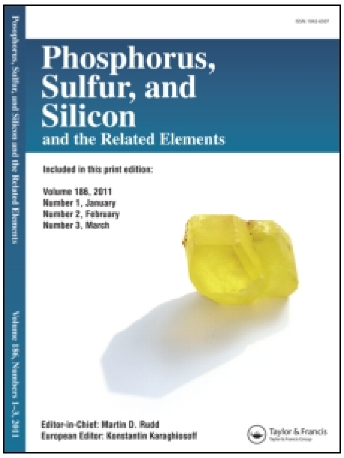

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Synthesis, Stereochemical, and Conformational Studies of Selected 3,7-Diheterabicyclo[3.3.1]nonan-9-ols: X-Ray Diffraction Analyses of 7-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol and 7-Benzyl-9-(4-<i>N,N'</i>-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol, a Rare Stable Chair-Boat Form With Trigonal Nitrogen

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Synthesis, Stereochemical, and Conformational Studies of Selected 3,7-Diheterabicyclo[3.3.1]nonan-9-ols: X-Ray Diffraction Analyses of 7-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol and 7-Benzyl-9-(4-*N,N′*-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol, a Rare Stable Chair–Boat Form With Trigonal Nitrogen

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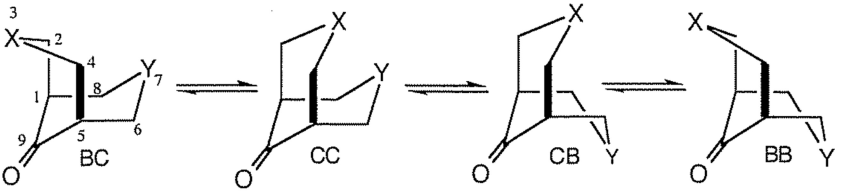
A systematic study of 1,2-additions to 3,7-diheterabicyclo[3.3.1]nonan-9-ones (3,7-DHBCN-9-ONES) by symmetrically substituted aryl Grignard reagents in anhydrous THF or ether has been conducted. 1,2-Additions of aryl Grignard reagents to the carbonyl group at C-9 in 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one and 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one resulted in the formation of tertiary alcohols with the aryl group "syn" to the oxygen or sulfur atoms in the respective rings. The X-ray analyses demonstrated that the solid, bicyclic, oxygen-containing alcohol was in chair–chair form while the solid, bicyclic, sulfur-containing alcohol existed in chair–boat form. A tentative mechanism is that the Grignard reagent may coordinate with the oxygen atom and/or sulfur atom in a boat conformer of the bicyclic system prior to the attack from the "oxygen or sulfur sides."

Keywords 1,2-additions of aryl Grignard reagents to selected 3,7-DHBCN-9-ONES; chair-chair and chair-boat alcohols; possible heteroatom mediation of the direction of attack

INTRODUCTION

Members of the family of 3,7-diheterabicyclo[3.3.1]nonanes have been well recognized for their antiarrhythmic[1,2] and analgesic[3] properties. Major starting materials for these heterocycles have been 3,7-diheterabicyclo[3.3.1]nonan-9-ones (3,7-DHBCN-9-ONES) **1** (Figure 1). Ketones **1** have not been extensively investigated in terms of 1,2-additions by organometallic reagents, and alcohols resulting from them could possess useful biological properties. It has been known for some time that **1a**, for example, has low energy barriers between the individual conformations illustrated.[4] However, relatively few studies have been reported on heterocyclic systems **1b** and **1c**.[5,6] Recent theoretical calculations on gas-phase conformers predicted that the introduction of heteroatoms such as oxygen (**1b**) and sulfur (**1c**) at the 3-position, along with $NCH_2C_6H_5$ at the 7-position, would result in low internal rotational barriers for such ring inversions.[7] Although **1c** was predicted to exist in an equilibrium between Chair–Chair (CC) and Chair–Boat



1 a. $X = Y = CH_2$
b. $X = O, Y = NCH_2Ph$
c. $X = S, Y = NCH_2Ph$

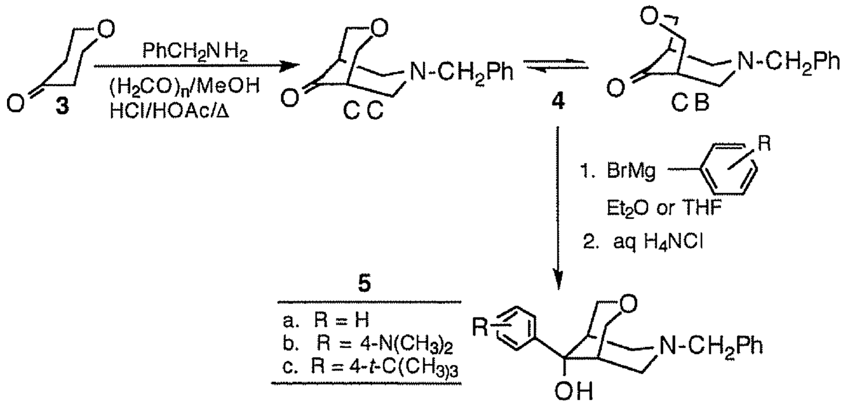
FIGURE 1 Possible conformations of members of **1**.

(CB) forms, an X-ray diffraction analysis of **1c** had previously revealed a CB form in the solid state with the sulfur atom being in the boat conformer.[1] No definitive evidence for a Boat–Boat (BB) form in this family of heterocycles has been reported. One product from the reaction of 2 equivalents of diiodomethane with *N,N′*-dimethylbispidine was tentatively identified as a BB salt.[8]

Investigations of 1,2-additions of nucleophiles to the carbonyl group at C-9 of members of 1 have been limited.[5,6] Reports on such additions to **1b** at r.t. by an aryl Grignard reagent in ether and by sodium borohydride in 2-propanol resulted in the formation of mixtures.[8,9] A separate examination of **1c** with an aryl Grignard reagent gave an amine that had to be converted to a salt.[1] Very few structure determinations have appeared on such products, and thus the overall stereochemistry of the systems and the configurations at C(9) have heretofore been questionable. The present work describes the additions of anyl Grignard reagents to **1b** and **1c** under specific conditions. Large, symmetrical Grignard reagents were employed and yielded solids.

