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Synthesis and conformational analysis of 2,6-dimethyl-1,5-diaza-*cis*-decalins

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Abstract—The stereoselective synthesis of 2,6-dimethyl-1,5-diaza-*cis*-decalins with the dimethyl groups *syn* or *anti* to the angular hydrogens has been accomplished starting from 1,5-diaza-*cis*-decalin. From an NMR study of the conformational properties of all three 2,6-dimethyl-1,5-diaza-*cis*-decalins, the components which affect the conformational equilibrium have been identified.

1. Introduction

1,5-Diaza-*cis*-decalins (Fig. 1) are unique diamine compounds which contain two amine functional groups as part of a *cis*-decalin framework. The two conformational isomers, *N*-in and *N*-out, when R=alkyl, can readily interconvert and the equilibrium between the two forms can be shifted by the additions of metals or acids.[1] As such, these compounds are potentially interesting chemically controllable conformational switches. In order to further examine these switches, compounds were desired in which the *N*-out form was stable under ordinary conditions and which when subjected to a metal source would undergo conversion to the *N*-in form. This goal could be accomplished by derivatizing the 1,5-diaza-*cis*-decalin core with groups that would be equatorial in the *N*-out form.

The conformationally well-defined 1,5-diaza-*cis*-decalin (R=H) is also the parent of a unique class of chiral diamine ligands. In the *N*-in conformation, the two amines can chelate a metal and, in doing so, position the metal within a well-defined chiral cavity.[2,3] A conformationally homogeneous system favoring the *N*-in conformation would serve to complex metals even if their complexation

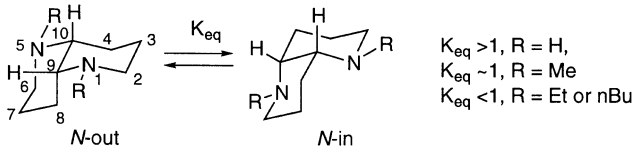

Figure 1.

constants are low. This goal could be accomplished by derivatizing the 1,5-diaza-*cis*-decalin core with groups that would be equatorial in the *N*-in form.[4,5] In addition, these substituents would allow the chiral cavity of the 1,5-diaza-*cis*-decalin to be extended and further defined.

Derivatization at the C^2 and C^6 positions of the 1,5-diaza-*cis*-decalins appeared the most straightforward means of achieving full conformational control of the structure to fulfill these goals. This paper describes the syntheses of the three isomeric 2,6-dimethyl-1,5-diaza-*cis*-decalins and the changes in the conformational properties of the 1,5-diaza-*cis*-decalins caused by methyl substitution.

2. Results and discussion

The synthesis of 2,6-dimethyl-1,5-diazadecalin with the C^2,C^6-methyl groups *syn* to the angular hydrogens began with compound **3** which had been prepared from **1** as illustrated in Scheme 1.[1] In the previous study,[1] the conformational behavior of **3** was rationalized and it was shown that **3** was isolated from the reaction medium as a mixture of two conformers (**3**-out and **3**-in) which interconvert slowly at 25°C. These two conformers can be purified by flash chromatography if special care is taken. Since the objective was to use **3** for the preparation of a C^2,C^6-dimethyl derivative, the stereochemical course of the lithiation with respect to each conformer would be important.

In the literature,[6] it has been reported that the Boc group directs alkylation to an equatorial position α to nitrogen in Boc-piperidine derivatives (Eq. (1)). If a second alkylation takes place on this conformationally-locked system (Eq. (2)), the net result is a *trans*-2,6-disubstituted compound. Steric hindrance between the Boc group and the adjacent

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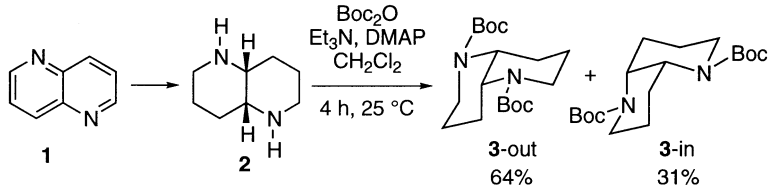
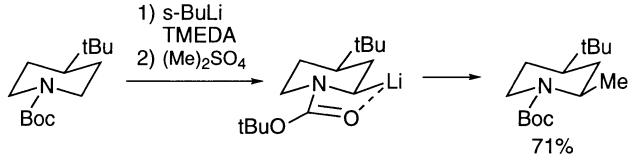
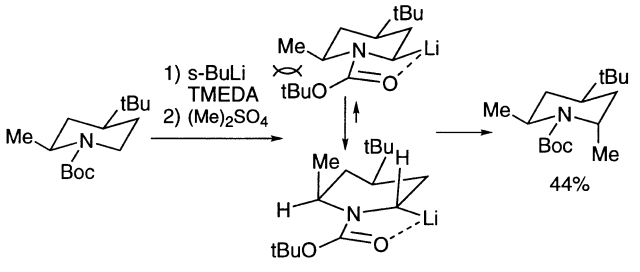


