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# Synthesis of Homoiceane (Tetracyclo$[6.3.1.1^{2,7}.0^{4,10}]$tridecane) and 3,13-Dehydrohomoiceane (Pentacyclo$[7.3.1.0^{2,4}.0^{3,8}.0^{5,11}]$-tridecane) through Homo-Diels–Alder Reaction[1]

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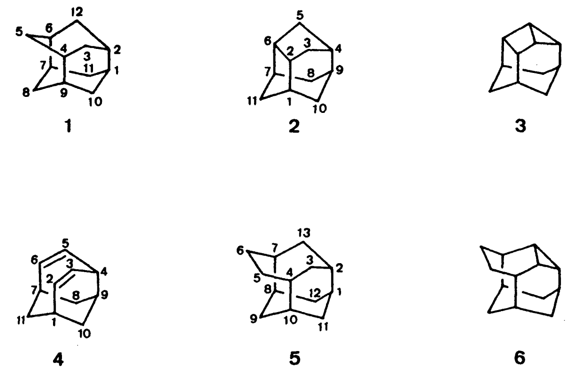
Homo-Diels–Alder reaction of tricyclo$[5.3.1.0^{4,9}]$undeca-2,5-diene with maleic anhydride proceeds very nicely in refluxed *o*-dichlorobenzene to give a single cycloadduct in 81% yield. The stereochemistry of the adduct is determined to be exo by leading to the *exo*-dimethyl ester and comparing it with the *endo*-dimethyl ester which is prepared by homo-Diels–Alder reaction of the above diene with dimethyl acetylenedicarboxylate followed by catalytic hydrogenation. Basic hydrolysis of the cycloadduct followed by oxidative decarboxylation with $Pb(OAc)_4$ in pyridine affords 3,13-dehydrohomoice-5-ene, catalytic hydrogenation of which gives 3,13-dehydrohomoiceane. Photoinduced intramolecular $[_{\pi}2+_{\sigma}2]$ cycloaddition of 3,13-dehydrohomoice-5-ene produces the compound which contains two cyclopropane rings in its rigid structure. When this strained cage compound is treated with Pd-black under $H_2$, hydrogenolysis of the two cyclopropane rings takes place simultaneously to afford homoiceane.

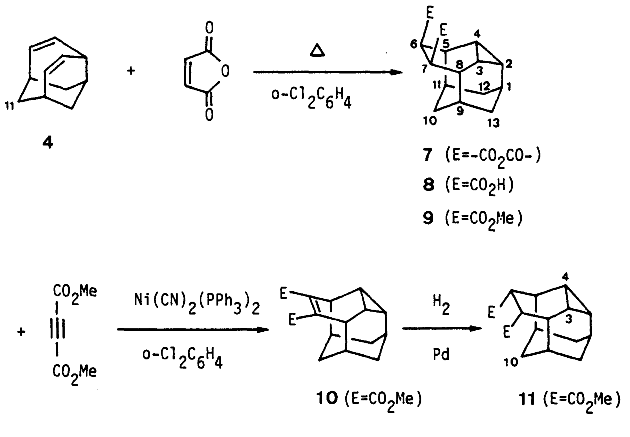
Iceane (**1**, tetracyclo$[5.3.1.1^{2,6}.0^{4,9}]$dodecane) is named after its geometrical similarity to one of the crystalline structure of water[2] and possesses a unique rigid structure that consists of two chair and three boat cyclohexane rings.[3–5] In the course of our works on synthesis and reactions of strained cage compounds related iceane,[6,7] we previously reported synthesis of a nor-analogue of iceane, i.e. noriceane (**2**) as well as its 3,5-dehydro derivative, i.e. 3,5-dehydronoriceane (**3**).[6] Recently we have found that tricyclo$[5.3.1.0^{4,9}]$undeca-2,5-diene (**4**) reacts with tetracyanoethene faster than norbornadiene to give the homo-Diels–Alder adduct, providing the first example of a 1,4-cyclooctadiene system participating as a diene partner in the homo-Diels–Alder reaction.[8] In addition to its mechanistic interest, the resulting adduct consists of a skeleton of homoiceane (a homologue of iceane). We now wish to report here the first synthesis of homoiceane (**5**) and its 3,13-dehydro derivative **6** by using this highly efficient one-step framework construction.[9]



Scheme 1.

