JOC The Journal of Organic Chemistry

Article

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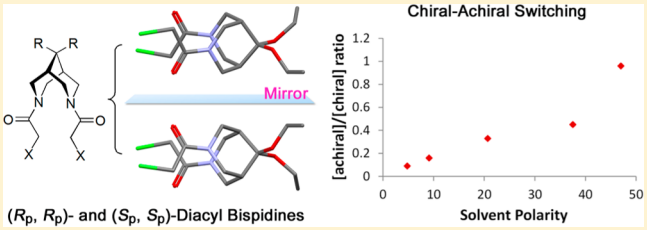
Conformational Study of *N,N′*-Diacyl Bispidines and Dioxo Bis-bispidines: Planar Chirality and Molecular Switching

Zhuo Wang,* Md. Jahirul Islam, V. Nicholas Vukotic, and Matthew J. Revington

Department of Chemistry and Biochemistry, University of Windsor, 401 Sunset Avenue, Windsor, Ontario N9B 3P4, Canada

Supporting Information

ABSTRACT: *N,N′*-Diacyl bispidines exhibit chirality in the absence of a chiral center and axis. Conformational analysis indicates planar chirality in the molecular structure as a result of open-ended chiral planes, which has been confirmed by X-ray diffraction studies. Substantial chiral−achiral molecular switching is observed in di(haloacetyl) bispidines upon changing the solvent polarity. Tethering the chiral planes with a bispidine linker alters the planar chirality significantly and renders the resulting bis-bispidine macrocycles achiral.



INTRODUCTION

Planar chiral compounds contain a plane of reference about which out-of-plane groups are arranged asymmetrically.[1] Although less common than central and axial chirality, planar chirality has been observed in cyclophanes, annulenes, *trans*-cycloalkenes, metallocenes, and transition metal complexes with arenes, some of which demonstrate interesting molecular recognition properties and asymmetric catalytic activities.[1,2] The chiral plane usually consists of an aromatic ring or C═C double bond, and in most nonmetal-containing organic compounds, is tethered at two ends by an out-of-plane linker to form a macrocycle. In this paper, we report planar chirality in *N,N′*-diacyl bispidines that possess open-ended chiral planes capable of substantial chiral−achiral molecular switching.

The stereochemistry of bispidine (**1**, R = R′ = H), bispidinone (**2**, R = R′ = H), and derivatives, which is of importance to their biological and pharmacological activities as well as asymmetric catalytic properties, can be influenced considerably by substituents on the bicyclic skeleton (Figure 1).[3] Most of the stereochemical studies have focused on the

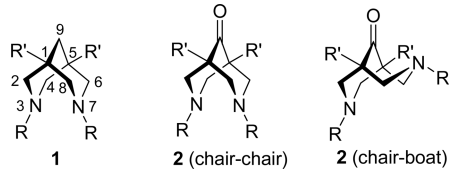


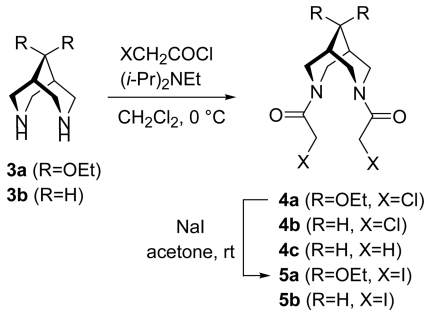
Figure 1. Bispidines (**1**) and bispidinones (**2**).

bicyclic structure, which may adopt a chair−boat or chair−chair conformation depending on the substituents, particularly at the C9, N3, and N7 positions (Figure 1).[3,4] Furthermore, it has been reported that adding lanthanide agents to *N,N′*-diacetyl bispidine **1** (R = COMe, R′ = Me) can induce significant conformational switching with respect to the amide groups.[5] In 2008, planar chirality was observed in bispidinones **2** (R = COMe, R′ = Ph) by Albeck and co-workers through NMR studies.[6] As part of our research on functionalized bis-bispidines,[7−9] it was found that bispidines **1** (R = $COCH_2X$, R′ = H) exhibit chirality in the absence of chiral centers. Analysis of the molecular structure indicates planar chirality, which has been confirmed by X-ray diffraction studies. Notably, a change in solvent polarity leads to substantial chiral−achiral switching in di(haloacetyl) bispidines. Moreover, the planar chirality can be affected significantly when the chiral planes are tethered by a second linker. The findings are reported herein.

