 (ddd, J = 11.8, 3.3. 0.8 Hz, 1 H, 4-H$_{ax}$), 3.52 (dd, J = 12.1, 2.0 Hz, 1 H, 2-H$_{ax}$), 3.88 (ddd, J = 11.8, 2.2, 2.1 Hz, 1 H, 4-H$_{eq}$), 3.93 (ddd, J = 12.1, 2.2, 2.0 Hz, 1 H, 2-H$_{eq}$), 6.82 (m, J = 8.7, 3.3, 2.4, 0.5 Hz, 2 H, 2′-H, 6′-H), 7.36 (m, J = 8.7, 3.3, 2.4, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.8 (C-7), 28.1 (Me), 34.0 (C-6), 36.5 (C-8), 47.2 (C-5), 56.3 (C-4), 57.4 (C-2), 62.3 (C-1), 111.9 (C-4′), 117.7 (C-2′, C-6′), 132.0 (C-3′, C-5′), 148.4 (C-1′), 207.0 (1-CO), 213.6 (C-9) ppm. IR (KBr): $\tilde{\nu}$ = 1700, 1714 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 358/360 (100) [M + Na]$^{+\cdot}$. $C_{16}H_{18}BrNO_2$ (336.22): calcd. C 57.16, H 5.40, N 4.17; found C 56.97, H 5.29, N 4.03.

Reaction of 4-Methoxyaniline, Formaldehyde and 2-Acetylcyclohexanone: A formaldehyde solution (37% in water, 9 mmol) was added to a solution of 4-methoxyaniline (**2b**, 1.0 mmol) in ethanol (15 mL), and the mixture was warmed gently for 5 min to dissolve all the reactants. 2-Acetylcyclohexanone (2.0 mmol) was added, and the mixture was heated under reflux for 5 min and was then stirred at room temperature overnight. The solvent was distilled off, and the resulting residue was subjected to column chromatography on silica gel with PE/EtOAc (10:1) as eluent to give, in elution order:

(i) 1-Acetyl-3-(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (3b): Yield 0.014 g (73%).

(ii) 1-Acetyl-3-(4-methoxyphenyl)-5-{[(4-methoxyphenyl)amino]-methyl}-3-azabicyclo[3.3.1]nonan-9-one (4b): Yield: 0.093 g, 22%. R_f = 0.11 (PE/EtOAc, 10:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.62–1.72 (m, 1 H, 7-H$_{eq}$), 2.12–2.23 (m, 2 H, 6-CH$_2$), 2.24–2.32 (m, 1 H, 8-H$_{eq}$), 2.30 (s, 3 H, COMe), 2.40–2.51 (m, 1 H, 8-H$_{ax}$), 2.65–2.80 (m, 1 H, 7-H$_{ax}$), 3.12 (d, J = 13.1 Hz, 1 H, NCH), 3.15 (d, J = 13.1 Hz, 1 H, NCH), 3.31 (dd, J = 11.5, 1.0 Hz, 1 H, 4-H$_{ax}$), 3.55 (dd, J = 11.5, 1.0 Hz, 1 H, 2-H$_{ax}$), 3.64 (dd, J = 11.5, 2.1 Hz, 1 H, 4-H$_{eq}$), 3.74–3.79 (m, masked by OMe signals, 2 H, 2-H$_{eq}$, NH), 3.75 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 6.61 (m, J = 8.4, 3.2, 2.4, 0.5 Hz, 2 H, 2′′-H, 6′′-H), 6.78 (d, J = 8.4, 3.2, 2.4, 0.5 Hz, 2 H, 3′′-H, 5′′-

H), 6.84 (m, J = 8.4, 2.5, 2.0, 0.5 Hz, 2 H, 3′-H, 5′-H), 6.92 (m, J = 8.4, 2.5, 2.0, 0.5 Hz, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.0 (C-7), 28.1 (Me), 36.3 (C-8), 38.1 (C-6), 49.5 (NCH_2), 51.5 (C-5), 55.6 (OMe), 55.8 (OMe), 59.1 (C-2), 61.3 (C-4), 62.9 (C-1), 114.5 (C-2′′, C-6′′), 114.6 (C-3′, C-5′), 114.9 (C-3′′, C-5′′), 118.8 (C-2′, C-6′), 142.9 (C-1′′), 143.7 (C-1′), 152.2 (C-4′′), 154.1 (C-4′), 207.1 (1-CO), 215.6 (C-9) ppm. IR (neat): $\tilde{\nu}$ = 1710, 1704 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 310 (100) [M + Na]$^{+\cdot}$. $C_{25}H_{30}N_2O_4$ (422.52): calcd. C 71.07, H 7.16, N 6.63; found C 70.85, H 7.33, N 6.77. When the reflux time was increased to 5 min, **3b** was isolated in 42% and **4b** in 55% yield, whereas – after an even longer reflux time (20 min) – the yield of **3b** was reduced to 5% and that of **4b** was increased to 81%.

