Synthesis and Formation Mechanism of a Compound with an Unprecedented Skeleton: Dodecahydro-4,10:5,9-diepoxydipyrrolo[3,4-b:3′,4′-f][1,5]diazocine

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The reaction of \( N\)-\((\text{2}((\text{tert-butyldimethyl}silyl)\text{oxy} \text{limino}) \text{ethyl})\text{-4-methyl} \text{N}-(3\text{-phenylprop-2-yn-1-yl})\text{-} \text{benzenesulfonyl} \text{amide} \text{6b} \) with \text{BF}_3 \cdot \text{OEt}_2 \text{ afforded a compound with an unprecedented dodecahydro-4,10:5,9-diepoxydipyrrolo[3,4-b:3′,4′-f][1,5]diazocine skeleton} \text{7} \text{ after aqueous work-up. The formation mechanism of meso-7 appears} \text{ to involve dimerization of the hydrated forms} \text{ of (6aS)-C} \text{ and (6aR)-C of the initial racemic product} \text{9 via cation B generated by facile protonation at the C3a position of 9. Extensive computational studies revealed} \text{ that the driving force of the facile hydration of 9 is probably the release of the ring strain of 9, which arises in part from the bent} \text{ sp^2-hybridized C3a carbon.}

Key words \text{ N-boranonitrone; cycloadDITION; o-acetylenic O-tert-butyldimethylsilyl oxime; dodecahydro-4,10:5,9-diepoxydipyrrolo[3,4-b:3′,4′-f][1,5]diazocine compound; ring strain}

Introduction

Intramolecular cycloaddition of nitrones containing an alkyne moiety is well known, \(^{1,2}\) \text{ and is frequently employed for the synthesis of nitrogen-containing natural products.} \(^{3-7}\) In contrast, the corresponding cycloaddition of nitrones having an alkyne moiety is much less well studied, \text{ and the products are often labile and undergo further transformation or rearrangement.} \(^{8-15}\) \text{ In particular, 2,3-dihydroisoxazoles fused with a five-membered ring at the 3,4 positions} \text{ are unstable due to ring strain, and to our knowledge, have never been isolated.} \(^{10,13-15}\) \text{ We have developed many intramolecular and intermolecular cycloadditions of N-borono-nitrones generated from O-silyl oxime and BF}_3 \cdot \text{OEt}_2, \text{ which generally take place under mild conditions (room temperature to 50°C).} \(^{16-20}\) \text{ and we considered that it might be possible to isolate a compound of type 1 formed from o-alkynyl O-silyl oximes and BF}_3 \cdot \text{OEt}_2. \text{ We report herein compound 7 having an unprecedented skeleton formed by the dimerization of 3-phenyl-5-tosyl-4,5,6,6a-tetrahydro-1H-pyrrolo[3,4-c]isoxazole} \text{ of 9 generated from o-alkynyl O-silyl oxime 6b and BF}_3 \cdot \text{OEt}_2. \text{ The mechanism of formation of 7 was explored by computational methods.}

