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Atropisomerism in the 2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepine Nucleus: Effects of Central Chirality at C3 on the N-Mesylation Reaction

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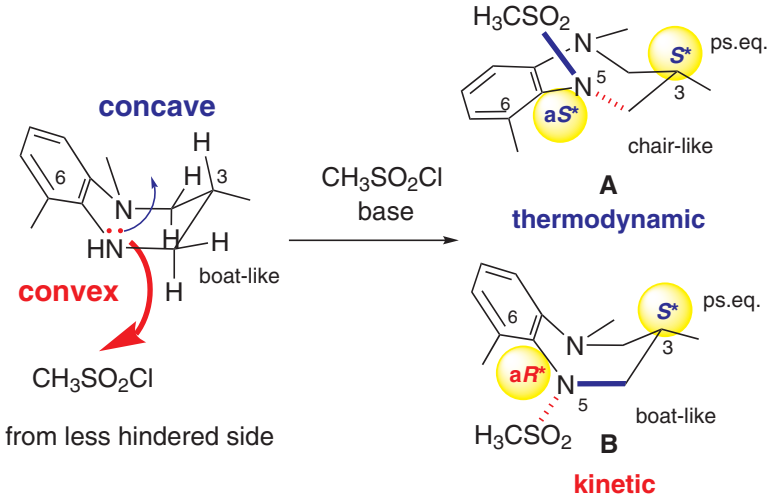

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Abstract The mesylation reaction of the 1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine nucleus was investigated in detail. Two diastereomers (**A** and **B**) of 5-mesyl-1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines, originating from chirality at C3 and at the Ar–N(SO_2) axis were formed, among which isomers of the derivative with a methyl group at C6 (R = CH_3) were separable at room temperature. **A** and **B** had chair-like and boat-like conformations, respectively, in which the C3-methyl group adopts a pseudoequatorial arrangement. Furthermore, **A** and **B** were shown to be the thermodynamically and kinetically controlled products, respectively.

Key words benzodiazepines, mesylation, atropisomerism, conformation, chirality

Benzo-fused seven-membered-ring nitrogen heterocycles (e.g., 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines) are found as important scaffolds in many biologically active molecules.[2] Because these heterocycles possess relatively flexible rings, the seven-membered ring often changes its conformation so as to exert biological activity. Although often overlooked, atropisomerism[2b,3] is latent in these heterocycles. In our previous papers, we have described the atropisomeric properties of these heterocycles in relation to their biological activities.[4] We first studied atropisomerism based on the Ar–N(CO) (sp^2–sp^2) axis in 5-benzoyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines **I**, which constitute a key core structure of the vaptan class of arginine–vasopressin (VP) receptor ligands. Although the conformational change in molecules without a substituent in the *ortho*-position of the benzene ring (R = H) was too rapid for isolation of the isomers at room temperature, molecules with a substituent (R = CH_3) at this position were conformationally 'frozen' and could be separated into the relatively stable (a*S*)- and (a*R*)-axial isomers[5] by chiral HPLC. That study revealed that the (a*S*)-isomer is the active structure (eutomer) in exerting the VP antagonistic activity.[4d,4h,4j]

In addition to the *N*-benzoyl derivatives of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines **I**, we recently investigated the congeneric *N*-*p*-tosyl and *N*-mesyl derivatives **II** and **III**, respectively (Figure 1).[4g] Although the sulfonamide group is an important functional moiety in various biologically active compounds,[6] its chemical nature is not well understood. Our study revealed atropisomeric properties of **IIa**/**b** and **IIIa**/**b** caused by the Ar–N(SO_2) axis.[7] Here again, the atropisomers for the **b**-series (R = CH_3) were stable and could be separated, although their chemical nature differed from that of the corresponding *N*-benzoyl compounds **Ib**. The 5-mesyl-3-methyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines **1** and **2**, which possess a stereogenic center at C3 in addition to the chirality due to the axis at Ar–N(SO_2), can theoretically exist as diastereomers. Here, we describe the N-mesylation reaction of 1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines, especially the effects of the central chirality at C3 on the reaction, and the detailed stereochemistry of the products **1** and **2**.

