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An Experimental and Theoretical Study of the Asymmetric Lithiation of 1,2,3,5,6,7-Hexahydro-3a,4a-diazacyclopenta[*def*]phenanthren-4-one

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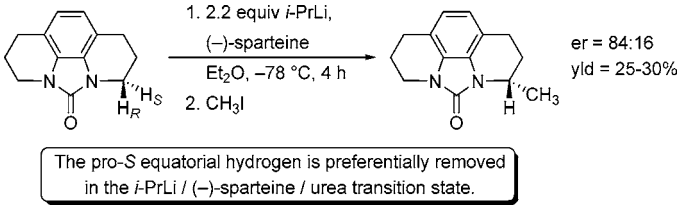

The inability of bis-*N*-Boc-protected octahydrophenanthroline to undergo asymmetric lithiation with (−)-sparteine is circumvented by use of a urea functionality as the directing group. Asymmetric lithiation followed by electrophile quench gives products substituted α to nitrogen in better yield (17−30%) but slightly lower enantiomeric ratio (er 84:16) than analogous lithiation of *N*-Boc-piperidine (er 87:13). Computational studies at the MP2/6-316(d)//B3LYP/6-316(d) level indicate that the prochiral equatorial *S*-hydrogen is removed preferentially over the pro-*R* hydrogen, with a difference in transition state activation energies of 1.26 kcal/mol, corresponding to a predicted er of 89:11. The predicted stereochemistry of the reaction was confirmed by single-crystal X-ray analysis of an aryl dibromide prepared from the enantiomerically enriched α-methyl-substituted product.

Introduction

The advent of the use of (−)-sparteine in asymmetric anionic chemistry by Hoppe[1] and Beak[2,3] has provided the synthetic community with many substrates for which stereogenic centers may be created at prochiral sp^3-hybridized carbon atoms.[4] For cyclic substrates, the enantioselective deprotonation of *N*-Boc-pyrrolidine[2,3] **1** sets a high standard for synthetic utility[5] which, unfortunately, is not equaled by the homologous piperidine analogue **3** (Scheme 1).[6] Although piperidyl substrates can in some cases be deprotonated and trapped with electrophiles in good yields under achiral conditions by using TMEDA,[7] the use of (−)-sparteine (**5**) for the enantioselective deprotonation of *N*-Boc-piperidine (**3**) furnishes the 2-trimethylsilyl adduct **4** in low yield (8%) and moderate enantioselectivity (87:13 er, 74% ee) (Scheme 1). Asymmetric deprotonation of **3** with other chiral diamines such as (*R*,*R*)-TMCDA (**6**) or O'Brien's (+)-sparteine surrogate[8] **7** gives the 2-trimethylsilyl product **4** in

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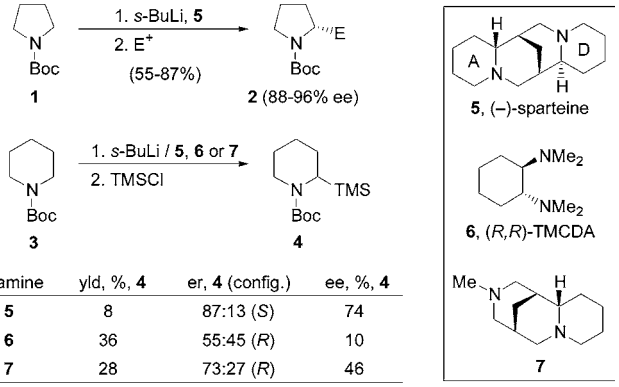
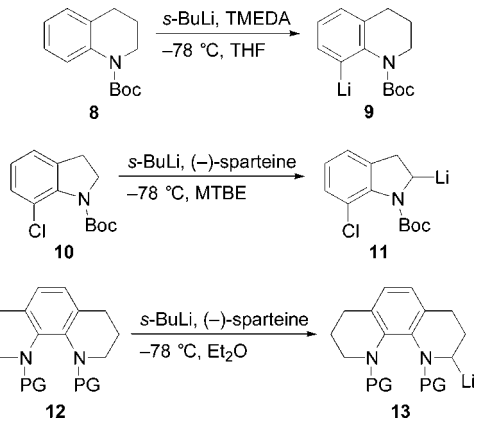
SCHEME 1. Asymmetric Deprotonation of *N*-Boc-Protected Pyrrolidine and Piperidine



Diamine	yld, %, **4**	er, **4** (config.)	ee, %, **4**
5	8	87:13 (*S*)	74
6	36	55:45 (*R*)	10
7	28	73:27 (*R*)	46

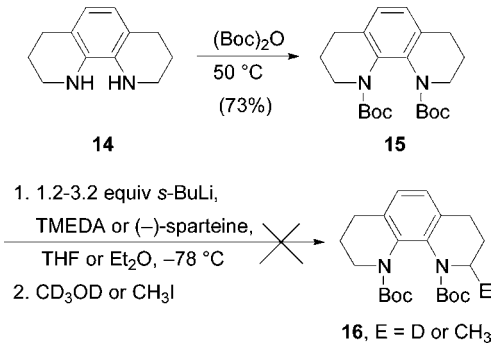
SCHEME 2. Lithiation of *N*-Boc-tetrahydroquinoline, 7-Chloro-*N*-Boc-indoline, and Bis-*N*-Protected Octahydrophenanthroline



better yield (28−36%), but lower enantiomeric purity (10−46% ee).[9] Seminal work by Bailey, Beak, and Wiberg[6] has provided mechanistic insight into the apparent discrepancy in lithiation behavior between *N*-Boc-pyrrolidine and *N*-Boc-piperidine.