Scheme 1.

equatorial methyl group disfavors formation of the equatorial lithium species in the chair conformation. Rather, a twist-boat conformation develops in which equatorial lithiation occurs.[7] In systems in which the substituent adjacent to the nitrogen is axial (Eq. (3)),[8] such a steric interaction does not arise and the normal equatorial lithiation/alkylation pathway predominates. Overall, lithiation of Boc-piperidines occurs at the less substituted position α to nitrogen and *trans* to a group on more substituted position α to nitrogen regardless of its orientation (equatorial or axial).[9]



(1)



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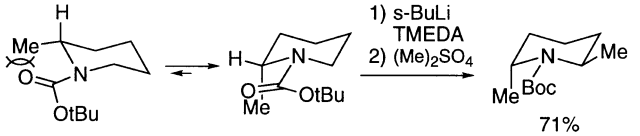
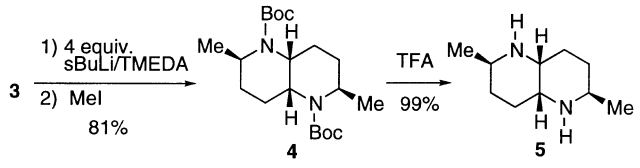


(3)

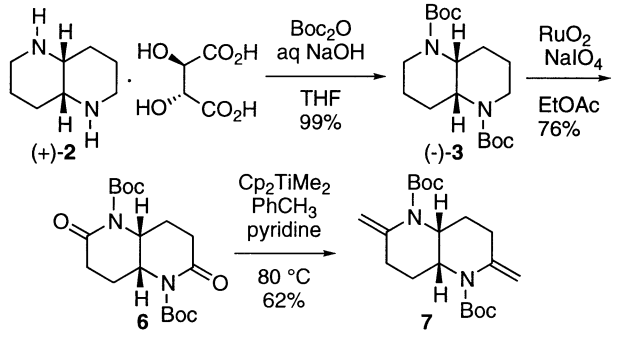
In the case of transforming **3** to **4** via dilithiation/dialkylation, a similar situation arises (Scheme 2). Treatment with two equivalents of sBuLi/TMEDA should lithiate the less hindered position α to the nitrogen in each ring of symmetric **3**. Using the principles from Eqs. (1)–(3), both **3**-out and **3**-in Scheme 1 are expected to undergo lithiation *trans* to the only α-amino substituents present (the ring fusion) regardless of the orientation (the ring fusion is axial for **3**-out and equatorial for **3**-in). This should cause equatorial lithiation for **3**-out and apparent axial lithiation for **3**-in, both of which produce the same stereochemical result. As such, the conformation of **3** is not expected to effect the overall course of the lithiation/alkylation and **4** should be the only product.



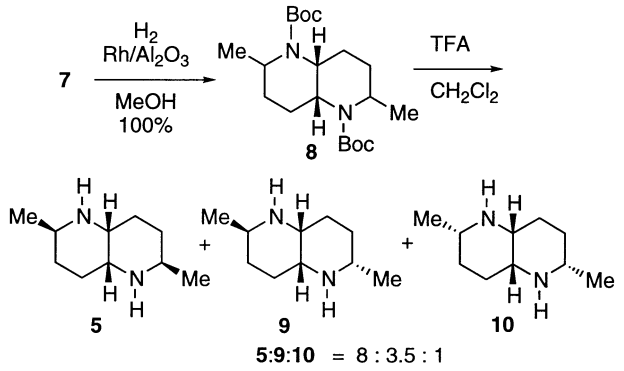
Scheme 2.