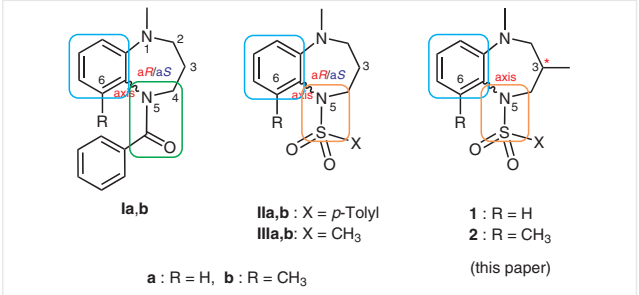


Figure 1 2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepines with an *N*-benzoyl group (**Ia**,**b**), an *N*-*p*-tosyl group (**IIa**,**b**), an *N*-mesyl group (**IIIa**,**b**), or both an *N*-mesyl group and a 3-methyl group (**1**, **2**; X = Me), all of which possess axial chirality

5-Mesyl-1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines **1** and **2** (X = Me) theoretically exist as diastereomers **A** (a*S**,*S**) and **B** (a*R**,*S**) as a result of chiralities at C3 and at the Ar–N(SO_2) axis, as shown in Figure 2. Compounds **2** (R = CH_3), which has a methyl group at C6 on the benzene ring, should provide a higher rotational barrier for the axis and thereby freeze the conformation of the molecule.

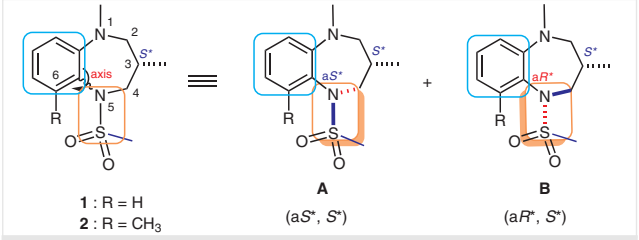
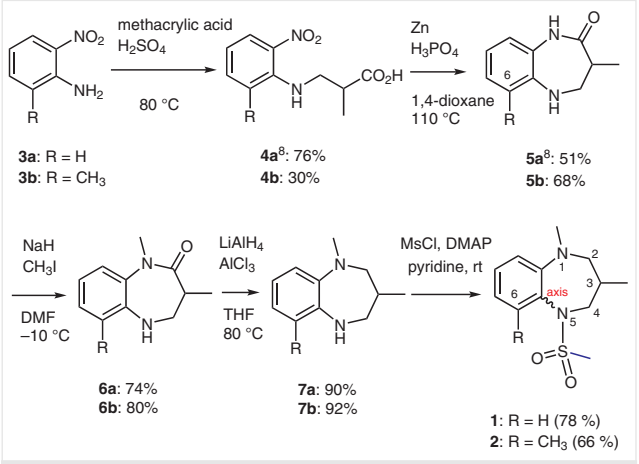


Figure 2 Plausible diastereomers originating from the (3*S**) central chirality and (a*R**)/(a*S**) axial chirality, i.e., (a*S**,3*S**) (**A**) and (a*R**,3*S**) (**B**).

5-Mesyl-1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**1**; X = Me) and 5-mesyl-1,3,6-trimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**2**; X = Me) were prepared starting from the corresponding *o*-nitroanilines **3a**,**b** as shown in Scheme 1. 3-Methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**5a**), lacking a methyl substituent at C6 (R = H), is a known compound[8] and was prepared from *o*-nitroaniline (**3a**) by *N*-alkylation with methacrylic acid in the presence of sulfuric acid, followed by reduction of the nitro group with zinc. 3,6-Dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**5b**, R = CH_3) with a methyl substituent at C6 was similarly prepared from 2-methyl-6-nitroaniline (**3b**) via **4b**. *N*-Methylation of the lactams **5a**,**b** with methyl iodide, followed by reduction of the lactam moiety with $LiAlH_4$ in the presence of $AlCl_3$, gave the corresponding methyl derivatives **7a**,**b**. Mesylation[9] of **7a**,**b** with mesyl chloride in the presence of DMAP in pyridine at room temperature afforded the 3-mesylated compounds **1** and **2**.