RESULTS AND DISCUSSION

The compounds used in this study were synthesized according to Scheme 1. Acylation of bispidine **3** afforded diacyl bispidine **4**, which can be converted to **5** via a Finkelstein reaction. The ^1H and ^{13}C NMR of **4a** show that the four CH_2N methylene groups are divided into two sets of signals with each comprising a pair of chemically equivalent methylenes (Figure 2). In addition, the two bridgehead protons exhibit a single peak at 2.12 ppm, which indicates that they are chemically equivalent

Scheme 1. Synthesis of *N,N′*-Diacyl Bispidines 4 and 5



Received: February 5, 2016
Published: March 9, 2016

DOI: 10.1021/acs.joc.6b00250
J. Org. Chem. 2016, 81, 2981−2986

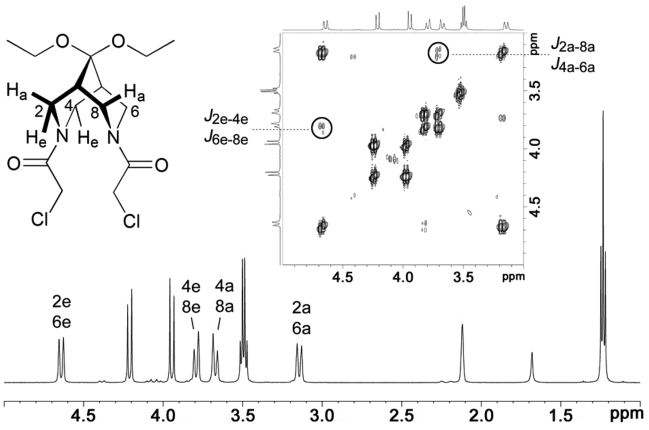


Figure 2. ^{1}H NMR spectrum of **4a** (500 MHz, $CDCl_3$) with "e" denoting equatorial and "a" axial. Inset: COSY spectrum of **4a** in the range of 3.0−5.0 ppm.

and that the CH_2N methylenes are equivalent at positions 2 and 6 and at 4 and 8. Because of the N−C═O ↔ N^+═C−O^- resonance,[10] each amide group in **4a** can adopt a planar geometry in which the C−N bond has substantial double bond character with restricted bond rotation. This may lead to two possible orientations of the carbonyl groups: *syn*, where they are parallel to each other, or *anti*, where they are antiparallel (Figure 3). The above NMR data are consistent with the *anti*

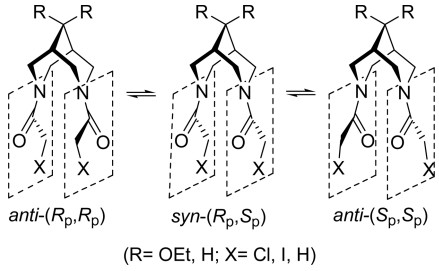


Figure 3. Planar chirality in *N*,*N*′-diacyl bispidines **4** and **5**. The two possible orientations of the carbonyl groups (*syn* or *anti*) are illustrated together with the designation of the chiral planes.

orientation. Furthermore, the COSY spectrum of **4a** displays two long-range ^{4}J couplings: between the equatorial protons $H_{2e}(H_{6e})$ (4.77 ppm) and $H_{4e}(H_{8e})$ (3.94 ppm) and between the axial protons $H_{2a}(H_{6a})$ (2.92 ppm) and $H_{8a}(H_{4a})$ (3.47 ppm) (Figure 2, inset). This is consistent with a chair−chair conformation in which the equatorial protons H_{2e} and H_{4e} (also H_{6e} and H_{8e}) form the ends of a W shape, and the axial protons H_{2a} and H_{8a} (also H_{4a} and H_{6a}) form the ends of another W, leading to the unusual long-range ^{4}J couplings in the saturated bicyclic system.[11] Because bispidines **4** and **5** exhibit comparable NMR data, it can be derived that they adopt the chair−chair conformation and the *anti* orientation of the amide groups. This corresponds to a bicyclic system that possesses a C_2 axis but lacks a plane or center of symmetry, which indicates that the molecular structures of **4** and **5** are chiral.

In the absence of a chiral center or axis in the structure, the chirality results from the asymmetric arrangement of out-of-plane groups with respect to each of the amide planes. The chirality of each plane can be assigned by defining as pilot atom the bridgehead carbon that is bonded to the methylene carbon which is in the plane and *Z* to the amide oxygen,[6] and observing the in-plane sequence by starting from the methylene carbon and continuing according to the Cahn−Ingold−Prelog priority rule.[12] As such, the chiral planes are denoted as (R_p, R_p) or (S_p, S_p) (Figure 3).[13] Because the two enantiomers differ from each other through a conceptual rotation of the amide planes, they are conformational but not configurational isomers.[12]

The planar chirality has been confirmed by an X-ray diffraction study of **4a**. The compound crystallizes from a solution of hexanes and ethyl acetate in the triclinic space group $P\bar{1}$. The molecule exhibits a chair−chair conformation and two planar amide groups that are *anti* to each other (Figure 4a). The unit cell contains two molecules that are nonsuperimposable mirror-images: one with (R_p, R_p) and the other with (S_p,

