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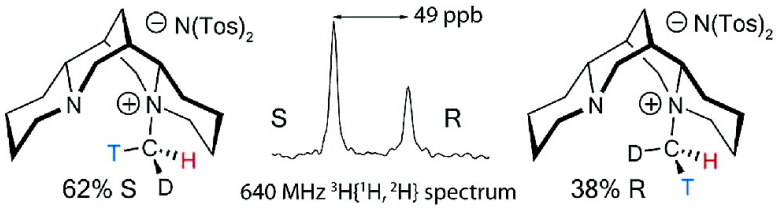

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An Isosparteine Derivative for Stereochemical Assignment of Stereogenic (Chiral) Methyl Groups Using Tritium NMR: Theory and Experiment

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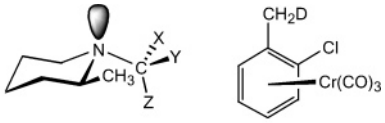
Abstract: (*N*-CHDT)-(α)-isosparteinium ditosylamide can be used in conjunction with tritium NMR spectroscopy to assign the configuration of an intact stereogenic (chiral) methyl group. The *S*-CHDT group has a ^{3}H chemical shift that is 49 ppb downfield of the *R*-CHDT resonance. The sign and magnitude of this chemical shift difference of these diastereotopic tritium nuclei are found to be in agreement with predictions made via a purely ab initio computational approach. The chemical shift difference is due to an equilibrium isotope effect originating from a novel $CH_3\cdots N$ hydrogen bond. Despite the improved tritium chemical shift dispersion, this method is not useful for determining the enantiopurity of $CHDTN(Tos)_2$ due to partial racemization that occurs during the derivatization step. Milder methylation conditions are described for reactions using methyl *p*-toluenesulfonate or methyl-d_3 triflate. These studies suggest that (−)-(α)-isosparteine is a potential new reagent for chirality analysis of methyl groups originating from suitably reactive electrophiles.

Introduction

The stereogenic (so-called chiral) methyl group has had significant utility in the mechanistic analysis of biosynthetic pathways involving methyl transfer reactions.[1] Configurational assignment of X-CHDT requires unique methodology due to the subtle structural features of this center of chirality. The original reports by the Cornforth and Arigoni laboratories described an enzymatic method that allowed assignment of configuration of chiral acetic acid based on a primary kinetic isotope effect and subsequent radiochemical assay of reaction products.[2,3] Reaction products arising from biochemical transformations of chiral methyl groups have also been analyzed with tritium NMR.[4]

In a conceptually different approach, Anet and Floss demonstrated that the configuration of *intact* chiral methyl groups could be directly analyzed with tritium NMR.[5,6] A prerequisite is an electrophilic agent as the chiral methyl source. The method involves reacting the ditosylate of chiral methylamine, $CHDTN(Tos)_2$, with excess 2-methylpiperidine for 24 h at 130 °C to provide (*N*-CHDT)-2-methylpiperidine (**1a**). In the demonstration case, the ditosylate was enriched in one enantiomer and the methylation was found to proceed with complete conversion and clean inversion. The observed chemical shift difference between the externally diastereotopic[7,8,9] tritium nuclei was found to be 14 ppb.



1a: X = H, Y = D, Z = T
1b: X = Y = H, Z = D

2

The Anet method was based on an NMR-observable equilibrium isotope effect[10,11] in (*N*-CH_2D)-2-methylpiperidine (**1b**) that causes the internally diastereotopic *N*-CH_2D protons to have different chemical shifts (these protons are also anisochronous by 14 ppb, with the *pro-R* proton shielded relative to the *pro-S* proton in (2*S*)-(*N*-CH_2D)-methylpiperidine).[12] The principal

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origin of the isotope effect is *n*-σ^* hyperconjugation involving the nitrogen lone pair of electrons and the anti methyl C−H(D) sigma bond. As the anti bond is weaker than the two gauche C−H(D) bonds, the molecule gains zero-point vibrational stabilization when deuterium partitions into the gauche bonds. A similar effect was investigated for (α-deutero-*o*-chlorotoluene)chromium tricarbonyl (**2**); a chemical shift difference of 8 ppb was found between the CH_2D protons.[13] Large equilibrium isotope effects are also known for organometallic $-CH_2D$ groups subject to agostic conformational perturbation, although to the best of our knowledge, a diastereotopic chemical shift difference has not been observed in these systems.[14,15] Each of the aforementioned molecules employs an isotope effect to cause a conformational perturbation for the methyl group. Alternatively, Courtieu has shown that a chiral liquid crystalline matrix can be used to partially align CHD_2OH to provide anisochronous ^2H NMR signals separated by 78 ppb.[16]

Although the enzymatic chirality analysis of acetic acid is a sensitive assay, it is usually only reproducible to ±7% ee.[17] Alternatively, tritium NMR analysis of intact chiral methyl groups can provide a very accurate measure of enantiopurity. One of the difficulties in implementing the NMR method with 2-methylpiperidine, however, is the relatively small chemical shift separation between the diastereotopic tritium chemical shifts. This small chemical shift separation results in slightly overlapping lines and requires careful integration or spectral deconvolution, even when the analysis is conducted at a tritium NMR frequency of 640 MHz.[18]

To improve on the NMR method, we sought to discover a molecule that would foment a larger chemical shift difference than the 1,2-dimethylpiperidine example. In so doing, we also wished to employ a fundamentally different type of equilibrium isotope effect to perturb the methyl rotameric equilibrium. Based on our work with isotopic perturbation of hydrogen bonding interactions[19] among hydroxyl groups, we hoped to utilize a novel C−H···X hydrogen bond to render the methyl C−H bonds suitably different from the bond strength standpoint (Figure 1).

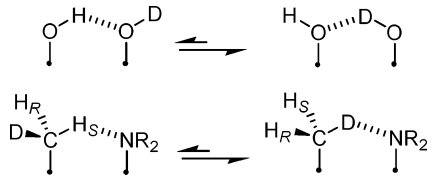
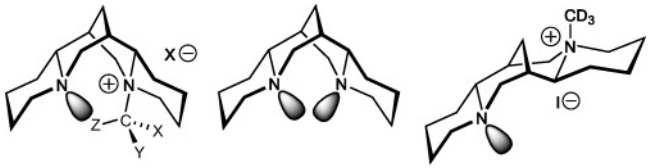


Figure 1. Design principle for provoking an equilibrium isotope effect to perturb the rotational equilibrium of an isotopically labeled methyl group.