RESULTS AND DISCUSSION

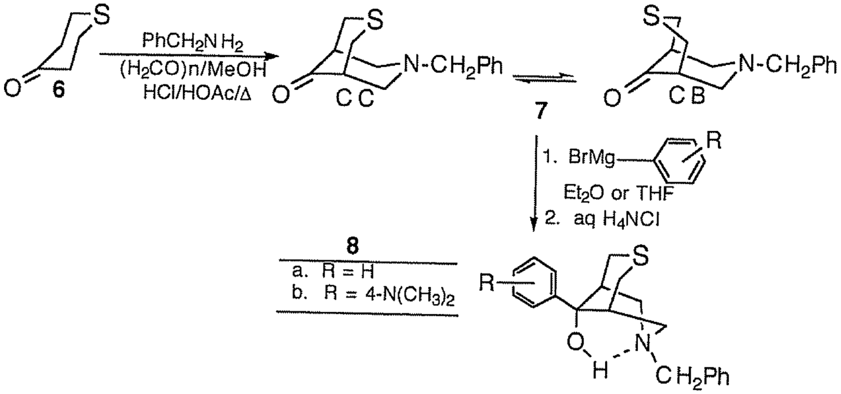
A double Mannich condensation[10] of ketone **3** was utilized in the synthesis of bicyclic ketone 4.[9] The 1,2-addition of selected aryl Grignard reagents to ketone **4**, in anhydrous (Scheme 1) ether (**5a**, **5c**) or THF (**5b**) at reflux, produced corresponding bicyclic alcohols **5** in moderate yields (39–48%). It is known that such yields are often encountered in the synthesis of tertiary alcohols from ketones with bulky alkyl groups[11] in different solvents.[12] An alcohol previously reported[9] in a low yield



SCHEME 1

from a complex mixture generated from a reaction of **4** with the phenyl Grignard reagent had an m.p. of 157–157°C, while that for the current **5a** melted at 91–92°C. Consequently, and in view of the X-ray diffraction data for **5a**, it is concluded that the higher melting compound recorded earlier[9] is an isomer of **5a**. It has not been possible to grow adequate crystals of the higher melting product for X-ray analysis. Conditions to derive the high melting product included a 1.5:1 ratio of Grignard reagent:**4** in ether with stirring overnight at r.t.[1] The generation of **5a** involved a 3:1 ratio of Grignard reagent:**4** in ether, with the resulting mixture being held at reflux for 1 h, followed by stirring overnight (r.t.). These slightly modified conditions invoked in the present work dramatically changed the reaction since **5a** formed in moderate yield (48%). A TLC analysis of the reaction mixture indicated several byproducts and unreacted starting material. This suggests that the reaction is slow and that the carbony group may be hindered to attack by the large solvated Grignard reagents. Surprisingly, **5a** crystallized with one molecule of water, also suggesting that partitioning of alcohols may have occurred between the organic and water layers and complicated the separation process. Several extractions of the water layer were required to obtain the reported yields of final product(s). Repeated recrystallizations of **5a**, **5b**, and **5c** gave solids, but suitable crystals could be obtained for X-ray analysis of only **5a**.

A Mannich condensation converted thiopyranone (**6**) to bicyclic ketone **7** using similar conditions as employed for bicyclic ketone 7 (Scheme 2). The treatment of ketone **7** with two aryl Grignard reagents in dry THF or ether gave tertiary, bicyclic alcohols **8**. Although presumed alcohol **8a** had been isolated previously,[1] no suitable crystals



SCHEME 2

for X-ray analysis could be grown although the hydroperchlorate was identified as a CC system. However, the treatment of **7** with 4-*N,N*′-dimethylaminophenylmagnesium bromide gave crystals that were useful for X-ray analysis. Alcohol **8b** crystallized in a CB form, *not a CC or BC form*, with the aryl group on the same side of the ring as the sulfur atom. The aryl ring was in a pseudo equatorial position with respect to the nitrogen atom at the 7-position. Crystallization of crude **8b** (denatured alcohol 3A:diethyl ether, 4:1) or crude **5a** (MeOH) gave only one pure isomer in each case. Although the addition appears to be stereoselective to some degree, several products were formed along with the starting material as indicated by TLC analysis. The presence of minor quantities of isomers of **5a** and **8b** in the individual very complex reaction mixtures cannot be eliminated. All attempted chromatographic/recrystallization methods to separate and purify byproducts from either reaction have been unsuccessful.

In an effort to ascertain the major conformer of **5a** present in solution, an NMR study was initiated. One set of configurational and conformational possibilities for **5a** in solution are shown in Figure 2. The ^{1}H spectrum of **5a** at 300 MHz showed 6 major signals at δ 2.72–2.78 [m, 2H, $H_{(1,5)}$], 3.31–3.36 [m, 4H, $H_{(6,8)}$], 3.54–3.63 [m, 4H, $H_{(2,4)}$], 3.60 [s, 2H, H_2C-Ph], 4.75 [s, 1H, OH], and 7.25–7.45 [m, 10H, 2 Ar-*H*]. Both rings in each conformer shown in the equilibrium can be considered as having axial and equatorial positions. Therefore, one might expect to observe 2 sets of peaks for $H_{(2,4)a}$ and $H_{(2,4)e}$ and 2 sets for $H_{(6,8)a}$ and $H_{(6,8)e}$. Unfortunately, at 300 MHz, the spectrum could not be unequivocally differentated in terms of axial or equatorial protons on the individual rings of the bicyclic system **5a**.

To determine which sets of axial and equatorial protons belong to specific carbons in the bicyclic system, a 2D gHMQC NMR (600 MHz) experiment was conducted on **5a** in $DCCl_3$. Figure 3 suggests that the signal centered at ~δ 2.76 arose from $H_{(1,5)}$. Moreover, at this frequency, another signal was noted, but it correlated with a different ^{13}C

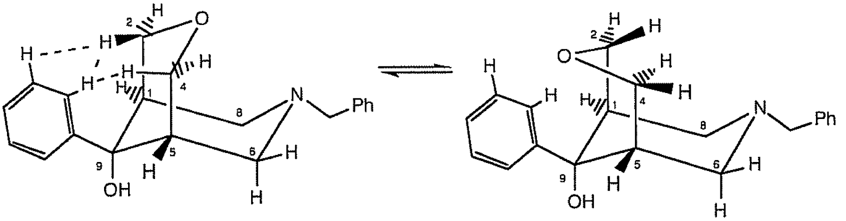


FIGURE 2 Major conformations expected for **5a** in $DCCl_3$ solution.

