JOC*Article*

Control of the Conformational Equilibria in Aza-*cis*-Decalins: Structural Modification, Solvation, and Metal Chelation

Puay-Wah Phuan and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104

marisa@sas.upenn.edu

Received January 21, 2002

A series of amino alcohol- and diamino-*cis*-decalins were synthesized and their conformational properties investigated. The equilibrium distributions of the conformational isomers were measured via NMR spectroscopy. The equilibrium ratios depend on the position of the substituents on the decalin ring system and the solvent. The 7-substituted 1-aza-*cis*-decalins are more likely to adopt the N-in form than the 5-substituted analogues. The N-in form is generally favored in nonpolar solvents, while the N-out form is favored in polar solvents. Complexation with $LiClO_4$ and Et_2Zn alters the equilibrium to favor the N-in decalin conformer. Both conformers coordinate lithium ions such that "on/off" conformational switching is not observed for these decalins. Comparison of the results with complexation studies of (−)-sparteine allows the criteria for an ideal "on/off" conformational switch to be defined.

Introduction

An ongoing research interest in our group is the utility of compounds containing a *cis*-decalin motif. We have developed novel ligands containing *cis*-decalin ring systems for use in asymmetric processes, including boron allylation, lithiation/substitution,[1] organozinc alkylation,[2] and oxidative biaryl coupling[3] reactions. As part of this effort, a series of C_2-symmetric (type I)[1,4] and non-C_2-symmetric (types II and III) diamines and amino alcohols containing this *cis*-decalin scaffold have been synthesized (Figure 1). In this paper, the conformational properties of the type II and III compounds are examined in the context of two objectives. First, understanding the conformational behavior of these types of *cis*-decalin molecules in the presence of metal additives and different solvents is crucial to using these compounds as chiral auxiliaries or in chiral catalysts. Second, the structural features needed for a binary conformational change in response to a chemical signal were identified.

cis-Decalin **1** exists predominantly in two enantiomeric, isoenergetic conformations (Figure 2). The addition of substituents or heteroatoms to **1** can break the symmetry such that the conformational isomers are diastereomeric and no longer isoenergetic. The position of the conformational equilibrium depends on the heteroatoms within the ring system and substituents on the ring, as well as the solvent and additives. Previously, Santos et al. had

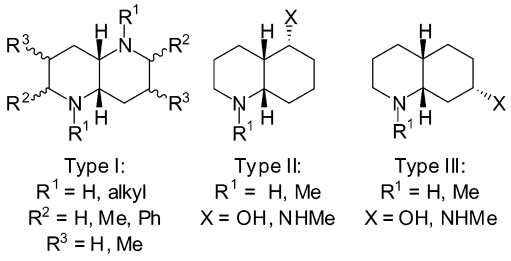


FIGURE 1. Potential *cis*-Decalin ligands.

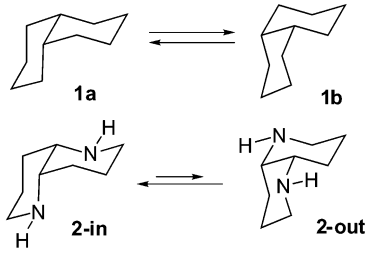


FIGURE 2. Conformational equilibria of *cis*-Decalins **1** and **2**.

examined the conformational equilibria of 1,5-diaza-*cis*-decalins (**2**, type I).[5] We have studied the conformation of **2** using ab initio and molecular mechanics calculations.[6] Steric effects control the equilibria between the two conformational isomers of **2**, while torsional effects dominate the equilibria of the *N*,*N*′-dialkyl derivatives.

Type II (**3**, **4**, **6**) and III (**5**, **7**) *cis*-decalins differ from type I (**2**) in that they contain only one endocyclic

(1) Li, X.; Schenkel, L.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875−878.
(2) Presented in part at the 220th American Chemical Society National Meeting, Washington, DC, August, 2000; Paper ORGN 113.
(3) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137−1140.
(4) (a) Kozlowski, M. C.; Xu, Z.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4537−4542. (b) Xu, Z.; Kozlowski, M. C. *J. Org. Chem.* **2002**, *67*, 3072−3078.
(5) Santos, A. G.; Klute, W.; Torode, J.; Bohm, V. P. W.; Cabrita, E.; Runsink, J.; Hoffmann, R. W. *New J. Chem.* **1998**, 993−997.
(6) Ganguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103−1108.

10.1021/jo025544t CCC: $22.00
Published on Web 07/17/2002

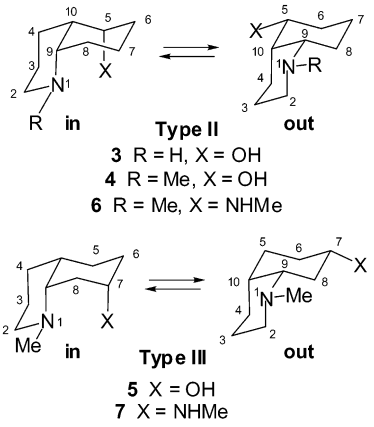
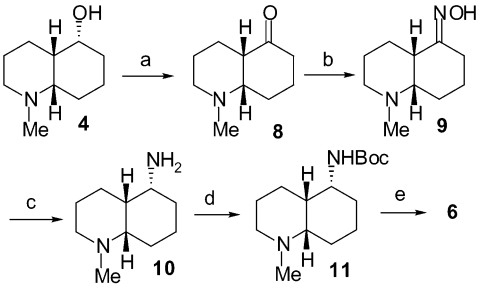


FIGURE 3. Conformational forms of type II and III *cis*-Decalins.

SCHEME 1[a]



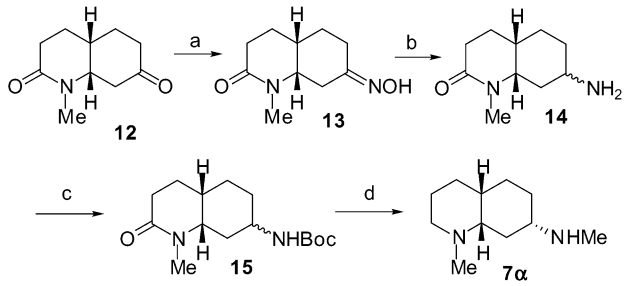
[a] Reagents and conditions: (a) MnO_2, CH_2Cl_2, rt, 50%; (b) $NH_2OH-HCl$, NaOAc, MeOH, 0 °C, 95%; (c) PtO_2, 50 psi H_2, AcOH, rt, 80%; (d) $(Boc)_2O$, CH_2Cl_2, rt, 68%; (e) $LiAlH_4$ THF, reflux, 99%.

heteroatom (Figure 3). The remaining heteroatom (amine or alcohol) is a pendant substituent facing the concave face of the *cis*-decalin ring system. While the backbone found in **3**−**7** is similar to that of **2**, it is not clear that the trends toward stabilization of **2-in** will hold for **3-in**−**7-in** especially because these structures may possess axial substituents. Type II is differentiated from type III by the position of the substituent on the ring; the nitrogen and the substituent are in a 1,5-relationship in type II and a 1,7-relationship in type III. Despite this difference, both sets of structures can form similar six-membered metal chelates from only one of the two possible conformers (the "in" form).