As part of a research program aimed at the preparation of chiral phenanthroline derived *N*-heterocyclic carbenes (NHCs),[10,11] we considered the possibility of developing an asymmetric route to these molecules by (−)-sparteine-mediated lithiation of bis-*N*-protected octahydrophenanthroline **12** (Scheme 2), which contains two benzo-fused piperidine rings. Despite previous results by Meyers et al.[12] which showed that lithiation of *N*-Boc-tetrahydroquinoline occurs ortho to the *N*-Boc group (**8** → **9**) rather than α to nitrogen, a derivative such as **12** would have the ortho positions blocked, thereby forcing deprotonation to take place in one of the piperidyl rings (**13**, Scheme 2). The blocking of an ortho position has previously been shown to be effective in the asymmetric lithiation of 7-chloro-*N*-Boc-indoline (**10** → **11**).[13] To the best of our knowledge, the current substrate (**12**) would represent the first (−)-sparteine-mediated α-deprotonation of a benzo-fused piperidine. Herein we report the outcome of the studies for asymmetric lithiation of **12** and its congeners, and offer a computational explanation for the observed results, including a prediction of the absolute stereochemistry. The predicted stereochemistry of the products has been confirmed by single-crystal X-ray analysis.

SCHEME 3. Preparation and Attempted Lithiation of 2,3,4,7,8,9-Hexahydro-1,10-phenanthroline-1,10-dicarboxylic Acid Di-*tert*-butyl Ester (15)



Results and Discussion

Attempted Lithiation of Bis-*N*-Boc-Protected Octahydrophenanthroline. Preliminary lithiation experiments required bis-*N*-Boc-protected octahydrophenanthroline (**15**, Scheme 3) to be prepared from octahydrophenanthroline (**14**).[10] It was necessary to use neat *tert*-butoxycarbonyl anhydride [$(Boc)_2O$] to obtain a good yield of **15**, as the use of any quantity of solvent afforded mixtures of mono- and bis-protected products. ^{1}H NMR analysis of **15** was complicated by the obvious presence of rotamers in solution, which may have been worsened by steric interactions between the neighboring Boc groups. All attempts to lithiate **15** under racemic (*s*-BuLi, TMEDA, −78 °C, THF) or chiral conditions (*s*-BuLi, (−)-sparteine, −78 °C, Et_2O) failed to provide any 2-substituted products (**16**) after electrophile quench with methanol-d_4 or iodomethane, even when 3.2 equiv of *s*-BuLi was used.

The recalcitrance of **15** to lithiation suggested that steric congestion between the Boc groups may have prevented them from adopting a conformation suitable to placing a coordinated alkyllithium in proximity of one of the neighboring methylene groups.[14] Validation of this assumption was secured through calculation of a Boltzmann ground state conformer distribution for di-*tert*-butyl carbamoyl protected **15**, which revealed that four conformationally different populations residing within 1 kcal/mol of the global minimum on the potential energy surface were present.[15] Readily apparent upon visual inspection of the lowest energy member within each of the four conformational groupings (Figure 1) was that both the top and bottom faces of the octahydrophenanthroline ring system are sterically shielded by the flanking bis-*N*-Boc groups, which are arranged in a geared orientation.[16] As such, the latter metric inhibits approach of the chiral *s*-BuLi·**5** complex, in effect shutting down a reaction pathway involving α-hydrogen removal.

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(15) Boltzmann distributions were calculated with Spartan02.
(16) See the Supporting Information for an overlay of the conformational groupings.

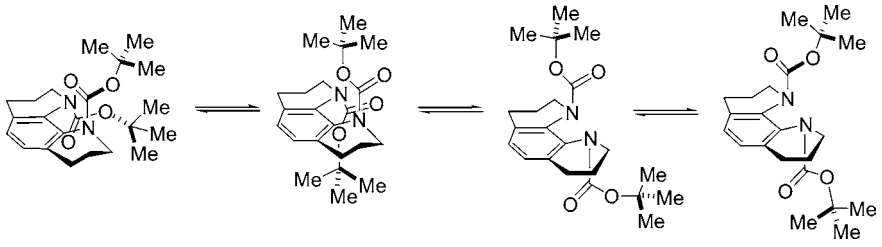

FIGURE 1. Depiction of the four lowest energy conformational states of **15** derived from a Boltzmann distribution.

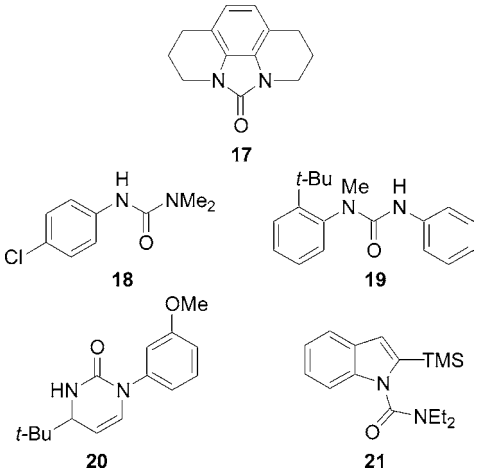

FIGURE 2. Urea substrates used in directed lithiation.

To improve the chances for successful lithiation, **14** required protection with a much smaller substituent, one that would mimic the electronic characteristics of Boc, but still be resistant to 1,2-addition of alkyllithium reagents. In principle, protecting both nitrogen atoms as part of the same functional group to give a urea derivative, and relying on the rigid tetracyclic shape of the molecule to provide sufficient steric protection to nucleophilic attack, could achieve this. It was anticipated that urea analogue **17** (Figure 2) may offer a better chance of α-methylene deprotonation owing to the approximate orientation of the carbonyl group within the plane of the adjacent piperidyl rings. Unlike carbamates, ureas have been used only sporadically as directed metalation groups[17] (DMGs) and, to the best of our knowledge, never in an asymmetric process with (−)-sparteine. Reported examples include *N*′-aryl-*N*,*N*-dimethylureas (**18**) by Smith,[18] *N*′-aryl-*N*-aryl-*N*-methylurea (**19**) by Clayden,[19] *N*-aryltetrahydropyrimidinones (**20**) by Joule,[20] and indolyl-*N*,*N*-diethylurea (**21**) by Snieckus[21] (Figure 2). The preceding cases typically involve deprotonation at aromatic sp^2-hydridized carbon[18−21] or non-prochiral *N*-Me groups.[19] The current example (**17**) is distinct in that lithiation is arranged to occur at a prochiral sp^3 center, and the "directing group" is locked within a ring that is in roughly the same plane as the remainder of the molecule.