Treatment of **3**-out as a single conformer with excess sBuLi/TMEDA followed by MeI produced one product in 81% yield which proved to be **4** (Scheme 2). Due to the Boc rotamers in **4**, the stereochemical determination was more readily made with the free diamine **5** after cleavage of the *N*-Boc groups with TFA (see below). As anticipated, alkylation had occurred on the *exo* face to produce **4** with the two C^2,C^6-methyl groups *syn* to the angular hydrogens. When a mixture of both conformers of **3** was alkylated under the same conditions, only **4** was observed providing experimental confirmation of the above hypothesis. Since the alkylation reaction was performed at a temperature (−78 to −35°C) at which conformational inversion does not occur,[1] the two conformers indeed appear to react via separate mechanisms. This result facilitates the preparation of **5** since there is no need to separate the isomeric forms of **3**, or even equilibrate them.

The synthesis of 2,6-dimethyl-1,5-diazadecalin with the C^2,C^6-methyl groups *anti* to the angular hydrogens began with the resolved tartrate salt of (+)-1,5-diaza-*cis*-decalin **2**,[2] which was directly converted to the corresponding *N,N′*-diBoc compound (−)-**3** by treatment with di-*tert*-butyl dicarbonate in the presence of aqueous NaOH (Scheme 3).[10] Protected diamine (−)-**3** was conveniently oxidized to the corresponding bislactam **6** using catalytic RuO_2 with excess 10% aqueous $NaIO_4$ in a two-phase EtOAc-H_2O system.[11] The subsequent chemoselective methylenation of the lactam carbonyl group was accomplished using dimethyltitanocene as the methylenation reagent. In related compounds, Herdeis et al.[12] have proposed that the



Scheme 3.



Scheme 4.

carbamate group serves both to protect the nitrogen and to activate the neighboring amide moiety.

With compound **7** in hand, catalytic hydrogenation of exocyclic double bonds was undertaken using Rh/Al_2O_3 as the catalyst. The reduced product was obtained in quantitative yield, but a complex mixture was observed which resisted characterization due to the carbamate rotamers and decalin conformers. Deprotection of *N,N′*-diBoc diamine **8** was readily achieved using TFA providing the three resultant isomers **5**, **9**, and **10** (**5:9:10**=8:3.5:1) which could be separated by column chromatography on basic Al_2O_3 (Scheme 4).

The structures of **5**, **9**, **10** were determined by ^1H and ^{13}C NMR spectral analysis. In the ^{13}C NMR spectra of **5** and **10**, only five peaks were found indicating that the compounds possessed C_2-symmetry. In contrast, 10 peaks were found in the ^{13}C NMR spectrum of **9**. On this basis, **9** was assigned as the non-C_2-symmetric derivative with one methyl group *syn* to the ring fusion and one methyl group *anti*.

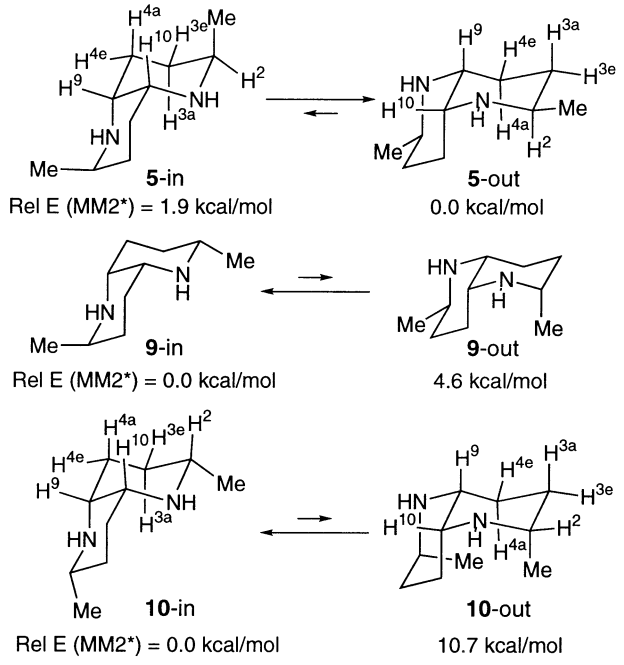


Figure 2.