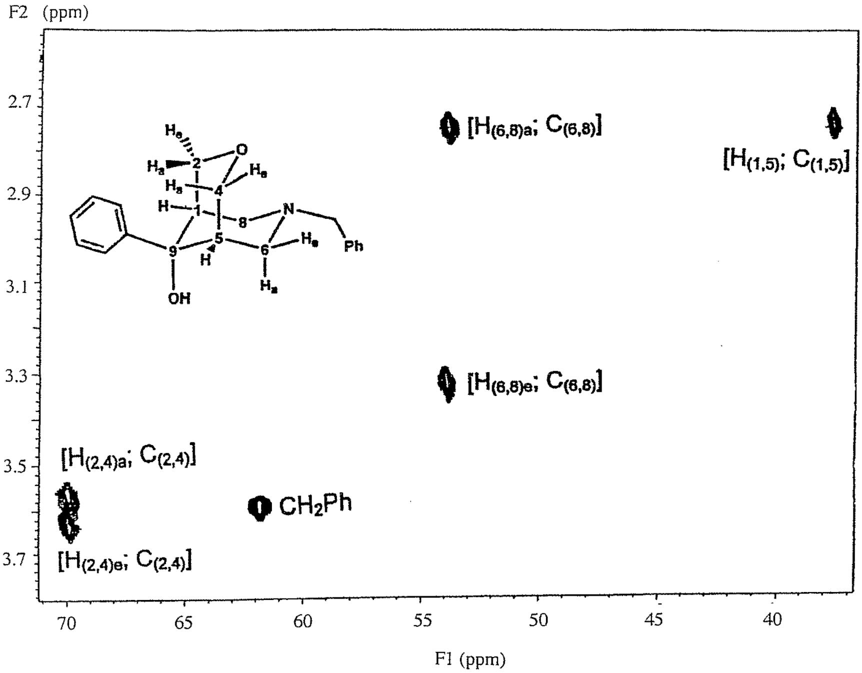


FIGURE 3 The 2D gHMQC spectrum of **5a** in $DCCl_3$.

frequency, namely with a proton at δ 3.33 of $H_{(6,8)e}$. Hence, the signal at δ 2.76 belonged to $H_{(6,8)a}$. This information also indicated that the signals of $H_{(1,5)}$ and $H_{(6,8)a}$ overlapped in the 1D ^1H NMR spectrum, and the signals were not resolved for these protons. However, the gHMQC spectrum did show that $H_{(2,4)a}$ and $H_{(2,4)e}$ appeared at δ 3.56 and δ 3.64, respectively. In addition, a signal for 2 protons on H_2C-Ph was also displayed at δ 3.58 and between the signals of $H_{(2,4)a}$ and $H_{(2,4)e}$ in the spectrum. This confirmed the singlet at δ 3.58 in the 1D ^1H spectrum was due to the methylene protons of the benzyl group H_2CPh.

A 2D COSY spectrum of **5a** was analyzed at a greater resolution and sensitivity (600 MHz, Figure 4). In Figure 4, an entry point of $H_{(1,5)}$ at δ 2.72 was chosen. Crosspeaks were observed for these protons with signals at δ 3.05, δ 3.47, δ 3.89, and δ 4.04. Since $H_{(2,4)ea}$ protons are close to O, which has a larger electronegativity value than N, the signals should be in the region downfield from that of $H_{(6,8)ea}$. Generally, in six-membered rings, axial protons usually appear further upfield than equatorial protons.[13] The signal at δ 3.89 was attributed to $H_{(2,4)a}$, and that due to $H_{(2,4)e}$ was at δ 4.04. The $H_{(6,8)a}$ signal was visible at δ

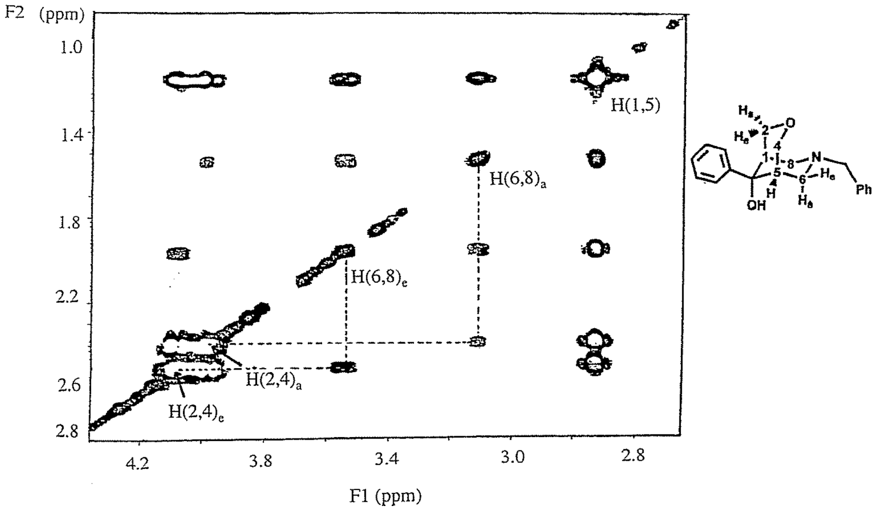


FIGURE 4 The 2D COSY spectrum of **5a** in $DCCl_3$.

3.05 and that of $H_{(6,8)e}$ at δ 3.47. A crosspeak was also observed for the geminal coupling between $H_{(2,4)e}$ and $H_{(2,4)a}$. Furthermore, the COSY spectrum (Figure 4) of **5a** also clearly showed crosspeaks that displayed the long range "W" pattern (4-bond coupling).[7,14] The dominant, 4-bond coupling is between $H_{(6,3)a}$ and $H_{(2,4)a}$ as a "W" pattern. This "W" type coupling is believed to occur when the tails of the orbitals of the first and fourth bond overlap.[14] This is only possible when both rings are in chair conformations in a CC form. The "W" pattern of 4-bond coupling is shown using thick bonds in Figure 5.

In order to extract and identify protons in the congested ^{1}H spectrum in $DCCl_3$, a few drops of pyridine-d_5 were added (Table I). It is known as a solvent for ASIS (Aromatic Solvent-Induced Shifts).[12] By adding pyridine-d_5, it was anticipated that the proton signals would be shifted

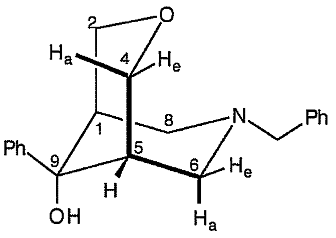


FIGURE 5 The "W" arrangement in **5a**.

TABLE I ^1H Chemical Shifts of 5a in $DCCl_3$ Without and With Pyridine-d_5

Protons	δ (Without)	δ (With)
$H_{(1,5\ \&\ 6,8)}$	2.72–2.78	2.54 (bs)
$H_{(2,4)}$	3.54–3.63$_{(a,e)}$	3.76–3.81$_{(a)}$
$H_{(2,4)}$	3.54–3.36$_{(ae)}$	3.87–3.92$_{(e)}$
$H_{(6,8)}$	3.31–3.36$_{(a,e)}$	2.90–2.93$_{(a)}$
$H_{(6,8)}$	3.31–3.36$_{(ae)}$	3.32–3.38$_{(e)}$
$PhCH_2$	3.60 (s)	3.65 (s)
OH	4.75 (s)	6.59 (s)

s = singlet; bs = broad singlet; the remaining signals are multiplets.

sufficiently to reveal individual patterns. The ^1H data illustrates that all proton signals were visible and experienced different chemical shifts than displayed in the 1D spectrum of **5a** in only $DCCl_3$. Thus, to further support the contention that the CC conformation predominated the bicyclic alcohol **5a** in $DCCl_3$, with pyridine-d_5 added, a 2D NMR NOESY experiment (Figure 6) was performed to examine through-space coupling of protons. If the NOESY spectrum showed through-space coupling between $H_{(2,4)a}$ and signals in the aromatic region of the aryl group at C-9, then the CC form would be suggested as the major conformer present. It is clear that in Figure 6 there are displayed crosspeaks of $H_{(2,4)a}$ with signals in the aromatic region and, moreover, with signals for $H_{(1,5)}$. This through-space coupling is only permitted with a CC form as the major conformer for **5a** (as the dotted lines show in Figures 4 and 6), a situation which is not possible in a BC conformer for **5a.** Thus, both rings of **5a** appear to be in chair conformations on the average in $DCCl_3$ at r.t.