First, we prepared \text{O-silyloximes 6a and 6b from N-tosyl glycine derivative 2 (Chart 1). Compound 2 was propargylated with 3a and 3b in the presence of cesium carbonate in acetone to give 4a and 4b in 51 and 62% yields, respectively. Reduction of the esters of 4a and 4b with sodium borohydride afforded 5a and 5b in 54 and 71% yields, respectively. Oxidation of alcohol 5a with pyridinium chlorochromate (PCC) followed by condensation with O-(tert-butyldimethylsilyl)hydroxylamine yielded O-(tert-butyldimethylsilyl)oxime 6a as a mixture of (E) and (Z)-isomers in 58% yield. O-(tert-butyldimethylsilyl)oxime 6b [(E) and (Z)-isomers, 22%] was obtained by three-step sequence; oxidation with PCC, condensation with hydroxylamine, \text{ and O-silylation with tert-butyldimethylchlorosilane. With 6a and 6b in hand, we next examined their cycloadDITION. O-Silyloxime 6a, on treatment with BF}_3 \cdot \text{OEt}_2 \text{ (3.3 equivalent (equiv.)) followed by extractive work-up with a saturated aqueous solution of NaHCO}_3 \text{ afforded a complex mixture from which no product was isolable. In sharp contrast, similar treatment of 6b afforded a crystalline compound in a moderate yield.} \(^{21}\) \text{ However, the spectral data were not consistent with the expected product, 3-phenyl-5-tosyl-4,5,6,6a-tetrahydro-1H-pyrrolo[3,4-c]isoxazole} \text{ of 9. Finally, the structure of the product was unambiguously established by X-ray diffraction analysis as 7} \text{ (Chart 2 and Fig. 1). ORTEP drawings of the top and side views revealed that 7 has a highly symmetric, ladder-shaped structure, probably formed by dimerization of the intramolecular cycloaddition product 9 of N-borononitrone A generated from oxime 6b and BF}_3. \text{ The six-membered ring in the middle of 7 has a chair conformation that connects two isoxazolidine rings derived from 9. Detailed examination showed that product 7 is a meso-compound constituted from both enantiomers of racemic 9. A plausible mechanism for the formation of 7 would involve hydrated compound C (Chart 3). Here, for convenience, we begin with the protonation of (6aS)-9. Thus, boron fluorides are removed from the initial cycloadduct (6aS)-8 by extractive work-up, which frees up the lone pair of oxygen in the cycloadduct. Then, (6aS)-9 is protonated at the 3a-position to generate oxonium cation (6aS)-B, which is hydrated to give (6aS)-C. Cation (6aS)-B undergoes an equilibrium addition reaction with (6aR)-C leading to D, which undergoes ring closure via oxonium ion E to provide the product 7.} \(^{23}\) \text{ The crucial step in this sequence should be facile hydration}

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of racemic 9 to afford (6aS)-C and (6aR)-C via oxonium ion B. To gain insight into the mechanism of formation of compound 7 from the initial cycloadduct 9, we turned our attention to a computational study of compound 9, which should be highly reactive, as well as 3,4-dimethyl-2,3-dihydroisoxazole (F) for comparison, because most monocyclic 2,3-dihydroisoxazoles are sufficiently stable to be isolated. M06-2X/6-31G(d) calculation of (6aR)-9 revealed high strain arising from the restriction imposed by the pyrrolidine ring (Table 1). The bicyclic structure of (6aR)-9 seems clearly strained compared to the mono-cyclic compound F (runs 1 and 2). In fact, the C4–C6 distance in (6aR)-9 is much shorter than the C6–C7 distance in monocyclic F (runs 3), and likewise the C4–C3a–C6a angle is much smaller than the C3–C4–C7 angle in F (run 4). The C4 and C5 in F and C3 in (6aR)-9 take planar forms (the sum of the three valence angles is 360°) and they are typical sp² hybrid carbons, whereas C3a of (6aR)-9 is slightly pyramidalized (runs 5 and 6). In monocyclic F, the dihedral angles O1–C5–C4–C3 (3.8°) and O1–C5–C4–C7 (177.5°) are normal values for an alkene (runs 7 and 8 for F). In bicyclic (6aR)-9, in contrast, the dihedral angle O2–C3–C3a–C6a (1.2°) takes a normal value, whereas O2–C3–C3a–C4 (160.3°) deviates from 180° by approx. 20° suggesting that the C3a–C4 bond is out of plane [runs 6 and 7 for (6aR)-9]. Accordingly, the high reactivity of 9 may derive mainly from the bent sp² carbon, C3a.

To obtain the strain energy due to the bicyclic system of (6aR)-9, heats of hydrogenation and hydration were calculated for (6aR)-9 and monocyclic 2,3-dihydroisoxazole F (runs 9 and 10). As a result, the strain energies associated with the bicyclic structure were estimated to be 10.4 kcal/mol from hydrogenation and 5.6 kcal/mol from hydration. These calculations are consistent with the experimental fact that bicyclic 2,3-dihydroisoxazoles 1 are highly reactive, whereas the monocyclic compounds are, in general, stable enough for isolation. Thus, the driving force for facile hydration of the initial cycloadduct (6aR)-9 to cation B would be release of the ring strain, partially arising from the bent sp² carbon, C3a.