In the OH/OD system, deuterium has a preference for the bridging position,[20] which is counterintuitive when one considers a reduced O−H stretching frequency is a hallmark of the hydrogen bond. However, theoretical studies of partially deuterated HF[21] and water dimer[22] systems have shown that while the major stretching frequency is reduced on formation of the hydrogen bond, frequencies of several bending and torsional modes increase more than enough to compensate. At the outset of our study, it was unknown whether the same behavior would operate in the hydrogen-bond-perturbed methyl group. Indeed, after a number of theoretical and experimental investigations of a variety of molecular systems, Buckingham concluded that predictions of relative stability in hydrogen bonding systems are difficult to make, due to the opposing nature of stretching and bending vibrational terms.[23]

To identify a candidate compound for our studies, the Cambridge Crystallographic Database was searched for molecules containing an *N*-CH_3 group in close proximity to another nitrogen atom. The search returned an interesting alkaloid derivative, (*N*-methyl)-(α)-isosparteinium iodide (**3a**).[24] A derivative of the C_2 symmetric (−)-(α)-isosparteine (**4**), which is readily available from enantiopure (−)-sparteine, this alkaloid provided all of the necessary structural features thought necessary to produce the desired interaction: (1) a nucleophilic site for methyl transfer, (2) a proximal Lewis basic functional group to serve as a hydrogen bond acceptor, and (3) an asymmetric environment in close proximity to the methyl group. The C_2 symmetry of (−)-(α)-isosparteine provides an added element of simplicity in that the nucleophilic and Lewis basic structural elements are one in the same; methylation at either nitrogen yields the same product.



3a: X = Y = Z = H, X = I **4** **5**
3b: X = H_R, Y = H_S, Z = D, X = I
3c: X = H, Y = D, Z = T (*S*), X = N(Tos)$_2$
3d: X = H, Y = T, Z = D (*R*), X = N(Tos)$_2$

In a preliminary study,[25] (−)-(α)-isosparteine was methylated with CH_2DI and the diastereotopic methyl protons in product **3b** were found to have a chemical shift difference of 43 ppb at room temperature. This shift difference could be increased to 106 ppb by cooling the sample to −110 °C in $CDFCl_2$. The experimental data were found to be in good agreement with a predicted chemical shift difference of 41 ppb made via a purely ab initio approach utilizing computed structures, vibrational frequencies, and proton chemical shifts. According to the ab initio predictions, the *R*- and *S*-CHDT methyl groups in methylated (−)-(α)-isosparteine would be expected to exhibit tritium NMR chemical shifts that differ by 49 ppb, with the *S*-CHDT group giving rise to the downfield resonance.

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Because the isosparteine system produced a 3-fold greater proton chemical shift separation than in (*N*-CH_2D)-2-methylpiperidine **1b**, we next wanted to explore its application as a tool for analyzing chiral methyl groups with tritium NMR. We were also intrigued by the excellent agreement between our preliminary computational predictions and experiment and wished to test this approach with different levels of theory and make the definitive comparison with experimental tritium NMR data. In the first section of this paper, we report a more extensive computational study of the isotope effect in (*N*-CH_2D)-2-methylpiperidine (**1b**) and the methyl isotopomers of (*N*-methyl)-α-isosparteinium (**3**). In the second part of the paper, we describe the reaction of (−)-(α)-isosparteine with *R*-CHDT-$N(Tos)_2$ and subsequent tritium NMR analysis of the methylated alkaloid. We conclude with a brief description of methylation reactions using electrophiles more reactive than $CH_3N(Tos)_2$.

Results and Discussion

Theoretical Considerations. A viable computational model for the NMR isotope effect must reproduce experiments to some standard of accuracy. In the testing of our method, we focused on reproducing the N−CH_2D proton chemical shift difference in Anet's 1,2-dimethylpiperidine[12] for several reasons: (1) this molecule had provided the largest chemical shift difference in the literature; (2) it is a small enough system to be amenable to quantum mechanical calculations; (3) it is structurally similar to our molecule of interest, (*N*-methyl)-(α)-isosparteinium (**3**).

As discussed above, a diastereotopic chemical shift difference can be provoked through the application of a population asymmetry to methyl rotation and distinct magnetic environments for the static methyl C−H(D,T) positions. Thus, the general computational strategy is to find the population in each isotopically substituted rotational conformation and to calculate the limiting proton chemical shifts in each methyl position; weighting the chemical shifts by the proper mole fractions for a given nucleus will give the averaged chemical shift for that nucleus on the NMR time scale.[26] The Gaussian computational package provides the necessary tools for this approach.[27]

The populations in each rotamer can be calculated by first finding an optimized structure and then computing the vibrational modes and standard free energies between each substituted rotamer based on this structure. Because there is no change in stoichiometry for conformational isomerization, one can solve the triangular equilibrium for methyl rotation (Figure 2) using these standard free energies, to yield the population in each rotamer.

Under the Born−Oppenheimer approximation, the electronic characteristics of a molecule are unchanged on isotopic labeling; in this way, the labeled rotamers can differ only with respect to vibrational free energies.[28] These free energies are dominated by the zero-point vibrational component; an analysis of the vibrational ΔU and ΔS terms for taking the molecule from 0 K up to room temperature showed them to be minimal. So while the accuracy of the energies in an absolute sense may not be particularly high, most errors should cancel out because the zero-point energy difference involves a single electronic structure.[29]

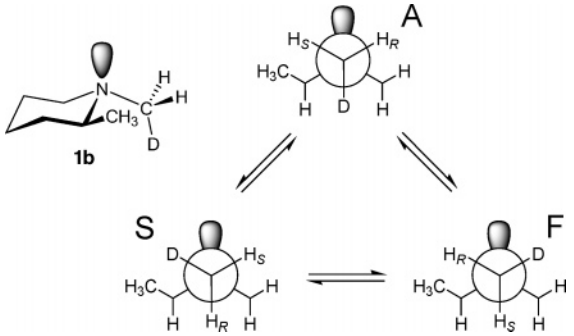

Figure 2. Triangular equilibrium for methyl rotation in (*N*-CH_2D)-2-methylpiperidine (**1b**). The methyl positions are labeled as follows: **S**, interacting sterically with the 2-methyl group; **F**, free from perturbing interactions; **A**, anti to nitrogen lone pair.