Although a few CB systems are known in the 3,7-diheterabicyclo-[3.3.1]nonane family,[6] such conformations are not common. The formation of bicyclic alcohol **8b** is a rare example of a CB form. One explanation might involve the following considerations. The sulfur atom is large (the covalent radius is 1.02 Å compared to 0.73 Å for O and 0.77 Å for C).[15] The high temperature[16,17] and the solvated, bulky aryl Grignard reagent may favor an attack on C-9 of ketone **7** opposite the N atom. The conformational change observed could result from the Grignard reagent forcing the sulfur atom in the flattened thiane ring toward the nitrogen atom. In turn, a repulsion could ensue between unshared electrons on sulfur and nitrogen and induce the nitrogen atom to bend away, creating a boat conformation for the nitrogen-containing

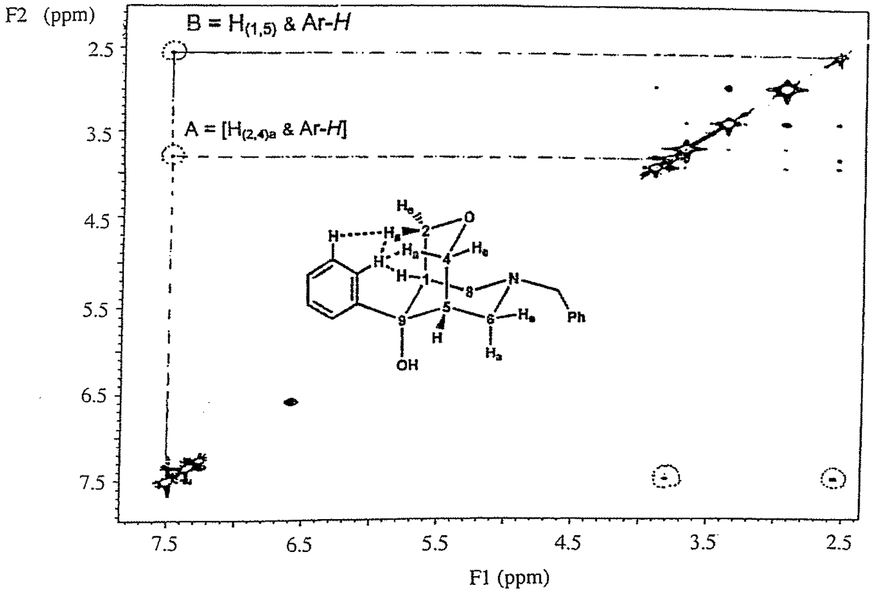
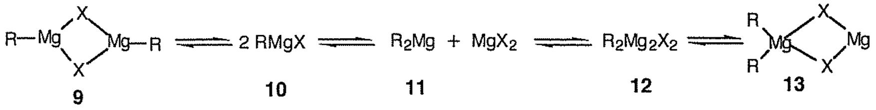


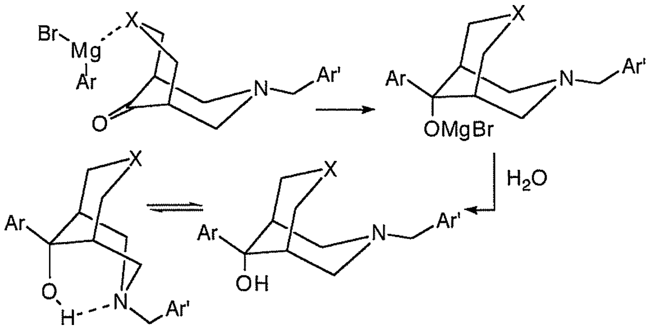
FIGURE 6 The 2D NOESY spectrum of **5a** with pyridine-d_5 added.

ring. Intramolecular hydrogen bonding between the hydrogen atom of the hydroxyl group and the unshared electron pair of the nitrogen atom is an additional stabilization factor that also may be necessary to accomplish the conformational transition from a CC into a CB form in alcohol **8b**. The aid of intramolecular hydrogen bonding in stabilizing certain structures, including some in the DHBCN family, has been recently reported.[18]



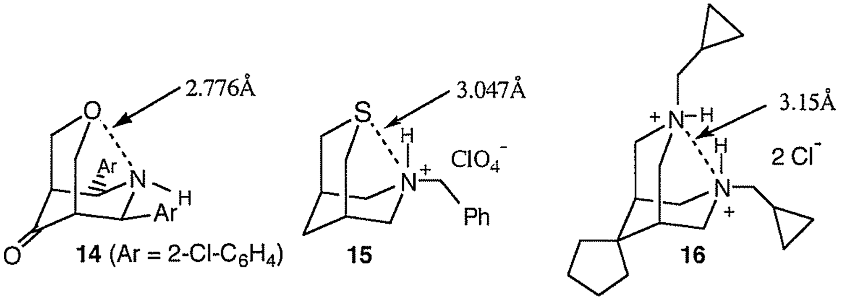
SCHEME 3

The solvent is a significant factor affecting the composition of Grignard reagents in solution.[11] It is well known that a Grignard reagent is not exclusively the simple monomeric species RMgX (Scheme 3). Instead, the term Grignard reagent normally refers to Schlenk equilibrium involving **9–13**.[19] It has been suggested that monomeric species (**10–11**) of a Grignard reagent are present in THF.[11,20] Monomeric



SCHEME 4

species in 1,2-carbonyl additions involving cyclohexanones attack in a direction to favor axial alcohols.[11,21] Thus, the one influential factor in the attack on **7** and in the flipping of the rings in the product **8b** may be associated with solvation of the Grignard reagent species in the THF solution of ketone **7** and/or in the aggregation of the Grignard reagent. In addition, the temperature also can play a significant role on the composition of Grignard reagents in solution.[11] Moreover, changing solution temperatures can significantly alter the solubility of the components of Grignard reagents.[16] Since the production of **8b** was performed (Scheme 4) under reflux, 4-*N,N*-dimethylaminophenylmagnesium bromide reagent in THF may be monomeric. Low temperatures are known to shift the monomer-dimer equilibrium toward a dimeric arylmagnesium complex in THF, and, at high temperatures, Grignard reagents in THF are often monomeric.[17] Possibly this could lead to a flipping of the nitrogen-containing ring perhaps through coordination between the ring N or S (or O) atom and ArMgX. Conceptually, coordination of the Grignard reagent–solvent complex could induce attack on a CB form