Experimental and Computational Studies of the (−)-Sparteine-Mediated Lithiation of Urea 17. To test the viability of a urea in piperidine ring deprotonation, diamine **14**[10] was converted to **17** with triphosgene/Et_3N in THF (Scheme 4). Asymmetric lithiation of **17** (2.2 equiv *s*-BuLi/(−)-sparteine, −78 °C, Et_2O, 4 h) followed by electrophile quench with methanol-d_4 afforded the deuterated product **22a** in 50% yield, along with amide **23** (18%) arising from competitive ring-opening of the urea. The low solubility of **17** in Et_2O at −78 °C necessitated the addition of *s*-BuLi to a stirred suspension of **17** and (−)-sparteine. Under these conditions, **17** gradually dissolved to give a homogeneous solution within 15 minutes. Both ^1H and ^{13}C NMR analysis indicated that **22a** was >95% monodeuterated α to nitrogen. The extent of deuteration of **22a** was also confirmed by low- and high-resolution mass spectrometry. These results resemble observations made by Beak et al.[6] for asymmetric lithiation of *N*-Boc-piperidine **3**, except that a shorter lithiation time for **17** gives a higher yield of the α-substituted product, at least when deuterium is the electrophile. Notably, the use of only 1.2 equiv of alkyllithium resulted in incomplete deuteration of urea **17**.

Encouraged by the yield obtained for **22a**, asymmetric lithiation of **17** with *s*-BuLi/(−)-sparteine was followed by quench with iodomethane. Under these conditions, the methyl-substituted product **22b** (Scheme 5) was obtained in yields ranging from 25% to 30% and with an enantiomeric ratio (er) of 80:20 (60% ee).[22] The use of *i*-PrLi in place of *s*-BuLi improved the er of **22b** to 84:16 (68% ee). Benzophenone was also an effective electrophile, providing **22c** in similar er (83.5:16.5, 67% ee), but slightly lower yield. Attempts to increase the enantioselectivity further by adding a pre-complexed solution of *i*-PrLi and (−)-sparteine at −78 °C to **17** diminished both the yield and er for **22b** and **22c**. In addition, it was found that better yields and enantiomeric ratios were obtained by transferring the α-carbanion to a solution of the electrophile in THF at −78 °C. This observation may be tentatively attributed to THF-induced dissociation of (−)-sparteine from the α-carbanion, which allows it to react more readily with the electrophile. The lack of racemization in the presence of THF during electrophile quench implies that the "naked" α-carbanion is configurationally stable and that the enantiodetermining step of the reaction is deprotonation[4a] as in *N*-Boc-pyrrolidine,[2,3] rather than asymmetric substitution,[23] as shown previously for lateral lithiations of benzamides.[24] Consequently, products **22b** and **22c** would be expected to have the same relative stereochemistry. Unlike *N*-Boc-piperidine **3**, several attempts to trap the putative α-carbanion of **17** with chlorotrimethylsilane (TMSCl) consis-

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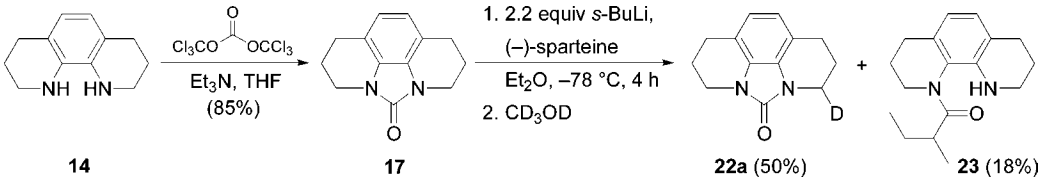
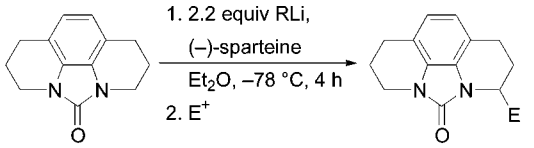
(22) All enantiomeric ratios were determined by chiral stationary phase (CSP) HPLC on a Chiralpak AS-H or a Chiralcel OD-H column.
(23) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *116*, 2516.
(24) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755.

SCHEME 4. Synthesis and Lithiation-Deuteration of Urea 17 (1,2,3,5,6,7-Hexahydro-3a,4a-diazacyclopenta[*def*]phenanthren-4-one)



14 **17** **22a** (50%) **23** (18%)

SCHEME 5. [a]Asymmetric Lithiation-Electrophile Quench of Urea 17



17 **22b** (E = CH_3) **22c** (E = Ph_2COH)

RLi	E^+	E	yld, % **22b,c**	er, **22b,c**
s-BuLi	CH_3I	CH_3	25-30	80:20
i-PrLi	CH_3I	CH_3	25-30	84:16
i-PrLi	Ph_2CO	Ph_2COH	17-27	83.5:16.5
i-PrLi[a]	CH_3I	CH_3	12	81:19
i-PrLi[a]	Ph_2CO	Ph_2COH	18	81:19

[a] *i*-PrLi pre-mixed with (−)-sparteine before addition to **17**.

tently gave only trace amounts of the TMS adduct, a phenomenon also observed in lithiations of *N*-Boc-protected piperazines.[25]

To gain insight into the electronic and structural elements governing pro-*R* versus pro-*S* deprotonation of urea **17** by the η_2-complex *i*-PrLi·**5**, an in-depth transition state analysis was undertaken with use of the Gaussian '03[26] suite of programs. Specifically, 16 different transition state geometries were considered corresponding to α-deprotonation of **17** by C_1-symmetric *i*-PrLi·**5**, wherein the relative positioning of the (−)-sparteine A and D rings was exchanged via a 180° rotation with respect to the principal axis of the urea. All reported structures were first optimized at the B3LYP[27]/6-31G(d,p)[28] level, and frequency calculations were carried out to ensure that the transition states were first-order saddle points. Subsequently, single-point MP2/6-31G(d) calculations were used to allow for a more accurate description of the transition state energies.

