Mechanistic Considerations for the Consecutive Cyclization of 2,3-Dibromopropylamine Hydrobromide Giving a Strained Molecule, 1-Azabicyclo[1.1.0]butane

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The effective formation of 1-azabicyclo[1.1.0]butane (2) by treatment of 2,3-dibromopropylamine hydrobromide (1) with *n*-BuLi could be understood considering a rational reaction pathway *via* both transition states 10 and 19 based on the intramolecular Br···Li$^+$ coordination. A similar cyclization pathway starting from *N*-benzyl-3-bromopropylamine hydrochloride (17) to afford *N*-benzylazetidine (18) could also be postulated on the basis of a transition state 20 involving the intramolecular Br···Li$^+$ coordination.

Key words azabicyclo[1.1.0]butane; lithium–bromine coordination; azetidene synthesis

Recently, we have developed an expeditious and good-yielding synthesis of 1-azabicyclo[1.1.0]butane (ABB) (**2**) bearing the high-strained bicyclic structure and established a facile synthetic method for various 3-substituted azetidine derivatives (**3**) from **2**, as represented in Chart 1.[1—3] The structure of **2** was comfirmed by ^{1}H- and ^{13}C-NMR analyses and its conversion to *N*-tosyl-3-chloroazetidine (**4**)[4] (Fig. 1, Table 1).[1,3] The optimization of the structure was carried out by DFT molecular orbital computation, as shown in Fig. 1.[1] Azetidine derivatives like **3** should be useful for syntheses of new pendant molecules of β-lactam and quinolone antibiotics.[1,5] As shown in Table 1, the desirable consecutive cyclization of 2,3-dibromopropylamine hydrobromide (**1**) giving ABB **2** proceeded only with the use of organolithium compounds and lithium amides (entries 6—9 in Table 1).[1] When other bases such as potassium, sodium, and magnesium species were employed, the reaction of **1** resulted in almost no yield of the product **2** (entries 1—5 and 10 in Table 1). The same reaction with *n*-BuLi or $LiNH_2$ in the presence of a crown ether, 12-crown-4, trapping a lithium cation afforded no significant product, respectively (entries 11 and 12 in Table 1). Thus a lithium cation of the lithium amide generated by treatment of **1** with the lithium species should play an essential role (*vide infra*) in the consecutive cyclization.

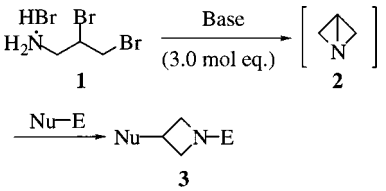
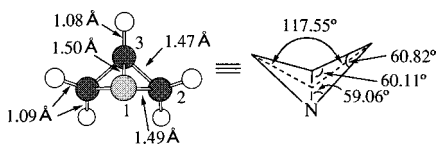


Chart 1



400 MHz ^{1}H-NMR (THF-*d8*, δ ppm)

H-2: 0.85 (2H, m)
2.07 (2H, m)
H-3: 2.29 (1H, m)

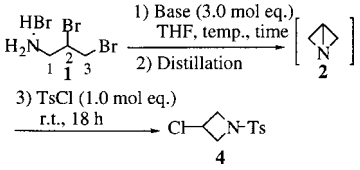
100 MHz ^{13}C-NMR (THF-*d8*, δ ppm)

C-2: 17.2
C-3: 51.1

Fig. 1. Optimized Structure of **2** and Its ^{1}H- and ^{13}C-NMR Spectral Data

Subsequently, we investigated the first cyclization step (*i.e.*, path A toward aziridine **6** and/or path B toward azetidine **7**) in the consecutive cyclization reactions of a free amine **5**,[6] as shown in Chart 2. First, we inspected the X-ray crystallographic structure (Fig. 2) of **1**, in which the relationship between C2–Br and C3–Br adopts an approximate antiperiplanar arrangement (torsion angle: Br–C2–C3–Br= 166.1°) due to the dipole–dipole and steric repulsion as anticipated.[7] This Br–Br anti-conformation even in the molecule of the free amine **5** (Chart 2) seemed to be preferable, which was supported by the ^{1}H-NMR analysis of a solution of **5** in THF-d_8 at 23 °C based on the coupling constants (J=10.0, 5.4 Hz) between C2–H and C3–H_2 (Ha and Hb in **5**). Then, on the basis of the conformational analysis of **5** de-

Table 1. Conversion of **1** to **4** *via* 1-Azabicyclo[1.1.0]butane (**2**)



Entry	Base	Additive (mol eq)	Temp.	Time	Yield (%)[a] of **4**
1	KOH	None	Reflux	1 h	2
2	DBU	None	Reflux	1 h	ND[c]
3	NaOMe	None	r.t.	24 h	2
4	NaH	None	r.t.	18 h	ND[c]
5	$NaNH_2$	None	r.t.	18 h	ND[c]
6	$LiNH_2$	None	r.t.	18 h	34
7	LDA	None	r.t.	18 h	39
8	*n*-BuLi[b]	None	−78 °C	1 h	82
9	PhLi[b]	None	−78 °C	1 h	87
10	PhMgBr[b]	None	−78 °C	1 h	1
11	*n*-BuLi[b]	12-Crown-4 (3.0)	−78 °C	1 h	1
12	$LiNH_2$	12-Crown-4 (3.0)	−78 °C	1 h	ND[c]

a) Determined by HPLC analysis. *b*) Quenched with 50% aq. KOH. *c*) Not detected.