SCHEME 5

since the space between the heteroatoms in the CC form of the ketones is small and cannot likely accommodate a large complex (Scheme 5). Model system **14**, for example, has an O...N distance of only 2.776 Å between the trigonal nitrogen atom and the oxygen atom in a slightly flattened CC form in the solid state.[9] Thus, the small "gap" of O...N in 4 or O...S in 7 may prevent coordination with ArMgBr but could induce an equilibrium with the formation of a CB form for enhanced coordination of ArMgBr with O (or S) and C=O. This suggests an attack by ArMgBr "syn" to the O or S atom side to give **5a** or **8b**, respectively. In contrast, salts **15**[1] and "Tedisamil" (**16**)[22] have longer N....S and N...N distances of 3.047 Å and 3.15 Å, respectively, in systems with tetrahedral nitrogen. This lends credence to the concept that coordination of a Grignard reagent with either heteroatom in ketones **4** or **7** with trigonal nitrogen would be difficult *if* the ketone conformer was a CC form rather than a CB form. Even with nitrogen in a chair ring in a CB system, the close proximity of the adjacent axial C—C bonds in the boat ring would retard coordination by a large Grignard–solvent complex. Hence, the approach of ArMgBr may favor a side of **4** and/or **7** syn to O and S in a CB system for maximum coordination.

Single-Crystal X-ray Diffraction Analyses

In the solid state, bicyclic alcohol **5a** was in CC conformation (Figure 7). The compound crystallized in the space group P2(1)/c of the monoclinic system (Table II). The elemental analysis suggested that there was one molecule of water trapped within the crystal of **5a**. The X-ray diagram of **5a** confirmed that a water molecule formed a weak hydrogen bond between the hydrogen atom of the OH group and the unshared electron pair on the nitrogen atom. The aryl and hydroxyl groups are bonded at C-9 with the C—C_6H_5 bond being equatorial with respect to the piperidine ring and axial with respect to the thiane ring. The crystal data for **5a** are given in Table II.

In contrast, analysis of a single crystal of alcohol **8b** demonstrated that the tertiary, bicyclic alcohol existed in a CB form with the nitrogen-containing ring in a boat (Figure 8). Moreover, the X-ray analysis also showed an intramolecular hydrogen bond between the hydrogen of the OH group and N atom in the piperidine ring. The distances for O...H, OH...N, and O...N were 0.87 Å, 1.88 Å, and 2.61(14) Å, respectively. The angle of the intramolecular hydrogen bond was 141.5°. Aryl and hydroxyl groups were bonded at C-9 with the C-C_6H_4-4-$N(CH_3)_2$ bond being equatorial with respect to the piperidine ring and pseudo axial with respect to the thiane ring. The crystal data for **8b** are given in Table II.

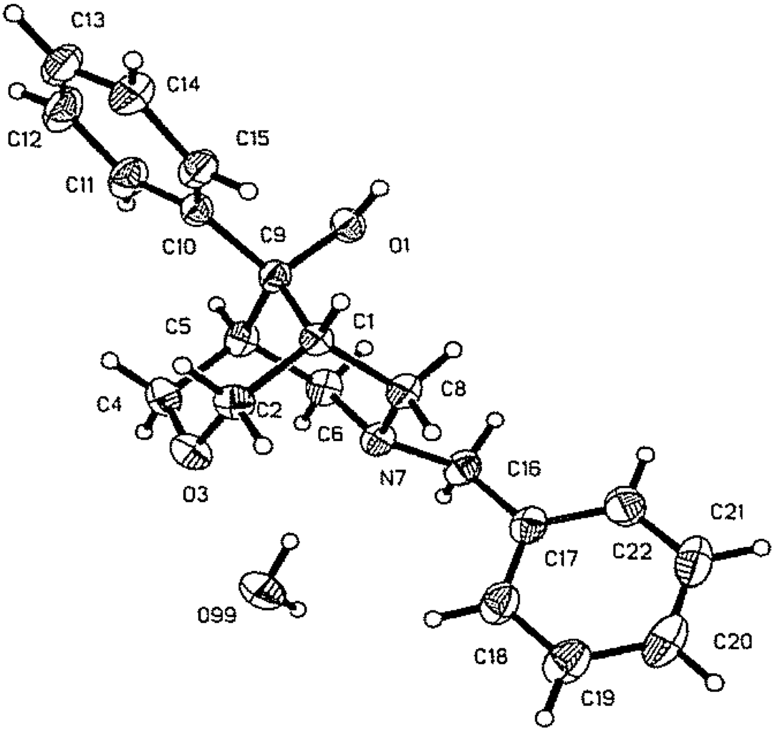


FIGURE 7 A stereo drawing of **5a**.

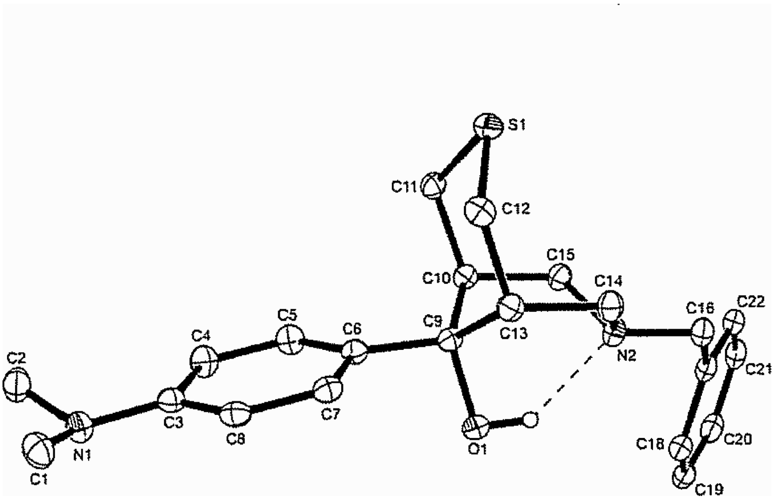


FIGURE 8 A perspective view of **8b**.