General Procedure for the Reaction of 4-Chloroaniline, Formaldehyde and 2-Acetylcyclohexanone without an Acid Catalyst: A formaldehyde solution (37%, 9 mmol) was added to a solution of 4-chloroaniline (**2e**, 1.0 mmol) in ethanol (15 mL), and the mixture was warmed gently for 5 min to dissolve all the reactants. 2-Acetylcyclohexanone (2.0 mmol) was added, and the mixture was heated under reflux for 5 min and then stirred at room temperature overnight. The solvent was evaporated, and the resulting residue was subjected to column chromatography on silica gel with PE/EtOAc (10:1) as eluent to give, in elution order:

(i) 1-Acetyl-3-(4-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (3e): Yield 0.015 g (5%).

(ii) 2-Acetyl-2-{[(4-chlorophenyl)amino]methyl}cyclohexanone (5e): Yield: 0.263 g, 91%. R_f = 0.14 (PE/EtOAc, 10:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.55–1.74 (m, 2 H, 4-H, 5-H), 1.75–1.85 (m, 2 H, 4-H, 5-H), 1.97–2.08 (m, 1 H, 3-H), 2.15 (s, 3 H, Me), 2.42–2.52 (m, 3 H, 3-H, 6-CH_2), 3.31 (dd, J = 12.7, 3.5 Hz, 1 H, 7-CH), 3.41 (dd, J = 12.7, 7.6 Hz, 1 H, 7-CH), 4.18 (br. s, NH), 6.53 (m, J = 8.5, 2.7, 2.2, 0.5 Hz, 2 H, 2′-H, 6′-H), 7.09 (m, J = 8.5, 2.7, 2.2, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.9 (C-4), 26.1 (Me), 26.7 (C-5), 33.4 (C-3), 41.5 (C-6), 48.2 (NCH_2), 67.7 (C-2), 114.4 (C-2′, C-6′), 122.5 (C-4′), 128.9 (C-3′, C-5′), 146.6 (C-1′), 207.2 (2-CO), 210.8 (C-1) ppm. IR (neat): $\tilde{\nu}$ = 1705, 1712 (C=O) cm^{-1}. MS (LCMS): m/z (%) = 302/304 (100) [M + Na]$^{+\cdot}$. $C_{15}H_{18}ClNO_2$ (279.76): calcd. C 64.40, H 6.49, N 5.01; found C 64.60, H 6.43, N 5.07.

General Procedure for the Reactions between the Azabicyclo-[3.3.1]nonan-9-ones 3 and Hydrazine. Syntheses of Compounds 6 and 7: A solution of the azabicyclo[3.3.1]nonan-9-one **3** (1.0 mmol) and hydrazine (1.2 mmol) in absolute ethanol (15 mL) was stirred at room temperature for 2 h, after which the starting material had been consumed. The solvent was distilled off, and the resulting residue was subjected to column chromatography on silica gel with PE/EtOAc (3:1) to give, in elution order, compounds **6** and **7**.

3-Methyl-9-phenyl-4,5,6,7-tetrahydro-3a,7-(methanoiminomethano)-indazole (6a): Yield: 0.203 g, 80%. R_f = 0.41 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.06–1.22 (m, 1 H, 6-H_{ax}), 1.53–1.72 (m, 1 H, 7-H_{ax}), 1.77–1.87 (m, 1 H, 6-H_{eq}), 1.98–2.10 (m, 1 H, 7-H_{eq}), 2.20 (s, 3 H, Me), 2.27–2.42 (m, 1 H, 8-H_{ax}), 2.50 (ddd, J = 15.6, 6.5, 0.8 Hz, 1 H, 8-H_{eq}), 2.75–2.84 (m, 1 H, 5-H_{eq}), 2.84 (t, J = 9.7 Hz, 1 H, 4-H_{ax}), 3.98 (dd, J = 9.7, 8.2 Hz, 1 H, 4-H_{eq}), 5.01 (d, J = 11.9 Hz, 1 H, 2-H_{ax}), 5.65 (d, J = 11.9 Hz, 1 H, 2-H_{eq}), 6.94 (t, J = 7.3 Hz, 1 H, 4′-H), 7.09 (d, J = 7.8 Hz, 2 H, 2′-H, 6′-H), 7.27 (dd, J = 7.8, 7.3 Hz, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.1 (Me), 19.6 (C-8), 23.1 (C-7), 25.7 (C-6), 30.7 (C-5), 53.2 (C-4), 65.3 (C-2), 112.6 (C-1), 118.1 (C-2′, C-6′), 121.2 (C-4′), 129.4 (C-3′, C-5′), 142.4 (C-9), 147.8 (C-1′), 148.6 (C-12) ppm. IR (neat): $\tilde{\nu}$ = 1599 (C=N and/or C=C) cm^{-1}. MS (LCMS): m/z (%) = 308 (40) [M + Na + MeOH]$^{+\cdot}$, 276 (20) [M + Na]$^{+\cdot}$, 254 (100) [M + H]$^{+\cdot}$. $C_{16}H_{19}N_3$ (253.34): calcd. C 75.85, H 7.56, N 16.59; found C 75.95, H 7.49, N 16.67.