Results and Discussion

Synthesis of *cis*-Decalin Diamines 6 and 7. Amino alcohols **3**[2,7] and **4**[2,7] were synthesized following the procedure of Lebel et al. Amino alcohol **5**[2,8] was synthesized following the procedure of Momose et al. with some modification. The synthesis of **6** (Scheme 1) began with amino alcohol **4**, which was oxidized to ketone **8** with MnO_2. Oxime formation gave **9**, which upon hydrogenation with catalytic PtO_2/HOAc yielded primary amine **10** stereoselectively. Unpurified **10** was subjected directly to Boc_2O to provide carbamate **11**. Subsequent reduction using $LiAlH_4$ then yielded diamine **6**.

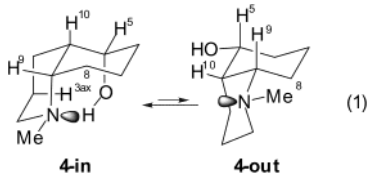
SCHEME 2[a]



[a] Reagents and conditions: (a) $NH_2OH-HCl$, NaOAc, MeOH, 0 °C, 40%; (b) PtO_2, 50 psi H_2, AcOH, rt, 80%; (c) $(Boc)_2O$, CH_2Cl_2, rt, 86%; (d) $LiAlH_4$, THF, reflux, 80%.

The synthesis of **7** followed a similar course (Scheme 2). Formation of oxime **13** from ketoamide **12**[2,8] was followed by hydrogenation using catalytic PtO_2 in HOAc. The ^{13}C NMR spectrum of the resultant primary amine **14** indicated a mixture of epimers. Protection of **14** yielded **15**α and **15***β*, which were not separable by chromatography. $LiAlH_4$ reduction of carbamate **15** provided diamine **7** as a mixture of epimers. With careful chromatography on Al_2O_3, epimer **7**α could be obtained in pure form.

Determining the Identity of the Conformational Isomers of 4. Initially, it was unclear if the conformational equilibrium would favor **4-in** or **4-out** (eq 1). On steric grounds, **4-in** is less favorable because of the axial hydroxyl and a disfavorable 1,4-steric interaction between the hydroxyl and H^{3ax}. However, an internal hydrogen bond may allow **4-in** to predominate. The signals in the room-temperature NMR spectra of **4** in $CDCl_3$ were broad. At 240 K, two sets of sharp signals in a 2.4:1 ratio were observed in the ^{13}C NMR spectrum, indicating the presence of two conformational isomers. The ^1H NMR spectrum at 240 K was complex even though the signals were sharp.



(1)

One- and two-dimensional NMR experiments were undertaken to identify the conformational isomers of **4** (Figure 4). The six methine carbon signals (C^5, C^{10}, and C^9), three for **4-in** and three for **4-out**, were identified using a DEPT-135 experiment (Figure 4a). Next, a HMQC experiment located the corresponding proton signals (Figure 4b). The H^5 proton adjacent to the hydroxyl group was assigned on the basis of its downfield chemical shift. With a gradient COSY (Figure 4c), it was then possible to assign the remainder of the $H^5-H^{10}-H^9$ spin system. Analysis of **4-in** and **4-out** indicates that only the **4-out** H^5 and H^9 should exhibit a NOE. A gradient NOESY (Figure 4d) pinpointed this NOE as well as other diagnostic NOEs. On this basis, **4-in** is definitively the major isomer in $CDCl_3$ at 240 K and **4-out** the

(7) (a) Grob, C. A.; Keifer, H. R. *Helv. Chim. Acta* **1965**, *48*, 799−808. (b) Lebel, N. A.; Caprathe, B. W. *J. Org. Chem.* **1985**, *50*, 3938−3940. (c) Comins, D. L.; Adbullah, A. H. *Tetrahedron Lett.* **1985**, *26*, 43−46.

(8) For the *N*-benzyl derivative, see: Momose, T.; Uchida, S.; Kinoshita, M.; Imanishi, T. *Chem. Pharm. Bull.* **1977**, *25*, 1797−1802.

