3,4-Homoadamantadiene: Generation and Regioselective [2+2] Cycloaddition of a Novel Tricyclic Bridgehead Allene

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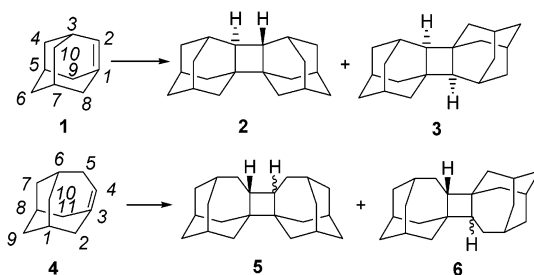
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Abstract: Dehalogenation of 3-bromo-4-iodo-4-homoadamantene with *n*-BuLi gave rise to 3,4-homoadamantadiene, a novel tricyclic bridgehead allene, which readily dimerized to head-to-head and head-to-tail [2+2] cycloadducts in a ratio of 96:4. Trapping with 1,3-diphenylisobenzofuran was successful to yield the corresponding Diels–Alder adduct.
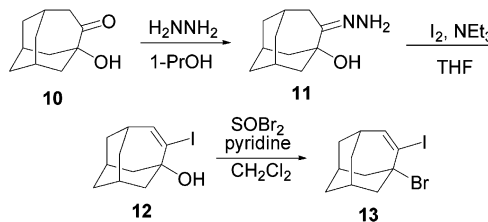
The synthesis of bridgehead olefins, which are known as highly strained organic compounds, has attracted organic and biological chemists.[1] Successful studies have been published recently on carbene–bridgehead olefin–carbene rearrangements,[2] the substitution effect on the reactivity of bridgehead olefins,[3] matrix isolation,[4] preparation of natural products,[5] and models of biologically active compounds.[6]

In general, as the size of carbocyclic rings decreases, double bonds are more bent and twisted and show increased reactivity. Furthermore, highly strained anti-Bredt olefins undergo [2+2] cycloaddition readily. 1-Tricyclo[3.3.1.1^{3,7}]decene (adamantene) (**1**)[7] affords head-to-head cycloadduct **2** and head-to-tail cycloadduct **3** in a 1:2 ratio, and 3-tricyclo[4.3.1.1^{3,8}]undecene (3-homoada-

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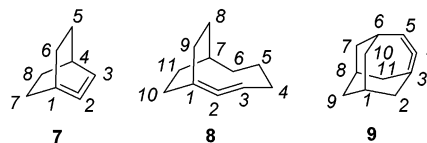
SCHEME 1

SCHEME 2

mantene) (**4**)[8] affords head-to-head and head-to-tail dimeric hydrocarbons (**5** and **6**) in low regioselectivity (Scheme 1).

"Bridgehead allenes" have the structural characteristics of both a bridgehead olefin and a cyclic allene. However, we can find only a few reports on the generation of bridgehead allenes.[1,9] Nathan investigated the generation of 1,2-bicyclo[2.2.2]octadiene (**7**).[10] Sy studied 1,2-bicyclo[5.2.2]undecadiene (**8**),[11] a reaction of which with 1,3-diphenylisobenzofuran gave a Diels–Alder adduct. In other systems the properties and reaction behavior of bridgehead allenes remain uncertain. Therefore, we now report the dehalogenation of a vicinal dihalide to 3,4-homoadamantadiene (**9**), whose allene bond locates in a seven-membered ring and at the bridgehead position of a homoadamantane framework, together with its structural character computed by DFT calculations.