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scribed above, we considered the first cyclization step in terms of both "acyclic transition state" and "cyclic transition state," as shown in Fig. 3. In the former, two kinds of Newman projection states **8** (toward aziridine **6**) and **9** (toward azetidine **7**) may be plausible. In the latter, the five-membered cyclic state **10** (toward **6**) and six-membered cyclic state **11** (toward **7**) consisting of the $Br\cdots Li^+$ coordination would also be plausible. Because of the greater instability of state **9** bearing two types of severe gauche repulsion than state **8** bearing one severe gauche repulsion (Fig. 3), path A toward aziridine **6** is predominant over path B toward azetidine **7** in the first cyclization step of **1**. In the assumed cyclic transition state, the five-membered cyclic state **10** must be kinetically predominant over the six-membered cyclic state **11** on the basis of the general aspect for the kinetic cyclization.[8)]

Thus, to clarify the first cyclization step, path A and/or path B, a competitive cyclization reaction of *N*-benzyl-2,3-dibromopropylamine hydrochloride (**12**) giving only two types of monocyclic products was examined. Treatment of **12** with *n*-BuLi under the same reaction conditions (entry 8 in Table 1) as in the case of **1** furnished aziridine **13**[9)] in 14% yield, a scarce amount of azetidine **14**, and allylamine **15**[10)] in 47% yield together with recovery (33%) of **12**, as shown in Chart 3 (HPLC analysis). The allylamine **15** was not derived from **13** or **14**, respectively, under the same reaction conditions. Compound **15** would be generated by the attack of *n*-BuLi on a bromine atom of *N*-benzyl-2,3-dibromopropylamine in competition with fairly difficult H-abstraction of the secondary NH group, followed by simultaneous exchange of Br for Li and then elimination of lithium bromide. The aziridine **13** proved not to be obtained from the azetidine **14** (Chart 3). Based on these results, it was strongly suggested that the first cyclization step in the consecutive cyclization of **5** is almost certainly path A. This outcome is consistent with the earlier kinetic studies of the cyclization of ω-(bromoalkyl)phenyl-

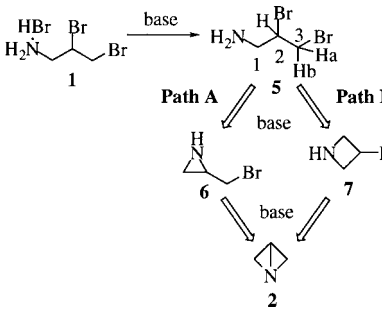


Chart 2

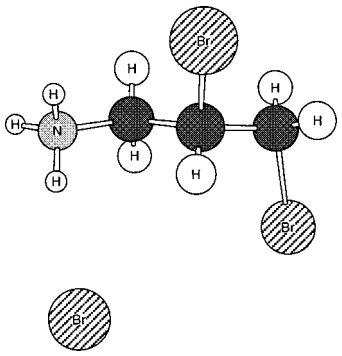


Fig. 2. Computer-Generated Drawing Derived from the X-Ray Coordinates of Compound **1**

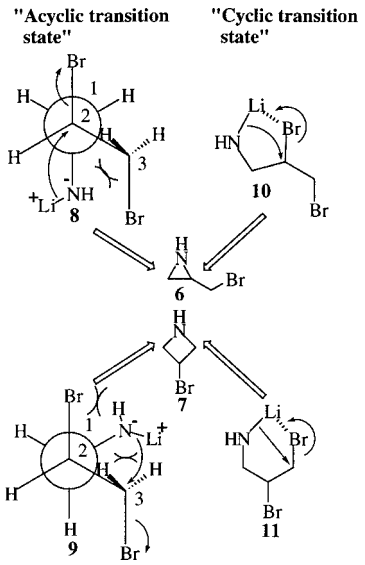
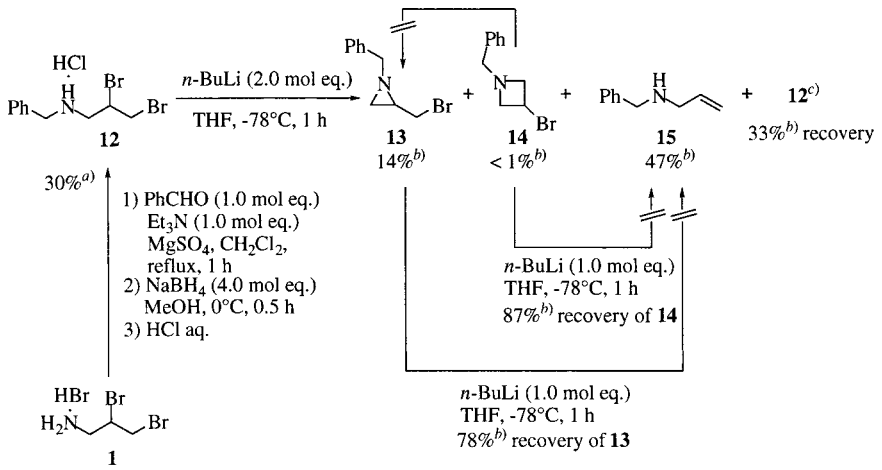