7-(Anilinomethyl)-3-methyl-4,5,6,7-tetrahydro-2*H*-indazole (7a): Yield: 0.029 g, 12%. R_f = 0.30 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.48–1.62 (m, 1 H, 6-H_{eq}), 1.62–1.76 (m, 1 H, 5-H_{eq}), 1.87–2.07 (m, 2 H, 5-H_{ax}, 6-H_{ax}), 2.18 (s, 3 H, 3-Me), 2.35–2.40 (m, 2 H, 4-CH_2), 3.02–3.09 (m, 1 H, 7-H_{eq}), 3.29 (d, J = 6.6 Hz, 2 H, 1′-CH_2), 5.62 (br. s, 2 H, 2 NH), 6.65–6.77 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.14–7.23 (m, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.5 (3-Me), 20.1 (C-4), 22.0 (C-5), 27.7 (C-6), 33.6 (C-7), 48.8 (7-CH_2), 113.4 (C-2′, C-6′), 113.5 (C-3a), 117.8 (C-4′), 129.3 (C-3′, C-5′), 139.9 (C-3), 147.0 (C-7a), 148.4 (C-1′) ppm. IR (neat): $\tilde{\nu}$ = 3198, 3148 (N–H) cm^{-1}. MS (LCMS): m/z (%) = 264 (100) [M + Na]$^{+\cdot}$, 242 (80) [M + H]$^{+\cdot}$. $C_{15}H_{19}N_3$ (241.33): calcd. C 74.65, H 7.94, N 17.41; found C 74.25, H 7.89, N 17.57.

3-Methyl-9-(4-tolyl)-4,5,6,7-tetrahydro-3a,7-(methanoiminomethano)indazole (6c): Yield: 0.200 g, 75%. R_f = 0.38 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.05–1.22 (m, 1 H, 6-H_{ax}), 1.53–1.72 (m, 1 H, 7-H_{ax}), 1.73–1.85 (m, 1 H, 6-H_{eq}), 1.97–2.09 (m, 1 H, 7-H_{eq}), 2.20 (s, 3 H, Me), 2.28 (s, 3 H, 4′-Me), 2.28–2.42 (m, 1 H, 8-H_{ax}), 2.50 (ddd, J = 15.6, 6.5, 0.8 Hz, 8-H_{eq}), 2.75–2.84 (m, 1 H, 5-H_{eq}), 2.85 (t, J = 9.7 Hz, 1 H, 4-H_{ax}), 3.91 (dd, J = 9.7, 8.2 Hz, 1 H, 4-H_{eq}), 5.01 (d, J = 11.9 Hz, 1 H, 2-H_{ax}), 5.65 (d, J = 11.9 Hz, 1 H, 2-H_{eq}), 7.01 (d, J = 8.6 Hz, 2′-H, 6′-H), 7.08 (d, J = 8.6 Hz, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.1 (Me), 19.7 (C-8), 20.5 (4′-Me), 23.1 (C-7), 25.7 (C-6), 30.5 (C-5), 53.6 (C-4), 65.7 (C-2), 112.6 (C-1), 118.6 (C-2′, C-6′), 129.9 (C-3′, C-5′), 130.9 (C-4′), 142.5 (C-9), 146.3 (C-1′), 147.7 (C-12) ppm. IR (neat): $\tilde{\nu}$ = 1606 (C=N, C=C) cm^{-1}. MS (LCMS): m/z (%) = 290 (30) [M + Na]$^{+\cdot}$, 268 (100) [M + H]$^{+\cdot}$. $C_{17}H_{21}N_3$ (267.37): calcd. C 76.37, H 7.92, N 15.72; found C 76.25, H 7.99, N 16.65.