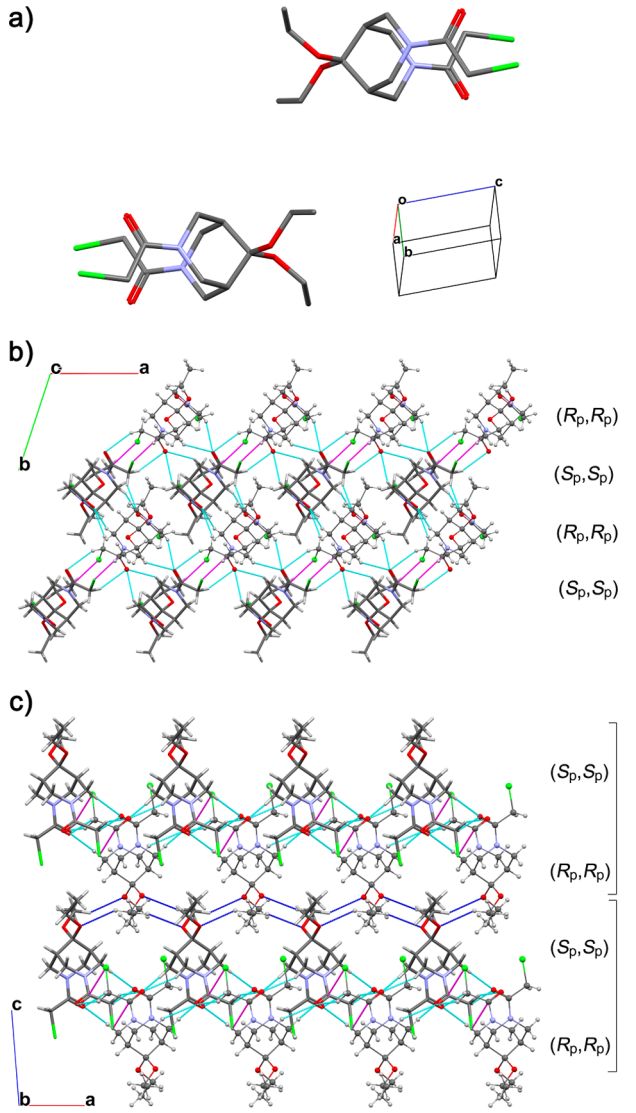


Figure 4. Crystal structure and molecular packing of **4a** in the crystal lattice with C (gray), O (red), N (blue), and H (white). (a) (R_p, R_p)- and (S_p, S_p)-**4a** in the unit cell. H atoms are omitted for clarity. (b) A 2D-network of (R_p, R_p)-**4a** (ball-and-stick) and (S_p, S_p)-**4a** (capped sticks) viewed down the *c*-axis. C−H···O hydrogen bonds and C−Cl···C═O dipole−dipole interactions are shown as light blue and pink dotted lines, respectively. (c) Stacking of two networks (viewed down the *b*-axis) showing infinite chains of C−H···O hydrogen bonds (blue dotted line) between the ethoxy groups.

DOI: 10.1021/acs.joc.6b00250
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S_p) chirality. The two enantiomers alternate with each other in three dimensions in the crystal lattice. A pair of neighboring enantiomers are related to each other through a center of inversion, and intermolecular short contacts occur in pairs.

Examination of the intermolecular short contacts indicates C−H···O hydrogen bonding[14] as the main driving force in the crystal packing of **4a**. The carbonyl oxygens in each molecule act as acceptors to the activated $COCH_2Cl$ or NCH_2 hydrogen atoms from three neighbors.[15] Together with the C−Cl···C═O dipolar interaction, this results in a two-dimensional network of interconnected (R_p, R_p) and (S_p, S_p) isomers (Figure 4b). The infinite chain motif of C−H···O hydrogen bonds between the ethoxy groups facilitates the stacking of the networks, leading to a crystal lattice with alternating (R_p, R_p) and (S_p, S_p) layers (Figure 4c).

The rotation of the amide C−N bond was investigated by dynamic NMR (DNMR) using *N*,*N*′-diacetyl bispidine **4c**, which is stable at high temperature. The ^{13}C spectra of **4c** in DMSO-d_6 were taken at various temperatures between 20 and 150 °C and subjected to total line-shape analysis.[15,16] This yields an enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation of 14 kcal/mol and −10 cal mol^{-1} K^{-1}, respectively, with a free energy of activation ($\Delta G^{\ddagger}_{298}$) of 17 kcal/mol.[15] The latter is comparable to the rotation barrier in various amides ($\Delta G^{\ddagger}$ = 15−20 kcal/mol)[16] and close to that in *N*,*N*′-diacetyl bispidine **1** (R = COMe, R′ = Me, $\Delta G^{\ddagger}_{298}$ = 18 kcal/mol),[5] suggesting that the two amide rotations are likely independent of each other and that substituents at the bridgeheads do not have discernible impact on the amide rotation dynamics. The rotation barrier also indicates that resolution of the enantiomers would be infeasible under ambient conditions.[1,16]

The chirality of diacyl bispidines **4** and **5** is influenced by solvent polarity as well as substituents on the bicyclic skeleton. In a nonpolar solvent, such as chloroform-*d*, the amide carbonyls adopt the *anti* orientation almost exclusively (Table 1). This corresponds to a chiral molecular structure of (R_p, R_p) or (S_p, S_p) (Figure 3). In a polar solvent, more amide carbonyls adopt the *syn* orientation, which corresponds to an achiral molecular structure of (R_p, S_p) due to mirror symmetry. The [*syn*]/[*anti*] ratio *K* can be determined by integration of the corresponding proton peaks. For **4c**, it increases from 0.06 in chloroform-*d* to 0.31 in DMSO-d_6, probably as a result of stronger dipole−dipole interactions between the polar *syn* isomer and DMSO (Table 1, Figure 5). In addition, the value of 0.31 is 50% higher than the largest [*syn*]/[*anti*] ratio of 0.20 previously observed for a bispidine compound in DMSO-d_6 (**1**, R = COMe, R′ = Me).[5] This indicates that the bridgehead substituents can affect the [*syn*]/[*anti*] ratio considerably and that, in their absence, *syn*-**4c** is stabilized more by DMSO due in part to less steric interference in the solute−solvent dipolar interactions.