Fig. 3. Hypothetic Transition States in Path A and Path B



a) Isolation yield. *b*) Determined by HPLC analysis. *c*) Compoud **12** was recovered as free amine.

Chart 3

amines[11] or ω-(bromoalkyl)dimethylamines[12] under totally different reaction conditions from our case. Namely, it was demonstrated that the cyclization rate toward aziridine is *ca.* 200 or 70 times that toward azetidine.[11,12]

We are now interested in the cyclization of *N*-benzyl-3-bromopropylamine hydrochloride (**17**) readily obtained from 3-bromopropylamine hydrochloride (**16**) to exploit our method for exclusive azetidine formation (Chart 4). Treatment of **17** with *n*-BuLi in THF at −78 °C for 1 h to give *N*-benzylazetidine (**18**)[13] in 73% yield (HPLC analysis) or in 64% isolation yield together with 22% or 14% recovery each of **17** (entries 1 and 2 in Table 2). Surprisingly, this cyclization reaction proceeded very rapidly (7 min) to give **18** in 67% yield (HPLC analysis) with 26% recovery of **17**[14] (entry 3 in Table 2). The ring strain of azetidine makes this class of amines one of the most difficult to prepare and the cyclization of 3-halogenopropylamines can be complicated by accompanying elimination, fragmentation, or dimerization.[14—16,17] The previous literature methods generally required drastic reaction conditions.[16,18,19] With the background described above, the cyclization procedure using *n*-BuLi should be more effective than the previous methods.[14—16,20,21] Interestingly, we again observed that the cyclization of **17** with *n*-BuLi did not proceed in the presence of 12-crown-4, but instead compound **17** was quantitatively recovered (entry 4 in Table 2).

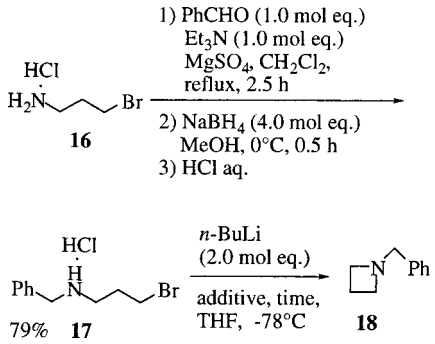


Chart 4

Table 2. Cyclization of *N*-Benzyl-3-bromopropylamine (**17**) with *n*-BuLi

Entry	Additive (mol eq)	Time	Yield (%)[a] of **18** [Recovery (%)[a] of **17**[b]]
1	None	1 h	73 [22]
2	None	1 h	64[c] [14][c]
3	None	7 min	67 [26]
4	12-Crown-4 (2.0)	1 h	0 [100]

a) Determined by HPLC analysis. *b*) Compound **5** was recovered as free amine. *c*) Isolation yield.

The fact that no *n*-BuLi-promoted cyclization reaction of **1** and **17** occurred in the presence of 12-crown-4 suggests that the attack of the naked amide anionic species involving a transition state **8** to the Br-attached carbon atom should be ruled out. Hence the five-membered cyclic transition state **10** consisting of the Br···Li^+ coordination must be the most possible in the first cyclization step of the facile consecutive cyclization of **5** with *n*-BuLi, giving the strained molecule ABB **2**. The significance of such a halogen···Li^+ coordination had been suggested in the stereoselective alkylation of the lithium enolate with alkyl halides by Meyers *et al.*[22] A similar suggestion has been made in an asymmetric alkylation reaction of chiral enamines by Ando *et al.*[23] Further, ^{1}H-NMR analysis of the intermolecular Br···Li^+ coordination between *n*-dodecylbromide and lithium diisopropylamide (LDA) was examined, as shown in Fig. 4. On the ^{1}H-NMR spectrum chart of a solution of *n*-dodecylbromide alone in THF-d_8 at 23 °C, one set of triplet signals due to –CH_2–Br was observed at 3.40 ppm (A in Fig. 4), whereas on that of a solution of *n*-dodecylbromide and 1 mol eq of LDA under the same conditions, two sets of triplet signals probably due to –CH_2–Br and –CH_2–Br···$Li^+N(i\text{-}Pr)_2^-$ could be observed in the presence of a free *n*-dodecylbromide and a weakly *n*-dodecylbromide-coordinated LDA at equilibrium (B in Fig. 4).[24] Tentative use of 3 mol eq of LDA showed one set of triplet signals, presumably due to an *n*-dodecylbromide-coordinated LDA alone, and two sets of triplet signals, in which each height of the triplet signals at the higher magnetic field is considerably higher than that of the corresponding triplet