A precursor of the target allene, 3-bromo-4-iodo-4-homoadamantene (**13**) was prepared from 3-hydroxy-4-homoadamantanone (**10**)[12] via a three-step synthesis summarized in Scheme 2. The reaction of **10** with hydrazine was almost quantitatively converted to **11**, whose reaction with iodine and subsequent bromination

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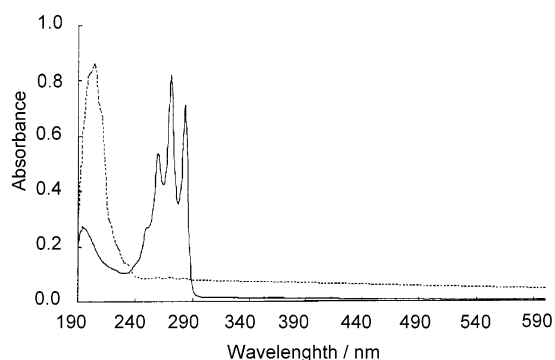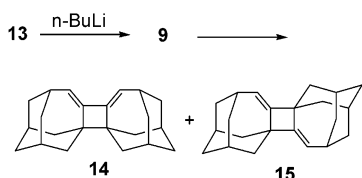
FIGURE 1. UV spectra for the dimeric products in hexane (**14**: solid line, 1.61×10^{-4} M, $\lambda_{max} = 270$ nm, $\epsilon = 5100$ M^{-1} cm^{-1}; **15**: dashed line, 6.85×10^{-5} M, $\lambda_{max} = 204$ nm, $\epsilon = 12600$ M^{-1} cm^{-1}).

SCHEME 3

with SOBr$_2$ yielded vicinal dihalide **13** in moderate overall isolated yield.

The obtained dihalide **13** was dehalogenated with *n*-BuLi in THF at 0 °C. After the usual aqueous workup, the reaction mixture was analyzed by NMR measurements, whose spectra showed the formation of two dimeric products, **14** and **15**, in a yield ratio of 96:4 (Scheme 3). Column chromatography on SiO$_2$ and subsequent recrystallization from ethanol afforded **14** as colorless crystals (67% isolated yield), whose UV spectrum in hexane showed absorption bands at 270 nm (Figure 1). This value indicates the existence of a conjugated butadiene structure.

The structure of minor product **15** was determined by comparison of its NMR spectra with those of an authentic sample that was synthesized in the following way. The coupling of **13** by an Ni(0) complex[13] gave mainly **14** and **15** in a 15:85 ratio. Following recycling GPC separation and SiO$_2$ column chromatography, recrystallization from ethanol gave **15** as colorless crystals in 22% yield. The UV spectrum showed an absorption band with $\lambda = 204$ nm and no distinct peaks around 270 nm. This observation evidences the absence of any conjugated double bonds (Figure 1).

The reaction of **13** with *n*-BuLi in the presence of 1,3-diphenylisobenzofuran at −78 °C in THF produced the Diels−Alder adduct (**16**) in 79% isolated yield, and the bridgehead double bond, C(3)=C(4), of **9** served as the dienophile. However, an attempted addition of a solution of 1,3-diphenylisobenzofuran in THF after the dehalogenation of **13** produced no Diels−Alder adduct **16**. The trapping experiments by the diene support the intermediacy of **9** as the product of the reaction of **13** with *n*-BuLi
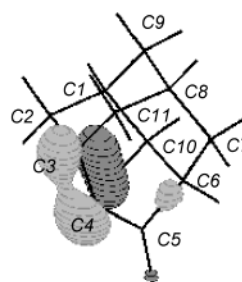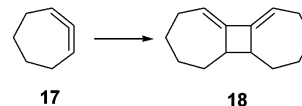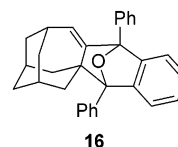
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FIGURE 2. A drawing of HOMO for **9** optimized by B3LYP/6-31G(d) calculations.

SCHEME 4

and manifest the high reactivity of **9** to [2+2] cycloaddition.