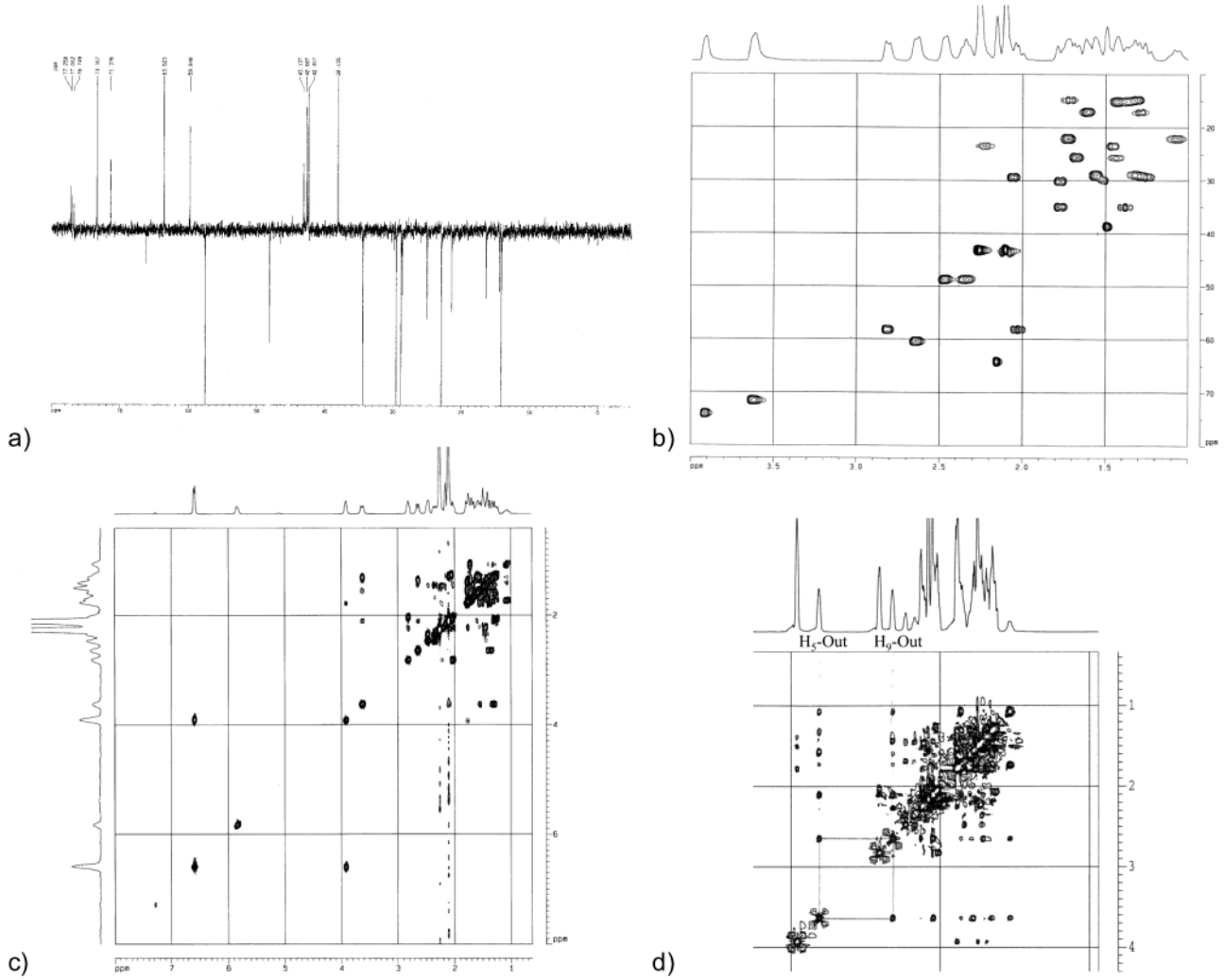


FIGURE 4. (a) DEPT-135 spectrum of **4** in $CDCl_3$ at 240 K. (b) HMQC of **4** in $CDCl_3$ at 240 K. (c) Gradient COSY relating H^5, H^{10}, and H^9. (d) Gradient NOESY of **4** showing a NOE observed between H^5 and H^9 in **4-out**.

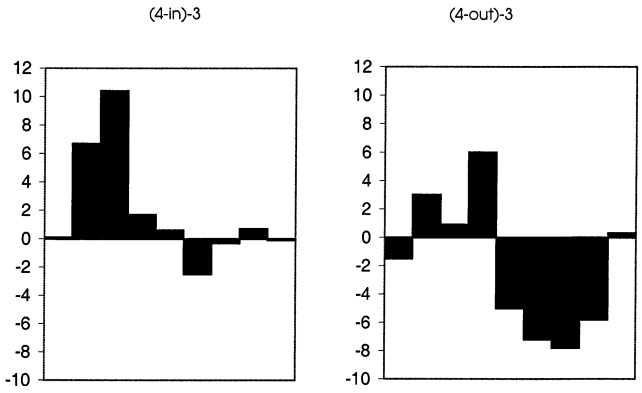
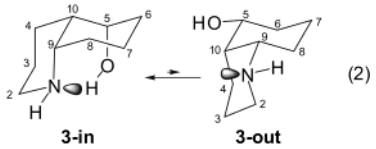


FIGURE 5. Difference in carbon chemical shifts of **3** with respect to **4-in** and **4-out**. The carbon number is listed on the *x*-axis and the $\Delta\delta$ (ppm) is listed on the *y*-axis.

minor isomer (2.4:1). This structural assignment was consistent with the sharp proton doublet at 6.52 ppm (major isomer) arising from the hydroxyl hydrogen of **4-in** participating in an internal hydrogen bond.

Assigning the Conformational Isomers of 3 and 5−7. In contrast to tertiary amine **4**, the NMR spectra at 240 K of secondary amine **3** in $CDCl_3$ are comprised of primarily one set of signals. The ^{13}C chemical shifts of **3** were compared with those of **4-in** and **4-out** to identify the conformational form of **3** (Figure 5).[9] The larger degree of similarity with **4-in** strongly points toward **3-in** as the major conformer (eq 2). As was the case for **4-in**, a downfield proton broad singlet (6.21 ppm) for the hydroxyl proton participating in the internal hydrogen bond of the "in" conformation was observed for **3**.



(2)

One set of sharp NMR signals was also observed for **6** at room temperature, indicating the prevalence of a single conformer. A doubled triplet at 2.65 ppm (J = 11.6, 4.3 Hz) unique to the "out" conformer was detected, indicating that **6-out** predominates (eq 3).

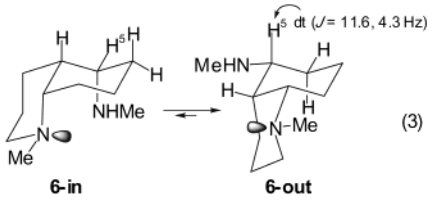
The 7-substituted-1-aza-*cis*-decalins (**5**, **7**) were examined next. At 240 K, the ^{13}C NMR of **5** in $CDCl_3$ is

(9) For an example of this analysis, see: Fidanze, S.; Song, F.; Szlosek-Pinaud, M.; Small, P. L. C.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10117−10118.

TABLE 1. Ratios of the "In" and "Out" Forms of 3−7 in Various Solvents[a]

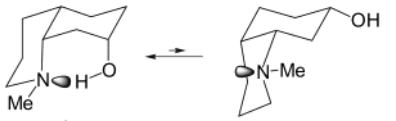
	type II						type III			
	3		4		6		5		7	
solvent	in	out	in	out	in	out	in	out	in	out
toluene-d_8	>20	1.0	>20	1.0	1.0	>20	>20	1.0	1.0	2.0
$CDCl_3$	14.0	1.0	2.4	1.0	1.0	>20	12.0	1.0	1.0	2.7
acetone-d_6	2.4	1.0			1.0	>0				
CD_3CN			1.0	1.3			2.6	1.0	1.0	1.3
THF-d_8			1.0	2.4			1.7	1.0		
CD_3OD	1.0	>20	1.0	>20	1.0	>20	1.0	>20	1.0	>20

[a] All spectra were taken at 240 K (broad signals observed at room temperature) with the exception of **6**, which was taken at room temperature.

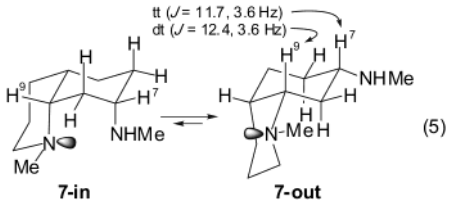


(3)

comprised of primarily one set of signals. These signals were assigned to **5-in** (eq 4) on the basis of the proton doublet at 5.90 ppm, which corresponds the hydroxyl proton participating in the internal hydrogen bond (similar to **4-in**). Diamine **7**, on the other hand, underwent conformational interchange as indicated by broad NMR signals at room temperature and two sets of signals (2.7:1.0) in $CDCl_3$ at 240 K. When MeOH was used (240 K), only the major set of signals was observed. From the diagnostic coupling patterns of H^7 and H^9, the major conformer could be assigned as **7-out** (eq 5).