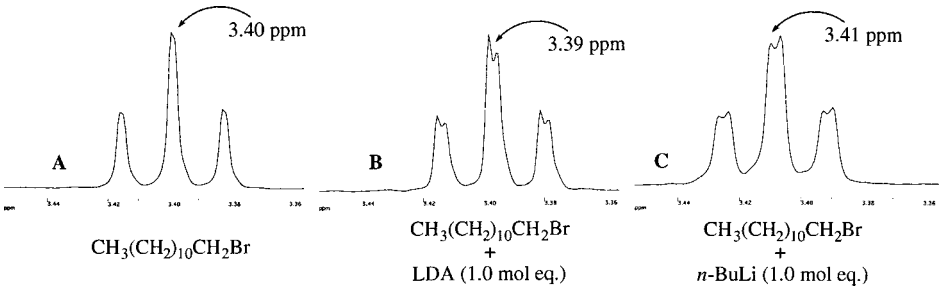


Fig. 4. Selected –CH_2–Br Peaks on the ^{1}H-NMR Chart (400 MHz) of *n*-Dodecylbromide in the Presence or Absence of LDA or *n*-BuLi in THF-d_8

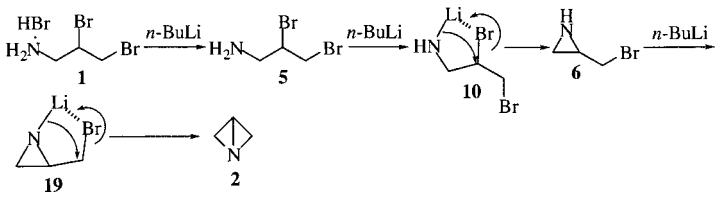


Chart 5

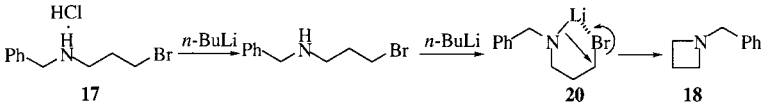


Chart 6

signals at the lower magnetic field, were observed in the presence of 0.5 mol eq of LDA. The same phenomenon was observed in the presence of *n*-dodesylbromide and 1 mol eq of *n*-BuLi (C in Fig. 4). Intramolecular Br···Li^+ coordination in state **10** seems to be stronger than that in the intermolecular Br···Li^+ coordination between *n*-dodecylbromide and LDA.

Based on all the related experiments and considerations described above, we propose a rational reaction pathway for the consecutive cyclization of **1** with *n*-BuLi involving the five-membered cyclic transition states **10** and **19** based on the intramolecular Br···Li^+ coordination, as shown in Chart 5. A similar reaction pathway for the cyclization of **17** *via* the six-membered cyclic transition state **20** can be postulated as shown in Chart 6.

In conclusion, we have established an efficient and facile method for the synthesis of small strained molecules such as 1-azabicyclo[1.1.0]butane and *N*-benzylazetidine using *n*-BuLi and postulated a rational mechanistic pathway for their cyclization reactions involving the intramolecular Br···Li^+ coordination.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO FT-IR 420 Fourier transform spectrometer. ^{1}H-NMR (300, 400 MHz) spectra were recorded on a JEOL JNM-AL300 or JEOL JNM-GSX400 spectrometer. ^{13}C-NMR (75, 100 MHz) spectra were recorded on a JEOL JNM-AL300 or JEOL JNM-GSX400 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS SX-102A spectrometer. Elementary combustion analyses were performed on a Yanaco CHN CORDER MT-5. HPLC analyses for the determination of yield were carried out on a SHIMADZU LC-6A and UV detector of 254 nm. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5-mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel (Katayama Chemical K070; 70—300 mesh, Merck 9385; 230—400 mesh). All solvents were distilled prior to use. All reagents were used as purchased.