Table 1. Equilibrium Constant *K* and ΔG° of Diacyl Bispidines 4c, 4b, and 5b in Various Solvents at 295 K[a]

	4c		4b		5b	
solvents	*K*	ΔG°	*K*	ΔG°	*K*	ΔG°
$CDCl_3$	0.06	1.65	0.08	1.48	0.09	1.41
CD_2Cl_2	0.14	1.15	0.15	1.11	0.16	1.07
$(CD_3)_2CO$	0.15	1.11	0.21	0.91	0.33	0.65
CD_3CN	0.26	0.79	0.29	0.73	0.45	0.47
DMSO-d_6	0.31	0.69	0.56	0.34	0.96	0.02

[a] *K* = [*syn*]/[*anti*]; ΔG° units in kcal mol^{-1}.

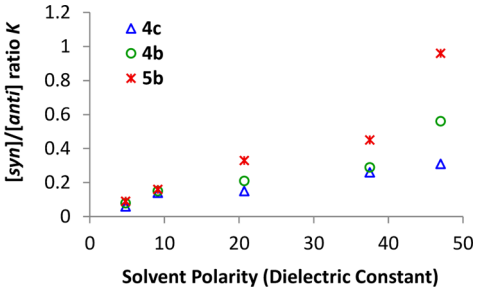
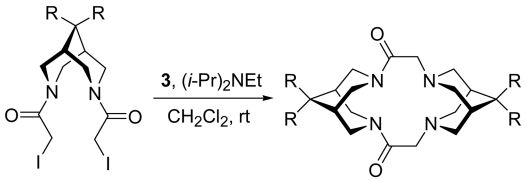


Figure 5. Plot of the [*syn*]/[*anti*] ratio of diacyl bispidines **4c**, **4b**, and **5b** vs the dielectric constant of various solvents (chloroform, 4.8; dichloromethane, 9.1; acetone, 21; acetonitrile, 38; and DMSO, 47)[17] at 295 K.

Notably, the [*syn*]/[*anti*] ratio increases substantially in **4b** and **5b** in polar solvents with the largest value observed in **5b** (0.96 in DMSO-d_6) (Table 1, Figure 5). Thus, by increasing the solvent polarity, up to half of **5b** can be switched from the chiral (*anti*) to the achiral (*syn*) structure. The substantial chiral−achiral transformation is unprecedented and may be accounted for by the orientation of the C−X bond (X = Cl, I) as well as the polarizability of the halogen atom. Previous studies of α-haloketones XCH_2COR have shown that the Cl and O atoms tend to adopt the *cisoid*-form in solution with a Cl−C−C═O dihedral angle of ∼0°.[18] In the haloacetyl groups of **4b** and **5b**, the *cisoid*-form would greatly reduce the steric repulsion between the halogen atom and the NCH_2 methylene group *trans* to the amide oxygen while at the same time enhancing the polarity of the *syn* isomer. Together with the fairly large polarizability of the halogen atoms,[19] this can lead to stronger dipolar interactions between the *syn* solute and polar solvent and thus substantial chiral−achiral switching.

Scheme 2. Synthesis of Dioxo Bis-bispidines 6



The planar chirality in **4** and **5** alters when the two amide planes are tethered by a second bispidine unit (Scheme 2). The ^1H NMR spectrum of dioxo bis-bispidine **6a** displays four sets of CH_2N signals, each comprising two chemically equivalent methylene groups (Figure 6). In addition, the bridgehead protons exhibit four distinct peaks, indicating that they are nonequivalent and that the amide carbonyls must be *syn* to each other. This suggests that the CH_2N methylenes are equivalent at positions 2 and 8, 4 and 6, 2′ and 8′, and 4′ and 6′. The equatorial protons H_{2e} (4.04 ppm) and H_{4e} (3.88 ppm) are chemically nonequivalent and exhibit long-range W-coupling (^4J) with each other (Figure 6, inset). As ^4J can be resolved from ^2J but not ^3J coupling, each proton appears as a slightly broadened doublet. By contrast, the axial protons H_{2a} and H_{8a}