Scheme 1 Preparation of 5-mesyl-1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**1**) and 5-mesyl-1,3,6-trimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**2**).

First, the conformations of the *N*-mesyl derivative **1** (R = H) were examined in detail. In the ^{1}H NMR (CD_2Cl_2) spectrum of **1**, each of the two methylene protons and the methine proton of the diazepine ring were observed as separated broad peaks (Figure 3a), indicating that the protons are diastereotopic due to the presence of the C3 central chirality. However, the presence of the signals due to the diastereomers **A** and **B** arising from the additional chirality at the Ar–N(SO_2) axis could not be detected, which suggests that at room temperature (295 K), rotation around the axis is too rapid on the NMR timescale to permit the observation of the diastereomers. A variable-temperature ^{1}H NMR (VT NMR) study of **1** at lower temperatures (295–183 K in CD_2Cl_2) revealed interesting conformational aspects of **1** (Figure 3b): On lowering the temperature, each diastereotopic proton signal split into paired signals showing the appearance of the diastereomers **A** and **B** in a ratio of ~5.3:1 at 183 K. From this ratio at 183 K, the energy difference (ΔG) between **1A** and **1B** was estimated to be ~2.9 kJ/mol by considering the Boltzmann distribution.[10] The activation free-energy barrier to rotation ($\Delta G^{\ddagger}$) between **1A** and **1B** was also estimated by using VT NMR: the coalescence spectra (T_c 243 K, C3 methyl) gave a $\Delta G^{\ddagger}$ value[11] of ~49 kJ/mol.

On the other hand, the crystal structure of **1** revealed a relative stereochemistry of (a*S**,3*S**), which also showed that the 1,5-benzodiazepine ring exists in a chair-like form and that the C3 methyl group adopts a pseudoequatorial orientation (Figure 4: **1**). The relative stereochemistry of the diastereomers of **1** in solution observed at lower temperatures was determined by comparison of the ^{1}H NMR spectrum (CD_2Cl_2) at 185 K with that of the separated diastereomers **A** and **B** of compound **2** (R = CH_3) with a methyl group at C6 on the benzene ring, which is described below. Thus

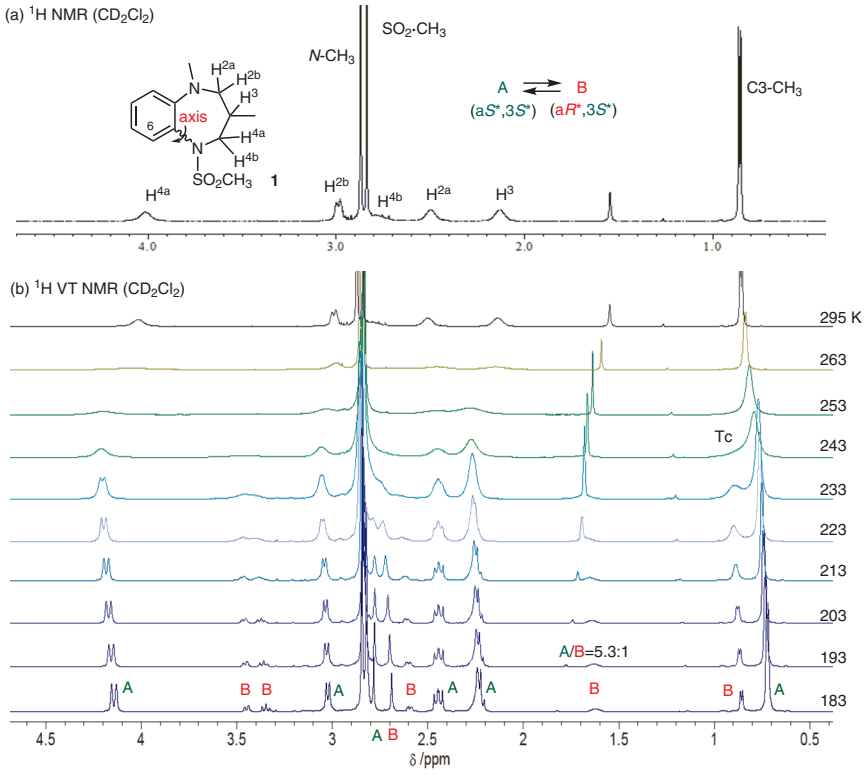


Figure 3 ^{1}H NMR (CD_2Cl_2) spectra (a), and VT ^{1}H NMR (CD_2Cl_2) spectra (b) of **1**.