3-Methyl-7-{[(4-tolyl)amino]methyl}-4,5,6,7-tetrahydro-2*H*-indazole (7c): Yield: 0.054 g, 21%. R_f = 0.27 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.42–1.57 (m, 1 H, 6-H_{eq}), 1.58–1.73 (m, 1 H, 5-H_{eq}), 1.87–2.06 (m, 2 H, 5-H_{ax}, 6-H_{ax}), 2.18 (s, 3 H, 3-Me), 2.24 (s, 3 H, 4′-Me), 2.35–2.40 (m, 2 H, 4-CH_2), 2.96–3.08 (m, 1 H, 7-H_{eq}), 3.27 (dd, J = 6.5, 2.6 Hz, 2 H, 7-CH_2), 4.80 (br. s, 2 H, 2 NH), 6.62 (d, J = 8.3 Hz, 2 H, 2′-H, 6′-H), 6.99 (d, J = 8.3 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.6 (3-Me), 20.1 (C-4), 20.4 (4′-Me), 22.1 (C-5), 27.7 (C-6), 33.6 (C-7), 49.4 (7-CH_2), 113.5 (C-3a), 113.8 (C-2′, C-6′), 127.2 (C-4′), 129.8 (C-3′, C-5′), 140.5 (C-3), 146.0 (C-1′), 146.7 (C-7a) ppm. IR (neat): $\tilde{\nu}$ = 3195, 3150 (N–H) cm^{-1}. MS (LCMS): m/z (%) = 278 (65) [M + Na]$^{+\cdot}$, 256 (100) [M + H]$^{+\cdot}$. $C_{16}H_{21}N_3$ (255.36): calcd. C 75.26, H 8.29, N 16.46; found C 75.13, H 8.19, N 16.55.

9-(4-Bromophenyl)-3-methyl-4,5,6,7-tetrahydro-3a,7-(methanoiminomethano)indazole (6f): Yield: 0.242 g, 73%. R_f = 0.38 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.06–1.20 (m, 1 H, 6-H_{ax}), 1.56–1.72 (m, 1 H, 7-H_{ax}), 1.79–1.86 (m, 1 H, 6-H_{eq}), 2.00–2.10 (m, 1 H, 7-H_{eq}), 2.19 (s, 3 H, Me), 2.26–2.42 (m, 1 H, 8-H_{ax}), 2.50 (ddd, J = 15.6, 6.5, 0.8 Hz, 1 H, 8-H_{eq}), 2.75–2.84 (m, 1 H, 5-H_{eq}), 2.87 (t, J = 11.5 Hz, 1 H, 4-H_{ax}), 3.93 (dd, J = 11.5, 8.2 Hz, 1 H, 4-H_{eq}), 4.98 (d, J = 11.9 Hz, 1 H, 2-H_{ax}), 5.58 (d, J = 11.9 Hz, 1 H, 2-H_{eq}), 6.96 (d, J = 8.9 Hz, 2′-H, 6′-H), 7.36 (d, J = 8.9 Hz, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.1 (Me), 19.7 (C-8), 23.1 (C-7), 25.7 (C-6), 30.8 (C-5), 53.2 (C-4), 65.3 (C-2), 112.9 (C-1), 113.6 (C-4′), 119.8 (C-2′, C-6′), 132.3 (C-3′, C-5′), 142.3 (C-9), 147.8 (C-1′), 148.1 (C-12) ppm. IR (neat): $\tilde{\nu}$ = 1591 (C=N, C=C) cm^{-1}. MS (LCMS): m/z (%) = 386/388 (100) [M + Na + MeOH]$^{+\cdot}$, 332/334 (60) [M + H]$^{+\cdot}$. $C_{16}H_{18}BrN_3$ (332.24): calcd. C 57.84, H 5.46, N 12.65; found C 58.06, H 5.32, N 12.55.