Table 1. Calculated and experimental coupling constants for the C_2-symmetric 2,6-dimethyl-1,5-diazadecalin isomers

Coupling	*J* (Hz) calcd[a]				*J* (Hz) expt.[b]	
	5-in	**5**-out	**10**-in	**10**-out	**5**-out	**10**-in
H^2–H^{3a}	5.0	**11.8**	**11.8**	5.3	**11.3**	**11.2**
H^2–H^{3e}	1.8	3.2	3.2	1.7	2.7	2.4
H^{3e}–H^{4a}	3.9	3.9	3.8	3.7	3.5	4.8
H^{3e}–H^{4e}	2.7	2.6	2.7	2.9	3.4	2.7
H^{3a}–H^{4a}	13.3	13.4	13.5	13.4	13.1	13.0
H^{3a}–H^{4e}	4.0	3.8	3.7	3.7	3.8	4.5
H^{4e}–H^9	2.7	4.0	2.7	3.6	4.0	2.7
H^{4a}–H^9	3.7	**11.7**	**3.6**	11.8	**13.6**	**4.0**

[a] Calculated using MacroModel 6.0.
[b] Values determined by simulation with PPC gNMR to reproduce the second order multiplets observed in the ^1H NMR spectra.

Close examination of the coupling patterns of the remaining two compounds **5** and **10** permitted assignment of the relative stereochemistry and the conformation of the decalin ring system for each (Fig. 2 and Table 1).[13,14] From ^1H-^1H COSY spectra, the H^2 of **5** and **10** was readily assigned on the basis of a crosspeak with the C^2-methyl group. In addition, the connectivity pattern of the ^1H-^1H COSY spectra allowed definitive assignment of H^3, H^4, and H^9. In **10**, H^2 undergoes one large (axial–axial) and one small coupling (axial–equatorial) with the two adjacent H^3 protons, implying that H^2 must be axial. Similarly, the angular hydrogen, H^9, can be assigned as equatorial due to two smaller couplings with the adjacent two H^4 protons. Comparison of calculated with the experimentally measured coupling constants (Table 1), reveals that such an arrangement is only possible if **10**-in is the predominant form. In **5**, H^2 and H^9 are both axial which is only consistent with **5**-out as the predominant form (Table 1).

Finally, an X-ray structure of crystalline **5** confirmed the configurational and conformational assignments (Fig. 3).[15]

Interestingly, from the NMR spectra of both **5** or **10**, one conformational form appears to greatly predominate for each. As described above, compound **5** is observed mainly in the **5**-out conformation with both methyl groups equatorial while **10** is observed mainly in the **10**-in conformation with both methyl groups equatorial. Since the parent, 1,5-diaza-*cis*-decalin lacking the C^2,C^6 dimethyl substitution mainly populates the *N*-in conformation under identical conditions ($CDCl_3$, rt), the equatorial orientation of the

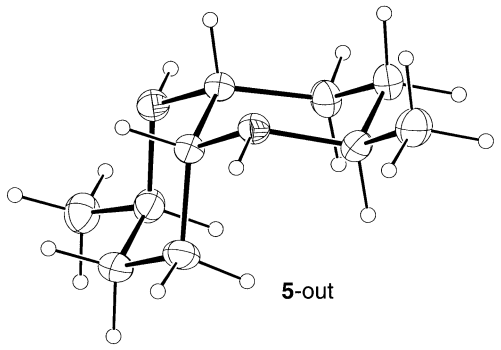
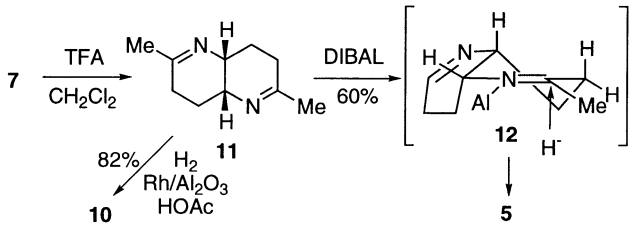


Figure 3. X-Ray structure of **5**.



Scheme 5.

additional methyl groups appears to dominate the conformational stability of these derivatives.[16] The NMR spectra of the isomer which has one Me *syn* and one Me *anti* to the angular hydrogens (**9**) was also examined. In this case, the coupling constants of H^9 and H^{10} were critical. For both of these protons, small vicinal couplings were observed (J=2.4 Hz) consistent only with the **9**-in as the predominant conformation. The greater stability of **9**-in over **9**-out is also expected, since the axial methyl group oriented toward the concave portion of the *cis*-decalin in **9**-out will have an $A^{1,3}$ and TMEDA interaction with a methylene and hydrogen, while the axial methyl group in **9**-in which is oriented towards the convex face undergoes $A^{1,3}$ interactions with only two hydrogens. Calculations of the relative energies (see Fig. 2) of the *N*-in and *N*-out conformations of **5**, **9**, and **10** using MM2* in MacroModel[13] were consistent with the experimental results. Overall, the conformational equilibria of **5**, **9**, and **10** were not controlled by the 1,5-diaza-*cis*-decalin core in which case the *N*-in form should have predominated.[16] Rather the substituent methyl groups directed the stability and the predominant conformers possessed the least disfavorable $A^{1,3}$ diaxial interactions.