DOI: 10.1021/acs.joc.6b00250
J. Org. Chem. 2016, 81, 2981−2986

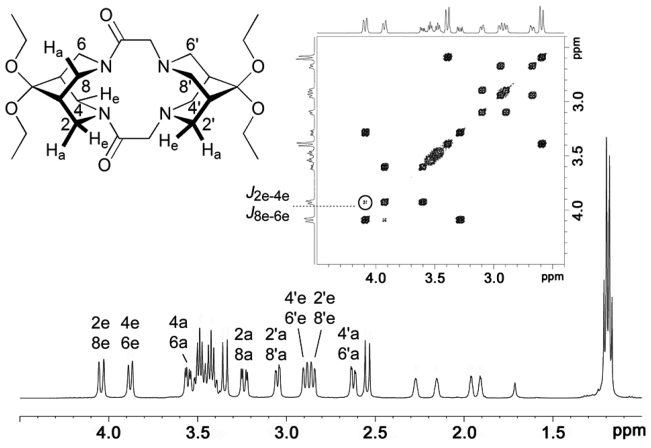


Figure 6. ^{1}H NMR spectrum of **6a** (500 MHz, $CDCl_3$) with "e" denoting equatorial and "a" axial. Inset: COSY spectrum of **6a** in the range of 2.4−4.5 ppm.

are chemically equivalent and do not couple with each other. Having only ^2J and ^3J couplings, they appear as a doublet of doublets (3.24 ppm). Thus, the axial and equatorial protons on both bispidine units can be determined based on the same analysis of coupling patterns. Notably, the equatorial protons $H_{2'e}$ and $H_{8'e}$ (2.85 ppm) appear more upfield from the axial protons $H_{2'a}$ and $H_{8'a}$ (3.05 ppm). This is in contrast to the general observation that an equatorial proton is more downfield than an axial proton in a rigid six-membered ring.[11] The unusual shift is also observed in **6b** and is probably caused by $H_{2'e}$ and $H_{8'e}$ lying in the shielding region of the carbonyls, indicating that the macrocycle may be rather rigid with a conformation similar to that in the solid state (see below). Unlike **4** and **5**, bis-bispidines **6** do not demonstrate chiral−achiral switching in solvents of various polarities.

The crystal structure of **6a** shows that the carbonyl groups are *syn* to each other and that the macrocycle adopts a chair conformation in addition to the chair−chair conformation of the bispidine units (Figure 7). Despite featuring a 14-membered ring, **6a** possesses two bispidine "caps" as well as two planar amide groups, which may significantly restrict bond rotations in the macrocycle. Molecular mechanics calculations indicate that *anti*-**6a** is approximately 9.4 kcal/mol higher in energy than *syn*-**6a** due to torsional and angle strains. This may account for the exclusive formation of the *syn* isomer during the macrocyclization and the lack of molecular switching in various solvents. Despite having a pair of R_p and S_p chiral planes, the molecular structure of **6** possesses a plane of symmetry and is therefore achiral.

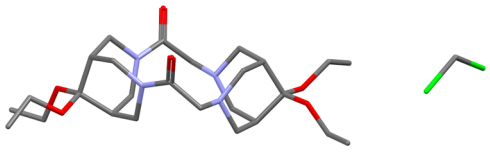


Figure 7. Crystal structure of **6a**·CH_2Cl_2 with C (gray), O (red), N (blue), and Cl (green). Hydrogen atoms are omitted for clarity.

CONCLUSIONS

Conformational analysis of *N*,*N*′-diacyl bispidines **4** and **5** by NMR indicates planar chirality with open-ended chiral planes, which has been confirmed by X-ray diffraction studies. The chirality arises from the asymmetric arrangement of out-of-plane groups with respect to each of the amide planes. Although the (R_p, R_p) and (S_p, S_p) enantiomers coexist in solution and pack alternately in three dimensions in the crystal lattice, DNMR study of the amide rotation barrier indicates that resolution of enantiomers would be infeasible at ambient temperature. Nonetheless, the amide rotation allows substantial chiral−achiral transformation in di(haloacetyl) bispidines, which may have implications in the development of molecular switches. The planar chirality is not only influenced by solvent polarity, bridgehead substituents, and α-halogen in the acetyl groups, but it can be altered by tethering the chiral planes with a second bispidine linker that renders the resulting dioxo bis-bispidines achiral.

EXPERIMENTAL SECTION

General Information. All reagents and anhydrous solvents were used as received from chemical companies unless otherwise indicated. Dichloromethane was further purified on a solvent purification system through double column filtration of the anhydrous solvents (99.8%). *N*-Boc-*N*′-allylbispidinone, **3a**, **4a**, **5a**, and **6a** were prepared according to literature procedures.[7,8,20] All manipulations of air-sensitive materials were performed under a nitrogen atmosphere either in a glovebox or by standard Schlenk line techniques. Column chromatography was carried out using silica gel (60 Å, 40−63 μm, 230−400 mesh) or alumina (activated, basic, Brockmann I). ^{1}H, ^{13}C, ^{1}H−^{1}H COSY as well as ^{1}H−^{13}C HSQC and HMQC NMR spectra were recorded on 300 and 500 MHz spectrometers and referenced to residual protonated solvent (^{1}H) or deuterated solvent (^{13}C) unless otherwise specified. Infrared (IR) spectra were recorded on an FT-IR spectrometer with a Platinum ATR module (single reflection diamond crystal). Elemental analysis was performed on a CHNS/O analyzer operating in CHN mode. High-resolution mass spectra were recorded on a micromass Electrospray Ionization Time of Flight Mass Spectrometer operating in positive mode. Various temperature ^{13}C NMR spectra of **4c** were recorded at 75 MHz between 20−150 °C. The temperature was calibrated using a standard sample for high temperature NMR values (80% ethylene glycol in DMSO). The total line shape analysis of the spectra was performed using the DNMR module included in Bruker's TopSpin 3.5 software package. Molecular mechanics calculations (MM2) of the energy of *syn*- and *anti*-**6a** were conducted using Chem3D Ultra 7.0 software.