A Computational Study of Equilibrium Isotope Effects in (*N*-CH_2D)-2-Methylpiperidine. Anet and Kopelevich predicted populations for each rotamer of (*N*-CH_2D)-2-methylpiperidine (**1b**) that were consistent with their experimental results; these predictions were based on analyses of analogous compounds and chemical intuition (Table 1).[12] We computed mole fractions for the rotamers **S**, **F**, and **A** (Figure 2) by the procedure outlined above using optimized structures, vibrational frequencies, and thermodynamics at four levels of theory. Table 1 illustrates the agreement between their predicted values and our theoretical results. While the results from the Møller−Plesset electron correlation method were slightly closer to Anet's predictions than the others, none of the computed values deviate from the predictions by more than 1%. Therefore, use of the less computationally intensive density functional theory procedures may be acceptable and, in fact, preferable for the analysis of larger systems.

Magnetic shielding values are far less frequently calculated than other molecular properties such as energies, orbitals, and vibrational modes, and these have mainly been applied to the ^{13}C nucleus. Our approach requires computational estimation of proton chemical shifts; recent studies of the accuracies of various basis sets and levels of theory have yielded differing conclusions.[30−32] We decided to compute proton chemical shifts at several levels of theory using the computationally inexpensive 6-311+G(2d,p) basis set suggested by Cheeseman.[30] Because our analysis depends on the accurate prediction of chemical shift *differences* and not absolute values, many of the errors associated with basis set choice may cancel. Comparison of the shieldings for each position within a single level of theory shows qualitative agreement with our expectations (Table 2). The anti position **A** is shielded via the hyperconjugation effect discussed

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Table 1. Calculation of the Mole Fractions x in Each Rotamer of (N-CH_2D)-2-Methylpiperidine Using Various Levels of Theory[a]

entry	Anet[12]	B3LYP/6-31G(d)	B3PW91/6-31G(d)	HF/6311+G(2d,p)	MP2/6-31G(d)
x_S	0.3472	0.350	0.349	0.349	0.346
x_F	0.3431	0.343	0.343	0.341	0.344
x_A	0.3097	0.307	0.308	0.310	0.310

[a] The rotamers **S**, **F**, and **A** are defined pictorially in Figure 2. In each case the optimized structure and vibrational frequencies were computed at the same level of theory. thermodynamic properties were calculated at 298.15 K and 1 atm. The corrective scaling factors applied to vibrational frequencies were as follows: density functional methods, 0.963; Hartree−Fock, 0.89; MP2, 0.95.[33] The designations B3LYP and B3PW91 indicate density function theory calculations using functionals as named.

Table 2. Chemical Shifts in ppm of the Limiting Positions **S**, **F**, and **A** of (N-CH_3)-2-Methylpiperidine, Referenced to Tetramethylsilane Computed at the Same Levels of Theory; Chemical Shifts Were Computed with the 6-311+G(2d,p) Basis Set in All Cases

	OPT: B3LYP/6-31G(d)			OPT: B3PW91/6-31G(d)		
δ	HF	B3LYP	B3PW91	HF	B3LYP	B3PW91
S	2.443	2.773	2.726	2.479	2.811	2.766
F	1.902	2.066	2.030	1.921	2.083	2.048
A	1.574	1.721	1.722	1.571	1.715	1.715
	OPT: HF/6-311+G(2d,p)			OPT: MP2/6-31G(d)		
δ	HF	B3LYP	B3PW91	HF	B3LYP	B3PW91
S	2.432	2.769	2.721	2.501	2.833	2.789
F	1.894	2.060	2.025	1.928	2.088	2.055
A	1.540	1.691	1.692	1.557	1.688	1.691

above, and position **S** is deshielded through its steric interaction with the neighboring 2-methyl group.

The computed chemical shift differences for (N-CH_2D)-2-methylpiperidine are given in Table 3. Compared to the experimental value[12] of 14 ppb as measured in CD_2Cl_2, all of the density functional theory methods overestimated the chemical shift difference by at least 20%, and in many cases much more. Interestingly, the chemical shifts computed at the Hartree−Fock level and with the same basis set exhibited uniformly better agreement with experiment than the density functional methods.

Inspection of Table 2 reveals that, while δ(**F**) and δ(**A**) exhibit constant ratios of proportionality between levels of theory, the ratio for δ(**S**) is markedly higher; that is, position **S** is too deshielded in the density function methods compared with the other positions. The best agreement was found when structures, vibrational modes, and thermodynamics were computed using the Hartree−Fock level of theory and a larger basis set 6-311+G(2d,p); this difference persists even for unscaled vibrational data (not shown). This effect may be attributed to the more accurate treatment of the anti rotamer **A** when polarization functions are included for hydrogen, since the hydrogen in the anti position has hydride character (compare values of x_A in Table 1). However, including such functions for large molecules requires unreasonable calculation times, even at the less expensive HF level. Fortunately, the qualitative accuracy (∼20%) given by the B3LYP/6-31G(d)//HF/6-311+G(2d,p) procedure seems sufficient to assess the ability of a given molecule to cause the chemical shift difference.

A Computational Study of Equilibrium Isotope Effects in (*N*-Methyl)-(α)-Isosparteinium. The structure of the parent compound, (−)-(α)-isosparteine, has been found by X-ray diffraction studies to have all four rings in the chair conformation, orienting the two nitrogen lone pairs toward each other[34] (e.g., **4**). A comparison of the basicities of sparteine and (−)-(α)-isosparteine indicates that this conformation persists in solution;[35] this result is corroborated by the reported ease of reaction between (−)-(α)-isosparteine and CH_2I_2 to yield the *endo*-methylene derivative.[24] (−)-(α)-Isosparteine is readily methylated with CH_3I to yield (*N*-methyl)-(α)-isosparteinium iodide. The solid-state X-ray structure of this compound is very similar to the parent compound.[24] This structure features a conspicuous close contact of the type $N^+-CH_3\cdots N$. The geometry of the interaction is comparable with the geometries of the strongest C−H···N hydrogen bonds, with the H···N distance noticeably shorter than that for most published cases.[36] These results allow the interaction to be cautiously designated a $N^+-C-H\cdots N$ hydrogen bond.