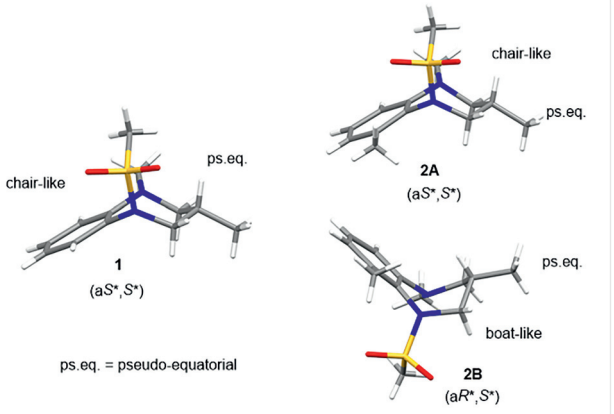


Figure 4 X-ray crystal structures of 5-mesyl-1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines **1**, **2A**, and **2B**. The crystal structures with 3*S* stereochemistry were extracted from the CIF data of the racemate.[18,20]

the ^{1}H NMR spectrum of **1** shown in Figure 3a was shown to correspond to that of the equilibrium state between the diastereomers **1A** and **1B**.

As described above, the **A** and **B** diastereomers of **2** were presumed to have a higher stability, permitting their separation at room temperature. Actually, the mesylation product **2** was obtained as a mixture of the diastereomers **2A** and **2B**, in a ratio of 1:2.6;[12] these were separated at room temperature by column chromatography on silica gel to afford **2A** and **2B** as colorless crystals. Both isomers were subjected to X-ray structural analysis[18,20] to reveal that the tetrahydrodiazepine nuclei of **A** and **B** exist in a chair-like and boat-like form, respectively, and that the C3 methyl group of both isomers adopts a pseudoequatorial orientation (Figure 4; **2A**, **2B**). The ^{1}H NMR spectra of **2A** and **2B** in CD_2Cl_2 are shown in Figure 5 and they reveal that structures similar to those demonstrated by the X-ray crystal analysis also exist in solution. Through detailed inspection of the 2D NMR spectra (NOESY, COSY, and HMQC), the methylene and methine protons were assigned as shown in Figure 5 and the stereochemistries of **2A** and **2B** in solution were deduced to be (a*S**,*S**) and (a*R**,*S**), respectively.

The diagnostic protons are H^{4a} and H^3, with the chemical shift of H^{4a} of **2A** being observed at a lower field (δ = 4.25 ppm) than that of **2B** (δ = 3.4 ppm). The markedly lower shift in **2A** can be explained as due to the H^{4a} atom being located within the deshielding cone of the sulfonyl group, whereas the chemical shift of H^3 of **2B** is observed at a higher field (δ = 1.6 ppm) compared with that of **2A** (δ = 2.3 ppm). The markedly higher shift in **2B** can be ex-