Crystal Structure. Crystals of **4a** (colorless plate shaped) and **6a** (colorless block shaped) suitable for X-ray diffraction were grown by slow evaporation of a solution of **4a** in a mixture of ethyl acetate and hexanes and **6a** in a mixture of dichloromethane and hexanes, respectively. The X-ray crystal structures of **4a** and **6a** were obtained at −123 °C, where the crystals were covered in paratone oil and placed rapidly into the cold N_2 stream of the Kryo-Flex low-temperature device. The data was collected using SMART software on a diffractometer equipped with a CCD area detector using a graphite monochromator with Mo Kα radiation (λ= 0.71073 Å).[21] A hemisphere of data was collected using a counting time of 30 s per frame. Data reductions were performed using SAINT software, and the absorption corrections of the raw data were performed using SADABS.[21] The structure was solved by direct methods using SHELX[22] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using the SHELX-97[23] software package. Evaluation of the thermal ellipsoid plot as well as crystal visualization and analysis were conducted using Mercury 3.1.[24]

3-Boc-7-allyl-3,7-diazabicyclo[3.3.1]nonane.[20] To a reaction flask containing *N*-Boc-*N*′-allylbispidinone (10.0 g, 35.7 mmol) and KOH (6.06 g 108 mmol) was added 71.0 mL of diethylene glycol followed by hydrazine monohydrate (4.32 mL, 89.2 mmol). The reaction mixture was stirred at 170 °C for 1 h and then cooled to ambient temperature. NaOH aqueous solution (15%, 30 mL) was added, and the mixture was extracted with dichloromethane (100 mL). The

DOI: 10.1021/acs.joc.6b00250
J. Org. Chem. 2016, 81, 2981−2986

aqueous layer was further re-extracted with dichloromethane (3 × 125 mL), and the combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by column chromatography (silica gel, hexanes → 10% EtOAc/hexanes) to afford *N*-Boc-*N*′-allylbispidine as a colorless oil (6.09 g, 22.9 mmol, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (ddt, J = 17.0, 10.5, 6.5 Hz, 1H), 5.01 (dm, J = 17.5 Hz, 1H), 4.93 (dm, J = 10.5 Hz, 1H), 4.12 (dd, J = 13.0, 1.0 Hz, 1H), 3.99 (dd, J = 13.0, 1.0 Hz, 1H), 2.94 (dm, J = 13.0 Hz, 1H), 2.89 (d, J = 11.0 Hz, 1H), 2.86−2.81 (m, 2H), 2.77 (dd, J = 13.5, 5.5 Hz, 1H), 2.63 (dd, J = 13.5, 6.5 Hz, 1H), 2.08 (d, J = 11.0 Hz, 1H), 1.99 (d, J = 11.0 Hz, 1H), 1.68 (br, 1H), 1.64 (br, 1H), 1.56 (dm, J = 12.5 Hz, 1H), 1.48 (dm, J = 12.5 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 136.6, 116.5, 78.6, 62.5, 58.9, 58.4, 49.0, 47.9, 32.1, 29.5, 29.4, 28.8; IR (liquid) 3075, 3006, 2974, 2906, 2856, 2767, 1687, 1473, 1456, 1421, 1389, 1363, 1323, 1266, 1236, 1173, 1133, 1126, 1056, 999, 946, 901, 872, 835, 756, 623, 539 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{26}N_2O_2H^+$ [M + H$^+$] 267.2072, found 267.2073.

*3,7-Diazabicyclo[3.3.1]nonane Hydrochloride (**3b**).*[20] To a clear colorless solution of *N*-Boc-*N*′-allylbispidine (7.16 g, 26.9 mmol) in anhydrous 1,2-dichloroethane (53.0 mL) was added 1-chloroethyl chloroformate (4.40 mL, 40.3 mmol) at ambient temperature under N_2. The reaction mixture was stirred at 50 °C overnight, and the solvent was removed under high vacuum (0.05 Torr). The crude residue was dissolved in methanol (53.0 mL), and to this solution was added HCl (67.2 mL of a 2.0 M solution in diethyl ether, 134 mmol) at ambient temperature. The reaction mixture was stirred at 50 °C for 1 h. The solvents were removed under high vacuum (0.05 Torr) at 50 °C, and the residue was washed with diethyl ether (3 × 50 mL) and dried under high vacuum to afford **3b** as a pale yellow solid (5.11 g, 25.7 mmol, 95% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 3.54 (d, J = 13.5 Hz, 4H), 3.41(dd, J = 13.5, 4.5 Hz, 4H), 2.42 (br, 2H), 2.02 (br, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 46.2, 26.3, 25.5; IR (solid) 2954, 2902, 2785, 2689, 2582, 2566, 2485, 2449, 2395, 1634, 1591, 1457, 1428, 1313, 1285, 1028, 1007, 958, 815, 562, 485 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{29}N_4ClH^+$ [M_2 + HCl + H$^+$] 289.2159, found 289.2170.