Close inspection of the environment inhabited by the bridging methyl group of (*N*-methyl)-(α)-isosparteinium (Figure **3**) reveals that the three static C−H positions should differ significantly with respect to magnetic shielding. Compared to the free position **F**, the crowded position **C** should be somewhat deshielded by the 1,3 diaxial interactions it experiences. Because the chemical shift is quite sensitive even to weak hydrogen bonding effects,[37] the bridging position **B** is expected to be significantly deshielded.[38]

Although the experimental evidence for the $N^+-C-H\cdots N$ hydrogen bond in (*N*-methyl)-(α)-isosparteinium is somewhat convincing, we endeavored to supplement this information by making a theoretical case for the effect. An optimized structure was computed for this molecule at the DFT/B3LYP/6-31G(d) level; in this structure, one of the methyl C−H bonds is directly oriented toward the opposing nitrogen lone pair. A full calculation of the vibrational modes for this structure gave no imaginary frequencies, nor any close to 0, indicating that the stationary point found by the optimization procedure was an energy minimum.[39] A comparison of the computed vibrational modes that best reflect each localized methyl C−H stretching motion indicates that the bridging stretch is red-shifted relative to the other two methyl C−H stretches by 102 and 173 cm^{-1}. These effects are consistent with a classical hydrogen bond.[40] The barrier for methyl rotation was estimated to be 5.8 kcal/mol by means of a torsional angle scan at the same level of theory. The geometric parameters for the $N^+-C-H\cdots N$ interaction in

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(39) This result is at odds with an earlier proposal, based on an analysis of infrared data, of a thermodynamic preference for a structure in which the *N*-methyl C−H bonds are eclipsed with the vicinal C−C bonds and the hydrogen bond is bifurcated, with the lone pair shared with two *N*-methyl C−H bonds; see: Majchrzak-Kuczynska, U.; Koziol, A. E.; Wiewiorowski, M. *J. Mol. Struct.* **1987**, *160*, 189−208.
(40) For a review of classical versus improper hydrogen bonds, see: Hobza, P.; Havlas, Z. *Chem. Rev.* **2000**, *100*, 4253−4264.

Table 3. Chemical Shift Differences (ppb, $\delta H_R - \delta H_S$) for the *N*-Methyl Protons of (*N*-CH_2D)-2-Methylpiperidine (**1b**); All Chemical Shifts Were Computed with a 6-311+G(2d,p) Basis Set

	populations			
	B3LYP/6-31G(d)	B3PW91/6-31G(d)	HF/6-311+G(2d,p)	MP2/6-31G(d)
HF	17.4	18.1	14.0	18.1
B3LYP	23.3	24.1	19.2	23.7
B3PW91	23.2	23.9	19.1	23.4

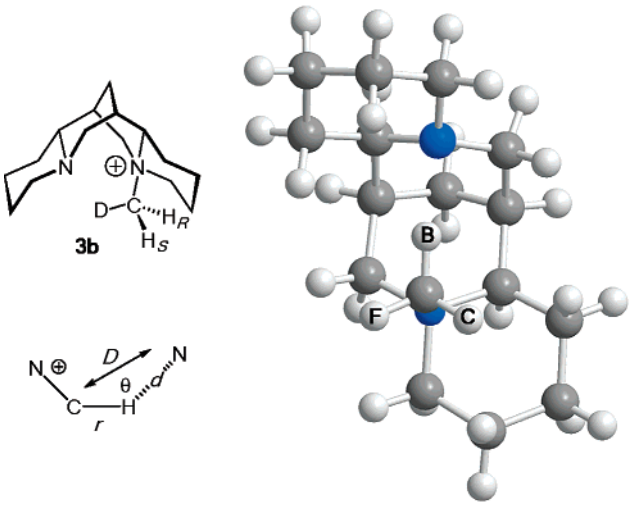

Figure 3. Stereochemical representations of (*N*-CH_2D)-(α)-isosparteinium (**3b**). The 3D structure has been optimized at the B3LYP/6-31G(d) level of theory. The methyl positions are labeled as follows: **B**, bridging; **C**, sterically compressed; **F**, free from interaction. Inset: geometric parameters for the $N^+-C-H\cdots N$ hydrogen bond.

the optimized structure are $r = 1.093$ Å, $d = 2.00$ Å, $D = 2.99$ Å, and $\theta = 148°$ (see Figure 3). These values compare very favorably with the shortest C−H···O hydrogen bonds, for which $d = 2.00$ Å and $D = 3.00$; since such values tend to be longer with an N acceptor atom, the geometry indicates that for its type this interaction should be quite strong. Although this interaction is not the optimal linear case, the value of $\theta = 148°$ is quite reasonable; strong C−H hydrogen bonds are found with values of θ in the range of 150° and higher.[36]

In calculating the rotameric populations for (*N*-CH_2D)-(α)-isosparteinium using the procedure outlined for 1,2-dimethylpiperidine **1b**, the increased size of the system prevented the use of explicit electron correlation or extended basis sets. Therefore, we relied on the DFT methods to produce the populations in each methyl group. Based on the results from **1b**, these methods should be acceptable; the deviation in that case was dominated by the contribution from the chemical shift calculations. The populations produced by the two DFT methods are in good agreement with each other; the B3LYP calculation favored deuterium in the bridging position more than the B3PW91 calculation by a small margin (see Figure 4 and Table 4). The calculations suggest that the *N*-CH_2D system behaves like the OD···OH system, in which deuterium prefers the bridging position. Although the bridging C−H stretching frequency is red-shifted, key torsional modes for this position are blue-shifted, causing a preference for the heavy isotope there.

The chemical shifts computed from structures optimized at the DFT levels match well with what one might expect for this system; the sterically crowded position **C** is significantly deshielded by the 1,3 diaxial interactions it experiences, while the bridging position **B** is extremely deshielded through the hydrogen bonding interaction (Table 5). As in the analysis of

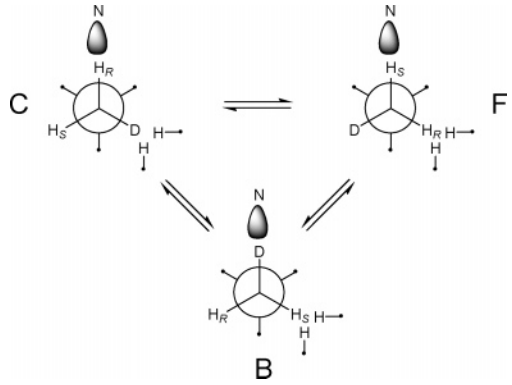

Figure 4. Triangular equilibrium between the three possible methyl rotamers of (*N*-CH_2D)-(α)-isosparteinium. The methyl positions are labeled as follows: **B**, bridging; **C**, sterically compressed; **F**, free from interaction. Each rotamer is named for the position occupied by deuterium.