The [2+2] cycloaddition of **9** was highly selective as described above. The regioselectivity is significantly higher than that of the bridgehead olefins and is similar to those of distorted monocyclic allenes.[9,14] Adamantene (**1**) was reported to afford head-to-head cycloadduct **2** and head-to-tail cycloadduct **3** in a 1:2 ratio (Scheme 1),[7] and 1,2-cycloheptadiene (**17**) was described to produce predominantly head-to-head cycloadduct **18** (Scheme 4).[15]

The optimized geometry of **9** by DFT calculations at the B3LYP/6-31G(d) level[16] has C_s symmetry with a bending angle of 135.9° for C(3)−C(4)−C(5) and with a pyramidalization angle[17] of 10.7° for C(3). Both the bridgehead double bond and the other double bond have 0° of twist angle, and there is no conjugation between the double bonds. A sketch of HOMO shown in Figure 2 indicates that the outer π-bond at the bridgehead double bond C(3)=C(4) is unusually constricted, where the reactive site is indicated by the experiments.

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In conclusion, we have shown 3,4-homoadamantadiene (**9**) could be generated by the dehalogenation from 3-bromo-4-iodo-4-homoadamantene (**13**) to afford head-to-head and head-to-tail [2+2] cycloadducts **14** and **15** in a ratio of 96:4. The selectivity was much higher than that of the known bridgehead olefins.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on 400 and 270 MHz instruments. IR spectra were obtained by using an FT-IR instrument. Elemental analyses were performed by the Microanalytical Center, Kyoto University, Kyoto. High-resolution mass spectra were obtained under electron impact conditions. 3-Hydroxy-4-homoadamantanone (**10**)[12] was prepared by the literature procedure. Anhydrous solvents were prepared according to standard methodologies. Other commercially available reagents were of reagent-grade quality and used as received. Medium-pressure liquid chromatography (MPLC) was conducted on silica gel (45−75 μm). Preparative recycling GPC separation was performed with GPC columns (ϕ 20 mm × 600 mm) with CHCl$_3$ as an eluent.

3-Hydroxy-4-homoadamantanone Hydrazone (11). To a solution of 3-hydroxy-4-homoadamantanone (**10**) (359 mg, 1.99 mmol) in absolute 1-propanol (3.1 mL) was added hydrazine (0.9 mL, 29 mmol). The solution was heated at 65 °C for 2.5 h. Evaporation of the solvent gave **11** as colorless crystals (382 mg) in 99% yield: colorless crystals; mp 81.0−82.0 °C; IR (KBr) 3378, 2916, 1446, 1067 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.45−1.70 (m, 6H), 1.90−2.00 (m, 4H), 2.08 (br s, 2H), 2.28 (br s, 1H), 2.35 (d, $J = 3.8$ Hz, 2H), 5.04 (br s, 3H); ^{13}C NMR (CDCl$_3$, 67.8 MHz) δ 27.4 (CH), 28.1 (2CH), 34.29 (CH$_2$), 34.34 (CH$_2$), 36.3 (2CH$_2$), 43.9 (2CH$_2$), 72.7 (C), 158.1 (C). Anal. Calcd for C$_{11}$H$_{18}$N$_2$O: C, 68.01; H, 9.34. Found: C, 67.83; H, 9.28.

3-Hydroxy-4-iodo-4-homoadamantene (12). To a solution of **11** (354 mg, 1.82 mmol) and dry triethylamine (2.2 mL) in dry THF (0.5 mL) was added dropwise iodine (853 mg, 3.36 mmol) in dry THF (1.3 mL). After being stirred for 100 min, the mixture was diluted with water. The solution was extracted with CH$_2$Cl$_2$. The organic layer was washed with saturated NaCl and dried (MgSO$_4$). Removal of the solvent afforded a pale yellow oil (529 mg), whose MPLC purification yielded **12** as colorless crystals (299 mg, 57%): mp 75.0−76.0 °C; IR (KBr) 3406, 2913, 1618, 1078 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.66−1.82 (m, 8H), 1.98 (br s, 1H), 2.02 (br s, 2H), 2.22 (m, 3H), 6.88 (d, $J = 9.9$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 67.8 MHz) δ 29.1 (2CH), 32.1 (2CH$_2$), 34.5 (2CH), 35.3 (CH$_2$), 40.6 (2CH$_2$), 73.2 (C), 120.4 (C), 144.2 (CH). Anal. Calcd for C$_{11}$H$_{15}$IO: C, 45.54; H, 5.21. Found: C, 45.41; H, 5.10.