## Results and Discussion

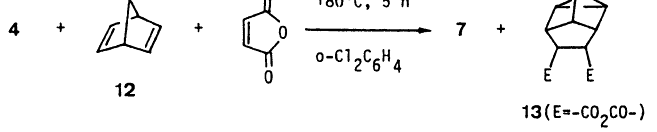
When a 2:3 mixture of **4** and maleic anhydride in *o*-dichlorobenzene was heated under reflux for 12 h, the homo-Diels–Alder reaction proceeded very nicely to give the [2+2+2] adduct **7** as the single stereoisomer in 81% yield (Scheme 2). The $^{13}C$ NMR spectrum of **7** showed 9 peaks, supporting the $C_s$ symmetry of **7**. Furthermore, the $^{13}C$-H coupling constants of two higher field signals ($\delta$=5.5 and 15.4) were 167 and 169 Hz, respectively, clearly indicating the presence of a cyclopropane ring. Thus, **4** demonstrated the remarkably high homo-Diels–Alder reactivity as a 1,4-cyclooctadiene derivative.[8]



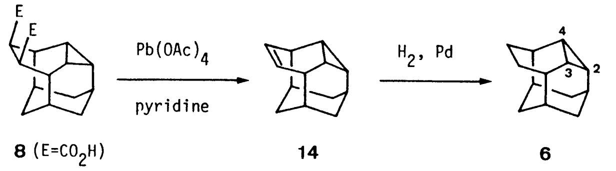
Scheme 2.

The stereochemistry of the adduct **7** was expected to be exo in consideration of the endo-selectivity of homo-Diels–Alder reaction and this expectation was further supported by the following experiments. Hydrolysis of **7** with potassium carbonate in $H_2O$ gave the dicarboxylic acid **8**, which was esterified with diazomethane to afford the *exo*-dimethyl ester **9** in 86% yield (Scheme 2). On the other hand, the *endo*-dimethyl ester **11** was prepared as follows; cycloaddition of **4** with dimethyl acetylenedicarboxylate in the presence of catalytic amount of $Ni(CN)_2(PPh_3)_2$[10] gave the cycloadduct **10** (45%), hydrogenation of which over Pd-black took place from the exo-side, probably owing to steric hindrance by $C^{10}$ methylene bridge, to give **11** (Scheme 2). The stereochemical assignments to **9** and **11** were compatible with a steric compression effect[11] observed in their $^{13}$C NMR spectra: the signal due to $C^3$ ($C^4$) appears at higher field ($\delta$=6.3) in **9** than in **11** ($\delta$=10.6), whereas the signal due to $C^{10}$ is at lower field ($\delta$=32.2) in **9** than in **11** ($\delta$=29.2). Thus, it is noteworthy that the present homo-Diels-Alder reaction proceeds exclusively in an endo-selective manner, since 67—79% endo-selectivity has been observed in the reaction of norbornadiene (**12**) with maleic anhydride.[12] The steric hindrance due to $C^{11}$ methylene bridge of **4** may enhance the endo-selectivity in the present case.

In order to compare the homo-Diels-Alder reactivity of **4** with that of norbornadiene (**12**), we undertook a competitive reaction of **3** and **12** (Scheme 3). When a 1 : 1 : 1 mixture of **4**, **12**, and maleic anhydride in *o*-dichlorobenzene was heated at 180 °C in a sealed tube for 5 h, the cycloadducts, **7** and **13**,[13] were obtained in a ratio of 67 : 33 by $^1$H NMR. This result suggested again the higher reactivity of **4** than that of **12**.[8]



Scheme 3.

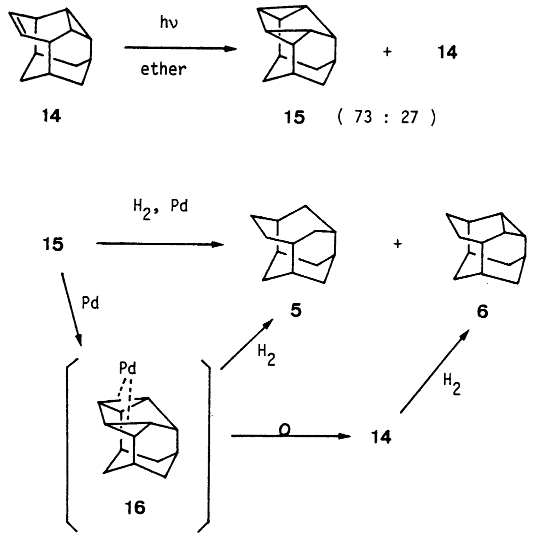


Scheme 4.