General Procedure of HPLC Analysis (Table 1) The reactions were performed by using a suspension of 2,3-dibromopropylamine hydrobromide (**1**) (5.00 g, 16.8 mmol) and each base (50.4 mmol) in THF (50 ml) under the conditions shown in Table 1. After the reaction was completed, the solution was distilled at atmospheric pressure. In the cases of entries 7—10, after the reaction was completed, the reaction mixture was quenched with 50% KOH (10 ml), and the whole mixture was distilled at atmospheric pressure. To the resulting distillate was added *p*-toluenesulfonyl chloride (3.20 g, 16.8 mmol) at 0 °C, and the mixture was stirred at room temperature for 18 h to afford a crude reaction solution, which was analyzed by HPLC under the following conditions. Mobil phase: phosphate buffer (pH=7.0, 0.05 mol/l)/MeCN=5/5, flow rate: 1.0 ml/min, column: TOSOH TSK-GEL 80Ts (4.6 mm ϕ* 25 cm). *N*-Tosyl-3-chloroazetidine (**4**) (retention time=9 min) was used as the standard sample.

Preparation of *N*-Tosyl-3-chloroazetidine (4)[4] To a suspension of 2,3-dibromopropylamine hydrobromide (**1**) (5.00 g, 16.8 mmol) in THF (50 ml) was added dropwise *n*-BuLi (1.61 mol/l, *n*-hexane solution, 31.3 ml, 50.4 mmol) at −78 °C under an N_2 atmosphere, and the reaction mixture was stirred at −78 °C for 1 h. Then the reaction mixture was quenched with 50% KOH (10 ml), and the whole mixture was distilled at atmospheric pressure. The distillate was dried over K_2CO_3 and filtered. To the resulting filtrate was added *p*-toluenesulfonyl chloride (3.20 g, 16.8 mmol) at 0 °C. Then the mixture was stirred at room temperature for 18 h and evaporated *in vacuo*. The residue was purified by column chromatography (eluent *n*-hexane–AcOEt, 3/1) to give **4** (3.38 g, 83%) as colorless needles, mp 110 °C (lit.,[4] 106 °C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.47 (3H, s), 3.84 (2H, dd, J=5.6, 8.3 Hz), 4.23 (2H, t, J=8.3 Hz), 4.3—4.5 (1H, m), 7.39 (2H, d, J=8.2 Hz), 7.73 (2H, d, J=8.2 Hz). IR (neat) 1596, 1343, 1162, 681 cm^{-1}. EI-MS calcd for $C_{10}H_{12}NO_2ClS$ MW245.0277, found *m/z* 245.0266 [M^+]. *Anal.* Calcd for $C_{10}H_{12}NO_2ClS$: C, 48.97; H, 4.94; N, 5.71. Found: C, 48.46; H, 4.86; N, 5.68.

Optimization of the Structure of 1-Azabicyclo[1.1.0]butane (2) DFT molecular orbital computation was performed with the GAUSSIAN 98 program obtained from Gaussian Inc. (Pittsburgh).[25] We used the B3LYP approach based on Becke's three-parameter nonlocal-exchange function after modification by using the nonlocal correlation of Lee, Yang, and Parr (B3LYP).[25] The structure was optimized using the 6-31G* basis set.

^{1}H- and ^{13}C-NMR Analysis of 1-Azabicyclo[1.1.0]butane (2) To a suspension of 2,3-dibromopropylamine hydrobromide (**1**) (1.00 g, 3.36 mmol) in THF-d_8 (10 ml) was added $LiNH_2$ (0.23 g, 10.1 mmol) at room temperature under an N_2 atmosphere, and the reaction mixture was stirred at room temperature for 18 h. Then the whole reaction mixture was distilled at atmospheric pressure and the resulting distillate was analyzed by ^{1}H- and ^{13}C-NMR at 23 °C. ^{1}H-NMR (400 MHz, THF-d_8) δ: 0.85 (2H, m), 2.07 (2H, m), 2.29 (1H, m). ^{13}C-NMR (100 MHz, THF-d_8) δ: 17.2, 51.2. The reported data[4,26]: ^{1}H-NMR (100 MHz, CCl_4) δ: 0.93 (2H, m), 2.13 (2H, m), 2.33 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.1, 51.1.

X-Ray Crystallographic Analysis of 2,3-Dibromopropylamine Hydrobromide (1) The crystalline compound **1** was prepared by bromination of allylamine, as reported previously,[2] and then recrystallized from MeOH for X-ray crystallographic analysis. The measurement was done on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo$K\alpha$ radiation. The data were processed using the PROCESS-AUTO program package. The linear absorption coefficient, μ, for Mo$K\alpha$ radiation is 1.0 cm^{-1}. A symmetry-related absorption correction using the program ABSCOR was applied.[27] The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods and expanded using Fourier techniques.[28,29] The nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. Natural atom scattering factors were taken from Cromer and Waber.[30] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[31] All calculations were performed using the teXsan crystallographic software package.[32]

Crystallographic Data for **1**: $C_3H_8NBr_3$, MW=297.81, colorless needle crystal, monoclinic, space group $P2_{1/c}$ (#14), a=7.973(3) Å, b=8.791(4) Å, c=11.225(5) Å, β=95.30°; V=783.4(6) Å^3; Z=4, D_{calcd}=2.525 g/cm^3, R=0.044, R_w=0.076; GOF=0.969.