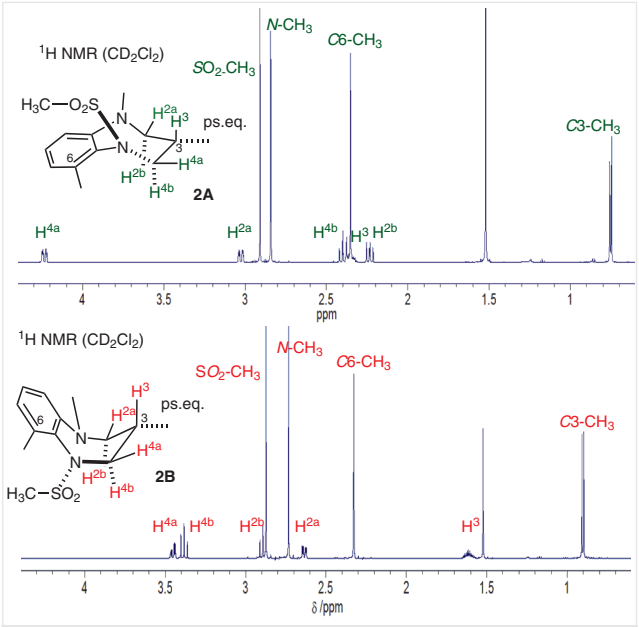


Figure 5 ^{1}H NMR (CD_2Cl_2) spectra of diastereomers **2A** and **2B**

plained as due to H^3 being located over the fused benzene ring.

Interestingly, the ratio of **2A** to **2B** was reversed by mesylation at elevated temperatures or on heating of the crude product mixture of **2A** and **2B** (e.g., at 100 °C in toluene) to afford **2A** in preference to **2B** (Figure 6). These results indicate that the mesylation of **7b** proceeds by a kinetically controlled reaction to form **2B** in preference to **2A**, but the isomer **2A** is the thermodynamically more stable than **2B**. The preferred approach of the mesyl chloride to the diazepine ring of **7b**, in which the chair-like form **7bA** and boat-like form **7bB** are in equilibrium, is presumed to be from the sterically less hindered side. In these forms (**7bA** and **7bB**), the sterically less hindered side is evidently

the lower (convex) side of the boat-like form (**7bB**). Thus, the reaction proceeded by following the bold red line in the bracketed section of Figure 6, affording **2B** as the major product.

To estimate the activation free-energy barrier to rotation ($\Delta G^{\ddagger}$) between the diastereomers **2A** and **2B**,[12] interconversion of the separated diastereomers was examined at 37 °C in toluene. The isomerization profile in Figure 7 shows that, upon heating, both isomers reach an equilibrium state in a ratio of **2A**/**2B** = 1.9:1. From this ratio, the energy difference (ΔG) between **2A** and **2B** is estimated to be 1.6 kJ/mol,[10] whereas the $\Delta G^{\ddagger}$ values calculated from the isomerization profile are 104 kJ/mol (from **2A** to **2B**) and 101 kJ/mol (from **2B** to **2A**),[13] giving a ΔG value of 3 kJ/mol, which suggests an equilibrium ratio of 3.4:1.[10]

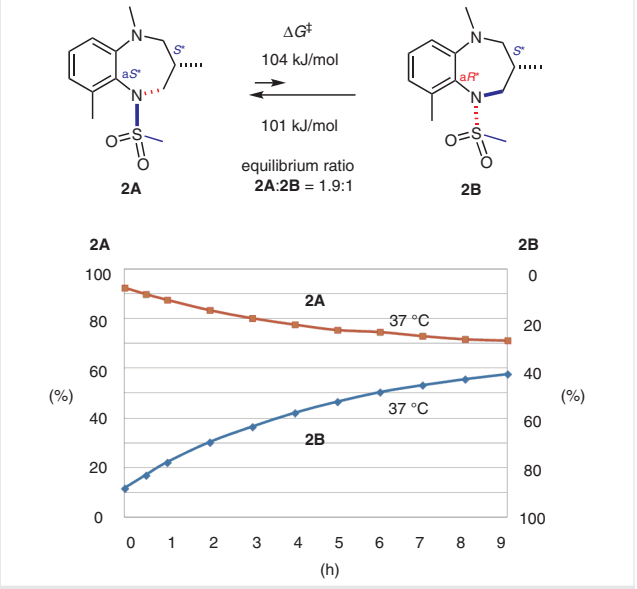


Figure 7 Interconversion between the diastereomers **2A** and **2B** at 37 °C in toluene