Inspection of the optimized first-order saddle points revealed that two distinct benzo-fused piperidyl ring conformational states were present which, collectively, reduced to either axial or equatorial hydrogen abstraction. Of these two sets, the lowest energy transition state for equatorial deprotonation was calculated to be 2.78 kcal/mol more stable than the most favorable mode of axial hydrogen abstraction. It is perhaps interesting that, in general, equatorial hydrogen removal was energetically favored over axial deprotonation, following a trend consistent with transition state models for *N*-Boc-pyrrolidine[29] and *N*-Boc-piperidine.[6] More relevant to the discussion of enantioselection, the pro-*S* and pro-*R* transition states (**TS1** and **TS2**) were found to have relative $\Delta\Delta E$ values of 0 and 1.26 kcal/mol, respectively (Figure 3). Again, this is consistent with the pro-*S*-selective lithiation observed for both cyclic[6,29] and acyclic derivatives such as *O*-alkyl-2-enyl carbamates.[30] It is worthy of note that the calculated $\Delta\Delta E$ of 1.26 kcal/mol corresponds to a predicted er of 89:11, which is close to the experimentally observed er of 84:16 for sequential lithiation−methylation.

Closer inspection of **TS1** and **TS2** revealed that the A-ring of the C_1-symmetric (−)-sparteine ligand lies directly atop the site of proton transfer (Figure 3). In this location, the methylene hydrogens β to nitrogen in the A-ring of (−)-sparteine are proximal to the octahydrophenanthroline core of **17** and appear to play a decisive role in determining pro-*R* versus pro-*S* selectivity. In this respect, a short H···H contact measured at 2.18 Å between the axial hydrogen of the α-carbon of urea **17** undergoing deprotonation and a β-methylene hydrogen of the (−)-sparteine A-ring leads to destabilization in **TS2**. In contrast, the shortest H···H contact found in **TS1** is 2.41 Å, a value greater than the sum of van der Waals radii for two hydrogen atoms (2.40 Å).[31] Once again, this interaction occurs between an α-axial hydrogen of urea **17** and the A-ring β-CH_2 group. This computational analysis corroborates previous studies that have confirmed that the A-ring of (−)-sparteine is essential for obtaining high levels of enantioinduction in lithiation−substitution reactions of *N*-Boc-pyrrolidine[32] and may serve as a general measure for predicting absolute stereochemistry in other (−)-sparteine-mediated lithiations.[33]

Crystallography. To determine the absolute stereochemistry of the products by X-ray diffraction, two derivatives containing

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(31) The sum of two hydrogen van der Waals radii is 2.40 Å: Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960; p. 260.

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(33) An in-depth study of the A-ring β-CH_2 effect will be discussed in a forthcoming communication.

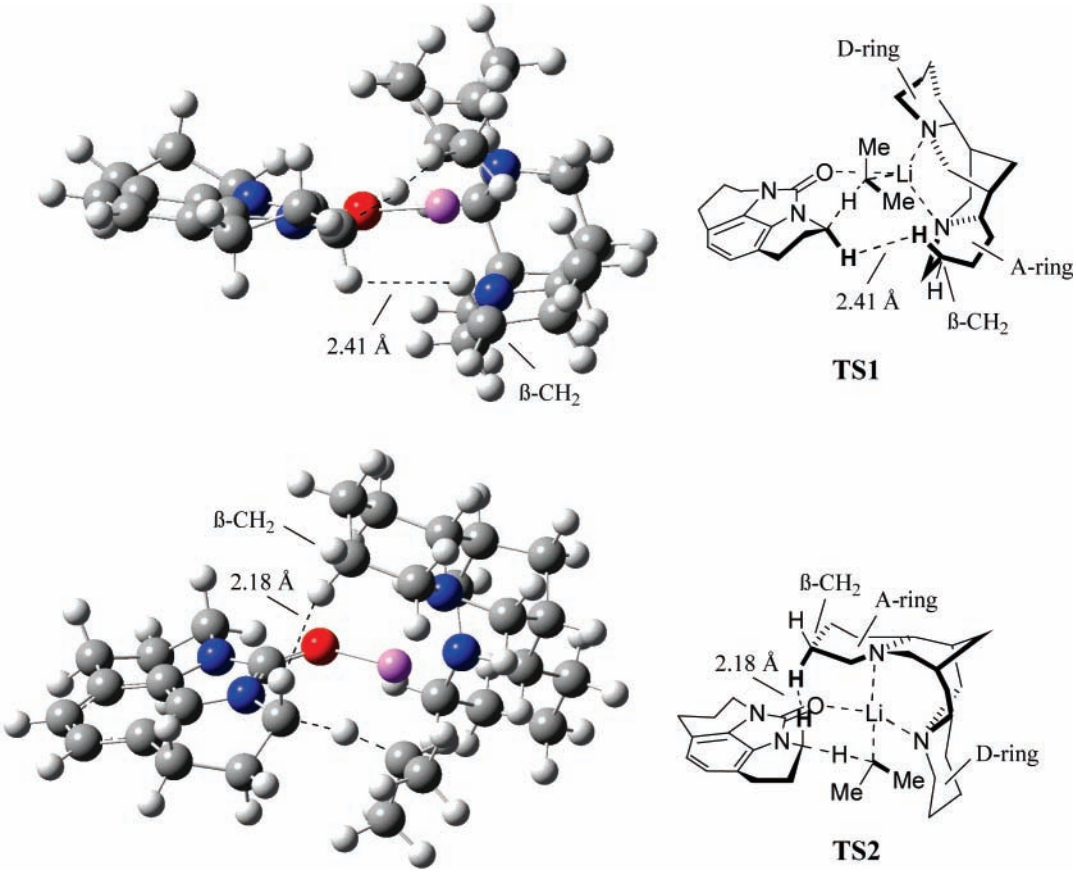
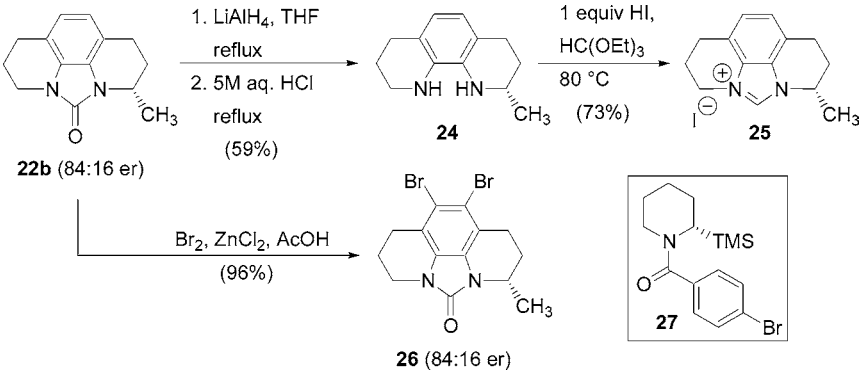