^{1}H-NMR Analysis of 2,3-Dibromopropylamine (5) The ether solution of **5** was obtained from 2,3-dibromopropylamine hydrobromide (**1**) by the method reported in the previous paper[6] and evaporated *in vacuo* to afford the crude **5** which was analyzed by ^{1}H-NMR at 23 °C. ^{1}H-NMR (300 MHz, THF-d_8) δ: 1.60 (2H, br s), 3.03 (1H, dd, J=5.4, 14.2 Hz), 3.14 (1H, dd, J=4.2, 14.2 Hz), 3.84 (1H, dd, J=5.4, 10.0 Hz), 3.91 (1H, t, J=10.0 Hz), 4.2—4.3 (1H, m).

***N*-Benzyl-2,3-dibromopropylamine Hydrobromide (12)** A suspension of 2,3-dibromopropylamine hydrobromide (**1**) (4.47 g, 15 mmol), benzaldehyde (1.59 g, 15 mmol), Et_3N (2.09 ml, 15 mmol), and $MgSO_4$ (1.8 g) in CH_2Cl_2 (60 ml) was refluxed for 1 h under an N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. Then Et_2O was added to the residue and the precipitate was filtered off. The filtrate was evaporated *in vacuo* to afford a crude imine product, whose structure was confirmed by ^{1}H-NMR analysis.^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.8—4.0 (2H, m), 4.0—4.2 (2H, m), 4.4—4.6 (1H, m), 7.3—7.5 (3H, m), 7.7—7.9 (2H, m), 8.30 (1H, s). The resultant crude imine was dissolved in MeOH (25 ml) and cooled to 0 °C. After addition of $NaBH_4$ (567 mg, 15 mmol) at 0 °C, the mixture was stirred at 0 °C for 0.5 h. Then the reaction mixture was quenched with 3.5% HCl at 0 °C followed by concentration *in vacuo* to remove MeOH. The concentrated solution was washed with Et_2O, adjusted to pH 8—9 with $NaHCO_3$, and extracted with Et_2O. The Et_2O layer was extracted with 3.5% HCl, and the water layer was evaporated *in vacuo*. The solid residue was recrystallized from MeOH–Et_2O to afford compound **12**

(1.53 g, 30%) as colorless prisms, mp 168—169 °C. ^{1}H-NMR (300 MHz, CD_3OD) δ: 3.45 (1H, dd, J=9.9, 13.9 Hz), 3.78 (1H, dd, J=3.3, 13.9 Hz), 3.84 (1H, dd, J=8.3, 11.2 Hz), 3.99 (1H, dd, J=4.6, 11.2 Hz), 4.33 (2H, s), 4.5—4.7 (1H, m), 7.4—7.6 (5H, m). IR (KBr) 2691, 2581, 1569, 1459, 1413, 1215, 939, 758, 704, 581 cm^{-1}. FAB-MS calcd for $C_{10}H_{14}NBr_2$ MW305.9493, found m/z 305.9509 [(M+1)$^+$]. *Anal.* Calcd for $C_{10}H_{15}NBrCl$: C, 34.97; H, 4.11; N, 4.08. Found: C, 34.76; H, 3.99; N, 4.01.

Preparation of *N*-Benzyl-2-(bromomethyl)aziridine (13) and *N*-Benzyllallylamine (15) To a suspension of *N*-benzyl-2,3-dibromopropylamine hydrobromide (**12**) (343 mg, 1.0 mmol) in THF (3.0 ml) was added *n*-BuLi (1.56 mol/l, *n*-hexane solution, 1.28 ml, 2.0 mmol) at −78 °C under an N_2 atmosphere. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with a phosphate buffer solution (pH=6.0, 0.05 mol/l, 10 ml) and extracted with AcOEt. The AcOEt extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by PTLC (eluent $CHCl_3$–MeOH, 9/1) to give the free amine of **12** (39 mg, 15%), **13** (72 mg, 39%), and **15** (20 mg, 19%).

Free Amine of **12**: Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.82 (1H, br s), 3.02 (1H, dd, J=6.8, 13.4 Hz), 3.20 (1H, dd, J=3.4, 13.4 Hz), 3.7—3.9 (4H, m), 4.2—4.4 (1H, m), 7.2—7.4 (5H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 34.2, 53.1, 53.3, 53.8, 127.7, 128.6, 129.0, 140.3. IR (neat) 3324, 3027, 2838, 1494, 1454, 1141, 738, 698, 570 cm^{-1}. EI-MS calcd for $C_{10}H_{13}NBr_2$ MW304.9415, found m/z 304.9420 [M$^+$].