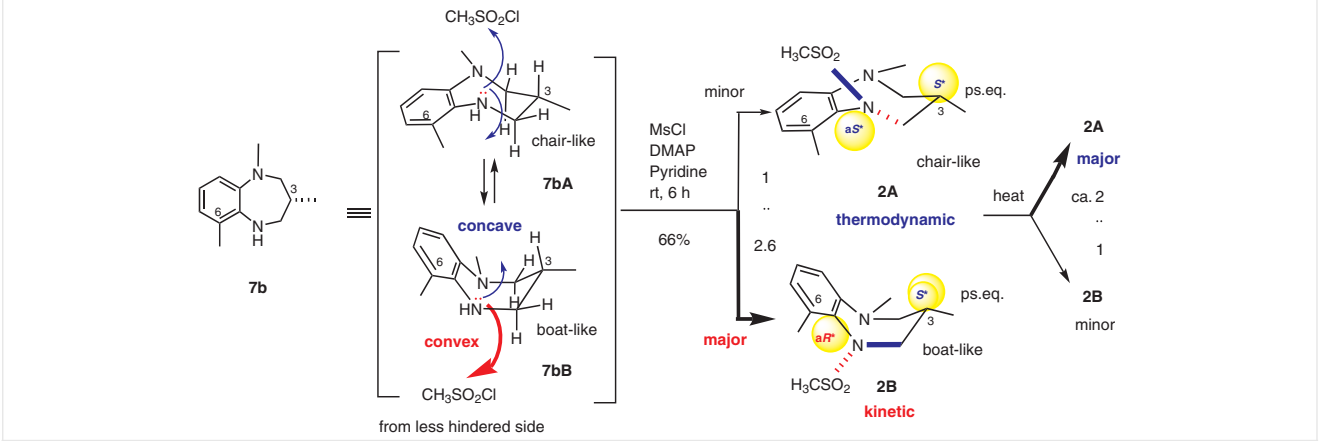


Figure 6 *N*-Mesylation of 3,5,7-trimethyl-1,5-benzodiazepine (**7b**); mesylation of **7b** proceeds preferentially from the convex side of **7bB** (boat-like form) to form **2B** predominantly.

For comparison, the ΔG value between the atropisomeric diastereomers **A** and **B** was also estimated by density functional theory (DFT) calculations.[14] Fourteen conformers for **2** were generated, starting from 2D chemical structures, among which the lowest-energy conformer was **2A** (a*S**, *S**) and the second-lowest was **2B** (a*R**, *S**). The structures for **A** and **B** obtained by calculation are in good agreement with the X-ray structures. Accurate analyses of the stabilities at the RB3LYP/6-31+G(d,p) level were performed both in the gas phase and in solution (toluene) at 310 K, revealing that the calculated ΔG values for **2A** versus **2B** are 4.98 and 2.37 kJ/mol, respectively; these data correspond to equilibrium ratios of 6.9:1and 2.5:1,[10] respectively. It is interesting to note that the ΔG values obtained in solution are smaller than those in the gas phase,[15] and that the data in solution have similar values to those obtained experimentally as described above.

In summary, the *N*-mesylation reaction of the 1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine nucleus, especially the effects of C3 central chirality on this reaction, has been clarified. Diastereomers **A** and **B** of the 5-mesyl-1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines **1** and **2**, originating from the chirality at C3 and the Ar–N(SO_2) axis, were formed, among which the isomers of **2** (R = CH_3) could be separated as stable forms at room temperature. Accompanied by rotation around the Ar–N(SO_2) axis, the 1,3-dimethyl-1,5-diazepine ring adopts chair-like and boat-like conformations **A** and **B**, respectively, in which the C3 methyl group is in a pseudoequatorial arrangement. Furthermore, structures **A** and **B** were shown to be the thermodynamically and kinetically controlled products, respectively. The knowledge regarding the conformation of 5-mesyl-1,3-dimethyl-1,5-benzodiazepines obtained here provides useful information, not only for sulfonamide chemistry, but also for future drug design. Currently, conformations of 1,3-dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines with 5-benzoyl and 5-tosyl groups are also being examined, and the application of the results to the synthesis of biologically active compounds is underway. These results will be reported later.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609868.

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(10) Estimated from the Boltzmann equation.

(11) For determination of $\Delta G^{\ddagger}$ values by VT NMR, see: Boiadjiev, S. E.; Lightner, D. A. *Tetrahedron* **2002**, *58*, 7411.