FIGURE 3. Transition states leading to pro-*S* (**TS1**) and pro-*R* (**TS2**) deprotonation. Shortest H···H contacts between β-CH_2 of the (−)-sparteine A-ring and α-CH_2 in urea **17** are indicated.

SCHEME 6. Conversion of 22b to Benzimidazolium Salt 25 and Dibromide 26



heavy atoms[34] were prepared by manipulation of urea **22b** (Scheme 6). First, reduction of **22b** to the aminal[35] ($LiAlH_4$, THF, reflux), followed immediately by acid hydrolysis (5 M HCl, reflux) afforded the enantiomerically enriched (−)-2-methyl-1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline **24**. Standard formylative ring-closure ($HC(OEt)_3$, 1 equiv of HI) gave the benzimidazolium iodide **25**. All attempts to grow crystals of **25** suitable for X-ray analysis were fruitless. As an alternative, **22b** was electrophilically brominated[36] (Br_2, $ZnCl_2$, AcOH) to furnish dibromide **26** in high yield, and with complete retention of stereochemistry.[22] Crystallographic analysis established the *S* absolute configuration for **26**,[37] and by inference also for **22b**. The relative and absolute stereochemistry of **26** is identical to *p*-bromobenzoyl-protected 2-trimethylsilyl piperidine **27** reported by Beak et al. previously,[6] and is in complete accord with the computationally predicted stereochemistry of the products.

Conclusions

It has been shown that (−)-sparteine-mediated lithiation may be applied to a benzo-fused piperidine (**17**) by using a urea

(34) Bijvoet, J. M.; Peerdeman, A. F.; Van Bommel, A. J. *Nature* **1951**, *168*, 271.

(35) Bates, H. A.; Condulis, N.; Stein, N. L. *J. Org. Chem.* **1986**, *51*, 2228.

(36) The procedure as used in the preparation of 1,2-dibromo-3,4,5,6-tetramethylbenzene was followed: (a) Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Tanaka, T.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 439. (b) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146.

(37) See the Supporting Information for an ORTEP plot of dibromide **26**.

directing group, thus circumventing steric encumberance in bis-*N*-Boc carbamate **15**. The yields obtained are somewhat higher than that observed previously in (−)-sparteine-mediated lithiation of *N*-Boc-piperidine,[6] although the enantiomeric ratios are slightly lower. On the basis of these results, the use of ureas as directing groups for asymmetric lithiation α to nitrogen in cyclic and acyclic substrates warrants further study. In addition, a quantum chemical transition state study predicted a $\Delta\Delta E$ value of 1.26 kcal/mol, corresponding to an enantiomeric ratio of 89:11 favoring pro-*S* equatorial deprotonation. The stereochemical course of the reaction was later confirmed by X-ray analysis of dibromide **26**. The key feature of the transition state analyses was a repulsive interaction between an A-ring β-CH_2-hydrogen of C_1-symmetric (−)-sparteine and an axial α-urea hydrogen at the carbon center undergoing deprotonation in **17**, which governs pro-*R* versus pro-*S* selectivity. The generality of this last point will be addressed in a forthcoming communication.

Experimental Section

2,3,4,7,8,9-Hexahydro-1,10-phenanthroline-1,10-dicarboxylic Acid Di-*tert*-butyl Ester (15). A round-bottomed flask was charged with diamine **14** (315 mg, 1.67 mmol) and di-*tert*-butyl dicarbonate (730 mg, 3.35 mmol), and heated to 50 °C for 12 h. After cooling to room temperature, column chromatography (silica, 4:1 hexanes/EtOAc, R_f 0.29) gave **15** as a yellow-orange semisolid that solidified on standing. Recrystallization from petroleum ether gave **15** as an amorphous off-white solid (473 mg, 73%): mp 113−114 °C (petroleum ether); IR (KBr) υ_{max} 3017, 2984, 2962, 2950, 2931, 2841, 1680, 1457, 1370, 1351, 1159, 1133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, rotameric) δ 6.83 (s, 2H), 4.08−3.93 (br, 2H), 3.39 (br, 2H), 2.62 (br, 4H), 2.07 (br, 2H), 1.70 (br, 2H), 1.44 (s, 18H); ^{13}C NMR (150.9 MHz, $CDCl_3$, rotameric) δ 153.6, 152.8, 134.8, 133.6, 133.3, 131.7, 124.3, 123.6, 122.8, 80.0, 79.3, 45.2, 43.2, 41.6, 28.2, 26.7, 24.7, 24.4; EIMS [*m/z* (%)] 388 (11), 188 (100), 57 (83); HRMS (EI) calcd for $C_{22}H_{32}N_2O_4$ 388.2362, found 388.2359.