In conclusion, we have found compound 7, which has an unprecedented skeleton, is formed by dimerization of (6aS)-9 and (6aR)-9 generated by intramolecular cycloaddition of α-acetylenic O-silyloxime via N-boranonitrone. Computational analysis of compound 9 revealed that the driving force of the facile hydration of 9, which is the crucial step in the...
to give 4a (1.77 g, 51%) as colorless crystals. mp 60–61 °C; IR (KBr) cm⁻¹: 3279, 2932, 2125, 1736, 1346, 1157; ¹H-NMR (300 MHz, CDCl₃) δ: 7.73 (2H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.4 Hz), 4.26 (2H, d, J = 4.1 Hz), 4.12 (2H, s), 3.70 (3H, s), 2.43 (3H, s), 2.14 (1H, t, J = 4.1 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ: 168.9, 143.9, 135.9, 129.6, 127.5, 74.3, 53.2, 46.7, 37.4, 21.6 (one signal overlapped); electrospray ionization (ESI)-MS m/z: 304.0616 (Calcd for C₉H₁₁NNaO₃S + [M + Na]⁺: 304.0620).

N-(2-Hydroxyethyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonylamide (5a) To a solution of 4a (0.10 g, 0.36 mmol) in MeOH (6 mL) was added NaBH₄ (0.082 g, 2.16 mmol) at 0 °C. The mixture was stirred at room temperature for 19 h, and then concentrated in vacuo. The residue was partitioned between water and CH₂Cl₂, and the organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt, 2/1) to give 5a (0.049 g, 54%) as colorless crystals. mp 57–58 °C; IR (KBr) cm⁻¹: 3516, 3260, 2951, 2116, 1344, 1167; ¹H-NMR (600 MHz, CDCl₃) δ: 7.5 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 4.21 (2H, d, J = 4.2 Hz), 3.80 (2H, q, J = 5.4 Hz), 3.36 (2H, t, J = 5.4 Hz), 2.43 (3H, s), 2.25 (1H, t, J = 5.4 Hz), 2.09 (1H, t, J = 2.4 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ: 143.8, 135.4, 129.6, 127.9, 76.9, 60.5, 49.0, 37.9, 21.5 (one signal overlapped); ESI-MS m/z: 276.0678 (Calcd for C₇H₁₁NNaO₃S + [M + Na]⁺: 276.0670).

N-(2-[[t(ert-Butyldimethylsilyl)oxy]limino]ethyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonylamide (6a) To a stirred mixture of MS 4A (2 g) and pyridinium chlorochromate (0.64 g, 2.96 mmol) in 1,2-dichloroethane (60 mL) was added a solution of alcohol 5a (0.50 g, 1.96 mmol) in 1,2-dichloroethane (20 mL) at 0 °C over 10 min. The mixture was stirred at room temperature for 3 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was partitioned between water and ether. The organic layer was washed with brine, dried (MgSO₄), and concentrated in vacuo, and the residue was dissolved in CH₂Cl₂ (2.5 mL). To this solution were added MS 4A (1 g), O tert-butyldimethylsilylhydroxylamine (0.29 g, 1.97 mmol) and PPTS (0.050 g, 0.20 mmol). The mixture was stirred at room temperature for 16 h, then filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt, 6/1) to give 6a (0.28 g, 37%) as a mixture of (E)- and (Z)-isomer. IR (NaCl) cm⁻¹: 3281, 2930, 2122, 1472, 1354, 1163; ¹H-NMR (300 MHz, CDCl₃) δ: 7.73 (2H, d, J = 8.1 Hz), 7.43 (2H, s, J = 8.1 Hz), 4.12 (2H, s, J = 4.2 Hz), 4.09 (2H, s, J = 4.2 Hz), 3.97 (2H × 5/9, s, J = 4.2 Hz, E-isomer), 2.97 (2H × 9/4, d, J = 4.2 Hz, Z-isomer), 2.43 (3H × 5/9, s, Z-isomer), 2.34 (3H × 9/4, s, Z-isomer), 1.70 (1H × 9/4, t, J = 2.4 Hz, E-isomer), 2.05 (1H × 5/9, s, E-isomer), 0.92 (9H × 4/9, s, Z-isomer), 0.91 (9H × 5/9, s, E-isomer), 0.16 (6H × 4/9, s, Z-isomer), 0.14 (6H × 5/9, s, E-isomer); ¹³C-NMR (75 MHz, CDCl₃) δ: 151.6, 149.5, 143.9, 134.8, 133.7, 129.7, 129.6, 127.7, 127.6, 74.1, 74.0, 45.6, 42.6, 38.2, 36.8, 26.0, 25.9, 21.5, 18.1, −5.4 (several signals overlapped); ESI-MS m/z: 403.1485 (Calcd for C₂₃H₂₄N₃NaO₃S + [M + Na]⁺: 403.1488).