Since the routes outlined above generate **5** as the predominant component, an alternative sequence toward **10** was developed. Reasoning that reduction of an endocyclic olefin (**11**) would be more selective than that of an exocyclic olefin, compound **7** was treated with TFA in CH_2Cl_2 which removed the Boc groups and isomerized the resultant bisenamine to provide bisimine **11**. The subsequent reduction of **11** with DIBAL provided **5** almost exclusively. Presumably, axial hydride delivery occurred on a conformation (**12**) which minimizes $A^{1,3}$-strain between the coordinated imine and the adjacent ring fusion. However, hydrogenation of **11** with Rh/Al_2O_3 in the presence of acetic acid permitted reduction from the less hindered convex face affording **10** in good yield. Since the previous methods generate **5** as the major product, these methods are complementary (Scheme 5).

3. Conclusion

In conclusion, the three isomers of 2,6-dimethyl-1,5-diaza-*cis*-decalin have been prepared starting from 1,5-diaza-*cis*-decalin. In particular, stereoselective syntheses of the C_2-symmetric isomers **5** and **10** were achieved. On the basis of NMR analyses of the stereoisomers of the 2,6-dimethyl-1,5-diaza-*cis*-decalins, the isomer with the C^2,C^6-methyl groups *syn* to the angular hydrogens (**5**) was found to exist in the *N*-out conformation while the isomer with the C^2,C^6-methyl groups *anti* to the angular hydrogens (**10**) was found to exist in the *N*-in conformation. The predominance of the *N*-in conformation for the isomer containing the C^2,C^6-methyl groups *anti* to each other (**9**), confirms that an axial methyl group on the concave face of a *cis*-decalin is more disfavorable compared to an axial methyl group on the convex face of a *cis*-decalin. As such, compounds like **10** are unlikely to undergo conformational exchange to the *N*-out form and should act as rigid chelating diamine ligands due to the *N*-in arrangement. Treatment with even weakly chelating metals would result in the metal being positioned within a well-defined extended chiral cavity. The application of such complexes is being pursued. Future work will also address the application of the other isomer (**5**) and related derivatives (i.e. with functional groups such as alkynes in place of the methyl groups) as chemically controllable conformational switches. Based on observations for **9** that axial methyl groups on the convex face are not as destabilizing, isomer **5** which ordinarily exists in the *N*-out form should isomerize to the *N*-in form upon addition of strongly chelating metals.

4. Experimental section

4.1. General

Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N_2 in dried glassware. When necessary, solvents and reagents were dried prior to use. Toluene, Et_2O, THF, and CH_2Cl_2 were de-oxygenated by purging with Ar and then dried by passing through activated alumina. MeI was distilled prior to use. Pyridine was distilled from CaH_2 and TMEDA was distilled from Na.

Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 60-F plates. Visualization was accomplished with UV light. Chromatography on silica gel was performed using a forced flow of solvent on EM Reagents Silica Gel 60 (230–400 mesh). NMR spectra were recorded on Bruker AM-500, AM-250, or AM-200 spectrometers. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants, and number of protons. Mass spectra were obtained on a low resonance Micromass Platform LC in electron spray mode and high resonance VG autospec with an ionization mode of either CI or ES. IR spectra were taken on a Perkin-Elmer FT-IR spectrometer. Melting points were obtained on Thomas Scientific Unimelt apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 and are reported as $[\alpha]_\lambda^T$, (c=g/100 mL, solvent).