(12) Although compound **2B** is the major product in the mesylation reaction at r.t. for 6 h in pyridine, the ratio of **2A**/**2B** (1:2.6) might not reflect the exact product ratio of the reaction because, presumably, **2B** was partially converted into **2A** during the reaction.

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(16) For general experimental methods, see the Supporting Information.

(17) **5-Mesyl-1,3-Dimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (1)**

DMAP (21 mg, 0.17 mmol) and MsCl (0.13 mL, 1.72 mmol) were added to a stirred solution of **7a** (61 mg, 0.35 mmol) in pyridine (3.5 mL) at 0 °C under argon. The mixture was stirred at 25 °C for 18 h and then the solvent was evaporated at 25 °C. H_2O (6.0 mL) and EtOAc (10 mL) were added to the residue, and the mixture was extracted with EtOAc (10 × 3 mL). The extracts were t washed with water, dried, and concentrated. The concentrate was purified by column chromatography [silica gel, EtOAc–hexane (1:5)] to give colorless crystals; yield: 68 mg (78%); mp 92–94 °C. IR (ATR): 2897, 1327 cm^{-1}. ^1H NMR (600 MHz, CD_2Cl_2): δ = 0.86 (d, *J* = 6.6 Hz, 3 H), 2.15 (br s, 1 H), 2.51 (br s, 1 H), 2.74–2.90 (m, 1 H), 2.85 (s, 3 H), 2.88 (s, 3 H), 2.97–2.99 (m, 1 H), 4.08 (br s, 1 H), 6.98–7.02 (m, 2 H), 7.26–7.30 (m, 1 H), 7.41 (dd, *J* = 1.0, 7.7 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.6, 32.9, 40.0, 42.5, 54.0, 62.1, 117.9, 122.2, 129.2, 131.3, 131.9. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{19}N_2O_2S$: 255.1162; found: 255.1164.

5-Mesyl-1,3,6-trimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (2)

In a similar manner to the synthesis of **1** from **7a** described above, compound **2** was prepared from **7b**, except that the reaction was conducted for 6 h at 25 °C instead of 18 h at 25 °C and gave separable diastereomers of **2** (**2A** and **2B**) in a ratio of 1:2.6 in 66% yield. These diastereomers were separated by column chromatography [silica gel, EtOAc–hexane (1:5)].

(a*S,3*S**)-5-Mesyl-1,3,6-trimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (2A)**

Colorless crystals; yield: 24.5 mg (47.7%); mp 133–135 °C; TLC: R_f = 0.38 (silica gel, 25% EtOAc–hexane). IR (ATR): 2892, 1322 cm^{-1}. ^1H NMR (600 MHz, CD_2Cl_2): δ = 0.77 (d, *J* = 6.3 Hz, 3 H), 2.25 (dd, *J* = 10.9, 13.3 Hz, 1 H), 2.35–2.40 (m, 1 H), 2.37 (s, 3 H), 2.41 (dd, *J* = 12.1, 14.0 Hz, 1 H), 2.86 (s, 3 H), 2.92 (s, 3 H), 3.04 (ddd, *J* = 1.6, 3.6, 13.3 Hz, 1 H), 4.25 (ddd, *J* = 1.6, 3.5, 14.0 Hz, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.94 (d, *J* = 7.8 Hz, 1 H), 7.18 (dd, *J* = 7.8, 7.8 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.0, 34.3, 34.9, 39.3, 50.3, 120.5, 129.1, 129.4, 130.1, 142.0, 143.2, 170.8. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2O_2S$: 269.1318; found: 269.1319.