Methyl N-(3-Phenylprop-2-yn-1-yl)-N-tosylglycinate (4b) To a mixture of 2 (1.00 g, 4.10 mmol) and Cs₂CO₃ (1.47 g, 4.65 mmol) in acetonitrile, is release of the high ring strain of 9.

Experimental

General Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8200A, and ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker-FTIR AV300 (300 MHz) or a Bruker-AV600 spectrometer. Measurements of MS and high-resolution MS (HRMS) were performed with a JEOL JMS-700 mass spectrometer. Column chromatography was carried out on silica gel (Silica Gel 60N, Kanto Chemical Co., Inc. or Silica Gel BW-127ZH, Fuji Silysia Chemical, Ltd.). Merck precoated TLC plates (silica gel 60 F₂₅₄, 0.25 mm, Art 5715) were used for the TLC analysis. The organic layer was washed with brine, dried (MgSO₄), and concentrated in vacuo. The residue was partitioned between water and ether. The organic layer was washed with brine, dried (MgSO₄), and concentrated in vacuo, and the residue was dissolved in CH₂Cl₂ (2.5 mL). To this solution were added MS 4A (1 g), O tert-butyldimethylsilylhydroxylamine (0.29 g, 1.97 mmol) and PPTS (0.050 g, 0.20 mmol). The mixture was stirred at room temperature for 16 h, then filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt, 6/1) to give 6a (0.28 g, 37%) as a mixture of (E)- and (Z)-isomer. IR (NaCl) cm⁻¹: 3281, 2930, 2122, 1472, 1354, 1163; ¹H-NMR (300 MHz, CDCl₃) δ: 7.73 (2H, d, J = 8.1 Hz), 7.43 (2H, s, J = 8.1 Hz), 4.12 (2H, s, J = 4.2 Hz), 4.09 (2H, s, J = 4.2 Hz), 3.97 (2H × 5/9, s, J = 4.2 Hz, E-isomer), 2.97 (2H × 9/4, d, J = 4.2 Hz, Z-isomer), 2.43 (3H × 5/9, s, Z-isomer), 2.34 (3H × 9/4, s, E-isomer), 1.70 (1H × 9/4, t, J = 2.4 Hz, E-isomer), 2.05 (1H × 5/9, s, E-isomer), 0.92 (9H × 4/9, s, Z-isomer), 0.91 (9H × 5/9, s, E-isomer), 0.16 (6H × 4/9, s, Z-isomer), 0.14 (6H × 5/9, s, E-isomer); ¹³C-NMR (75 MHz, CDCl₃) δ: 151.6, 149.5, 143.9, 134.8, 133.7, 129.7, 129.6, 127.7, 127.6, 74.1, 74.0, 45.6, 42.6, 38.2, 36.8, 26.0, 25.9, 21.5, 18.1, −5.4 (several signals overlapped); ESI-MS m/z: 403.1485 (Calcd for C₂₃H₂₄N₃NaO₃S + [M + Na]⁺: 403.1488).
4.50 mmol) in acetone (50 mL) was added 3-chloro-1-phenyl-1-propyne (3b, 0.60 mL, 4.50 mmol) at room temperature. The mixture was stirred at 60 °C for 3 h, then cooled and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane–AcOEt, 2/1) to give 4b (0.91 g, 62%) as colorless crystals. mp 80–81 °C; IR (KBr) cm\(^{-1}\): 2959, 2239, 1759, 1348, 1163; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.77 (2H, d, \(J = 8.1\) Hz), 7.30–7.24 (5H, m), 7.15 (2H, d, \(J = 8.1\) Hz), 4.48 (2H, s), 4.16 (2H, s), 3.72 (3H, s), 2.37 (3H, s); \(^1\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\): 168.9, 143.8, 136.0, 131.6, 129.6, 128.6, 128.2, 127.6, 121.9, 86.1, 81.4, 52.3, 47.1, 38.4, 21.5; ESI-MS \(m/z\): 380.0927 (Calcd for C\(_{19}\)H\(_{19}\)NNaO\(_4\)S [M + H]\(^+\): 380.0933).