(4)



(5)

Conformational Analysis of 4−7. The ratios of the "in" and "out" conformational isomers for **3**−**7** were measured in a series of solvents (Table 1). Comparison of **5** with **3**−**4** and of **7** with **6** indicates that the type III aza-*cis*-decalins (**5**, **7**) have a greater tendency to populate the "in" conformation compared to the type II aza-*cis*-decalins (**3**, **4**, **6**). A simple explanation for this phenomenon is based on the larger steric hindrance found in type II aza-*cis*-decalins relative to that in type III derivatives. An unfavorable 1,4-interaction occurs between H^{3ax} and the hydroxyl or amino substituent of the "in" form of the type II compounds (eq 1). This interaction is absent in type III aza-*cis*-decalins.

A favorable internal hydrogen bond from the hydroxyl group to the ring nitrogen in **3** and **4** (type II) is sufficient to compensate for this unfavorable 1,4-interaction and to shift the equilibrium to the "in" conformer. Amino alcohol **3** has a higher ratio of "in":"out" relative to **4** (14:1 vs 2.4:1 in $CDCl_3$) due to destabilizing gauche interactions between the *N*-Me and C^8 of **4-in**.[6] Strongly polar solvents such as MeOH disrupt the internal hydrogen bonding and solvate the hydroxyl or amine substituent, causing an increase in its A value. The result is a shift in the equilibrium to the "out" form (equatorial hydroxyl or amine substituent) in all cases (Table 1). Conversely, nonpolar solvents such as $PhCH_3$ stabilize the internal hydrogen bonding and shift the equilibrium to the "in" form in all cases except for **6**.

Replacement of the hydroxyl group in **4** with a secondary amine yields **6** for which the "out" form predominates under all circumstances. The secondary amine substituent of **6** is a much poorer hydrogen bond donor. In the absence of the internal hydrogen bond, minimization of the 1,4-interaction between the amine substituent and H^{3ax} destabilizes **6-in**. For the type III aza-*cis*-decalins, replacement of the hydroxyl group in **5** with a secondary amine (**7**) causes a different result. In hydroxylic solvents, the **7-out** form predominates. In nonhydroxylic solvents, the equilibrium shifts toward **7-in** ("in":"out" = 1:2 in $PhCH_3$). The amine substituent may participate in a weak hydrogen bond or electrostatic interaction with ring nitrogen, stabilizing **7-in**, which is disrupted in hydroxylic solvents (Figure 3). Alternatively, the inherent steric interactions of **7-in** may balance those of **7-out**, but solvation in MeOH increases the steric size of the C^7 amino substituent, causing a shift to **7-out** where this group is equatorial.

Complexation Studies. Conformational changes upon complexation of a metal have been described for a number of flexible diamines, including 3,7-diaza-bicyclo-[3.3.1]nonane-9-one,[10] 1,5-diaza-*cis*-decalin,[5] and (−)-sparteine.[11] We have examined the conformational properties of the aza-*cis*-decalins with the goal of identifying a molecule capable of a complete conformational switch (from "out" to "in"). Such an "on/off" switch would be useful as a sensor and for the construction of chemically responsive molecular devices. For example, a switch attached to two short peptides could alternate between random coil and β-sheet forms. Complexation of type II and III aza-*cis*-decalins has not been reported, although 1,5-diaza-*cis*-decalin (type I) has been titrated with H^+ and Li^+ and undergoes partial conformational switching.[5] With the intent of generating a metal-triggered "on/off" conformational switch, we selected diamines **6** and **7** for further study.

(10) (a) Sadykow, S.; Kamayev, F. G.; Korenevsky, V. A.; Leont'ev, V. B.; Ustynyuk, Y. A. *Org. Magn. Reson.* **1972**, *4*, 837. (b) Zefirov, N. S. *Russ. Chem. Rev. (Engl. Trans.)* **1975**, *44*, 185.

(11) Zefirov, N. S.; Palyulin, V. A. *Top. Stereochem.* **1991**, *20*, 171.

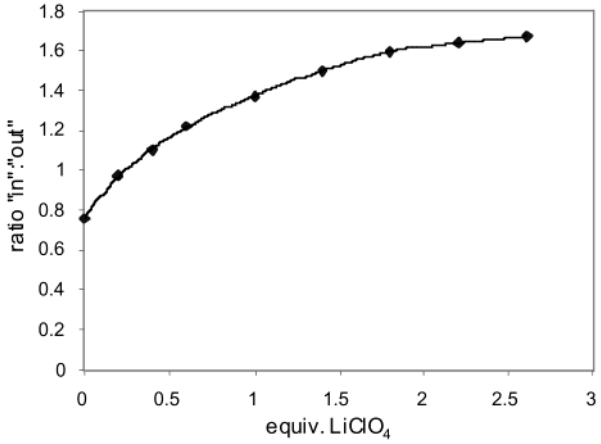
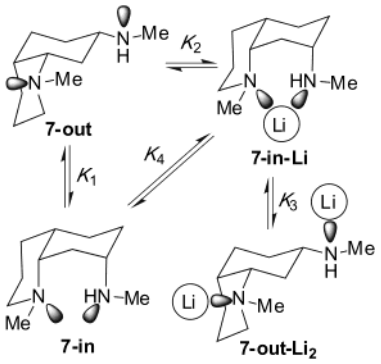


FIGURE 6. Titration of **7** in CD_3CN with $LiClO_4$.

SCHEME 3



Since MeOH may inhibit metal complexation, the choice of solvent is crucial. Since **6** was insoluble in CD_3CN, titration with $LiClO_4$ was performed in acetone-d_6. No **6-in** was observed even in the presence of excess Li^+. Even when diamine **6** was treated with Et_2Zn in toluene-d_8, **6-in** was not observed. Titration of **7** with $LiClO_4$ in CD_3CN showed a 2-fold increase of **7-in** over **7-out** (Figure 6). With Et_2Zn in toluene-d_8, **7** showed almost a 10-fold increase (from 0.29 to 2.40 in:out) of **7-in** over **7-out**. At ≥1.05 equiv of Et_2Zn, additional zinc species formed analogous to **7-out-Li$_2$** (see below).