4.1.1. (±)-(2*R*,6*R*,9*R*,10*R*)-*N*,*N*′-Di-*tert*-butoxycarbonyl-2,6-dimethyl-1,5-diaza-*cis*-decalin (4). To a solution of **3**[1] (0.30 g, 0.88 mmol) and TMEDA (0.53 mL, 3.53 mmol, 4.0 equiv.) in Et_2O (6.0 mL) at −78°C was slowly added a 1.0 M solution of s-BuLi in hexane (3.53 mL, 3.53 mmol, 4.0 equiv.). The temperature was slowly raised to −35°C and the mixture stirred for 2.3 h. The temperature was then lowered again to −78°C and MeI (0.22 mL, 3.53 mmol, 4.0 equiv.) was slowly added. The reaction was stirred for about 6 h, with the temperature slowly rising to ambient. A saturated solution of NaCl (6.0 mL) was added and the

mixture was stirred for a few minutes. The organic layer was separated and the aqueous phase extracted with Et_2O (3×4 mL). The organic extracts were combined and dried with anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography (10% EtOAc/pet. ether). Compound **4** was obtained as white crystals (0.26 g, 81%).

Further characterization was accomplished after removing the Boc groups. Compound **4** was treated directly with neat TFA for 10 min, made basic, and extracted to yield the corresponding free diamine **5** (0.12 g, 99%) which possessed spectral data identical to that prepared via **8** (see below).

4.1.2. (9*R*,10*R*)-*N*,*N*′-Di-*tert*-butoxycarbonyl-1,5-diaza-*cis*-decalin (3). A mixture of (9*R*,10*R*)-1,5-diaza-*cis*-decalin (*R*,*R*)-tartrate salt (**2**, 1.51 g, 5.19 mmol),[2] NaOH (2.03 g, 50.6 mmol) and ice water (20 mL) was cooled in an ice bath and then a solution of Boc_2O (4.68 g, 21.4 mmol) in THF (40 mL) was added dropwise. The resulting mixture was stirred for 10 min and then the ice bath was removed. After stirring further at rt for 21 h, the organic solvent was removed in vacuo, and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over K_2CO_3. After concentration, the residue was chromatographed (SiO_2; 15% EtOAc/hexanes) to give (−)-**3** (1.75 g, 99%) with spectral data matching that previously reported.[1] R_f=0.51 (50% EtOAc/hexanes); $[\alpha]_D^{20}$=−16.1 (*c* 3.07, $CHCl_3$).

4.1.3. (9*R*,10*R*)-*N*,*N*′-Di-*tert*-butoxycarbonyl-2,6-dioxo-1,5-diaza-*cis*-decalin (6). To a solution of $NaIO_4$ (11.95 g, 55.8 mmol) in water (100 mL) was added RuO_2xH_2O 0.16 g, 1.2 mmol) generating a bright yellow solution followed by a solution of (−)-**3** (1.75 g, 5.15 mmol) in EtOAc (150 mL). The resulting mixture was vigorously stirred in a sealed flask at rt for 20 h. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered through celite to remove a black precipitate, and concentrated. The residue was chromatographed (SiO_2; 30% EtOAc/hexanes) to afford **6** (1.45 g) in 76% overall yield from **2**. R_f=0.27 (50% EtOAc/hexanes); Mp 100–101.5°C; $[\alpha]_D^{20}$=−100.0 (*c* 1.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (dm, *J*=11.7 Hz, 2H), 2.59–2.63 (m, 4H), 2.26–2.32 (m, 2H), 1.95–2.02 (m, 2H), 1.53 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 152.2, 83.8, 53.2, 32.5, 27.9, 24.3; IR (film) 1770, 1717, 1149 cm^{-1}; MS (ES) *m/z* 391.3 (MNa^+); Anal. calcd for $C_{18}H_{28}N_2O_6$: C, 58.68; H, 7.66; N, 7.60. Found: C, 58.84; H, 7.94; N, 7.40.