1,2,3,5,6,7-Hexahydro-3a,4a-diazacyclopenta[*def*]phenanthren-4-one (17). A solution of diamine **14** (1.63 g, 8.65 mmol) and triphosgene (2.57 g, 8.65 mmol) in dry THF (180 mL) was treated carefully (exothermic) with anhydrous triethylamine (2.40 mL, 17.3 mmol), and the resulting mixture was stirred at room temperature for 12 h. Water (50 mL) was added and the THF was removed in vacuo. The remaining aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to approximately 10% of its original volume. The concentrated solution was passed through a short column of silica gel, eluting with 1:1 hexanes/EtOAc (R_f 0.19) to give the crude product as an off-white solid. Recrystallization from hexanes/EtOAc gave **17** as colorless needles (1.58 g, 85%) in two crops: mp 160−162 °C (hexanes/EtOAc); IR (KBr) υ_{max} 3053, 2954, 2920, 2857, 1701, 1631, 1514, 1411, 1342, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 2H), 3.85 (t, 4H, J = 5.6 Hz), 2.81 (t, 4H, J = 6.3 Hz), 2.12 (quintet, 4H, J = 5.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.9, 125.1, 118.4, 116.9, 38.9, 23.3, 22.7; EIMS [*m/z* (%)] 214 (M^+, 100), 185 (12); HRMS (EI) calcd for $C_{13}H_{14}N_2O$ 214.1106, found 214.1109. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59. Found: C, 72.75; H, 6.61.

3-Deuterio-1,2,3,5,6,7-hexahydro-3a,4a-diazacyclopenta[*def*]-phenanthren-4-one (22a) and 1-(2,3,4,7,8,9,10-Heptahydro[1,-10]phenanthrolin-1-yl)-2-methylbutan-1-one (23). A solution of urea **17** (107 mg, 0.5 mmol) and (−)-sparteine (0.25 mL, 1.1 mmol) in Et_2O (15 mL) under argon was cooled to −78 °C with stirring. The resulting suspension was treated with a solution of *s*-BuLi (0.93 mL, 1.18 M, 1.1 mmol) added dropwise over 10 min, giving a red-brown solution that was stirred for 4 h. Methanol-d_4 (0.45 mL) was added to quench the reaction mixture, resulting in a rapid change in color to pale yellow, and the mixture was allowed to warm to room temperature. Water (10 mL) was added, and the reaction mixture was extracted with Et_2O (3 × 10 mL) and CH_2Cl_2 (1 × 10 mL). The combined organic extract was washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (silica, 64:35:1 hexanes:EtOAc:MeOH) gave, sequentially, amide **23** (24 mg, 18%, R_f 0.40) and urea **22a** (54 mg, 50%, >95% monodeuterated, R_f 0.10).

23: off-white solid; mp 84−85 °C (EtOAc/hexanes); IR (KBr) υ_{max} 3393, 2957, 2931, 2872, 2839, 1643 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, rotameric) δ 6.71 (d, 0.5H, J = 7.2 Hz), 6.69 (d, 0.5H, J = 7.5 Hz), 6.33 (d, 0.5H, J = 7.2 Hz), 6.31 (d, 0.5H, J = 7.5 Hz), 5.25 (br, 0.5H), 5.16 (br, 0.5H), 4.60−4.51 (m, 1H), 3.23−3.11 (m, 2H), 2.68−2.39 (m, 4H), 2.28−2.21 (m, 1H), 2.08−2.02 (m, 1H), 1.79−1.65 (m, 3H), 1.52−1.47 (m, 1H), 1.25−1.09 (m, 2H), 1.04 (d, 1.5H, J = 6.6 Hz), 0.81 (t, 1.5H, J = 7.5 Hz), 0.66 (d, 1.5H, J = 7.2 Hz), 0.52 (t, 1.5H, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6, rotameric) δ 176.9, 176.5, 140.1, 139.9, 134.6, 134.5, 127.1, 127.0, 125.0, 124.8, 119.5, 119.3, 114.0, 113.9, 41.1, 40.9, 40.7, 38.4, 37.8, 27.6, 27.0, 26.9, 26.3, 25.8, 25.5, 23.93, 23.88, 21.6, 18.0, 17.1, 12.3, 11.4; EIMS [*m/z* (%)] 272 (M^+, 26), 215 (74), 187 (100); HRMS (EI) calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1900.

22a: off-white solid; mp 156−158 °C; IR (KBr) υ_{max} 3054, 2953, 2922, 2854, 2162, 1703, 1631, 1510, 1415, 1343, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 2H), 3.86−3.81 (m, 3H), 2.81 (t, 4H, J = 5.9 Hz), 2.16−2.08 (m, 4H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 153.0, 125.2, 118.4, 117.0, 39.0, 38.7 (t, $^1J_{^{13}C-^2H}$ = 21.9 Hz), 23.4, 23.3, 22.8, 22.7; EIMS [*m/z* (%)] 215 (M^+, 100), 186 (12); HRMS (EI) calcd for $C_{13}H_{13}DN_2O$ 215.1168, found 215.1163.