Equilibria relevant to the complexation of **7** are depicted in Scheme 3. The two conformers, **7-in** and **7-out**, exist in dynamic equilibrium. At 250 K, in CD_3CN, the K_1 value is simply the ratio of the **7-in**:**7-out**. Addition of increasing amounts of Li^+ (from 0.2 to 2.6 equiv) could, in principle, cause three events to occur. First, **7-in** could chelate to Li^+ and form complex **7-in-Li**. This would perturb the equilibrium between **7-in** and **7-out** allowing more **7-in** to form, which would then further complex to form **7-in-Li**. Second, **7-out** could coordinate to Li^+ and then undergo a chair−chair inversion to form **7-in-Li**. Third, with increasing amounts of Li^+, **7-in-Li** could undergo further coordination to form **7-out-Li$_2$.** All three pathways were used in generating an equation to fit the experimental data shown in Figure 6.

The equilibrium equations in eqs 6−9 describe the equilibria in Scheme 3. Combining eqs 6−9 affords an equation describing the ratio of the species occupying the "in" conformation to those in the "out" conformation (eq 10). This expression should equal the experimental ratio

TABLE 2. *K* and Δ*G*° Values for Scheme 3[a]

K[b]	values	error (±)	ΔG° (kcal/mol)
K_1	0.81		0.10
K_2	0.69	0.05	0.18
K_3	0.12	0.01	1.03
K_4	0.85	0.08	0.08

[a] Obtained by a least-squares fit of eq 11 to the curve in Figure 6. [b] K values were measured or calculated at 250 K.

of the "in" and "out" conformers (eq 11). This ratio was measured spectroscopically via integration of the ^1H NMR spectra assuming that chemical shift was the same for **7-in** and **7-in-Li** as well as for **7-out** and **7-out-Li$_2$**.

$$[\mathbf{7\text{-}in}] = K_1[\mathbf{7\text{-}out}] \quad (6)$$

$$[\mathbf{7\text{-}in\text{-}Li}] = K_2[Li^+][\mathbf{7\text{-}out}] \quad (7)$$

$$[\mathbf{7\text{-}out\text{-}Li_2}] = K_3[Li^+][\mathbf{7\text{-}in\text{-}Li}] \quad (8)$$

$$[\mathbf{7\text{-}in\text{-}Li}] = K_4[Li^+][\mathbf{7\text{-}in}] \quad (9)$$

$$([\mathbf{7\text{-}in\text{-}Li}] + [\mathbf{7\text{-}in}])/([\mathbf{7\text{-}out\text{-}Li_2}] + [\mathbf{7\text{-}out}]) = \{(K_2[Li^+]) + (K_2/K_4)\}/(1 + K_2K_3[Li^+]^2) \quad (10)$$

$$\text{ratio of "in":"out"} = \{(K_2[Li^+]) + (K_2/K_4)\}/(1 + K_2K_3[Li^+]^2) \quad (11)$$

Fitting the curve in Figure 6 to eq 11 affords values for K_2, K_3, and K_4. These values are collected in Table 2 together with the corresponding ΔG° values. Chelation of **7-in** with Li^+ to give **7-in-Li** appears to be the dominant pathway with the largest equilibrium constant of $K_4 = 0.85$. Further coordination of **7-in-Li** with another Li^+ to give **7-out-Li$_2$** appears to be least likely, which may be due to an unfavorable entropy component. Titration with an increasing amount of Li^+ did not lead to complete formation of **7-in-Li**. The "in":"out" conformer ratio leveled off at about 1.7:1.0.

In general, chelation is a favored process, which is confirmed by the increasing amount of **7-in** with an increasing amount of $LiClO_4$. However, with diamine **7**, why does the amount of the "in" conformer level off upon addition of further Li^+ (i.e., incomplete formation of **7-in-Li**)? To answer this question, a study with the related diamine, (−)-sparteine (**16**), was undertaken.

Titration experiments with (−)-sparteine **16**,[12] were performed with Et_2Zn and $LiClO_4$ to analyze the equilibrium processes in the presence of exogenous metals.[13] The NMR spectra of **16** with increasing amounts of Et_2-

(12) For reviews on (−)-sparteine, see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282−2316. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan *Acc. Chem. Res.* **1996**, *29*, 552−560.

(13) Examples of the complexation of sparteine with other species have been reported. For complexation of (−)-sparteine with R_2Mg, see: (a) Fraenkel, G.; Cottrell, C.; Russel, R. J. *Chem. Commun.* **1971**, 273−274. (b) Fraenkel, G.; Appleman, B.; Ray, G. *J. Am. Chem. Soc.* **1974**, *96*, 5113−5119. For complexation with organolithium, see: (c) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707−10718. (d) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567−5572. (e) Remenar, J. F.; Lucht, B. L.; Kruglyak, D.; Romesberg, F. E.; Gilchrist, J. H.; Collum, D. B. *J. Org. Chem.* **1997**, *62*, 5748−5754. (f) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810−5811.

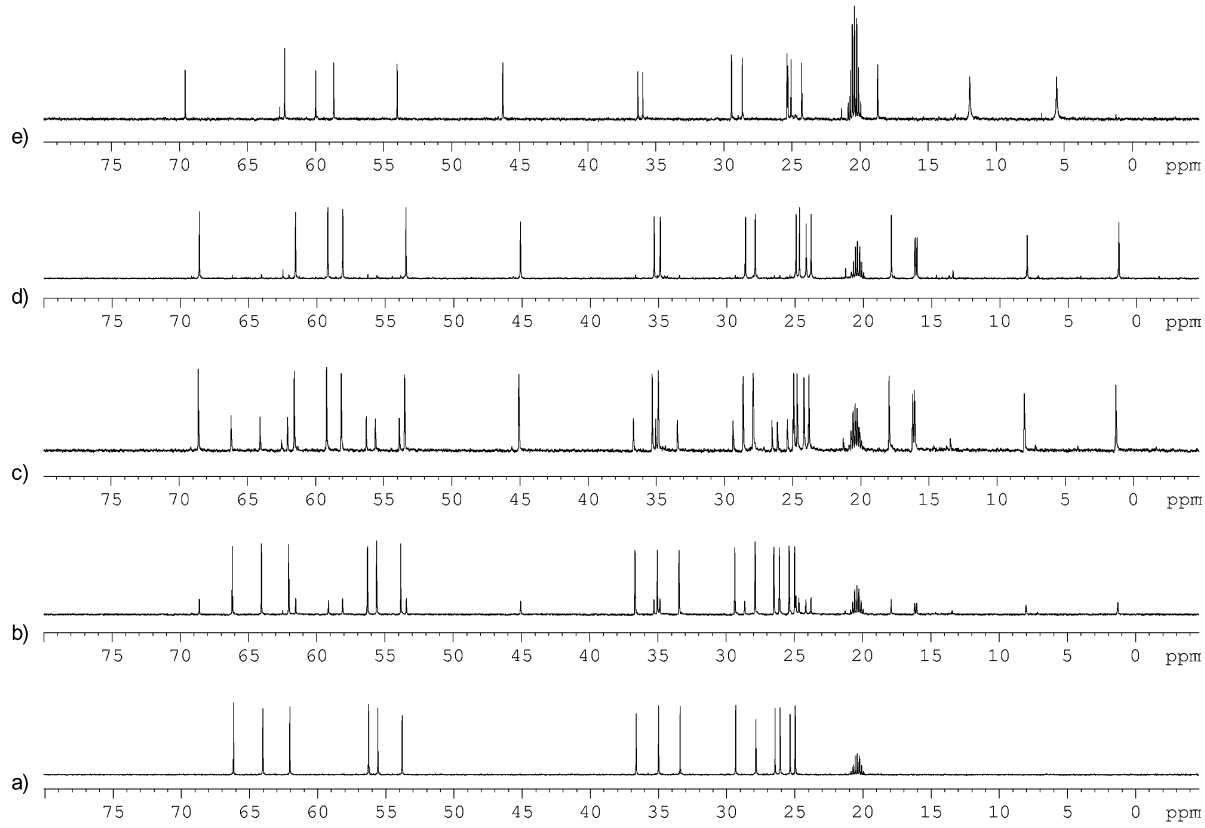
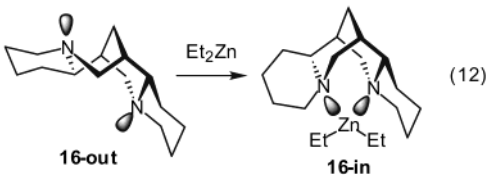