4.1.4. (9*R*,10*R*)-*N*,*N*′-Di-*tert*-butoxycarbonyl-2,6-dimethylene-1,5-diaza-*cis*-decalin (7). Dimethyltitanocene was prepared according to a procedure analogous to that described by Dollinger et al.[17] Cp_2TiCl_2 (6.25 g, 25.1 mmol) and toluene (75 mL) was added to a dry Schlenk flask. The resulting mixture was degassed and then cooled in an ice-salt bath (−15°C) under N_2. A solution of MeLi in Et_2O (1.6 M, 36.5 mL, 58.4 mmol) was added dropwise. The mixture was stirred at −15 to −5°C for 3 h and then was allowed to stand in a 0°C freezer overnight. The reaction mixture was quenched with ice-cold saturated brine (50 mL). The organic layer was separated, and the aqueous phase was extracted once with toluene. The combined organic layers were dried over $MgSO_4$ and filtered through filter paper to give a red solution which was suitable for use without further purification. To this Cp_2TiMe_2 solution in toluene, were added dry pyridine (2 mL) and **6** (1.45 g, 3.93 mmol) in toluene (20 mL). The mixture was degassed and then heated at 80°C for 18 h under N_2. The solvent was removed in vacuo, and the residue was chromatographed twice (SiO_2; 10% EtOAc/hexanes for the first column and 5% for the second) to afford **7** (0.889 g, 62%). R_f=0.40 (25% EtOAc/hexanes); $[\alpha]_D^{20}$=−192.9 (*c* 1.41, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.93 (s, 2H), 4.78 (s, 2H), 4.35–4.39 (m, 2H), 2.15–2.30 (m, 4H), 1.63–1.83 (m, 4H), 1.45 (s, 18H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 193.8, 140.3, 108.6, 80.3, 51.7, 31.6, 28.3, 24.6; IR (film) 1691, 1651, 1298 cm^{-1}; HRMS (ES) calcd for $C_{20}H_{32}N_2O_4Na$ (MNa^+) 387.2260, found 387.2262.

4.1.5. (9*R*,10*R*)-*N*,*N*′-Di-*tert*-butoxycarbonyl-2,6-dimethyl-1,5-diaza-*cis*-decalin (8). A mixture of **7** (0.878 g, 2.4 mmol), 5% Rh/Al_2O_3 (0.30 g) in MeOH (25 mL) was placed under 180 psi H_2 at rt. After 35 min, the pressure of H_2 was reduced to 140 psi, and after 7 h, to 120 psi. After an additional 28 h, the catalyst was filtered off. The filtrate was concentrated, and the residue was chromatographed (SiO_2; 10% EtOAc/hexanes) to give **8** (0.887 g, 100%) as an inseparable mixture of isomers. R_f=0.37 (25% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18–4.49 (m, 2H), 3.80–3.93 (m, 2H), 2.25–2.33 (m, 2H), 1.93–2.00 (m, 2H), 1.72–1.78 (m, 1H), 1.56–1.62 (m, 2H), 1.35–1.41 (m, 1H), 1.46 (s, 18H), 1.21 (d, *J*=6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 79.3, 47.9, 46.1, 28.5, 26.4, 23.5, 20.9; IR (film) 1688, 1365, 1173 cm^{-1}; HRMS (ES) calcd for $C_{20}H_{37}N_2O_4$ (MH^+) 369.2753, found 369.2737.

4.1.6. (2*R*,6*R*,9*R*,10*R*)-2,6-Dimethyl-1,5-diaza-*cis*-decalin (5) and (2*R*,6*S*,9*R*,10*R*)-2,6-dimethyl-1,5-diaza-*cis*-decalin (9) from 8. A solution of **8** (0.887 g, 2.4 mmol) and TFA (5 mL) in CH_2Cl_2 (30 mL) was stirred at rt for 11 h, and then the solvents were removed in vacuo. The residue was treated with 30% NaOH, and extracted three times with $CHCl_3$. The combined organic layers were dried over K_2CO_3. After the solvent was evaporated under reduced pressure, the residue was chromatographed (basic Al_2O_3; 2% MeOH/CH_2Cl_2 for first fraction **10** (0.017 g, 4%), 5% MeOH/CH_2Cl_2 for second fraction **9** (0.058 g, 14%), and then 10% MeOH/CH_2Cl_2 for third fraction **5** (0.126 g, 31%).

9: R_f=0.43 (10% MeOH/CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.22–3.26 (m, 1H), 2.84–2.87 (m, 1H), 2.61–2.63 (m, 1H), 2.52–2.59 (m, 1H), 1.82–1.87 (m, 2H), 1.41–1.65 (m, 4H), 1.17–1.33 (m, 4H), 1.12 (d, *J*=7.0 Hz, 3H), 1.01 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 53.4, 52.4, 47.3, 44.4, 30.9, 28.7, 25.7, 24.6, 22.8, 17.4.