(+)-(3*S*)-Methyl-1,2,3,5,6,7-hexahydro-3a,4a-diazacyclopenta-[*def*]phenanthren-4-one (22b). A solution of urea **17** (643 mg, 3.00 mmol) and (−)-sparteine (1.52 mL, 6.60 mmol) in dry Et_2O (70 mL) under argon was cooled to −78 °C with stirring. The resulting suspension was treated with a solution of *i*-PrLi in pentane (3.73 mL, 1.77 M, 6.60 mmol), added dropwise over 10 min, to give a red-brown solution that was stirred at −78 °C for 4 h. The reaction mixture was then transferred by cannula to a precooled (−78 °C) solution of iodomethane (0.65 mL, 10.5 mmol) in dry THF (80 mL), and stirred for a further 2 h. The resulting pale yellow solution was treated with saturated aqueous NH_4Cl solution (10 mL) and allowed to warm up to room temperature. Water (30 mL) was added, the phases were separated, and the remaining aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with 5% aqueous H_3PO_4 (2 × 10 mL), water (30 mL), and brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (silica, 4:1 Et_2O/CH_2Cl_2, R_f 0.32) gave **22b** (170 mg, 25%) as a pale yellow oil, which solidified on standing: mp 57−59 °C; $[\alpha]^{20}_D$ +21.0 (*c* 4.37, $CHCl_3$); CSP HPLC analysis (Chiralpak AS-H; eluent: 80:20 hexanes:*i*-PrOH, 1.0 mL/min) determined 84:16 er, 68% ee [t_R(major) = 11.03 min, t_R(minor) = 13.34 min]; IR (KBr) υ_{max} 2965, 2933, 2893, 1705, 1505, 1414, 1334, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 2H), 4.45−4.39 (m, 1H), 3.87−3.82 (m, 2H), 2.87−2.73 (m, 4H), 2.12 (quintet, 2H, J = 5.7 Hz), 2.07−1.99 (m, 2H), 1.40 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.6, 125.1, 118.4, 118.2, 116.9, 116.73, 116.66, 45.3, 38.9, 29.3, 23.3, 22.7, 20.1, 19.1; EIMS [*m/z* (%)] 228 (M^+, 100), 213 (87), 185 (17); HRMS (EI) calcd for $C_{14}H_{16}N_2O$ 228.1263, found 228.1260. Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06. Found: C, 73.16; H, 7.01.

(−)-(3*R*)-(Diphenylhydroxy)methyl-1,2,3,5,6,7-hexahydro-3a,-4a-diazacyclopenta[*def*]phenanthren-4-one (22c). A solution of urea **17** (214 mg, 1.00 mmol) and (−)-sparteine (0.51 mL, 2.20 mmol) in dry Et_2O (25 mL) under argon was treated with a solution of *i*-PrLi in pentane (1.29 mL, 1.70 M, 2.20 mmol), added dropwise over 10 min, to give a red-brown solution that was stirred at −78 °C for 4 h. The reaction mixture was then transferred by cannula to a

precooled (−78 °C) solution of benzophenone (638 mg, 3.50 mmol) in dry THF (18 mL) and stirred for a further 2 h. The resulting blue-green solution was treated with saturated aqueous NH_4Cl (3 mL) and allowed to warm to room temperature. Water (10 mL) was added, the phases were separated, and the resulting aqueous mixture was extracted with Et_2O (3 × 20 mL). The combined organic extract was washed with 5% aqueous H_3PO_4 (3 × 10 mL), water (15 mL), and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (silica, 3:1 hexanes/EtOAc, R_f 0.23) gave **22c** as a colorless solid (107 mg, 27%): mp 257−259 °C (hexanes/EtOAc); $[\alpha]^{20}_D$ −77.0 (*c* 2.25, $CHCl_3$); CSP HPLC analysis (Chiralcel OD-H; eluent: 90:10 hexanes:*i*-PrOH, 1.0 mL/min) determined 83.5:16.5 er, 67% ee [t_R(major) = 12.09 min, t_R(minor) = 21.14 min]; IR (KBr) υ_{max} 3387, 3056, 2963, 2938, 2912, 2883, 2831, 1689, 1501, 1349, 1234, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.28 (m, 8H), 7.24−7.19 (m, 2H), 6.79 (d, 1H, J = 7.8 Hz), 6.77 (s, 1H), 6.71 (d, 1H, J = 7.8 Hz), 4.80 (dd, 1H, J = 8.1, 3.3 Hz), 3.84−3.70 (m, 2H), 2.92−2.73 (m, 2H), 2.54−2.25 (m, 3H), 2.20−2.03 (m, 2H), 1.77−1.67 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.3, 146.0, 143.9, 127.9, 127.8, 127.7, 127.5, 127.4, 127.2, 125.8, 125.4, 119.1, 118.6, 118.1, 117.0, 79.9, 62.7, 39.2, 27.1, 23.3, 23.0, 22.5; EIMS [*m/z* (%)] 396 (M^+, 3), 378 (16), 214 (51), 105 (57), 43 (100); HRMS (EI) calcd for $C_{26}H_{24}N_2O_2$ 396.1838, found 396.1832. Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10. Found: C, 78.23; H, 6.31.

(−)-(2*S*)-Methyl-1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline (24). A stirred solution of urea **22b** (154 mg, 0.67 mmol) in THF (6.5 mL) under argon was cooled to 0 °C and treated with $LiAlH_4$ (128 mg, 3.37 mmol) in two portions. The resulting mixture was heated to reflux for 2 h. After cooling to room temperature, the reaction mixture was worked up by sequential addition of water (0.1 mL), 10% aqueous NaOH solution (0.1 mL), and water (0.3 mL). The precipitated aluminum salts were removed by filtration through Celite, and the filtrate was extracted with Et_2O (4 × 10 mL) and concentrated in vacuo. The resulting residue was treated with 5 M aqueous HCl solution (6.5 mL) and heated to 60 °C for 2 h. After cooling to room temperature, the mixture was treated with 10% aqueous NaOH solution to approximately pH 12, and the product was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (silica, 9:1 hexanes:EtOAc, R_f 0.27) gave diamine **24** (80 mg, 59%) as a clear viscous oil: $[\alpha]^{20}_D$ −41.4 (*c* = 1.7, acetone); IR (KBr, neat) υ_{max} 3333, 3036, 2924, 2842, 1582, 1487, 1332, 1255 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 6.24 (ABq, 2H), 3.73 (br, 1H), 3.56 (br, 1H), 3.32−3.19 (m, 3H), 2.81−2.55 (m, 4H), 1.90−1.76 (m, 3H), 1.51−1.38 (m, 1H), 1.21 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 133.5, 133.0, 119.9, 119.4, 119.0, 118.8, 48.4, 43.0, 31.2, 27.9, 27.5, 23.3, 22.8; EIMS [*m/z* (%)] 202 (M^+, 100); HRMS (EI) calcd for $C_{13}H_{18}N_2$ 202.1470, found 202.1466.