TABLE II Crystal Data and Structure Refinement for Alcohols 5a and 8b

	5a	**8b**
Mol. formula	$C_{20}H_{25}NO_3$	$C_{22}H_{28}N_2OS$
MWT	327.41	368.52
Temperature	301 (2) K	100 (2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$	Orthorhombic, $P2_12_12_1$
Cell dimensions	a = 7.664 (2)Å, $\alpha = 90°$	a = 9.1781 (6) Å, $\alpha = 90°$
	b = 10.652 (2)Å, $\beta = 97.370°$ (10)	b = 11.1062(8) Å, $\beta = 90°$
	c = 21.229 (3)Å, $\gamma = 90°$	c = 18.3868(13) Å, $\gamma = 90°$
Volume	1718.8 (6) $Å^3$	1874.2(2) $Å^3$
Z, Calculated density	4, 1.265 Mg/m^3	4, 1.306 Mg/m^3
Absorption coefficient	0.084 mm^{-1}	0.187 mm^{-1}
F(000)	704	792
Crystal size	0.1 × 0.1 × 0.1 mm^3	0.36 × 0.16 × 0.10 mm^3
Theta range-data collection	1.93°–26.37°	2.14°–27.50°
Index ranges	$-1 \leq h \leq 9$, $-13 \leq k \leq 1$, $-26 \leq l \leq 26$	$-11 \leq h \leq 11$, $-14 \leq k \leq 14$, $-23 \leq l \leq 23$
Reflections collected/unique	4790/3518 [R(int) = 0.0277]	16383/4293 [R (int) = 0.0193]
Completeness to 2 theta = 27.50°	94.4%	99.7%
Absorption correction		Semi-empirical from equivalents
Max. and min. transmission		0.9816 and 0.9359
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3518/0/218	4293/0/237
Goodness of fit on F^2	1.052	1.045
Final R indices [$I > 2sigma(I)$]	R1 = 0.0592, wR2 = 0.1570	R1 = 0.0271, wR2 = 0.0713
R indices (all data)	R1 = 0.0991, wR2 = 0.1833	R1 = 0.0276, wR2 = 0.0716
Absolute structure parameter	0.006 (2)	0.01 (5)
Largest diff. peak and hole	0.227 and −0.315 e.$Å^{-3}$	0.312 and −0.168 e.$Å^{-3}$

CONCLUSIONS

Although reactions mixtures were complex with several byproducts formed, along with starting material, it was possible to isolate several members of the title compounds. In the examples studied, 1,2-additions of selected Grignard reagents to 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one and 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one resulted in the generation of alcohols with the aryl groups "syn" to the oxygen and sulfur atom in the respective rings under the conditions employed. Spectral and X-ray diffraction analyses strongly imply that the oxygen-containing systems exist in CC forms in a solid state and in solution, while the one sulfur-containing system is in a CB form in the solid state. Specifically, 7-benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (**5a**) was a CC form, and 7-benzyl-9-(4-*N,N*-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (**8b**) was a rare CB form in the solid state. Presumably the CB form **8b** was generated because of the internal repulsion of the ring heteroatoms, the large sulfur atom, the flattening of the thianol ring, and the enhanced stabilization conferred on the CB conformation via H-bonding involving the proton of the alcohol at C-9 with the nitrogen atom in the piperidine ring. Since it has not been possible to ascertain if another isomer is formed in each reaction, it is tentatively concluded that final configurations of alcohols generated from such bicyclic ketones may be influenced by the type of Grignard reagent, reaction temperature, and nature of the solvent utilized. The compounds await biological screening.

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer 2000 FTIR as liquid films or KBr pellets. All ^{1}H and ^{13}C NMR spectra were taken either on a Varian Unity Gemini 300 MHz spectrometer operating at 300.082 MHz and 75.463 MHz, respectively, or on a Varian Unity Inova 600 MHz spectrometer operating at 598.724 MHz and 150.57 MHz, respectively. Chemical shifts for the ^{1}H and ^{13}C spectra were recorded ($DCCl_3$; in the case of **5a**, a few drops of pyridine-d_5 were added) in δ or ppm values downfield from TMS. All 2D NMR experiments for bicyclic alcohol **5a**, including COSY, NOESY, HMQC, and HMBC, were recorded on a Varian Unity Inova 600 MHz spectrometer. All reactions were performed under nitrogen unless otherwise specified. All Grignard reagents were purchased from Rieke Metals, Inc. (Lincoln, NE). Ketones **4**[1] and **7**[5] and alcohol **8a**[1] were prepared as reported and possessed all properties that corresponded to literature values. Attempts to crystallize **8a** for X-ray analysis failed. TLC analyses were performed on all reactions mixtures (silica gel 60 F_{254}-EM Science). Analyses of reaction mixtures indicated several minor products, a small amount of starting material, and the major product. Purification of the major products was achieved by flash chromatography (J. T. Baker silica gel, 40 μm particle size). Elemental analyses were by Atlantic Microlab, Inc. (Norcross, GA).

7-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (5a)

A system under N_2 was charged with phenylmagnesium bromide in ether (2.16 mL; 6.48 mmol, 3*M*), and the mixture was stirred at r.t. for 5 min. A solution of ketone **4** (0.5 g, 0.002 mol) in anhydrous ether (35 mL) was added dropwise to the Grignard reagent. After 1 h of gentle reflux, heating was discontinued, but stirring of the mixture was maintained overnight at r.t. To the resulting mixture was added dropwise, with a cooling ice bath (~0°C), H_2SO_4 (20 mL, 9 *M*) with stirring. Adding aq H_4NCl for decomposition of the reaction led to severe emulsions. After 1 h, the water layer was separated and made basic via the addition of KOH pellets with a cooling ice bath followed by dilution with distilled water (100 mL). The mixture was extracted with ether (3 × 50 mL), and the extracts were dried (KOH) overnight. The solution was filtered and treated dropwise with $HClO_4$ (60%), with stirring, which resulted in the formation of a white precipitate. The solid was then washed with cold ether and recrystallized (ethanol). The new solid was redissolved in distilled water (50 mL), and the solution was made basic with NaOH (pH ~2). Extracts with ether (3 × 50 mL) were combined and dried (Na_2SO_4) overnight. Evaporation of the solvent yielded a final product (TLC analysis indicated the presence of two impurities, product, and starting material) **5a** (0.24 g, 0.78 mmol, 48%, recrystallized (methanol) as a white solid m.p., 91–92°C. IR (film) 3344 cm^{-1} (O—H). ^1H NMR (300 MHz, $DCCl_3$ without pyridine-d_5) δ 2.72–2.78 [m, 4 H, $H_{(1,5\&6,8)]}$, 3.31–3.36 [m, 2 H, $H_{(6.8)}$], 3.54–3.63 [m, 4 H, $H_{(2,4)}$], 3.60 [s, 2 H, H_2C-Ph], 4.75 [s, 1 H, OH], and 7.25–7.45 [m, 10 H, 2 Ar-*H*]. ^1H NMR (600 MHz, $DCCl_3$ + a few drops of pyridine-d_5) δ 2.54 [bs, 2 H, $H_{(1,5)}$], 2.90–2.93 [m, 2 H, $H_{(6,8)a}$; the axial-equatorial coupling was not discernable in this signal], 3.32–338 [m, 2 H, $H_{(6.8)e}$], 3.65 [s, 2 H, CH_2], 3.76–3.81 [m, 2 H, $H_{(2.4)a}$], 3.87–3.92 [m, 2 H, $H_{(2.4)e}$], 6.59 [bs, 1 H, OH], 7.20–7.55 [m, 10 H, Ar-*H*]. ^{13}C NMR ($DCCl_3$ + a few drops of pyridine-d_5) ppm 37.5 [$C_{(2,4)}$], 52.8 [$C_{(1,5)}$], 61.7 [$C_{(6.8)}$], 69.7 [CH_2], 72.3 [$C_{(9)}$], 125.4 [$C_{(4'')}$], 126.7 [$C_{(4')}$], 127.8 [$C_{(3'',5'')}$], 128.0 [$C_{(3',5')}$], 128.5 [$C_{(2'',6'')}$], 128.9 [$C_{(2',6')}$], 138.9 [$C_{(1')}$], 142.4 [$C_{(1'')}$]. Anal. calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Anal. calcd. for $C_{20}H_{23}NO_2H_2O$: C, 73.36; H, 7.69; N, 4.27. Found: C, 73.54; 73.41; H, 7.80, 7.69; N, 4.33, 4.33. In view of the presence of a water molecule, two separate analyses were obtained.