3-Bromo-4-iodo-4-homoadamantene (13). To a solution of **12** (514 mg, 1.77 mmol) in dry CH$_2$Cl$_2$ (15 mL) containing dry pyridine (0.35 mL, 4.33 mmol) at 0 °C was dropwise added SOBr$_2$ (0.33 mL, 4.36 mmol). The mixture was stirred at 0 °C for 15 min, warmed to room temperature, and stirred for an additional 1.5 h. Water was added, and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was washed with 10% HCl and saturated NaCl and dried (MgSO$_4$). Removal of the solvent gave a pale yellow oil, whose recycling GPC separation and recrystallization from hexane−CH$_2$Cl$_2$ (3:1) afforded **13** as colorless crystals in 39% yield: mp 95.0−95.5 °C; IR (KBr) 2918, 2848, 1439, 931, 916, 841, 810 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.51−1.99 (m, 6H), 2.19 (br s, 3H), 2.52−2.81 (m, 4H), 7.04 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 67.8 MHz) δ 31.6 (2CH$_2$), 31.7 (2CH), 35.2 (CH$_2$), 35.3 (CH), 45.9 (2CH$_2$), 74.2 (C), 111.9 (C), 147.2 (CH). Anal. Calcd for C$_{11}$H$_{14}$BrI: C, 37.42; H, 4.00. Found: C, 37.41; H, 3.94.

Reaction of 3-Bromo-4-iodo-4-homoadamantene (13) with *n*-BuLi. A solution of **13** (94 mg, 0.27 mmol) in dry THF (0.64 mL) was cooled to 0 °C under argon atmosphere. To the solution was added dropwise 2.57 M *n*-BuLi in hexane (0.37 mL, 0.95 mmol), and the resulting solution was stirred for 15 min. After being stirred at room temperature for an additional 45 min, the reaction mixture was quenched by addition of water.

The mixture was extracted with CH$_2$Cl$_2$, and the organic layer was washed with saturated NaCl and dried (MgSO$_4$). The removal of the solvent gave colorless crystals, whose ^{1}H NMR indicated the formation of **14** and **15** (96:4) with trace amounts of unknown compounds. Recrystallization from ethanol gave pure **14** as colorless crystals (18.6 mg, 67%): mp 175.5−176.0 °C; IR (KBr) 2913, 1654, 1443, 1348, 810 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.47−1.55 (m, 6H), 1.68−1.80 (m, 10H), 1.88 (br s, 2H), 1.92 (br s, 2H), 2.20 (m, 4H), 2.30 (m, 2H), 6.09 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 67.8 Hz) δ 31.0 (4CH), 32.1 (2CH), 34.0 (4CH$_2$), 34.4 (4CH$_2$), 36.6 (2CH$_2$), 47.3 (2C), 126.5 (2CH), 149.4 (2C). Anal. Calcd for C$_{22}$H$_{28}$: C, 90.35; H, 9.65. Found: C, 90.09; H, 9.43. A UV spectrum in hexane is shown in Figure 1.