Table 4. Calculation of the Mole Fractions *x* in Each Rotamer of (*N*-CH_2D)-(α)-Isosparteinium Using Various Levels of Theory[a]

rotamer	B3LYP/6-31G(d)	B3PW91/6-31G(d)
x_C	0.333	0.333
x_F	0.318	0.321
x_B	0.349	0.346

[a] The rotamers **C**, **F**, and **B** are defined pictorially in Figure 4. In each case the optimized structure and vibrational frequencies were computed at the same level of theory and using the same basis set. Thermodynamic properties were calculated at 298.15 K and 1 atm. A corrective scaling factor of 0.963 was applied to vibrational frequencies before thermodynamic calculations were performed.[52]

Table 5. Chemical Shifts in ppm of the Limiting Positions **C**, **F**, and **B** of (*N*-CH_3)-(α)-Isosparteinium, Referenced to Tetramethylsilane Computed at the Same Levels of Theory; the 6-311+G(2d,p) Basis Set Was Used for All Chemical Shift Calculations

	OPT: B3LYP/6-31G(d)			OPT: B3PW91/6-31G(d)		
δ	HF	B3LYP	B3PW91	HF	B3LYP	B3PW91
C	2.649	3.192	3.198	2.915	3.207	3.214
F	1.586	1.829	1.830	1.813	1.804	1.804
B	6.707	7.324	7.317	7.322	7.669	7.668

(*N*-CH_2D)-2-methylpiperidine, the two DFT methods agreed fairly well, while the Hartree−Fock gave substantially different values. Interestingly, the chemical shifts produced by the HF method were much closer to those given by the DFT methods when a structure optimized at the B3PW91 level rather than the B3LYP level was used. This result is in agreement with that of Cheeseman, who found that structures optimized with the B3PW91 functional produced slightly more accurate chemical shielding constants than those optimized with the more common B3LYP functional.[30] In contrast, no significant difference in agreement between the HF and DFT methods was found for (*N*-CH_2D)-2-methylpiperidine on going from B3LYP to B3PW91 optimized structures (Table 2).

Weighting these computed chemical shifts in Table 5 with the theoretical populations given above (Table 4) yields the

Table 6. Chemical Shift Differences between the pro-*R* and pro-*S* Protons of (*N*-CH_2D)-(α)-Isosparteinium in ppb; All Chemical Shifts Were Computed with a 6-311+G(2d,p) Basis Set

	populations	
NMR	B3LYP/6-31G(d)	B3PW91/6-31G(d)
HF	44.7	42.4
B3LYP	40.9	39.4
B3PW91	40.6	39.2

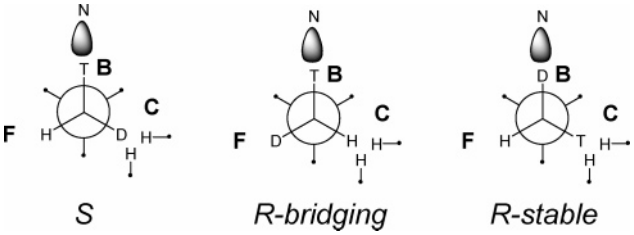

Figure 5. *S* and *R* forms of the CHDT group are shown in the context of (*N*-CHDT)-(α)-isosparteinium; the limiting methyl positions **B**, **F**, and **C** are labeled in bold. Structure ***S*** shows the most stable rotamer for the *S* form of the CHDT group in α-isosparteinium. Structure ***R*-bridging** shows the analogous conformation for the *R*-CHDT group with tritium in the bridging position; this form is not the most stable because it places deuterium in the disfavored open position **F**. Structure ***R*-stable** shows the preferred orientation of the *R*-CHDT group, in which deuterium occupies the bridging position.

expected chemical shift difference between the diasteretopic methylene protons of the CH_2D group. The computed values (Table 6) are remarkably close to the experimentally observed shift difference of 43 ppb. The chemical shift differences calculated using shieldings at the HF and DFT levels vary only by 3−4 ppb or less than 10% of the total value; this compares very favorably to the (*N*-CH_2D)-2-methylpiperidine case, where analogous differences between results at the HF and DFT levels were 30−40%. In contrast, the fractional differences between values produced with optimized structures and thermodynamics at the B3LYP and B3PW91 levels are approximately 5% for both molecules. Because the isosparteinium calculations are less sensitive to changes in level of theory than is the piperidine derivative, the theoretical picture that the calculations give seems clearer; this bodes well for a meaningful comparison to experiment. Even if the values given in Table 6 are in error by as much as those in Table 3, the chemical shift difference given by (*N*-CH_2D)-(α)-isosparteinium are predicted to be significantly in excess of that given by (*N*-CH_2D)-2-methylpiperidine.

In contrast to 1,2-dimethylpiperidine **1b**, for which two of the rotamers were found to be nearly degenerate (Table 1), the three rotamers for the isosparteinium compound have distinct conformational energies (Table 4**)**; a heavy atom is strongly favored in the **B** position, somewhat favored in the **C** position, and unfavored in the **F** position. This might help distinguish the two CHDT configurations in the ^3H NMR spectrum by creating a single favored rotamer. The *S* form of the CHDT group would fit perfectly in the space created by the (−)-(α)-isosparteine enantiomer (Figure 5, left); the lowest-energy rotamer of this compound would have tritium in the most favored position **B**, deuterium in the next favored position, **C**, and hydrogen in the least favored position, **F.** However, this conformation is impossible for the *R* configuration of the CHDT group: if tritium is in the bridging position **B** in that case, deuterium would be forced into the least favorable position **F** (see Figure 5, center). The most favored rotamer for the *R*-CHDT is as shown, with tritium taking on the second-best position and deuterium taking on the best position; because positions **B** and **C** have very different limiting chemical shifts (Table 5), the two configurations of the CHDT group would be expected to exhibit different averaged shifts as well.

Table 7. Populations in Each of the Three Possible Rotamers C, F, and B, as Defined in Figure 5[a]

	rotamer		
diastereomer	x_C	x_F	x_B
S-CHDT	0.318	0.327	0.355
R-CHDT	0.349	0.312	0.339

[a]For example, the label x_B for the *S*-CHDT group refers to the fractional population of molecules in the conformer for which tritium takes on the bridging position **B**. These populations were calculated using optimized structures, frequencies, and thermodynamics at the DFT/B3LYP/6-31G(d) level of theory; thermodynamics were calculated at 298.15 K, 1 atm, and scaled by a factor of 0.963[33]

Table 8. Expected ^3H Chemical Shift Differences in ppb between the *S* and the *R* Configurations of the CHDT Group in (*N*-CHDT)-(α)-Isosparteinium[a]

	populations	
NMR	B3LYP/6-31G(d)	B3PW91/6-31G(d)
HF	49.4	43.4
B3LYP	46.2	41.1
B3PW91	45.9	40.9

[a] Levels of theory and basis sets used to calculate populations are listed going across. Levels of theory for NMR chemical shifts are listed going down; all chemical shifts were computed with a 6-311+G(2d,p) basis set

The populations of the CHDT-labeled isosparteinium compound may be modeled in a manner analogous to what has been shown so far for the CH_2D isotopomer. The above calculations were repeated once for the *R* form and once for the *S* form of the CHDT group to find the populations in each rotamer for each configuration (Table 7). These populations were used to weight the limiting chemical shifts, yielding the averaged chemical shift differences reported in Table 8.