\(N\)-(2-Hydroxyethyl)-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (5b) To a solution of 4b (0.10 g, 0.28 mmol) in MeOH (7 mL) was added NaBH\(_4\) (0.042 g, 1.20 mmol). After the reaction was complete, the mixture was concentrated in vacuo and the residue was chromatographed on silica gel (hexane–AcOEt, 2/1) to give 5b (0.08 g, 72%) as colorless crystals. mp 100–101 °C; IR (KBr) cm\(^{-1}\): 3459, 3239, 2929, 1719, 1648, 1519, 1378, 1092; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.77 (2H, d, \(J = 8.1\) Hz), 7.30–7.24 (5H, m), 7.15 (2H, d, \(J = 8.1\) Hz), 4.48 (2H, s), 4.16 (2H, s), 3.72 (3H, s), 2.37 (3H, s); \(^1\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\): 168.9, 143.8, 136.0, 131.6, 129.6, 128.6, 128.2, 127.6, 121.9, 86.1, 81.4, 52.3, 47.1, 38.4, 21.5; ESI-MS \(m/z\): 380.0927 (Calcd for C\(_{19}\)H\(_{19}\)NNaO\(_4\)S [M + H]\(^+\): 380.0933).

\(N\)-(2-Hydroxyethyl)-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (5b) To a solution of 4b (0.10 g, 0.28 mmol) in MeOH (7 mL) was added NaBH\(_4\) (0.042 g, 1.20 mmol). After the reaction was complete, the mixture was concentrated in vacuo and the residue was chromatographed on silica gel (hexane–AcOEt, 2/1) to give 5b (0.08 g, 72%) as colorless crystals. mp 100–101 °C; IR (KBr) cm\(^{-1}\): 3459, 3239, 2929, 1719, 1648, 1519, 1378, 1092; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.77 (2H, d, \(J = 8.1\) Hz), 7.30–7.24 (5H, m), 7.15 (2H, d, \(J = 8.1\) Hz), 4.48 (2H, s), 4.16 (2H, s), 3.72 (3H, s), 2.37 (3H, s); \(^1\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\): 168.9, 143.8, 136.0, 131.6, 129.6, 128.6, 128.2, 127.6, 121.9, 86.1, 81.4, 52.3, 47.1, 38.4, 21.5; ESI-MS \(m/z\): 380.0927 (Calcd for C\(_{19}\)H\(_{19}\)NNaO\(_4\)S [M + H]\(^+\): 380.0933).
1.12 mmol) at 0°C. The mixture was stirred at room temperature for 19 h, and then concentrated in vacuo. The residue was partitioned between water and CH₂Cl₂, and the organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1) to give 5b (0.065 g, 71%) as colorless crystals.