Reaction of 3-Bromo-4-iodo-4-homoadamantene (13) with *n*-BuLi in the Presence of 1,3-Diphenylisobenzofuran. A solution of **13** (34 mg, 0.097 mmol) and 1,3-diphenylisobenzofuran (190 mg, 0.70 mmol) in dry THF (1.5 mL) was cooled to −78 °C under argon atmosphere. To the solution was added dropwise 1.48 M of *n*-BuLi in hexane (0.30 mL, 0.43 mmol), and the mixture was stirred for 1 h. After being stirred at room temperature for an additional 15 min, the mixture was quenched by addition of water. The resulting mixture was extracted with CHCl$_3$, and the organic layer was washed with saturated NaCl and dried (MgSO$_4$). Removal of the solvent gave colorless crystals, whose recycling GPC separation and MPLC afforded **16** as colorless crystals (32 mg) in 79% yield: mp 169.0−170.0 °C; IR (KBr) 2909, 2874, 2847, 1684, 1459, 1444, 1300, 1007, 990, 757, 704 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.82 (d, $J = 12.4$ Hz, 1H), 1.29 (dd, $J = 13.2$, 4.4 Hz, 1H), 1.44−1.71 (m, 6H), 1.81 (d, $J = 13.2$ Hz, 1H), 1.99−2.09 (m, 3H), 2.25 (m, 1H), 5.97 (d, $J = 8.0$ Hz, 1H), 7.16 (m, 2H), 7.33−7.56 (m, 8H), 7.80 (d, $J = 7.6$ Hz, 2H), 7.84 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 67.8 Hz) δ 29.3 (CH), 29.7 (CH), 30.9 (CH), 33.5 (CH$_2$), 33.6 (CH$_2$), 35.97 (CH$_2$), 36.04 (CH$_2$), 37.4 (CH$_2$), 51.0 (C), 88.5 (C), 91.6 (C), 119.0 (CH), 120.9 (CH), 125.8 (2CH), 126.0 (CH), 126.2 (CH), 126.6 (2CH), 126.7 (CH), 127.1 (CH), 127.5 (CH), 128.15 (2CH), 128.19 (2CH), 136.7 (C), 137.9 (C), 145.3 (C), 145.8 (C), 151.6 (C). Anal. Calcd for C$_{31}$H$_{28}$O: C, 89.38; H, 6.78. Found: C, 89.13; H, 6.91.

Head-to-Tail [2+2] Cycloadduct (15). A suspension of NiBr$_2$(PPh$_3$)$_2$ (221 mg, 0.30 mmol), PPh$_3$ (155 mg, 0.59 mmol), and activated Zn (155 mg) in dry benzene (1.8 mL) was heated to 50 °C under argon atmosphere. After 15 min, the mixture became a dark-red suspension. To the mixture was added dropwise a solution of **13** (208 mg, 0.59 mmol) in dry benzene (1.5 mL) at ambient temperature. The mixture was stirred for 1.3 h, and then filtered through neutral Al$_2$O$_3$ with benzene. Removal of the solvent afforded a 15:85 mixture of **14** and **15** as dark-black crystals, whose recycling GPC separation and MPLC (SiO$_2$), and recrystallization from ethanol gave head-to-tail [2+2] cycloadduct **15** as colorless crystals in 22% yield. **15**: colorless crystals; mp 264.0−264.5 °C; IR (KBr) 2908, 2838, 2362, 2344, 1561, 1438 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.57−2.00 (m, 20H), 2.13 (br s, 4H), 2.27 (m, 2H), 5.81 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 67.8 Hz) δ 31.0 (4CH), 31.9 (2CH), 34.6 (4CH$_2$), 36.4 (2CH$_2$), 39.6 (4CH$_2$), 48.9 (2C), 125.9 (2CH), 158.1 (2C); HRMS calcd for C$_{22}$H$_{28}$ 292.2192, found 292.2186. A UV spectrum in hexane is shown in Figure 1.

Calculations. DFT calculations were performed with Gaussian-98 software,[16] and geometry optimizations were verified by frequency calculations. A Molden program package was used for drawing molecular orbitals.[18]

Supporting Information Available: Selected NMR spectra for **11**, **12**, **13**, **14**, **15**, and **16**, and calculated energies and Cartesian coordinates for **9** optimized by DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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