The relative magnitudes of the values as a function of theory levels and basis sets follow those given in Table 6 for the CH_2D analogue; here, each value is 1−5 ppb higher than those in the previous case. These results suggested that the deuterium and tritium isotope effects combine to provide an even larger tritium chemical shift difference for the CHDT groups than the proton chemical shift difference for the CH_2D group in the isosparteinium system, whereas these values were nearly the same in the 1,2-dimethylpiperidine example.

Methylation of (−)-(α)-Isosparteine with $CHDTN(Tos)_2$ and Tritium NMR Analysis of Reaction Products. The ditosylmethylamine reagent, $CHDTN(Tos)_2$, has served as a chiral methyl source[5,18] in prior direct tritium NMR analyses of configuration. The reason for its use stems from the fact that it can be prepared from chiral acetic acid using a stereochemically well-defined sequence of reactions.[17] An improved enantioselective synthesis of this reagent has been reported.[18] Methylamine ditosylate is a much poorer electrophile than CH_3I, which readily alkylates (−)-(α)-isosparteine in warm acetone. We therefore investigated the alkylation chemistry of isosparteine in trial reactions with $CH_3N(Tos)_2$. A one-pot procedure was also desirable, so that eventual manipulations with the radioactive material might be minimized. It was found that when 3:1 molar ratios of (−)-(α)-isosparteine to $CH_3N(Tos)_2$ of about 15 mg total mass were heated at 130 °C in a sealed tube with

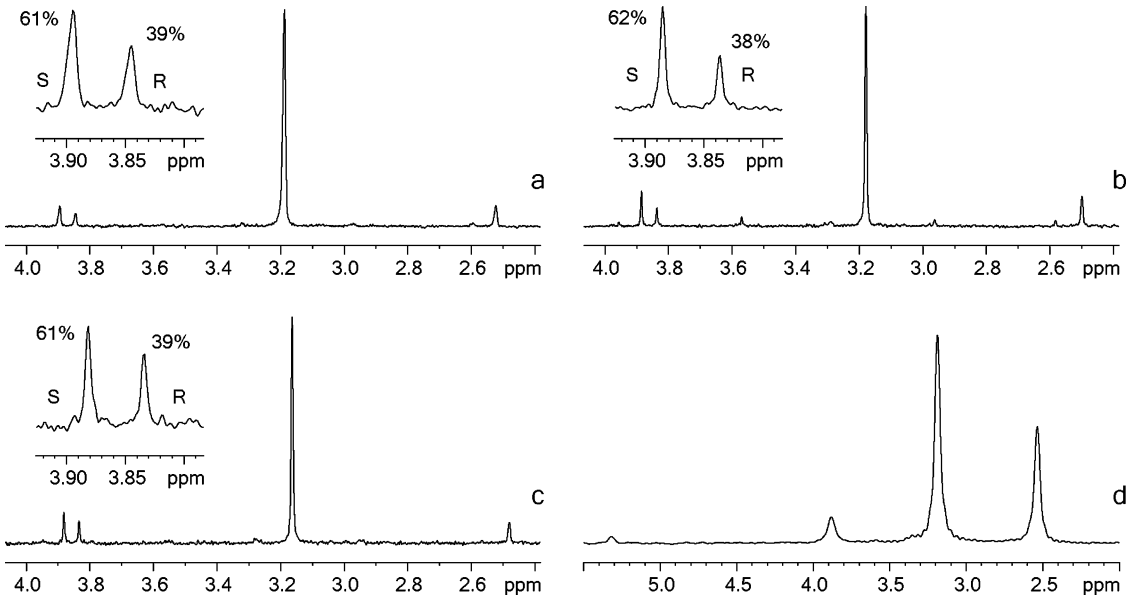

Figure 6. (a−c) $^3H\{^1H, ^2H\}$ 640 MHz NMR spectra of the reaction products of *R*-CHDTN(Tos)$_2$ (66% ee) with (−)-α-isosparteine (**4**) for reaction times of (a) 24 h, 11% conversion; (b) 48 h, 16% conversion; and (c) 48 h, 11% conversion. The low-field peaks arise from the *S* and *R* forms of (*N*-CHDT)-(α)-isosparteinium ditosylamide (**3c**, **3d**). The peak at 3.19 ppm is unreacted starting material, CHDTN(Tos)$_2$. The high-field peak is CHDTNH(Tos). The percent conversion for each reaction is estimated by comparing the product and unreacted starting material integrals. Relative integrations of the *S* and *R* peaks are indicated in the expanded region of each spectrum. The chemical shift difference between the signals arising from the *S* and *R* stereogenic methyl groups is 49 ppb in each case. (d) 61 MHz ^2H spectrum of the reaction products of $CD_3N(Tos)_2$ with (−)-α-isosparteine following a 24 h reaction period in acetone at 130 °C. The natural abundance ^2H signal from the solvent was used as the chemical shift reference at 5.32 ppm, and the sample has been spiked with $CD_3NH(Tos)$. The high-field peak was not observed in the unaltered reaction mixture.

25 μL of acetone, about 15% of the desired product (*N*-CH_3)-(α)-isosparteinium ditosylamide was formed. A few milligrams of BHT were added to the reaction mixture to reduce the amount of oxidized byproducts and slightly increase the yield of the desired compound.

Although the given yield is fairly low, better conditions were never identified. Reactant ratios other than 3:1 and lower temperatures resulted in lower yields; higher temperatures and nonevacuated reaction vessels gave oxidative decomposition products. Reactions in the presence of other solvents, including DMF and methanol, were attempted, although the latter solvent proved problematic. For example, sealed-tube reactions at 130 °C using $CD_3N(Tos)_2$ in CH_3OH were found to produce some of the desired (*N*-CD_3)-(α)-isosparteinium ditosylamide but also a significant amount of $CD_3NH(Tos)$. The latter presumably forms as a result of a nucleophile, perhaps methoxide, attacking at sulfur rather than at the methyl group. Under these reaction conditions, the (*N*-CH_3)-(α)-isosparteinium species was also produced, likely via transient formation of methyl *p*-toluenesulfonate by the S-attack mechanism described above.