FIGURE 7. ^{13}C NMR spectra from titration of sparteine (**16**) with Et_2Zn in toluene-d_8 at 250 K (eq 12): (a) no Et_2Zn; (b) 0.5 equiv of Et_2Zn; (c) 1.0 equiv of Et_2Zn; (d) 1.25 equiv of Et_2Zn; (e) 3.25 equiv of Et_2Zn (355 K).

Zn[14] in toluene-d_8 at 250 K showed only **16-out** and **16-in** (eq 12, Figure 7). Initially, only **16-out** was observed, which is consistent with reports that this form is more stable.[15] After addition of 1.25 equiv of Et_2Zn, only **16-in** was observed, indicating a complete conformational shift in response to the additive. Notably, excess Et_2Zn did not cause **16-in** to switch back to **16-out**. Another titration study of **16** was performed with $LiClO_4$ at 250 K. Since **16** was not entirely soluble in CD_3CN, CD_3OD was added. Upon addition of 0.25−1.0 equiv of $LiClO_4$ (dissolved in CD_3CN), no **16-in** was observed. With excess $LiClO_4$ (2.5 equiv), the ratio of **16-in**:**16-out** increased to 1:1. Thus, a coordinating solvent like MeOH can inhibit chelation by sequestering the cation.



(12)

Comparison of the results from sparteine (**16**) and **7** provides insight into the structural features that promote metal chelation in molecules that can exchange between two conformational forms. In general, metal chelation is a favored process, which is supported by the increasing amount of "in" conformer with increasing amounts of metal, observed in both **16** and **7**. The key difference between **16** and **7** can be found in the structures of the putative 2:1 metal−diamine complexes.

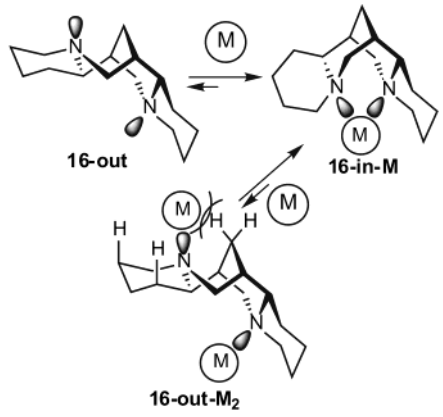


FIGURE 8. Plausible (−)-sparteine complexation pathway.

Analysis of **16** reveals that a 2:1 metal−diamine complex such as **16-out-M_2** would be disfavored due to unfavorable steric interactions from the bridging methylene (Figure 8). Since the predominate species is **16-in-M** even in the presence of the excess metal, it appears that **16-in-M** is the most thermodynamically stable adduct.[16] For diamine **7**, such a steric factor is not present and 2:1 metal−diamine complexes such as **7-out-Li_2** or **7-out-Zn_2** (see Scheme 3) can form. From the calculated free energies, the energy differences are not large enough to favor exclusive formation of **7-in-Li**. We conclude that

(14) An X-ray crystal structure of Me_2Zn and (−)-sparteine has been reported; see: Motevalli, M.; O'Brien, P.; Robinson, A. J.; Walsh, J. R.; Wyatt, P. B.; Jones, A. C. *J. Organomet. Chem.* **1993**, *461*, 5−7.

(15) Wysocka, W.; Bruwicki, T. *J. Mol. Struct.* **1996**, *385*, 23−33.

a metal-triggered "on/off" conformational switch under thermodynamic control in the presence of excess metal is only possible if the "out" conformer does not undergo double metal binding (in other words **16-in-M** is much more stable than **16-out-M_2**). A structurally less discriminating molecule such as diamine **7** will result in a mixture of conformational isomers and will be less likely to serve as an effective "on/off" switch.

Concluding Remarks

The azaalcohols (**3**−**5**) and azaamines (**6**, **7**) of both types of type II and III *cis*-decalins were synthesized and their conformational isomer ratios measured in various solvents. In general, the equilibria favor the "in" conformers more for type III than for type II. Furthermore, the "out" conformer of azaamines **6** and **7** is more stable than for the corresponding azaalcohols. Nonpolar solvents such as toluene stabilize the "in" conformer. The highly polar protic solvent MeOH shifts the equilibrium to the "out" conformer in all cases.

Neither lithium ion or Et_2Zn chelation with **7** caused complete formation of **7-in**. Instead, an increase in the ratio of "in":"out" was observed. This stands in contrast to (−)-sparteine (**16**) for which addition of Et_2Zn causes a complete conformational switch from "in" to "out". This phenomenon occurs because a 2:1 metal−sparteine complex is energetically unfavorable due to steric interactions with the second metal. Thus, even if chelation is a favored process, competition for formation of 1:1 and 2:1 complexes may result in a mixture of conformational isomers at equilibrium. For the successful development of a system in which a biconformational molecule undergoes a metal-dependent "on/off" switch from one conformer to another, the molecule must contain structural features that discourage formation of the 2:1 complex. Examination of compounds that exhibit these characteristics is underway and will be reported in due course.