13: Colorless oil.[9] ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.54 (1H, d, J=5.9 Hz), 1.71 (1H, d, J=3.3 Hz), 1.8—1.9 (1H, m), 3.20 (1H, dd, J=6.3, 10.2 Hz), 3.25 (1H, dd, J=6.9, 10.2 Hz), 3.30 (1H, d, J=13.2 Hz), 3.49 (1H, d, J=13.2 Hz), 7.1—7.3 (5H, m). The ^{1}H-NMR data of **13** were identical to those of the known compound.[9]

15: Colorless oil.[10] ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45 (1H, br s), 3.28 (2H, dt, J=5.9, 1.3 Hz), 3.79 (2H, s), 5.1—5.2 (2H, m), 5.8—6.0 (1H, m), 7.2—7.4 (5H, m). The ^{1}H-NMR data of **15** were identical to those of the known compound.[10]

Preparation of *N*-Benzyl-3-bromoazetidine (14) To a solution of *N*-benzyl-3-hydroxyazetidine[33] (163 mg, 1.0 mmol) and CBr_4 (445 mg, 1.34 mmol) in CH_2Cl_2 (1.0 ml) was added PPh_3 (393 mg, 1.5 mmol) at 0 °C. After being stirred for 0.5 h at 0 °C, the reaction mixture was evaporated *in vacuo* to give a residue. The residue was purified by column chromatography (eluent *n*-hexane–AcOEt, 2/8) to afford **14** (80 mg, 35%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.3—3.4 (2H, m), 3.62 (2H, s), 3.7—3.9 (2H, m), 4.3—4.5 (1H, m), 7.2—7.3 (5H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 34.3, 63.3, 64.6, 126.9, 128.0, 128.1, 137.1. IR (neat) 3027, 2953, 2832, 1495, 1453, 1362, 1234, 1178, 758, 712, 696 cm^{-1}. EI-MS calcd for $C_{10}H_{12}NBr$ MW225.0153, found m/z 225.0143 [M$^+$].

General Procedure for HPLC Analysis (Chart 3) To a suspension of **12** (172 mg, 0.5 mmol) in THF (1.5 ml) was added *n*-BuLi (1.56 mol/l, *n*-hexane solution, 0.64 ml, 1.0 mmol) under an N_2 atmosphere at −78 °C and the mixture was stirred at −78 °C for 1 h. In the reaction of **13** or **14** with *n*-BuLi, a solution of **13** (20 mg, 0.089 mmol) or **14** (20 mg, 0.089 mmol) in THF (0.3 ml), and *n*-BuLi (1.56 mol/l, *n*-hexane solution, 0.057 ml, 0.089 mmol) was employed. The resulting reaction mixture was worked up in a similar manner to the preparative syntheses of **13** and **15** to furnish the crude reaction solution, which was subjected to HPLC analysis. Mobil phase: phosphate buffer (pH=6.0, 0.05 mol/l)/MeCN=6/4, flow rate: 2.0 ml/min, column: Wakopack Fluofix (4.6 mm ϕ* 25 cm). The isolated compounds **12** (retention time=13 min), **13** (retention time=8.5 min), **14** (retention time=10.5 min), and **15** (retention time=4.5 min) were used as each corresponding standard sample.

***N*-Benzyl-3-bromopropylamine Hydrobromide (17)** A suspension of 3-bromopropylamine hydrochloride (**16**) (3.29 g, 15 mmol), benzaldehyde (1.59 g, 15 mmol), Et_3N (2.09 ml, 15 mmol), and $MgSO_4$ (1.8 g) in CH_2Cl_2 (60 ml) was refluxed under an N_2 atmosphere for 1.5 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. Then Et_2O was added to the residue and the precipitate was filtered off. The filtrate was evaporated *in vacuo* to afford a crude imine product, of which the structure was confirmed by ^{1}H-NMR. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.25 (2H, m), 3.49 (2H, t, J=6.3 Hz), 3.74 (2H, t, J=6.6 Hz), 7.3—7.5 (3H, m), 7.5—7.8 (2H, m), 8.32 (1H, s). The resulting crude imine was dissolved in MeOH (25 ml) and cooled to 0 °C. After the addition of $NaBH_4$ (567 mg, 15 mmol) at 0 °C, the mixture was stirred at 0 °C for 0.5 h. Then the reaction mixture was quenched with 3.5% HCl at 0 °C and concentrated *in vacuo* to remove MeOH. The concentrated solution was washed with Et_2O, adjusted to pH 8—9 with $NaHCO_3$, and extracted with Et_2O. The Et_2O layer was extracted with 3.5% HCl, and the water layer was evaporated *in vacuo*. The solid residue was recrystallized from EtOH to afford **17** (3.14 g, 79%) as colorless plates, mp 186—187 °C. ^{1}H-NMR (400 MHz, CD_3OD) δ: 2.2—2.3 (2H, m), 3.26 (2H, t, J=7.8 Hz), 3.54 (2H, t, J=6.4 Hz), 4.87 (2H, s), 7.4—7.6 (5H, m). IR (KBr) 2941, 2799, 1445, 1245, 745, 697 cm^{-1}. FAB-MS calcd for $C_{10}H_{15}NBr$ MW 228.0388, found m/z 228.0387 [(M+1)$^+$]. *Anal.* Calcd for $C_{10}H_{15}NBrCl$: C, 45.39; H, 5.71; N, 5.29. Found: C, 45.78; H, 5.71; N, 5.37.