7-{[(4-Bromophenyl)amino]methyl}-3-methyl-4,5,6,7-tetrahydro-2*H*-indazole (7f): Yield: 0.070 g, 22%. R_f = 0.35 (PE/EtOAc, 9:1); yellow crystals, m.p. 115–117 °C. ^{1}H NMR ($CDCl_3$): δ = 1.48–1.61 (m, 1 H, 6-H_{eq}), 1.62–1.73 (m, 1 H, 5-H_{eq}), 1.76–2.04 (m, 2 H, 5-H_{ax}, 6-H_{ax}), 2.18 (s, 3 H, 3-Me), 2.36–2.51 (m, 2 H, 4-CH_2), 2.96–3.07 (m, 1 H, 7-H_{eq}), 3.20 (dd, J = 12.1, 8.7 Hz, 1 H, 7-CH), 3.28 (dd, J = 12.1, 6.2 Hz, 1 H, 7-CH), 5.33 (br. s, 2 H, 2 NH), 6.54 (d, J = 8.9 Hz, 2 H, 2′-H, 6′-H), 7.23 (d, J = 8.9 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.2 (Me), 20.1 (C-4), 22.0 (C-5), 27.8 (C-6), 33.6 (C-7), 48.8 (7-CH_2), 113.6 (C-3a), 114.9 (C-2′, C-6′), 127.2 (C-4′), 132.0 (C-3′, C-5′), 138.5 (C-3), 147.6 (C-1′), 148.5 (C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3413, 3198 (N–H), 1618, 1593 (C=N, C=C) cm^{-1}. MS (LCMS): *m*/*z* (%) = 374/376 (40) [M + Na + MeOH]$^{+\cdot}$, 342/344 (100) [M + Na]$^{+\cdot}$, 320/322 (100) [M + H]$^{+\cdot}$. $C_{15}H_{18}BrN_3$ (320.23): calcd. C 56.26, H 5.67, N 13.12; found C 56.38, H 5.74, N 13.05. Compounds **6f** and **7f** were also obtained in about the same yields and ratios when the reactions were performed at –10 °C or at –78 °C (Table 3).

General Procedure for the Reactions between Compounds 3 and Methylhydrazine. Syntheses of Compounds 8 and 9: A solution of **3a** (1.0 mmol) and methylhydrazine (1.2 mmol) in anhydrous ethanol (15 mL) was stirred at room temperature for 36 h, after which the starting material had been consumed. The solvent was distilled off, and the resulting residue was subjected to column chromatography on silica gel with PE/EtOAc (3:1) to give, in elution order, compounds **8** and **9**.

7-[(Anilino)methyl]-2,3-dimethyl-4,5,6,7-tetrahydro-2*H*-indazole (8a): Yield: 0.120 g, 47%. R_f = 0.32 (PE/EtOAc, 3:1); yellow crystals, m.p. 119–121 °C. ^{1}H NMR ($CDCl_3$): δ = 1.52–1.70 (m, 2 H, 5-H_{ax}, 6-H_{ax}), 1.82–1.90 (m, 1 H, 5-H_{eq}), 1.90–2.00 (m, 1 H, 6-H_{eq}), 2.11 (s, 3 H, 3-Me), 2.33–2.41 (m, 2 H, 4-CH_2), 2.95–3.05 (m, 1 H, 7-H_{eq}), 3.28 (d, J = 7.2 Hz, 2 H, 7-CH_2), 3.71 (s, 3 H, 2-Me), 4.50 (br. s, 1 H, NH), 6.62–6.72 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.10–7.17 (m, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.4 (3-Me), 20.6 (C-4), 21.9 (C-5), 28.2 (C-6), 33.6 (C-7), 36.0 (2-Me), 48.6 (7-CH_2), 113.2 (C-2′, C-6′), 113.8 (C-3a), 117.0 (C-4′), 129.2 (C-3′, C-5′), 134.4 (C-3), 149.0 (C-1′), 149.5 (C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3319 (NH), 1606 (C=C, C=N) cm^{-1}. MS (LCMS): *m*/*z* (%) = 278 (80) [M + Na]$^{+\cdot}$, 256 (100) [M + H]$^{+\cdot}$. $C_{16}H_{21}N_3$ (255.36): calcd. C 75.26, H 8.29, N 16.46; found C 75.38, H 8.35, N 16.31.