Experimental Section

General Information. Unless otherwise noted, all nonaqueous reactions and distillations were carried out under an atmosphere of dry N_2 in dried glassware. When necessary, solvents and reagents were dried prior to use. THF and CH_2Cl_2 were dried and deoxygenated using a solvent column purification system. A 450 mL reactor (No. N4767 from Parr) was used for the high-pressure reactions with stirring by an external magnetic stirrer.

1-Methyl-octahydroquinolin-5-one (8). To a solution of **4** (200 mg, 1.2 mmol) in CH_2Cl_2 (50 mL) was added MnO_2 (5.14 g, 59 mmol), and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite and concentrated to give **8** (100 mg, 50%) as an oil: IR (film) 2943, 2862, 2778, 1709, 1447 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.12−1.31 (m, 1H), 1.36−1.40 (m, 1H), 1.68−1.74 (m, 3H), 1.96−2.03 (m, 3H), 2.11 (s, 3H), 2.13−2.20 (m, 3H), 2.37−2.45 (m, 2H), 2.76−2.73 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.3, 22.3, 23.9, 27.8, 41.1, 42.5, 49.4, 57.1, 65.0, 210.9; HRMS (CI^+) calcd for $C_{10}H_{18}NO$ (MH^+) 168.1388, found 168.1395.

1-Methyl-octahydroquinolin-5-one Oxime (9). To a solution of ketone **8** (100 mg, 0.6 mmol) in MeOH (2 mL) at 0 °C were added $NH_2OH{\cdot}HCl$ (46 mg, 0.66 mmol) and NaOAc (108 mg, 1.32 mmol). The solution was further stirred at 0 °C for 30 min. The mixture was concentrated into a solid residue and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (neutral Al_2O_3, 10% MeOH/CH_2Cl_2) yielded **9** (90 mg, 85%, 1.2:1.0 *E*/*Z* mixture) as an oil: IR (film) 3201, 2938, 2860, 2801, 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19−1.28 (m, 2H), 1.34 (m, 1H), 1.42−1.60 (m, 4H), 1.66−1.71 (m, 3H), 1.78−1.85 (m, 3H), 2.03 (dt, J = 4.6, 14.8 Hz, 1H), 2.16 (m, 1H), 2.24 (s, 2H), 2.35 (s, 3H), 2.44−2.61 (m, 4H), 2.71 (m, 1H), 3.72 (dt, J = 4.9, 11.7 Hz, 1H), 8.43 (bs, 1H), 8.60 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 20.9, 21.6, 21.8, 23.3, 23.6, 24.3, 24.6, 28.5, 29.7, 34.6, 42.0, 42.6, 42.7, 47.5, 52.0, 59.9, 62.5, 161.0, 162.2; HRMS (CI^+) calcd for $C_{10}H_{19}N_2O$ (MH^+) 183.1497, found 183.1489.

1-Methyl-decahydroquinolin-5-ylamine (10). A solution of oxime **9** (100 mg, 0.6 mmol) in glacial HOAc (3 mL) and PtO_2 (10 mg) was stirred under H_2 (50 psi) overnight at room temperature. The solution was filtered through a plug of cotton and concentrated to an oily residue, which was basified with cold 30% NaOH until pH > 14. The aqueous solution was then saturated with NaCl and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated to give amine **10** (81 mg, 80%) as an oil: IR (film) 3341, 2929, 2858, 2791, 1483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01−1.19 (m, 3H), 1.30−1.48 (m, 5H), 1.55−1.57 (m, 1H), 1.61−1.64 (m, 1H), 1.84 (dq, J = 12.9, 3.9 Hz, 1H), 2.21 (s, 3H), 2.29−2.36 (m, 2H), 2.54 (dt, J = 11.7, 4.5 Hz, 1H), 2.65 (dt, J = 4.2, 10.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.0, 16.5, 22.8, 24.9, 30.5, 42.9, 48.2, 52.5, 61.1; HRMS (CI^+) calcd for $C_{10}H_{19}N_2$ ($M - H^+$) 167.1548, found 167.1548.

(1-Methyl-decahydroquinolin-5-yl)-carbamic Acid *tert*-Butyl Ester (11). A solution of crude amine **10** (200 mg, 1.20 mmol) and Boc_2O (300 mg, 1.31 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 3 h. The solution was concentrated to an oily residue. Purification by chromatography (neutral Al_2O_3, 2.5% MeOH/CH_2Cl_2) yielded **11** (220 mg, 68%) as an oil: IR (film) 3339, 2932, 2863, 1707, 1364 cm^{-1}; ^1H NMR (500 MHz, 90 °C, toluene-d_8) δ (broad) 1.01−1.07 (m, 1H), 1.17−1.22 (m, 3H), 1.25−1.26 (m, 2H), 1.31−1.40 (m, 2H), 1.44 (s, 9H), 1.49−1.56 (m, 2H), 1.73 (m, 1H), 1.85 (m, 1H), 2.04 (s, 3H), 2.19 (m, 1H), 2.42 (m, 1H), 3.74 (bs, 1H), 5.20 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (broad) 15.6, 17.6, 22.8, 24.6, 27.6, 28.4, 39.7, 42.7, 48.0, 51.7, 60.7, 78.9, 155.1; HRMS (CI^+) calcd for $C_{15}H_{28}N_2O_2$ (M^+) 268.2151, found 268.2147.

Methyl (1-Methyl-decahydroquinolin-5-yl)amine (6). To a solution of **11** (115 mg, 0.43 mmol) in THF was added $LiAlH_4$ (163 mg, 4.3 mmol) at 0 °C. The mixture was heated to reflux overnight. Rochelle's salt (1.21 g, 4.3 mmol) was added at room temperature, and the mixture was stirred for 5 h, filtered, and concentrated. The residue was chromatographed (basic Al_2O_3, 15% MeOH/CH_2Cl_2) to provide **6** (70 mg, 99%) as an oil: IR (film) 3297, 2931, 2857, 2784, 1636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13−1.19 (m, 2H), 1.29 (qd, J = 13.0, 4.3 Hz, 1H), 1.46 (dt, J = 12.4, 4.1 Hz, 1H), 1.51−1.54 (m, 2H), 1.55−1.61 (m, 2H), 1.68 (m, 1H), 1.77−1.79 (m, 1H), 2.16 (dq, J = 12.9, 4.1 Hz, 1H), 2.36 (s, 3H), 2.38 (s, 3H), 2.40−2.51 (m, 3H), 2.67 (dt, J = 11.6, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.8, 16.9, 23.0, 25.2, 27.5, 33.6, 49.5, 48.4, 61.0, 61.1; HRMS (ES^+) calcd for $C_{11}H_{23}N_2$ (MH^+) 183.1681 found 183.1854.