*3,7-Bis(chloroacetyl)-3,7-diazabicyclo[3.3.1]nonane (**4b**).*[20] To a suspension of bispidine hydrochloride **3b** (8.23 g, 41.3 mmol) in anhydrous dichloromethane (154 mL) at 0 °C under N_2 was added *N*,*N*-diisopropylethylamine (23.7 mL, 136 mmol) followed by chloroacetyl chloride (8.30 mL, 103 mmol) at 0 °C under a N_2 atmosphere. The resulting solution was stirred for 15 min at 0 °C before being quenched with a saturated aqueous NH_4Cl solution. The dichloromethane layer was separated, and the aqueous layer was re-extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by column chromatography (silica gel, hexanes → 75% EtOAc/hexanes) to give **4b** as a white solid (8.67 g, 31.1 mmol, 75% yield); mp 201−202 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (d, J = 13.5 Hz, 2 H), 4.22 (d, J = 12.5 Hz, 2H), 3.95 (d, J = 13.0 Hz, 2H), 3.94 (d, 2H), 3.47 (dt, J = 13.5, 2.5 Hz, 2H), 2.92 (dt, J = 14.0, 2.5 Hz, 2H), 2.03 (s, br, 2H), 1.97 (s, br, 2H); ^{1}H NMR (500 MHz, C_6D_6) δ 4.38 (d, J = 14.0 Hz, 2H), 4.01 (d, J = 12.5 Hz, 2H), 3.89 (d, J = 13.0 Hz, 2H), 3.19 (d, J = 13.5 Hz, 2H), 2.55 (d, J = 13.5 Hz, 2H), 2.08 (d, J = 14.0 Hz, 2H), 0.94 (s, br, 2H), 0.83 (s, br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 51.2, 46.5, 41.4, 31.9, 28.2; ^{13}C NMR (125 MHz, C_6D_6) δ 166.0, 50.6, 45.7, 41.7, 31.6, 28.0; IR (solid) 3032, 2956, 2909, 2857, 1647, 1631, 1443, 1415, 1348, 1308, 1296, 1247, 1224, 1212, 1130, 1102, 990, 824, 783, 732, 594, 560, 467 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{16}N_2O_2Cl_2H^+$ [M + H$^+$] 279.0667, found 279.0674.

*3,7-Diacetyl-3,7-diazabicyclo[3.3.1]nonane (**4c**).* To a suspension of bispidine hydrochloride **3b** (0.488 g, 2.45 mmol) and crushed sodium hydroxide (0.600 g, 15.0 mmol) in dichloromethane at ambient temperature was added acetic anhydride (0.71 mL, 7.50 mmol) dropwise. After 30 min of stirring, the mixture was filtered through Celite. Evaporation of the filtrate followed by recrystallization of the residue in ethyl acetate gave **4c** as a colorless crystal (462 mg, 2.20 mmol, 90% yield); mp 91−92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (d, J = 13.5 Hz, 2 H), 3.95 (d, J = 13.0 Hz, 2H), 3.33 (dt, J = 13.0, 2.5 Hz, 2H), 2.81 (d, J = 14.0 Hz, 2H), 2.06 (s, 6H), 1.93 (s, br, 2H), 1.90 (s, br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 50.7, 45.7, 31.6, 27.7, 21.5; IR (solid): 3280, 2866, 1605, 1465, 1445, 1359, 1255, 1236, 1023, 990, 589 cm^{-1}; Anal. Calcd for $C_{11}H_{18}N_2O_2$ C 62.84, H 8.63, N 13.32; found C 62.76, H 8.68, N 13.28.