The CHDTN(Tos)$_2$ used in this study had been determined to consist of 83% *R*-CHDT and 17% *S*-CHDT by the Anet method[5] and had been stored in a dilute methanol solution for over a year at −20 °C. A limited supply of this material provided for three small-scale methylation reactions (see the Experimental Section for details). Ampules 1 and 2 were prepared identically, with approximately 3:1 stoichiometry of (−)-(α)-isosparteine hydrate and CHDTN(Tos)$_2$, 25μL of acetone, and 2 mg of BHT. The two reactions were allowed to proceed in sealed tubes for 24 and 48 h, respectively. A larger batch of less pure ditosylmethylamine was taken from storage in an NMR tube for the third ampule; in this case, approximately double the quantities used for the previous two ampules was used, and the BHT was omitted.

The results of these three experiments are shown in Figure 6. The prominent peak at 3.19 ppm in each spectrum is unreacted CHDTN(Tos)$_2$; the high field peak at 2.52 ppm arises from a small amount of CHDTNH(Tos) that is present in the ditosylamine starting material. The low field peaks are due to the methyl tritium resonances of diastereomeric **3c** and **3d**, with the downfield major peak arising from the *S*-CHDT group, assuming S_N2 inversion of the starting material. The general features of the tritium spectra could be replicated using ^2H NMR analysis of reactions employing $CD_3N(Tos)_2$ as a substitute for the radiolabeled material (Figure 6d).

After 24 h at 130 °C, only 11% of the CHDTN(Tos)$_2$ was converted to (*N*-CHDT)-(α)-isosparteinium ditosylamide (Figure 6a). The two remaining reactions were each heated for 48 h, though each ampule gave a slightly different result. The contents of ampule 2 showed 16% conversion but also exhibited a number of small peaks throughout the spectrum; these are assumed to be oxidative decomposition products of (*N*-CHDT)-(α)-isosparteinium and CHDTN(Tos)$_2$ (Figure 6b). The contents of ampule 3 exhibited a cleaner reaction profile (Figure 6c) than ampule 2, and the tritium spectrum was nearly identical with that obtained from ampule 1.

The (*N*-CHDT)-(α)-isosparteinium ^3H NMR region illustrates a chemical shift difference of 49 ppb in each case, which is in excellent agreement with the predicted values given in Table 8. The 3.5-fold increase in chemical shift separation, relative to the 2-methylpiperidine case, offers baseline separation between the two peaks. From these results, we conclude that (−)-(α)-isosparteine can produce a chemical shift difference between the *S* and *R* forms of the CHDT group and thus be used to assign the configuration of an intact stereogenic methyl group. However, the relative integrations of the CHDT peaks are less encouraging. Assuming a clean S_N2 inversion, we expected to see an 83:17 *S*/*R* ratio in the methyl tritium

resonances. However, in each case a 61:39 *S*/*R* ratio was observed. Initially, we assumed that the methylating agent had partially racemized over time while in storage; however, the ee was rechecked by the Anet method and was found to be the same as originally reported.

These results indicate that a fixed amount of racemization of the CHDT center takes place during the reaction period. The similar degree of racemization and product formation seems to suggest that the reaction proceeds for a period of time and then somehow becomes inhibited. When acetone is used as solvent, the reaction vials are found to contain a substantial amount of unchanged (−)-(α)-isosparteine and distosylate, so the reactants are not being lost to other reactions. The partial racemization might be caused by either intramolecular S_N2 attack by the opposing nitrogen in (*N*-CHDT)-(α)-isosparteinium or intermolecular attack by a molecule of (−)-(α)-isosparteine. The intramolecular mechanism, which is formally a 6-endo-tet ring closure, is disfavored according to Baldwins's rules.[41] The intermolecular methyl transfer mechanism is more likely, although we have not conducted double labeling experiments to provide definitive evidence for such a pathway. We have, however, observed intermolecular methyl transfer from the closely related *exo*-(*N*-CD_3)-sparteinium iodide (**5**)[42,43] to (−)-(α)-isosparteine using conditions similar to those used in the tritium labeling experiments, the only difference being the use of DMF as solvent to dissolve the methiodide.[44] Although the iodide counterion may well be participating in this particular chemistry, limited intermolecular methyl transfer is a reasonable explanation for the observed partial racemization observed in these reactions.

Methylation of (−)-(α)-Isosparteine with Methyl *p*-Toluenesulfonate and Methyl-d_3 Triflate. It was apparent from our studies that isosparteine offered a significant improvement in terms of resolving the diastereotopic tritium resonances associated with *R*- and *S*-CHDT groups. However, the vigorous conditions necessary for reaction with methylamine ditosylate renders isosparteine unsuitable for ee determinations employing this electrophile using the conditions described above. To conclude our studies, we studied the methylation of (−)-(α)-isosparteine with the more reactive trifluoromethanesulfonate and *p*-toluenesulfonate ester derivatives of methanol.[45]

We knew from our earlier work that (−)-(α)-isosparteine was methylated over the course of several hours in reactions with methyl iodide in refluxing acetone (ca. 55 °C). Given the relative reactivity of these electrophiles,[46] CH_3I:CH_3OTs:CH_3OTf = 1:10:∼10^5, we were confident that (−)-(α)-isosparteine could be methylated at this temperature or below. We were less certain about the likelihood of inter-alkaloid methyl transfer reactions under these reaction conditions. Accordingly, the methylation reaction was studied with ^1H and ^2H NMR studies and methyl *p*-toluenesulfonate and methyl-d_3 triflate, respectively.[44] The reaction conditions were kept similar to the tritium labeling studies with regard to stoichiometry and concentration. The reaction time, temperature, and solvent were adjusted so as to define the mildest methylating condition.

Methyl *p*-toluenesulfonate was found to readily react with (−)-(α)-isosparteine in *N*,*N*-dimethylformamide (DMF) at 45 °C, with 92% conversion to the desired product after 4 h and complete conversion after 7.5 h. In this reaction, DMF was substituted for acetone because (−)-(α)-isosparteine is not appreciably soluble in acetone at this temperature. Isosparteine also cleanly reacts with methyl-d_3 triflate after 40 min in acetone at 65 °C.[47] To test for the occurrence of intermolecular methyl transfer reactions during a reaction period of 8 h at 65 °C, we again employed the isosparteine/(*N*-CD_3)-sparteinium iodide/DMF system described earlier.[48] With these conditions, we did not observe any methyl transfer to isosparteine. If this is the case for reactions at 65 °C, then it is reasonable to assume that the same is true for methylation reactions held at 45 °C.