Preparation of *N*-Benzylazetidine (18) (Table 2, Entry 2) To a suspension of *N*-benzyl-3-bromopropylamine hydrochloride (**17**) (396 mg, 1.50 mmol) in THF (4.5 ml) was added *n*-BuLi (1.56 mol/l, *n*-hexane solution, 1.92 ml, 3.0 mmol) at −78 °C under N_2 atmosphere. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with a phosphate buffer solution (pH=6.0, 0.05 mol/l, 10 ml) and then extracted with AcOEt. The AcOEt extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography (eluent $CHCl_3$–MeOH, 9/1) to give **18** (142 mg, 64%), and the free amine of **17** (46 mg, 14%) as each colorless oil.

18: Colorless oil, bp 70—75 °C/5 mmHg (lit.,[13] bp 65—70 °C/4 mmHg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.06 (2H, quintet, J=7.1 Hz), 3.20 (4H, t, J=7.1 Hz), 3.55 (2H, s), 7.2—7.4 (5H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 17.7, 55.1, 63.9, 126.9, 128.3, 128.4, 138.3. IR (neat) 2957, 2818, 1493, 1453, 1361, 1187, 733, 698 cm^{-1}. EI-MS calcd for $C_{10}H_{14}NBr$ MW 148.1126, found m/z 148.1108 [(M+1)$^+$].

Free Amine of **17**: Colorless oil.[21] ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.07 (2H, m), 2.79 (2H, t, J=6.9 Hz), 3.25 (1H, br s), 3.48 (2H t, J=6.6 Hz) 3.81 (2H, s), 7.2—7.4 (5H, m).

General Procedure for HPLC Analysis (Table 2, Entries 1, 3, 4) Each reaction was carried out using a suspension of **17** (265 mg, 1.0 mmol) and *n*-BuLi (1.56 mol/l, *n*-hexane solution, 1.28 ml, 2.0 mmol) in THF (5 ml) under the conditions shown in Table 2 (entries 1, 3). In the case of entry 4, *n*-BuLi (1.56 mol/l, *n*-hexane solution, 1.28 ml, 2.0 mmol) was added to a solution of 12-crown-4 (352 mg, 2.0 mmol) in THF (3 ml) at −78 °C, and then the mixture was added to a suspension of **17** (265 mg, 1.0 mmol) in THF (2 ml). The whole mixture was stirred at −78 °C for 1 h. Each reaction mixture was worked up in a similar manner to the case of preparative synthesis of **18**. The corresponding resulting solution was analyzed by HPLC under the following conditions. Mobil phase: phosphate buffer (pH=6.0, 0.05 mol/l)/MeCN=6/4, flow rate: 1.0 ml/min, column: Wakopack Fluofix (4.6 mm ϕ* 25 cm). The isolated compounds **18** (retention time=10 min) and **17** (retention time=14 min) were used as the standard sample.

^{1}H-NMR Analysis of the Intermolecular Br$\cdots$Li$^+$ Coordination (Fig. 4) (A) To THF-d_8 (1.0 ml) were added *n*-hexane (0.21 ml) and *n*-dodecylbromide (0.081 ml, 0.34 mmol) at 0 °C. The mixture was stirred at room temperature for 10 min, and the resulting solution was analyzed by ^{1}H-NMR (400 Mz) at 23 °C.

(B) To a solution of diisopropylamine (0.047 ml, 0.34 mmol) in THF-d_8 (1.0 ml) was added *n*-BuLi (1.58 mol/l, *n*-hexane solution, 0.213 ml, 0.34 mmol) at 0 °C. Then *n*-dodecylbromide (0.081 ml, 0.34 mmol) was added to the mixture at 0 °C and stirred at room temperature for 10 min. The resulting solution was analyzed by ^{1}H-NMR (400 Mz) at 23 °C.

(C) To a solution of *n*-dodecylbromide (0.081 ml, 0.34 mmol) in THF-d_8 (1.0 ml) was added *n*-BuLi (1.58 mol/l, *n*-hexane solution, 0.213 ml, 0.34 mmol) at 0 °C. Then the mixture was stirred at room temperature for 10 min, and the resulting solution was analyzed by ^{1}H-NMR (400 Mz) at 23 °C.

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