5: R_f=0.37 (10% MeOH/CH_2Cl_2); mp 116–118°C; $[\alpha]_D^{20}$=+21.3 (*c* 1.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)[14] δ 3.090 (ddd, *J*=4.00, 5.65, 13.60 Hz, 1H), 3.091 (ddd, *J*=4.00, 5.65, 13.60 Hz, 1H), 2.85 (dqd, *J*=2.7, 6.2, 11.3 Hz, 2H), 2.02 (dddd, *J*=3.5, 12.5, 13.1, 13.6 Hz, 2H), 2.01 (br s, 2H), 1.72 (dddd, *J*=2.7, 3.4, 3.5, 13.1 Hz, 2H), 1.49 (dddd, *J*=3.4, 3.8, 4.0, 12.5 Hz, 2H),

1.14 (dddd, J=3.8, 11.3, 13.1, 13.1 Hz, 2H), 1.02 (d, J=6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.7, 44.3, 34.8, 25.3, 22.8; IR 3406, 2928 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{20}N_2$ (M^+) 168.1626, found 168.1632.

4.1.7. (9*R*,10*R*)-2,6-Dimethyl-3,4,7,8,9,10-hexahydro-1,5-naphthyridine (11). A solution of **7** (1.154 g, 3.17 mmol) and TFA (7 mL) in CH_2Cl_2 (40 mL) was stirred at rt for 24 h, and then the volatiles were removed in vacuo. The residue was treated with 5% NaOH, and extracted twice with CH_2Cl_2. The combined organic layers were dried over $K_2CO_3/MgSO_4$. Filtration and concentration yielded bisimine **11**, which was unstable and was used in the next step without further purification. R_f=0.67 (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (br s, 2H), 2.02–2.13 (m, 4H), 1.89 (br s, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 52.6, 27.2, 27.0, 25.2.

4.1.8. (2*R*,6*R*,9*R*,10*R*)-2,6-Dimethyl-1,5-diaza-*cis*-decalin (5) from 11. To a solution of **11** (prepared from 0.093 g of **7** as described above) in CH_2Cl_2 (5 mL) was added DIBAL (1.0 M in hexanes, 1 mL) at −78°C under N_2. The resulting mixture was stirred overnight, with the temperature slowly rising to ambient. After 18 h, MeOH (1 mL) was added and the mixture was stirred at rt overnight, filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated and purified by chromatography to afford 0.021 g (60%) of **5**, which possessed identical spectral data to that described above.

4.1.9. (2*S*,6*S*,9*R*,10*R*)-2,6-Dimethyl-1,5-diaza-*cis*-decalin (10) from 11. A mixture of **11** (prepared from 1.154 g of **7** as described above) and 5% Rh/Al_2O_3 (0.122 g) in MeOH (5 mL) /HOAc (5 mL) was placed under 160 psi H_2 at rt. After 36 h, the mixture was diluted with CH_2Cl_2 and washed with 30% NaOH. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over K_2CO_3. After the solvent was evaporated under reduced pressure, the residue was chromatographed (basic Al_2O_3; 2% MeOH/CH_2Cl_2) to give 82% of **10** (0.435 g) in two steps from **7**. Further purification could be accomplished by sublimation to yield pure **10** (0.261 g). Chromatography of the residue from sublimation (basic Al_2O_3; 1% MeOH/CH_2Cl_2) provided additional pure **10** (0.119 g) for a total purified yield of 71%. R_f=0.51 (10% MeOH/CH_2Cl_2); Mp 67.5–69.0°C; $[\alpha]_D^{20}$=+45.6 (c 1.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)[14] δ 2.681 (ddd, J=2.7, 2.8, 4.0 Hz, 1H), 2.680 (ddd, J=2.7, 2.8, 4.0 Hz, 1H), 2.64 (dqd, J=2.4, 6.3, 11.2 Hz, 2H), 1.71 (dddd, J=2.4, 2.7, 4.8, 13.0 Hz, 2H), 1.66 (dddd, J=4.0, 4.8, 13.0, 13.0 Hz, 2H), 1.56 (br s, 2H), 1.355 (dddd, J=2.7, 2.7, 4.5, 13.0 Hz, 2H), 1.245 (dddd, J=4.5, 11.2, 13.0, 13.0 Hz, 2H), 1.07 (d, J=6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.9, 52.7, 31.3, 29.1, 23.0; IR (film) 3242, 2922 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{20}N_2$ (M^+) 168.1626, found 168.1631; Anal. calcd for $C_{10}H_{20}N_2$: C, 71.38; H, 11.98; N, 16.64. Found: C, 71.24; H, 12.24; N, 17.13.

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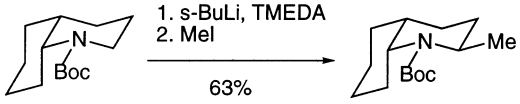

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