As the dehydrohomoiceane skeleton could be obtained in one step, we next examined transformation of **7** into **5** and **6**. Oxidative decarboxylation of **7** with lead tetraacetate in pyridine[14] gave the cage olefin **14** in 65% yield (Scheme 4). It should be noted that **14** contains a rigid chair bicyclo[4.1.0]hept-3-ene system, in which the $\pi$-$\sigma$ interaction between the double bond and the cyclopropane ring has been of great interest.[15,16] Catalytic hydrogenation of **14** with Pd-black gave 3,13-dehydroiceane (**6**) in 97% yield.

On the other hand, transformation into homoiceane (**5**) was not so straightforward as above, because hydrogenolysis of the cyclopropane ring of **6** gave a unsymmetrical product which might be formed by hydrogenolysis of the side C-C bond ($C^2$-$C^3$ or $C^2$-$C^4$) of the cyclopropane ring: treatment of **6** with $PtO_2$ under $H_2$ in AcOH at 50 °C gave a compound, the $^{13}$C NMR spectrum of which showed a lack of symmetry. In order to accomplish a regioselective cleavage of the central C-C bond ($C^3$-$C^4$), we have noticed an intramolecular $[_{\pi}2+_{\sigma}2]$ cycloaddition[16] between the olefin and the cyclopropane moieties in **14**. Thus, irradiation of **14** in ether by a medium-pressure mercury lamp through a quartz filter afforded a 73 : 27 mixture of the $[_{\pi}2+_{\sigma}2]$ cycloadduct **15** and unchanged **14** in 83% yield (Scheme 5). The $^1$H NMR spectrum of **15** showed no olefinic protons and its $^{13}$C NMR spectrum showed 8 peaks, suggesting $C_s$ symmetry. The ratio of **15** to **14** was not changed after prolonged irradiation, suggesting a photostationary state between **14** and **15**.[17]

Since **15** contains two cyclopropane rings in its rigid cage structure, **15** is expected to be reactive toward transition metals.[18] When **15** was treated with Pd-black under $H_2$, hydrogenolysis of the two cyclopropane rings took place simultaneously to afford a 1 : 1 mixture of homoiceane (**5**) and **6**, along with a small amount of an unidentified compound (Scheme 5). The $^{13}$C NMR spectrum of **5** clearly indicated $C_s$ symmetry. The successful simultaneous hydrogenolysis of the two cyclopropane rings and the formation of **6** could be rationalized as follows (Scheme 5). The reaction would be probably initiated through complexation of Pd to the two cyclopropane rings, such as **16**. When **16** would undergo a valence isomerization to **14**, **6** would be produced after hydrogenation of the olefinic group. On the other hand, reaction of **16** with $H_2$ *before the isomerization* could afford **5**.



Scheme 5.

## Experimental

All the temperatures were uncorrected. The IR spectra were obtained on a Hitachi 215 spectrometer. The mass spectra were taken by using a Hitachi RMS-4 mass spectrometer. The $^1$H and $^{13}$C NMR spectra were obtained on Varian EM-390 and CFT-20 or a JEOL FX-90Q spectrometer, $Me_4Si$ being chosen as an internal standard. Analytical

GLC were carried out on a Shimadzu GC-4C gas chromatography with 10% SE-30 and 10% PEG-20M on Chromsorb W columns. Preparative GLC were performed on a Varian 920 gas chromatography with a 10% PEG-20M on Chromsorb W column. The microanalyses were carried out by Kyoto University Elemental Analysis Center.