mp 85–86°C; IR (KBr) cm⁻¹: 3547, 2918, 2239, 1321, 1163; ¹H-NMR (300 MHz, CDCl₃) δ: 7.80 (2H, d, J = 8.4 Hz), 7.31–7.20 (5H, m), 7.10 (2H, dd, J = 8.4, 1.5 Hz), 4.42 (2H, s), 3.84 (2H, q, J = 7.5 Hz), 3.42 (2H, t, J = 5.7 Hz), 2.36 (3H, s), 2.16 (1H, t, J = 5.7 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ: 143.6, 135.3, 131.3, 129.4, 128.3, 128.0, 127.6, 121.8, 85.5, 81.8, 60.3, 48.8, 38.5, 21.2; ESI-MS m/z: 352.0983 (Calcd for C₉H₇N₃NaO₃S [M + Na⁺]: 352.0983).

N-[2-(Hydroxyimino)ethyl]-4-methyl-N-(3-phenylprop-2-yny-1-yl)benzenesulfonamide

To a stirred mixture of MS 8 mL). To the solution were added NH₂OH·HCl (0.046 g, in vacuo was dried (MgSO₄) and concentrated for 19 h, and then concentrated. The residue was added BF₃·OEt₂ (0.083 mL, 0.66 mmol) at 0°C, and the mixture was stirred at room temperature. After 22 h, a saturated aqueous solution of NaHCO₃ (0.2 mL) was further added, and the mixture was stirred for 30 min. The mixture was diluted with H₂O (20 mL) and extracted with CHCl₃ (30 mL x 3). The organic layer was dried (MgSO₄) and concentrated in vacuo to give crystalline solid. Trituration of the solid with hexane–CHCl₃ afforded colorless crystals of 7 (26 mg) after filtration. The filtrate was concentrated and chromatographed on silica gel (hexane–CH₂Cl₂–ether, 5:1) to give 7 (8 mg, total 52%) as colorless crystals. mp >300°C (CDCl₃–hexane); IR (KBr) cm⁻¹: 2859, 1597, 1474, 1342, 1167; ¹H-NMR (300 MHz, CDCl₃) δ: 7.48 (4H, d, J = 8.4 Hz), 7.40–7.20 (12H, m), 7.16 (2H, brd, J = 8.4 Hz), 3.99 (2H, td, J = 8.1, 3.6 Hz), 3.74 (2H, td, J = 8.1, 6.3 Hz), 3.36 (2H, dd, J = 10.2, 8.1 Hz), 3.03 (2H, dd, J = 10.2, 8.1 Hz), 2.82 (2H, dd, J = 10.2, 6.3 Hz), 2.43 (6H, s), 2.29 (2H, dd, J = 10.2, 6.3 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ: 143.8, 133.6, 131.4, 129.5, 129.3, 129.0, 128.4, 128.0, 126.8, 126.0, 102.2, 66.0, 53.4, 52.3, 50.0, 21.6; ESI-MS m/z: 707.1963 (Calcd for C₉H₇N₃NaO₃S [M + Na⁺]: 707.1974).

X-Ray Diffraction Analysis

Crystallographic data of compound 7 are given in Supplementary Materials.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains supplementary materials.

References and Notes

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21) Whether the reaction is intramolecular or intermolecular, cycloaddition of O-silyl oximes requires at least two equivalents of BF$_3$·OEt$_2$, probably because the active species is the N-boranonitrone activated by further coordination of boron fluoride species.\(^{30}\)
22) Crystallographic data (excluding structural factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1981260.
23) Equilibrating addition reaction between the same enantiomers leads to an adduct that would not undergo cyclization due to severe intramolecular steric interaction. See Supplementary Materials.
24) LeBel and Banucci observed addition of a protic solvent (EtOH) to the 4,5-double bond of a 2,3-dihydroisoxazole; see ref. 10. Schreiber and co-workers also reported addition of H$_2$O to the double bond of a similar ring system to that of 9; see ref. 15. Other examples of protonation at the 4-position of monocyclic 2,3-dihydroisoxazoles under acidic conditions are described in refs. 25–27.
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