(a*R,3*S**)-5-Mesyl-1,3,6-trimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (2B)**

Colorless crystals; yield: 9.4 mg (18.3%); mp 127–130 °C; TLC: R_f = 0.31 [silica gel, 25% EtOAc–hexane]. IR (ATR): 2876, 1324 cm^{-1}. ^1H NMR (600 MHz, CD_2Cl_2): δ = 0.92 (d, *J* = 6.7 Hz, 3 H), 1.59–1.66 (m, 1 H), 2.34 (s, 3 H), 2.65 (ddd, *J* = 1.5, 4.0, 10.9 Hz, 1 H), 2.75 (s, 3 H), 2.89 (s, 3 H), 2.91 (dd, *J* = 10.9, 12.4 Hz, 1 H), 3.40 (dd, *J* = 11.9, 12.4 Hz, 1 H), 3.47 (ddd, *J* = 1.5, 4.2, 12.4 Hz, 1 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 6.89 (d, *J* = 7.7 Hz, 1 H), 7.18 (dd, *J* = 7.7, 7.8 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.3, 18.3, 30.0, 37.8, 39.8, 52.1, 60.6, 123.7, 128.5, 140.5, 147.5, 155.5. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2O_2S$: 269.1318; found: 269.1319.

(18) **Crystal Data for 1, 2A, and 2B**

All measurements were made on a RIGAKU RAXIS RAPID imaging-plate area detector with graphite monochromated Cu Kα radiation. The data were collected at a temperature of –100 °C. The structure was solved by the SIR92 direct method and expanded by using Fourier techniques. The nonhydrogen atoms were refined anisotropically. All calculations were performed by using the *CrystalStructure* crystallographic software package except for the refinement, which was performed by using SHELXL97 (See Ref. 19).

Crystal data of 1 (see Ref. 20): $C_{12}H_{18}N_2O_2S$; mp 92–94 °C, M_r = 254.35, Cu Kα (λ = 1.54187 Å), monoclinic, $P2_1/n$, colorless prism: 0.25 × 0.20 × 0.05 mm, crystal dimensions: *a* = 7.83330(14) Å, *b* = 9.04486(16) Å, *c* = 18.1712(3) Å, β = 91.5053(10)°, *T* = 173 K, *Z* = 4, *V* = 1287.01(4) Å^3, D_{calc} = 1.313 g/cm^3, μCu Kα = 21.802 cm^{-1}, F_{000} = 544.00, GOF = 1.063, R_{int} = 0.0376, R_1 = 0.0389, wR_2 = 0.1016.

Crystal data of 2A (see Ref. 20): $C_{13}H_{20}N_2O_2S$: mp 133–135 °C, M_r = 268.37, Cu Kα (λ = 1.54187 Å), monoclinic, $P2_1/n$, colorless prism: 0.40 × 0.35 × 0.20 mm, crystal dimensions: *a* = 8.38672(15) Å, *b* = 8.82991(16) Å, *c* = 18.4671(4) Å, β = 92.8791(13)°, *T* = 173 K, *Z* = 4, *V* = 1365.84(4) Å^3, D_{calc} = 1.305 g/cm^3, μCu Kα = 20.811 cm^{-1}, F_{000} = 576.00, GOF = 1.014, R_{int} = 0.0410, R_1 = 0.0348, wR_2 = 0.0906.

Crystal data of 2B (see Ref. 20): $C_{13}H_{20}N_2O_2S$: mp 127–130 °C, M_r = 268.37, Cu Kα (λ = 1.54187 Å), triclinic, *P*-1, colorless prism: 0.35 × 0.20 × 0.08 mm, crystal dimensions *a* = 8.33(4) Å, *b* = 8.71(6) Å, *c* = 9.82(5) Å, α = 96.87(11)°, β = 106.76(8)°, γ = 94.85(14)°, *T* = 173 K, *Z* = 4, *V* = 672(7) Å^3, D_{calc} = 1.325 g/cm^3, μCu Kα = 21.137 cm^{-1}, F_{000} = 288.00, GOF = 0.950, R_{int} = 0.1560, R_1 = 0.0719, wR_2 = 0.1790.

(19) Sheldrick, G. M. *SHELX97 [Includes SHELXS97, SHELXL97 and CIFTAB]: Programs for Crystal Structure Analysis (Release 97-2)*; Institüt für Anorganische Chemie der Universität: Göttingen, **1998**.

(20) CCDC 1837601, 1837602 and 1837601 contain the supplementary crystallographic data for compounds **1**, **2A**, and **2B**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.