7-Benzyl-9-(4-*N,N*-dimethylaminophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (5b)

A system under N_2 was charged with 4-*N,N*-dimethylaminophenylmagnesium bromide in THF (18 mL, 0.0085 mol, 0.5 *M*), and the mixture was stirred at r.t (5 min). A solution of ketone **4** (1.0 g, 0.0043 mmol) in anhydrous THF (25 mL) was added dropwise (~0.5 h) to the Grignard reagent, and the solution was stirred at r.t (10 min). Upon applying heat (~1 h), the light-yellow solution turned copper color. After heating for 24 h at gentle reflux, heat was discontinued, but stirring of the solution was continued overnight (r.t). To the new solution was added dropwise, with a cooling ice bath, aq. NH_4Cl (39 mL, 10%), followed H_2SO_4 (9 *M*, 6.4 mL) with stirring. After 1 h, the mixture was made basic (KOH pellets, pH ~12) with a cooling ice bath. Extracts with ether (4 × 50 mL) were combined and dried (Na_2SO_4) overnight. The solution was treated with decolorized charcoal and filtered (celite pad). Evaporation of the solvent gave a brown solid, which was stirred in petroleum ether (3 × 30 mL, each for 0.5 h). The petroleum ether was discarded. Evaporation of the residual solvent gave a brown solid (TLC analysis indicated two impurities, product, and starting material), which was recrystallized [denatured alcohol 3A:ether (4:1)] and yielded colorless crystals of **5b** (0.33 g, 45%); m.p. 155–156°C; IR (film) 3383 (O—H) cm^{-1}. ^1H NMR (600 MHz, $DCCl_3$ + a few drops of pyridine-d_5 δ 1.82 [bs, 1 H, OH], 2.38 [s, 2 H, $H_{(1,5)}$], 2.47–2.51 [m, 2 H, $H_{(6,8)a}$], 2.88–2.92 [m, 2 H, $H_{(6,8)e}$], 2.98 [s, 6 H, $N(CH_3)_2$], 3.31 [s, 2 H, CH_2Ph], 3.95–3.99 [m, 2 H, $H_{(2,4)a}$], 4.45–4.49 [m, 2 H, $H_{(2,4)e}$], 6.74 [d, 2 H, Ar-*H*], 7.21–7.31 [m, 7 H]. ^{13}C NMR ($DCCl_3$) ppm 38.2 [$C_{(2,4)}$], 40.4 [$N(CH_3)_2$], 55.7 [$C_{(1,5)}$], 62.3 [$C_{(6,8)}$], 67.7 [CH_2], 71.6 [$C_{(9)}$], 112.5 [$C_{(3'',5'')}$], 126.4 [$C_{(4')}$], 126.6 [$C_{(3',5')}$], 128.1 [$C_{(2',6')}$], 128.5 [$C_{(2'',6'')}$], 130.1 [$C_{(1'')}$], 139.2 [$C_{(1')}$], 149.9 [$C_{(4'')}$]. Anal. calcd. for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.83; H, 8.15; N, 8.06. Attempts to grow crystals of **5b** for X-ray analysis were unsuccessful.

7-Benzyl-9-(4-*t*-butylphenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (5c)

A system under N_2 was charged with *tert*-butylphenylmagnesium bromide in ether (3.24 mL, 0.0065 mol, 2 *M*), and the mixture was stirred at r.t. (5 min). A solution of ketone **4** (0.5 g, 0.0022 mol) in anhydrous THF (5 mL) was added dropwise to the Grignard reagent in a flask over 0.5 min. Upon applying heat for 1 h, the light-yellow mixture turned to brown and then to a clear orange liquid. After 60 h at reflux, heating was discontinued, but stirring of the solution was maintained overnight (r.t). To the new solution was added dropwise, with a cooling ice bath, aq. NH_4Cl (15 mL, 20%). The organic layer was separated, and the aqueous layer was extracted (ether, 3 × 50 mL). The combined extracts were dried (K_2CO_3) overnight, were treated with decolorizing charcoal, and were filtered (celite pad). Evaporation of the solvent gave a yellow oil, which, upon adding ethyl acetate:hexanes (1:2), produced a precipitate (TLC indicated at least two impurities, product, and starting material), which was filtered and dried (60–68 °C) overnight. Recrystallization (denatured alcohol 3A) of the solid yielded white flakes of **5c** (0.31 g, 39%); m.p. 163.5–164°C. IR (film) 3378 (O—H), 1109 (C—O) cm^{-1}. ^1H NMR (600 MHz, $DCCl_3$ + a few drops of pyridine-d_5) δ 1.28 [s, 9 H, CH_3], 2.62 [s, 2 H, $H_{(1,5)}$], 3.00–3.02 [m, 2 H, $H_{(6,8)a}$], 3.50–3.53 [m, 2 H, $H_{(6,8)e}$], 3.63 [s, 2 H, N—CH_2], 3.96–3.99 [m, 2 H, $H_{(2,4)a}$], 4.02–4.05 [m, 2 H, $H_{(2,4)e}$], 6.62 [s, 1 H, OH], 7.26–7.63 [m, 9 H, Ar-H]. ^{13}C NMR ($DCCl_3$) ppm 29.9 [CH_3], 32.9 [$C(CH_3)_3$], 37.3 [$C_{(6,8)}$], 52.4 [$C_{(1,5)}$], 61.2 [N-CH_2], 68.1 [$C_{(2,4)}$], 68.6 [$C_{(9)}$], 124.1 [$C_{(4'')}$], 124.4 [$C_{(1'')}$], 125.4 [$C_{(1')}$], 126.9 [$C_{(2',6')}$], 127.4 [$C_{(2'',6'')}$], 138.2 [$C_{(3',5')}$], 139.5 [$C_{(4')}$], 147.7 [$C_{(3'',5'')}$]. Anal. calcd. for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55. Found: C, 78.70; H, 8.64. All attempts to grow crystals of **5c** for X-ray work were unsuccessful.