*3,7-Bis(iodoacetyl)-3,7-diazabicyclo[3.3.1]nonane (**5b**).*[20] To a clear colorless solution of **4b** (5.68 g, 20.3 mmol) in acetone (300 mL) at ambient temperature was added a solution of NaI (12.2 g, 81.3 mmol) in acetone (100 mL). After overnight stirring, the reaction mixture was concentrated under reduced pressure, dissolved in dichloromethane (150 mL), and filtered. The filtrate was washed with water (30 mL), and the aqueous layer was re-extracted with dichloromethane (4 × 150 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by column chromatography (silica gel, hexanes → 75% EtOAc/hexanes) to give **5b** as a white solid (8.52 g, 18.4 mmol, 91% yield); mp 160−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (d, J = 13.5 Hz, 2 H), 3.89 (d, J = 10.5 Hz, 2H), 3.87 (d, J = 13.5 Hz, 2H), 3.60 (d, J = 10.5 Hz, 2H), 3.34 (dt, J = 13.5, 2.5 Hz, 2H), 2.86 (dt, J = 13.5, 2.5 Hz, 2H), 2.04 (s, br, 2H), 1.92 (s, br, 2H); ^{1}H NMR (500 MHz, C_6D_6) δ 4.40 (d, J = 14.0 Hz, 2H), 3.67 (d, J = 10.5 Hz, 2H), 3.53 (d, J = 10.5 Hz, 2H), 3.15 (d, J = 13.5 Hz, 2H), 2.50 (d, J = 13.0 Hz, 2H), 2.08 (d, J = 13.5 Hz, 2H), 0.94 (s, br, 2H), 0.87 (s, br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 52.2, 46.7, 31.6, 28.2, −2.8; ^{13}C NMR (125 MHz, C_6D_6) δ 166.8, 51.6, 45.9, 31.4, 28.1, −1.7; IR (solid) 3043, 2992, 2917, 2866, 1621, 1459, 1443, 1404, 1343, 1251, 1233, 1161, 1084, 1064, 991, 594, 513, 472, 454 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{16}N_2O_2I_2H^+$ [M + H$^+$] 462.9380, found 462.9377.

*3,6,12,15-Tetraazapentacyclo [13.3.1.1^{3,17}.1^{6,10}.1^{8,12}]docosane-4,14-dione (**6b**).*[20] To a suspension of bispidine hydrochloride **3b** (2.26 g, 11.4 mmol) in dichloromethane (100 mL) at ambient temperature was added *N*,*N*-diisopropylethylamine (9.90 mL, 56.8 mmol) followed by a solution of bis(iodoacetyl) bispidine **5b** (3.28 g, 7.09 mmol) in dichloromethane (260 mL). After overnight stirring, the reaction mixture was washed with 10% Na_2CO_3 (150 mL) and separated. The aqueous layer was re-extracted with dichloromethane (4 × 125 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure to afford crude **6b** as a light yellow solid (3.30 g, 9.92 mmol, 96% yield). The crude product (1.467 g) was further purified by column chromatography (basic alumina, hexanes → 75% THF/hexanes) to give **6b** as a pale yellow solid (1.095 g, 3.29 mmol, 75% yield from the crude product). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (d, J = 14.0 Hz, 2H), 3.99 (d, J = 11.5 Hz, 2H), 3.32 (dd, J = 11.5, 4.5 Hz, 2H), 3.31 (d, J = 12.5 Hz, 2H), 3.04−2.96 (m, 6H), 2.73 (dd, J = 10.0, 2.5 Hz, 2H), 2.51 (d, J = 13.0 Hz, 2H), 2.32 (dd, J = 11.0, 3.0 Hz, 2H), 2.18 (m, br, 1H), 2.07 (m, br, 1H), 1.83 (m, br, 1H), 1.80 (m, br, 2H), 1.78 (m, br, 1H), 1.53 (m, br, 2H); ^{1}H NMR (500 MHz, C_6D_6) δ 4.31 (d, J = 13.5 Hz, 2H), 3.39 (d, J = 11.5 Hz, 2H), 3.26 (d, J = 11.5 Hz, 2H), 2.91 (d, J = 12.5 Hz, 2H), 2.70 (dd, J = 14.0, 4.5 Hz, 2H), 2.58 (d, J = 12.5 Hz, 2H), 2.54 (dd, J = 11.5, 4.5 Hz, 2H), 2.42 (d, J = 10.5 Hz, 2H), 2.33 (dd, J = 10.5, 2.5 Hz, 2H), 2.19 (dd, J = 11.0, 3.0 Hz, 2H), 1.42 (s, br, 1H), 1.36−1.32 (m, 3H), 1.18 (s, br, 3H), 1.12 (s, br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 60.4, 59.5, 57.5, 50.6, 46.9, 32.1, 31.4, 29.6, 28.5, 27.9, 27.2; ^{13}C NMR (125 MHz, C_6D_6) δ 171.1, 60.5, 59.4, 57.7, 50.3, 47.0, 32.4, 31.7, 29.9, 28.7, 28.1, 27.4; IR (solid) 2928, 2897, 2845, 2821, 2705, 1626, 1421, 1256, 1143, 1129, 1108, 1074, 1010, 984, 978, 847, 775, 738, 672, 619, 576, 529, 484, 473 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{28}N_4O_2H^+$ [M + H$^+$] 333.2291, found 333.2281.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00250.

^{1}H and ^{13}C NMR chemical-shift assignments for compounds **4**−**6**, NMR spectra of compounds *N*-Boc-

DOI: 10.1021/acs.joc.6b00250
J. Org. Chem. 2016, 81, 2981−2986

N′-allylbispidine, **3b**, and **4**−**6**, single crystal X-ray diffraction data, and DNMR data (PDF)
CIF file for compound **4a** (CIF)
CIF file for compound **6a** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: zhuowang@uwindsor.ca.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada and the University of Windsor. We thank Dr. Janeen Auld at the University of Windsor for HRMS and elemental analysis.

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DOI: 10.1021/acs.joc.6b00250
J. Org. Chem. 2016, 81, 2981−2986