7-(Anilino)methyl-1,3-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole (9a): Yield: 0.112 g, 44%. R_f = 0.27 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.65–1.82 (m, 3 H, 5-CH_2, 6-H_{ax}), 1.95–2.08 (m, 1 H, 6-H_{eq}), 2.15 (s, 3 H, 3-Me), 2.25–2.45 (m, 1 H, 4-H), 2.42–2.52 (m, 1 H, 4-H), 2.98–3.08 (m, 1 H, 7-H_{eq}), 3.19 (dd, J = 13.0, 8.8 Hz, 1 H, 7-CH), 3.31 (dd, J = 13.0, 8.0 Hz, 1 H, 7-CH), 3.70 (s, 3 H, 1-Me), 4.02 (br. s, 1 H, NH), 6.56–6.63 (m, 2 H, 2′-H, 6′-H), 6.66–6.72 (m, 1 H, 4′-H), 7.12–7.19 (m, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.4 (3-Me), 18.4 (C-4), 19.9 (C-5), 25.4 (C-6), 31.1 (C-7), 35.8 (2-Me), 46.2 (7-CH_2), 112.3 (C-2′, C-6′), 114.3 (C-3a), 117.2 (C-4′), 129.2 (C-3′, C-5′), 139.5 (C-7a), 144.5 (C-3), 147.6 (C-1′) ppm. IR (neat): $\tilde{\nu}$ = 3308 (N–H), 1602 (C=N, C=C) cm^{-1}. MS (LCMS): *m*/*z* (%) = 278 (70) [M + Na]$^{+\cdot}$, 256 (100) [M + H]$^{+\cdot}$. $C_{16}H_{21}N_3$ (255.36): calcd. C 75.26, H 8.29, N 16.46; found C 75.18, H 8.13, N 16.30.

2,3-Dimethyl-7-{[(4-tolyl)amino]methyl}-4,5,6,7-tetrahydro-2*H*-indazole (8c): Yield: 0.110 g, 41%. R_f = 0.32 (PE/EtOAc, 3:1); brown crystals, m.p. 40–42 °C. ^{1}H NMR ($CDCl_3$): δ = 1.50–1.64 (m, 1 H, 6-H_{ax}), 1.58–1.70 (m, 1 H, 5-H_{ax}), 1.83–1.92 (m, 1 H, 5-H_{eq}), 1.88–2.01 (m, 1 H, 6-H_{eq}), 2.11 (s, 3 H, 3-Me), 2.21 (s, 3 H, 4′-Me), 2.33–2.42 (m, 2 H, 4-CH_2), 2.94–3.05 (m, 1 H, 7-H_{eq}), 3.26 (dd, J = 11.3, 4.5 Hz, 1 H, 7-CH), 3.28 (dd, J = 11.3, 10.0 Hz, 1 H, 7-CH), 3.72 (s, 3 H, 2-Me), 4.50 (br. s, 1 H, NH), 6.62 (d, J = 8.4 Hz, 2 H, 2′-H, 6′-H), 6.96 (d, J = 8.4 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.3 (3-Me), 20.3 (4′-Me), 20.4 (C-4), 21.8 (C-5), 28.0 (C-6), 33.5 (C-7), 35.8 (2-Me), 48.9 (7-CH_2), 113.3 (C-2′, C-6′), 113.7 (C-3a), 126.0 (C-4′), 129.8 (C-3′, C-5′), 134.2 (C-3), 146.6 (C-1′), 149.4 (C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3362 (NH), 1617 (C=C, C=N) cm^{-1}. MS (LCMS): *m*/*z* (%) = 270 (100) [M + H]$^{+\cdot}$. $C_{17}H_{23}N_3$ (269.38): calcd. C 75.80, H 8.61, N 15.60; found C 75.88, H 8.52, N 15.47.

1,3-Dimethyl-7-{[(4-tolyl)amino]methyl}-4,5,6,7-tetrahydro-1*H*-indazole (9c): Yield: 0.112 g, 42%. R_f = 0.27 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.65–1.78 (m, 3 H, 5-CH_2, 6-H_{ax}), 1.96–2.04 (m, 1 H, 6-H_{eq}), 2.16 (s, 3 H, 3-Me), 2.23 (s, 3 H, 4′-Me), 2.25–2.52 (m, 2 H, 4-CH_2), 3.00–3.08 (m, 1 H, 7-H_{eq}), 3.24 (dd, J = 13.0, 9.1 Hz, 1 H, 7-CH), 3.31 (dd, J = 13.0, 4.9 Hz, 1 H, 7-CH), 3.72 (s, 3 H, 1-Me), 4.02 (br. s, 1 H, NH), 6.54 (m, J = 8.1, 2.5, 2.0, 0.5 Hz, 2 H, 2′-H, 6′-H), 6.99 (m, J = 8.1, 2.5, 2.0, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.5 (3-Me), 18.5 (C-4), 20.0 (C-5), 20.3 (4′-Me), 25.5 (C-6), 31.3 (C-7), 35.8 (2-Me), 46.7 (7-CH_2), 112.7 (C-2′, C-6′), 114.4 (C-3a), 126.6 (C-4′), 129.8 (C-3′, C-5′), 139.7 (C-7a), 144.6 (C-3), 145.4 (C-1′) ppm. IR (neat): $\tilde{\nu}$ = 3310 (N–H), 1601 (C=N, C=C) cm^{-1}. MS (LCMS): *m*/*z* (%) = 292 (75) [M + Na]$^{+\cdot}$, 270 (100) [M + H]$^{+\cdot}$. $C_{17}H_{23}N_3$ (269.38): calcd. C 75.80, H 8.61, N 15.60; found C 75.70, H 8.54, N 15.40.