These results suggest that (−)-(α)-isosparteine holds promise for ee determination of chiral methyl groups, provided the source is a suitably reactive electrophile. The benefits of using isosparteine are 2-fold: (1) an increased chemical shift difference for the diastereotopic tritium resonances, and (2) because (−)-(α)-isosparteine is prepared in one step from a naturally occurring alkaloid, it is essentially enantiopure and thus well-suited as a diastereomeric derivatizing agent. On the other hand, enantiopure 2-methylpiperidine must be prepared from racemic commercial material using an optical resolution employing the mandelate salts.[49] As a secondary amine, however, 2-methylpiperidine is a better nucleophile than isosparteine and when used in excess produces a tertiary amine product that is not prone to further methyl transfer reactions. In our view, it remains the reagent of choice for analyses of chiral methyl groups arising from weak electrophiles such as CHDTN$(Tos)_2$.

Conclusion

In this paper we have described a molecular system that uses a novel C−H(D,T)···N hydrogen bond to perturb the rotameric equilibrium of an isotopically labeled methyl group. In (*N*-CHDT)-(α)-isosparteinium ditosylamide, this effect is large enough to produce an experimental tritium chemical shift separation of 49 ppb between the *S*- and *R*-CHDT groups, with the *S*-CHDT group giving rise to the downfield resonance. These spectral parameters showed excellent agreement with theoretical predictions, and it is clear from these studies that theory can make useful predictions for effects even as subtle as these. On the basis of the 3.5-fold increase in CHDT chemical shift

(41) For a discussion of Baldwin's rules, see ref 9, p 434.
(42) Majchrzak-Kuczynska, U.; Koziol, A. E.; Langowska, K.; Wiewiorowski, M. *Bull. Polish Acad. Sci.* **1984**, *32*, 233−253. We prepared this compound by reacting sparteine with 4 equiv of methyl iodide in refluxing acetone for 3.5 h. The acetone was removed in vacuo, and the residue was washed thoroughly with refluxing ethyl acetate. The resulting solid was isolated by filtration. In our hands, this procedure provided a major and minor form (as judged by ^2H NMR spectroscopy); the major product in this reaction has been shown to the *exo* N-16 methiodide **5**. The minor form is presumably an *endo* isomer formed by methylation of either N-1 or N-16.
(43) In the methylation of isosparteine at 130 °C, a qualitative comparison of the amount of *endo*- versus *exo*-methyl transfer was possible because a mixture of the *endo*- and *exo*-(*N*-CD_3)-sparteinium iodides was used in the reaction. The formation of a ^2H resonance arising from (*N*-CD_3)-(α)-isosparteinium appears to occur with concomitant disappearance of the resonance from the *exo* isomer; the *endo* resonance is largely unchanged.
(44) Procedures and NMR spectra are provided as Supporting Information.
(45) Chiral methanol, CHDTOH, has been utilized in biosynthetic studies of methanogenic bacteria (ref 17). In this study, the ee of chiral methanol was determined via the enzymatic assay following a four-step conversion of methanol to acetic acid.
(46) Kurz, J. L.; El-Nasr, M. M. Seif. *J. Am. Chem. Soc.* **1982**, *104*, 5823−5824.
(47) Reactions employing methyl triflate in DMF produced multiple products and were noticeably exothermic upon the addition of methyl triflate, presumably due to solvent alkylation.
(48) The contents of an identically prepared vial held for 8 h at 45 °C were not sufficiently soluble to provide a meaningful result.
(49) Craig, J. C.; Pinder, A. R. *J. Org. Chem.* **1971**, *36*, 3648−3649.

separation relative to (*N*-CHDT)-2-methylpiperidine, the new procedure holds promise as an improved method for assigning the configuration of stereogenic methyl groups using tritium NMR spectroscopy. These preliminary studies suggest that (−)-(α)-isosparteine should be a viable reagent for chiral methyl ee determinations, provided the methyl source is suitably electrophilic.

Experimental Section

Computational Methodology. Molecular modeling was performed using *Gaussian 98W* on Microsoft Windows XP workstations with dual 1.7 GHz Xeon processors; some calculations were also performed using *Gaussian 98* on a Silicon Graphics Indigo^2 R10000 workstation running under IRIX 6.5. Thermodynamic parameters for isotopomers were computed using the Freqchk utility program in *Gaussian 98*.

Methylation of (−)-(α)-Isosparteine with CHDTN(Tos)$_2$ and Tritium NMR Analysis. (−)-(α)-Isosparteine hydrate was prepared from commercially available (−)-sparteine (Aldrich) by the method of Galinovsky.[50] Reactions between (CHDT)NTos$_2$ and (−)-(α)-isosparteine were carried out in sealed 2 mL ampules under nitrogen. Ampules 1 and 2 contained (−)-(α)-isosparteine (11.5 mg, 0.049 mmol, 3.2 equiv), CHDTN(Tos)$_2$ (5.3 mg, 0.016 mmol, 2.4 mCi, 1 equiv), 2,6-di-*tert*-butyl-4-methylphenol (2.1 mg, 0.010 mmol), and acetone-d_6 (25 μL). Ampule 3 contained (−)-(α)-isosparteine (28.9 mg, 0.114 mmol, 3.2 equiv), CHDTN(Tos)$_2$ (13.3 mg, 0.039 mmol, 6.0 mCi, 1 equiv), and acetone-d_6 (50 μL). The ampule contents were then frozen in liquid nitrogen, and the ampule was evacuated. The internal pressure was then adjusted to about 300 Torr with nitrogen gas, and the neck was sealed with an oxygen−acetylene torch. The ampules were submerged in silicone oil at 130 °C for 24 h (ampule 1) or 48 h (ampules 2 and 3).

After cooling to room temperature, the ampules were opened and the reaction mixtures were dissolved in CD_2Cl_2 for 640 MHz $^3H\{^1H, ^2H\}$ NMR analysis using a Bruker DRX spectrometer. The tritium NMR spectra shown in Figure 6 were acquired using identical acquisition parameters, which consisted of 8000 scans, a 6400 Hz spectral width, an 8K file size, a 0.78 Hz/pt digital resolution, a 0.314 s acquisition time, and a 2 s relaxation delay.

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Supporting Information Available: Experimental procedures and spectroscopic data for reactions of (−)-(α)-isosparteine with (*N*-CD_3)-sparteinium iodide, methyl *p*-toluenesulfonate, and methyl-d_3 triflate. This material is available free of charge via the Internet at http://pubs.acs.org.

JA045265I

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