1-Methyl-hexahydroquinoline-2,7-dione-7 Oxime (13). To a solution of ketone **12** (565 mg, 3.12 mmol) in MeOH (5 mL) at 0 °C were added $NH_2OH{\cdot}HCl$ (238 mg, 3.43 mmol) and NaOAc (562 mg, 6.86 mmol). The solution was stirred for 30 min at 0 °C during which a white precipitate was formed. The solution was concentrated to a solid residue and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (SiO_2, 10% MeOH/CH_2Cl_2) to provide oxime **13** (240 mg, 40%)

(16) Since similar six-membered chelates are involved in the complexed species of **7** and **16**, similar complexation energies were anticipated. Similar trends from addition of less than 1 equiv of $LiClO_4$ and Et_2Zn corroborate this estimate; however, a significantly stronger complexation energy for **16** relative to that for **7** would provide an alternate explanation for our observations.

as an oil: IR (film) 3174, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ + MeOH-d_4) δ 1.60−1.70 (m, 2H), 1.79−1.89 (m, 2H), 2.04−2.08 (m, 1H), 2.15−2.24 (m, 2H), 2.39−2.49 (m,5H), 2.66−2.70 (m, 1H), 2.90 (s, 3H), 3.98−3.12 (m, 1H), 3.34−3.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$ + MeOH-d_4) δ 19.4, 21.36, 21.40, 25.7, 26.6, 27.6, 28.7, 31.0, 31.1, 33.23, 33.29, 33.32, 33.33, 33.5, 59.3, 60.3, 156.2, 156.9, 170.11, 170.13; HRMS (ES^+) calcd for $C_{10}H_{17}N_2O_2$ (MH^+) 197.1290, found 197.1292.

7-Amino-1-methyl-octahydro-quinolin-2-one (14α + 14*β*). To oxime **13** (240 mg, 1.3 mmol) in glacial HOAc (3 mL) was added PtO_2 (20 mg), and the mixture was stirred under H_2 (40 psi) overnight at room temperature. The solution was filtered through a plug of cotton and concentrated to give an oily residue, which was basified with cold 30% NaOH until pH > 14. The aqueous solution was saturated with NaCl and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated to give crude **14**α and **14***β* as a 1.6:1 mixture (220 mg, 95%) in the form of an oil: IR (film) 3350, 2933, 1619 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16−1.46 (m, 3H), 1.46−1.69 (m, 3H), 1.69−2.20 (m, 3H), 2.30−2.43 (m, 2H), 2.61 (tt, J = 11.5, 3.8 Hz, 1H, α), 2.88 (s, 3H), 3.10 (bs, 1H, *β*), 3.20 (dt, J = 11.9 Hz, 1H, α), 3.59 (dt, J = 8.9, 4.3 Hz, 1H, *β*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 22.5, 23.8, 27.3, 28.4, 30.1, 30.3, 30.9, 31.5, 32.1, 32.6, 33.6, 35.6, 37.1, 45.3, 49.5, 56.1, 59.7, 68.9, 169.5, 170.1; HRMS (ES^+) calcd for $C_{10}H_{19}N_2O$ (MH^+) 183.1497, found 183.1488.

(1-Methyl-2-oxo-decahydro-quinolin-7-yl)-carbamic Acid *tert*-Butyl Ester (15α + 15*β*). To a solution of the epimeric mixture of amine **14** (220 mg, 1.21 mmol) in CH_2Cl_2 (5 mL) was added $(Boc)_2O$ (420 mg, 1.92 mmol) at room temperature, and the solution was stirred for 6 h. The solution was concentrated, and the mixture was purified by chromatography (SiO_2, 5% MeOH/dichloromethane) to afford **15** (318 mg, 86%) as an oil: IR (film) 3304, 2935, 1707, 1625, 1525, 1420 cm^{-1}; ^1H NMR (500 MHz, 90 °C, toluene-d_8) δ 0.78 (q, J = 12.0, 1.5H), 0.82−0.93 (m, 2H), 1.00−1.04 (m, 1.7H), 1.08−1.33 (m, 8H), 1.46 (s, 19H), 1.50−1.72 (m, 7H), 1.85−2.00 (m, 2.4H), 2.04−2.31 (m, 7.5H), 2.68 (s, 3H), 2.74 (m, 1.5H), 2.80 (s, 1.5H), 2.99 (m, 0.6H), 3.19 (m, 1.5H), 3.54 (m, 0.7H), 4.50 (bs, 0.6H); ^{13}C NMR (125 MHz, 90 °C, toluene-d_8) δ 22.4, 23.7, 25.0, 27.86, 27.89, 28.12, 28.14, 28.80, 28.83, 31.6, 32.0, 33.2, 33.5, 33.7, 34.1, 34.3, 46.2, 49.1, 49.2, 56.8, 59.8, 78.78, 78.85, 79.0, 155.18, 155.20, 168.1, 168.8; HRMS (ES^+) calcd for $C_{15}H_{27}N_2O_3$ (MH^+) 283.2022, found 283.2035.

Methyl (1-Methyl-decahydro-quinolin-7-yl) Amine (7α). To a solution of **15**α and *β* (580 mg, 2.05 mmol) in THF was added $LiAlH_4$ (781 mg, 20.56 mmol), and the mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and treated with Rochelle's salt (5.80 g, 20.56 mmol). After stirring 8 h at room temperature, the mixture was filtered and concentrated to provide **7** (300 mg, 80%) as an oil. Purification by chromatography (neutral Al_2O_3, 2% MeOH/CH_2Cl_2) yielded **7**α (100 mg): IR (film) 3399, 2928, 1446, 1380 cm^{-1}; ^1H NMR (500 MHz, 250 K, CD_3OD) δ 1.28−1.37 (m, 2H), 1.49 (q, J = 12.0 Hz, 1H), 1.55−1.68 (m, 4H), 1.68−1.73 (m, 1H), 1.76−1.78 (m, 1H), 1.94 (m, 2H), 2.37 (s, 3H), 2.44 (td, J = 11.8, 2.6 Hz), 2.52 (s, 3H), 2.67 (tt, J = 11.7, 3.6 Hz, 1H), 2.90 (dt, J = 12.4, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, 250 K, CD_3OD) δ 21.8, 23.4, 25.8, 26.0, 29.6, 31.8, 42.3, 48.3, 58.8, 60.4; HRMS (ES^+) calcd for $C_{11}H_{23}N_2$ (MH^+) 183.1861, found 183.1857.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM59945) and the University of Pennsylvania Research Foundation. Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The invaluable assistance of Dr. George Furst in collecting the NMR spectroscopic data is gratefully acknowledged.

Supporting Information Available: ^1H and ^{13}C NMR spectra of **8**−**11**, **13**, and **14**, low-temperature spectra for **3**−**7**, and HMQC, DEPT-135, COSY, and NOESY spectra of **4** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025544T