(−)-Benzimidazolium Iodide 25. A solution of **24** (31 mg, 0.15 mmol) in $HC(OEt)_3$ (3 mL) in a round-bottomed flask equipped with a reflux condenser under argon was treated with concentrated HI (21 μL, 0.15 mmol) and warmed to 80 °C for 1 h. The reflux condenser was removed, and heating was continued for an additional 2 h in the open air. After cooling to room temperature, the yellow reaction mixture was poured into Et_2O (15 mL), and the precipitated product was collected on a Hirsch funnel and dried in vacuo to give **25** (37 mg, 73%) as an off-white powder: mp 219−221 °C (CH_2Cl_2/pentane); $[\alpha]^{20}_D$ −3.8 (*c* 0.4, $CHCl_3$); IR (KBr) υ_{max} 3091, 3064, 2963, 2917, 2838, 1509, 1320, 1200 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.25 (s, 2H), 4.90−4.85 (m, 1H), 4.74 (t, 2H, J = 6.0 Hz), 3.08−3.01 (m, 4H), 2.44−2.40 (m, 1H), 2.40−2.36 (m, 2H), 2.09 (sextet, 1H, J = 6.0 Hz), 1.85 (d, 3H, J = 6.0 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 137.4, 127.8, 127.4, 124.2 (2C), 122.8, 122.5, 52.6, 45.4, 30.7, 22.8, 22.7, 22.0, 20.3; FABMS [*m/z* (%)] 213 ($M - I^-$, 100); HRMS (FAB) calcd for $C_{14}H_{17}N_2$ 213.1392, found 213.1384. Anal. Calcd for $C_{14}H_{17}IN_2$: C, 49.43; H, 5.04. Found: C, 49.39; H, 5.06.

(+)-8,9-Dibromo-(3*S*)-methyl-1,2,3,5,6,7-hexahydro-3a,4a-diazacyclopenta[*def*]phenanthren-4-one (26). A solution of **22b** (228 mg, 1.00 mmol) in glacial acetic acid (5 mL) was treated with $ZnCl_2$ (290 mg, 2.13 mmol), and the mixture was stirred until a homogeneous solution had formed. The solution was treated with Br_2 (0.11 mL, 2.1 mmol) by syringe, and stirred at room temperature for 12 h. The slight excess of bromine persisted as an orange color in solution for the duration of the reaction. A saturated solution of aqueous Na_2SO_3 (5 mL), water (5 mL), and CH_2Cl_2 (20 mL) was added, and the mixture was stirred at room temperature for approximately 20 min. The organic phase was collected, and the remaining aqueous mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was washed with 10% aqueous NaOH (3 × 10 mL), water (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was passed through a short column of silica gel eluting with CH_2Cl_2 to give **26** (370 mg, 96%) as a colorless oil that solidified on standing: mp 119−123 °C (absolute EtOH); $[\alpha]^{20}_D$ +20.5 (*c* 1.0, $CHCl_3$); CSP HPLC analysis (Chiralpak AS-H; eluent: 80:20 hexanes:*i*-PrOH, 1.0 mL/min) determined 84:16 er, 68% ee [t_R(major) = 13.48 min, t_R(minor) = 15.27 min]; X-ray analysis (CCDC 620846) was performed on a colorless triangular needle fragment (0.22 × 0.14 × 0.12 mm^3), which was obtained by crystallization from EtOAc. $C_{14}H_{14}Br_2N_2O$: M = 385.08 g/mol, triclinic, $P1$, a = 7.7309(3) Å, b = 9.8742(4) Å, c = 10.3595(4) Å, V = 672.57(5) $Å^3$, α = 63.330(1)°, β = 85.655(1)°, γ = 72.561(1)°, Z = 2, D_c = 1.906 g/cm^3, $F(000)$ = 380, T = 180(1) K. Data were collected on a Bruker APEX CCD system with graphite monochromated Mo Kα radiation (λ = 0.71073 Å); 7506 data were collected. The structure was solved by Patterson and Fourier (SHELXTL) and refined by full-matrix least-squares on F^2 resulting in final R, R_w, and GOF [for 6187 data with $F > 2\sigma(F)$] of 0.0259, 0.0484, and 1.30, respectively, for solution using the *S* enantiomer model, Flack parameter = −0.017(6); IR (KBr) υ_{max} 2934, 2892, 1704, 1507, 1399, 1331 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42−4.35 (m, 1H), 3.85−3.75 (m, 2H), 2.93−2.76 (m, 4H), 2.15 (quintet, 2H, J = 6.0 Hz), 2.08−2.04 (m, 2H), 1.38 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.1, 125.2, 124.7, 119.0, 118.9, 115.2 (2C), 45.2, 38.5, 29.2, 25.7, 22.7, 22.5, 18.9; EIMS [*m/z* (%)] 386 (M^+, 100), 371 (38), 185 (17); HRMS (EI) calcd for $C_{14}H_{14}{}^{79}Br^{81}BrN_2O$ 385.9453, found 385.9454. Anal. Calcd for $C_{14}H_{14}Br_2N_2O$: C, 43.55; H, 3.65. Found: C, 43.69; H, 3.68.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all compounds and an X-ray plot of **26** (pp S1−S12) plus computational data (pp S13−S46). This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 620846 contains the supplementary crystallographic data (CIF file format) for compound **26**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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