7-{[(4-Bromophenyl)amino]methyl}-2,3-dimethyl-4,5,6,7-tetrahydro-2*H*-indazole (8f): Yield: 0.211 g, 63%. R_f = 0.32 (PE/EtOAc, 3:1); yellowish crystals, m.p. 52–54 °C. ^{1}H NMR ($CDCl_3$): δ = 1.48–1.60 (m, 1 H, 6-H_{ax}), 1.60–1.72 (m, 1 H, 5-H_{ax}), 1.82–1.92 (m, 1 H, 5-H_{eq}), 1.90–2.02 (m, 1 H, 6-H_{eq}), 2.13 (s, 3 H, 3-Me), 2.36–2.41 (m, 2 H, 4-CH_2), 2.93–3.06 (m, 1 H, 7-H_{eq}), 3.20 (dd, J = 11.7, 7.7 Hz, 1 H, 7-CH), 3.26 (dd, J = 11.7, 6.5 Hz, 1 H, 7-CH), 3.73 (s, 3 H, 2-Me), 4.80 (br. s, 1 H, NH), 6.56 (m, J = 8.5, 2.7, 2.0, 0.5 Hz, 2 H, 2′-H, 6′-H), 7.22 (m, J = 8.5, 2.7, 2.0, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.4 (3-Me), 20.5 (C-4), 21.9 (C-5), 28.1 (C-6), 33.4 (C-7), 36.0 (2-Me), 48.6 (7-CH_2), 108.4 (C-4′), 113.8 (C-3a), 114.8 (C-2′, C-6′), 131.7 (C-3′, C-5′), 134.4 (C-3), 147.9 (C-1′), 149.3 (C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3332 (N–H), 1595 (C=N, C=C) cm^{-1}. MS (LCMS): *m*/*z* (%) = 388/390 (30) [M + Na + MeOH]$^{+\cdot}$, 356/358 (40) [M + Na]$^{+\cdot}$, 334/336 (40) [M + H]$^{+\cdot}$. $C_{16}H_{20}BrN_3$ (334.25): calcd. C 57.49, H 6.03, N 12.57; found C 57.60, H 5.89, N 12.42.

7-{[(4-Bromophenyl)amino]methyl}-1,3-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole (9f): Yield: 0.107 g, 32%. R_f = 0.27 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.65–1.82 (m, 3 H, 5-CH_2, 6-H_{ax}), 1.96–2.04 (m, 1 H, 6-H_{eq}), 2.16 (s, 3 H, 3-Me), 2.27–2.40 (m, 1 H, 4-H), 2.42–2.52 (m, 1 H, 4-H), 3.00–3.10 (m, 1 H, 7-H_{eq}), 3.22 (dd, J = 13.0, 8.5 Hz, 1 H, 7-CH), 3.30 (dd, J = 13.0, 5.2 Hz, 1 H, 7-CH), 3.72 (s, 3 H, 1-Me), 4.02 (br. s, 1 H, NH), 6.49 (m, J = 8.5, 2.7, 2.0, 0.5 Hz, 2 H, 2′-H, 6′-H), 7.26 (m, J = 8.5, 2.7, 2.0, 0.5 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.6 (3-Me), 18.7 (C-4), 20.1 (C-5), 25.7 (C-6), 31.3 (C-7), 36.1 (2-Me), 46.5 (7-CH_2), 109.1 (C-4′), 114.2 (C-2′, C-6′), 114.7 (C-3a), 132.1 (C-3′, C-5′), 139.4 (C-7a), 144.9 (C-3), 146.8 (C-1′) ppm. IR (neat): $\tilde{\nu}$ = 3305 (NH), 1601 (C=C, C=N) cm^{-1}. MS (LCMS): *m*/*z* (%) = 388/390 (50) [M + Na + MeOH]$^{+\cdot}$, 356/358 (100) [M + Na]$^{+\cdot}$, 334/336 (30) [M + H]$^{+\cdot}$. $C_{16}H_{20}BrN_3$ (334.25): calcd. C 57.49, H 6.03, N 12.57; found C 57.40, H 6.10, N 12.46.