7-Benzyl-9-(4-*N,N*-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (8b)

A system under N_2 was charged with 4-*N,N*-dimethylaminophenylmagnesium bromide in THF (24 mL, 0.012 mol, 0.5 *M*), and the solution was stirred at r.t (5 min). A solution of ketone **7** (0.5 g, 0.002 mol) in anhydrous THF (10 mL) was added dropwise (0.5 h) to the Grignard reagent. Upon applying heat (~1 h), the light-yellow mixture turned copper color. After heating for 24 h at a gentle reflux, heating was discontinued, but stirring of the solution was maintained overnight (r.t). To the new mixture was added dropwise, with a cooling ice bath, aq. NH_4Cl (60 mL, 10%), followed by H_2SO_4 (5 mL, 18 *M*) with stirring. After 1 h, the mixture was made basic (cooling ice bath) via the addition of KOH pellets (pH ~12). The mixture was extracted with ether (3 × 50 mL), and the combined extracts were dried (KOH) overnight and then were treated with charcoal (Norit

A) and filtered (celite pad). Evaporation of the solvent gave a brown oil, which was purified via flash column chromatography with ethyl acetate:hexanes (1:8) and methanol:CH_2Cl_2 (1:35). Evaporation of the solvent (methanol:CH_2Cl_2) and, upon standing at r.t, produced an oil, which solidified to a brown solid (TLC indicated 2–3 impurities, product, and starting material). Recrystallization [denatured alcohol 3A:ether (4:1)] of the solid yielded colorless crystals of **8b** (0.33 g, 44%); m.p. 168–169.5°C. IR (film) 3276 (O—H) cm^{-1}. ^1H NMR (600 MHz, $DCCl_3$ + a few drops of pyridine-d_5) δ 2.22–2.26 [m, 2 H, $H_{(6,8)a}$], 2.65–2.69 [m, 2 H, $H_{(6,8)e}$], 2.89 [bs, 2 H, $H_{(1,5)}$], 2.95 [s, 6 H, $N(CH_3)_2$], 3.33–3.37 [m, 2 H, $H_{(2,4)e}$], 3.42 [s, 2 H, CH_2Ph], 3.48–3.52 [m, 2 H, $H_{(2,4)a}$], 4.75 [s, 1 H, OH], 6.67 [s, 1 H, Ar-H], 6.70 [s, 1 H, Ar-H], 7.20–7.40 [m, 7 H, Ar-H]. ^{13}C NMR ($DCCl_3$) ppm 40.1 [$(H_3C)_2N$], 40.2 [$C_{(2,4)}$], 53.7 [$C_{(1,5)}$], 54.9 [$C_{(6,8)}$], 61.9 [CH_2], 69.4 [$C_{(9)}$], 112.2 [$C_{(3'',5'')}$], 126.6 [$C_{(4')}$], 127.1 [$C_{(3',5')}$], 128.3 [$C_{(2',6')}$], 129.0 [$C_{(2'',6'')}$], 129.6 [$C_{(1'')}$], 137.7 [$C_{(1')}$], 149.8 [$C_{(4'')}$]. Anal. calcd. for $C_{22}H_{28}N_2OS$: C, 71.70; H, 7.66. Found: C, 71.80; H, 7.66.

Crystallographic Data-Analysis of Structure 5a

A single crystal of 7-benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (**5a**) with dimensions of 0.1 × 0.1 × 0.1 mm was mounted on a Bruker-Siemens-Nicolet P4 diffractometer equipped with a molybdenum source (graphite monochromator, MoKα radiation, $\lambda = 0.71073$ Å) and θ–2θ data collection (variable scan rate between 10 and 30 seconds per degree, based on the intensity observed during a prescan). The unit cell was determined by least-squares refinement 301 K (Table II) and corrected for Lorentz, polarization, and background effects.[23] Intensities of three standard reflections were monitored after every 97 reflections. Crystal decomposition was found to be insignificant. After removal of redundant and space group forbidden data, atomic positions were determined with SHELXS[24], and 3518 observed data ($I > 2.0\ \sigma(I)$) were refined using full-matrix least squares [function minimized, $\Sigma w(Fo^2 - Fc^2)^2$] until convergence (SHELXL[25]). Hydrogen positions were calculated and included in the final cycles of refinement in constrained positions and with fixed isotropic thermal parameters and with a C–H distance of 0.97 Å. Extinction was refined but was minimal. Molecular graphics were prepared using the program XP[26] (supplementary material) and present positional parameters, which are the basis for the bond angles and distances (supplementary material). The final cycle of refinement led to an agreement factor of $R = 5.92\%$, $R_w = 15.70\%$, and $R = 9.91\%$ for all data, with 218 parameters refined.

Crystallographic Analysis of Structure 8b

A single crystal of 7-benzyl-9-(4-*N,N*-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (**8b**) was mounted on a Bruker APEX[27] diffractometer equipped with a molybdenum source (graphite monochromator, MoKα adiation, $\lambda = 0.71073$ Å) and a total of 16383 intensity data, which approximately covered the full sphere of the reciprocal space, was measured as a series of ω oscillation frames each 0.3 γ for 25 s/frame. The detector was operated in 512×512 mode and was positioned at 6.12 cm from the crystal. Data were collected at 100(2) K. Coverage of unique data was 99.7% complete to $55.0\gamma 2\theta$. The unit cell was determined by a nonlinear least-squares fit of 4123 reflections in the range of $3.2 < \theta < 26.9\gamma$. After removal of redundant and space group forbidden data, atomic positions were determined with SHELXTL,[28] and 4222 observed data ($I > 2.0\sigma(I)$) were refined using full-matrix least-squares [function minimized, $\Sigma w(Fo^2–Fc^2)^2$] until convergence. Hydrogen positions were calculated and included in the final cycles of refinement in constrained positions and with fixed isotropic thermal parameters and with a C–H distance of 0.97 Å. Absorption corrections were made using a semiempirical method based on equivalents. The final cycle of refinement led to an agreement factor of $R = 2.7\%$, $R_w = 7.13\%$, and $R = 7.16\%$ for all data (4293 reflections), with 237 parameters refined.

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