Reaction between 3f and Hydroxylamine. Synthesis of Compounds 10f and 11f: A solution of **3f** (1.0 mmol) and hydroxylamine (1.2 mmol) in absolute ethanol (15 mL) was stirred at room temperature for 24 h (until the starting material had been consumed). The solvent was distilled off, and the resulting residue was sub-

jected to column chromatography on silica gel with PE/EtOAc (3:1) to give, in elution order:

(i) 7-{[(4-Bromophenyl)amino]methyl}-3-methyl-4,5,6,7-tetrahydro-2,1-benzisoxazole (10f): Yield: 0.132 g, 41%. R_f = 0.35 (PE/EtOAc, 3:1); yellow crystals, m.p. 60–62 °C. ^{1}H NMR ($CDCl_3$): δ = 1.42–1.60 (m, 1 H, 6-H_{ax}), 1.55–1.68 (m, 1 H, 5-H_{ax}), 1.85–1.95 (m, 1 H, 5-H_{eq}), 1.90–2.03 (m, 1 H, 6-H_{eq}), 2.29 (s, 3 H, 3-Me), 2.30–2.50 (m, 2 H, 4-CH_2), 3.00–3.10 (m, 1 H, 7-H_{eq}), 3.32 (d, J = 5.8 Hz, 2 H, 7-CH_2), 4.60 (br. s, 1 H, NH), 6.55 (d, J = 8.8 Hz, 2 H, 2′-H, 6′-H), 7.22 (d, J = 8.8 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.8 (3-Me), 18.8 (C-4), 21.3 (C-5), 27.0 (C-6), 33.1 (C-7), 47.3 (7-CH_2), 108.9 (C-4′), 110.5 (C-3a), 114.8 (C-2′, C-6′), 131.8 (C-3′, C-5′), 147.1 (C-1′), 162.8 (C-7a), 163.2 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3326 (NH) cm^{-1}. MS (LCMS): *m/z* (%) = 375/377 (80) $[M + Na + MeOH]^{+\cdot}$, 343/345 (100) $[M + Na]^{+\cdot}$, 321/323 (100) $[M + H]^{+\cdot}$. $C_{15}H_{17}BrN_2O$ (321.21): calcd. C 56.09, H 5.33, N 8.72; found C 56.21, H 5.38, N 8.61.

(ii) 3-(4-Bromophenyl)-1-(*N*-hydroxyethanimidoyl)-3-azabicyclo-[3.3.1]nonan-9-one (11f): Yield: 0.070 g, 20%. R_f = 0.43 (PE/EtOAc, 3:1); oil. ^{1}H NMR ($CDCl_3$): δ = 1.55–1.65 (m, 2 H, 7-H_{eq}, 6-H), 1.96 (s, 3 H, Me), 2.12–2.35 (m, 3 H, 6-H, 8-CH_2), 2.45–2.60 (m, 1 H, 7-H_{ax}), 2.60–2.64 (m, 1 H, 5-H_{eq}), 3.34 (ddd, J = 11.6, 2.4, 0.8 Hz, 1 H, 4-H_{ax}), 3.45 (dd, J = 12.3, 1.0 Hz, 1 H, 2-H_{ax}), 3.88 (ddd, J = 11.6, 2.0, 2.0 Hz, 1 H, 4-H_{eq}), 4.00 (dd, J = 12.3, 2.0 Hz, 1 H, 2-H_{eq}), 6.81 (d, J = 8.9 Hz, 2 H, 2′-H, 6′-H), 7.36 (d, J = 8.9 Hz, 2 H, 3′-H, 5′-H), 7.45 (s, 1 H, NOH) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.2 (Me), 20.2 (C-7), 34.2 (C-6), 37.6 (C-8), 47.4 (C-5), 56.1 (C-4), 56.7 (C-1), 58.6. (C-2), 111.7 (C-4′), 117.6 (C-2′, C-6′), 132.0 (C-3′, C-5′), 148.5 (C-1′), 158.7 (C=N), 213.9 (C-9) ppm. The numbering follows that of compounds **3**. IR (neat): $\tilde{\nu}$ = 1716 (C=O) cm^{-1}. MS (LCMS): *m/z* (%) = 373/375 (100) $[M + Na]^{+\cdot}$. $C_{16}H_{19}BrN_2O_2$ (351.24): calcd. C 54.71, H 5.45, N 7.98; found C 54.83, H 5.30, N 7.75.

Supporting Information (see footnote on the first page of this article): Cartesian coordinates of conformations **3a-A** to **3a-D** and product **10f**, and ^{1}H and ^{13}C NMR spectra.

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Received: May 19, 2011
Published Online: August 12, 2011