**Pentacyclo[7.3.1.$0^{2,4}$.$0^{2,8}$.$0^{5,11}$]tridecane-*exo,exo*-dicarboxylic Anhydride (7).** A mixture of tricyclo[5.3.1.$0^{4,9}$]undeca-2,5-diene (146 mg, 1.0 mmol), maleic anhydride (147 mg, 1.5 mmol), and a small amount of hydroquinone in *o*-dichlorobenzene (15 mL) was heated at reflux under Ar for 12 h. The reaction mixture was chromatographed on silica gel. Elution by hexane and, then, a mixture of hexane and $CH_2Cl_2$ (1 : 1) gave **7** (198 mg, 81%): mp 153—155 °C; MS *m/z* (%) 244 ($M^+$, 100); IR (Nujol): 1845, 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=3.09 (s, 2H), 2.80—3.05 (m, 2H), 1.84—2.30 (m, 3H), 1.10—1.73 (m, 7H), 0.67—1.04 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$=174.7 (s), 44.1 (d), 32.6 (t), 31.9 (t), 31.0 (d), 28.4 (d), 18.4 (d), 15.4 (d, $^1J_{C-H}$=169 Hz), 5.5 (d, $^1J_{C-H}$=167 Hz). Found: C, 73.60; H, 6.60%. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%.

***Dimethyl* Pentacyclo[7.3.1.$0^{2,4}$.$0^{3,8}$.$0^{5,11}$]tridecane-*exo,exo*-6,7-dicarboxylate (9).** A mixture of **7** (305 mg, 1.3 mmol) in 5% aqueous $K_2CO_3$ (10 mL) was heated at reflux for 2 h. The reaction mixture was acidified by 10% aqueous HCl and extracted with AcOEt. The organic solution was washed with $H_2O$ and dried ($Na_2SO_4$). Evaporation of the solvent gave pentacyclo[7.3.1.$0^{2,4}$.$0^{3,8}$.$0^{5,11}$]tridecane-*exo-,exo*-6,7-dicarboxylic acid (**8**, 317 mg, 97%). A solution of **8** (123 mg, 0.5 mmol) in diethyl ether (30 mL) was treated with $CH_2N_2$ generated from $C_7H_7SO_2N(NO)CH_3$ and KOH. Usual work-up and chromatography on silica gel gave **9** (117 mg, 86%): mp 98—101 °C; MS *m/z* (%) 290 ($M^+$, 30), 258 (100); IR (Nujol): 1760, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=3.61 (s, 6H), 2.94 (s, 2H), 2.53—2.80 (m, 2H), 1.57—2.20 (m, 4H), 0.93—1.53 (m, 7H); $^{13}C$ NMR ($CDCl_3$) $\delta$=174.8 (s), 51.4 (q), 44.1 (d), 32.8 (t), 32.2 (t), 31.9 (d), 30.7 (d), 18.8 (d), 16.3 (d), 6.3 (d). Found: C, 70.07; H, 7.57%. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64%.

**Dimethyl Pentacyclo[7.3.1.$0^{2,4}$.$0^{3,8}$.$0^{5,11}$]tridec-6-ene-6,7-dicarboxylate (10).** A mixture of **4** (146 mg, 1.0 mmol), dimethyl acetylenedicarboxylate (710 mg, 5.0 mmol), $Ni(CN)_2(PPh_3)_2$ (12 mg, 0.02 mmol), and a small amount of hydroquinone in *o*-dichlorobenzene (5 mL) was heated at reflux under Ar for 4 h. The reaction mixture was chromatographed on silica gel. Elution by hexane, hexane-$CH_2Cl_2$ (1 : 1), and $CH_2Cl_2$ gave a mixture of **10** and some by-products, which was distilled (Kugelrohr, 130 °C/53 Pa) to give **10** (131 mg, 45%, 95% pure by $^1H$ NMR). Further purification by using a Lobar column (10% AcOEt-hexane) gave pure **10**: mp 63—4 °C; MS *m/z* (%) 288 ($M^+$, 28), 256 (83), 228 (100); IR (Nujol): 1720 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$=3.77 (s, 6H), 3.07—3.33 (m, 2H), 2.00—2.33 (m, 1H), 1.43—1.97 (m, 3H), 0.73—1.37 (m, 8H); $^{13}C$ NMR ($CDCl_3$) $\delta$=168.6 (s), 143.5 (s), 51.9 (q), 34.2 (d), 31.5 (t), 30.2 (t), 24.3 (d), 23.8 (d), 18.5 (d), 15.6 (d). Found: C, 70.86; H, 6.80%. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99%.

**Dimethyl Pentacyclo[7.3.1.$0^{2,4}$.$0^{3,8}$.$0^{5,11}$]tridecane-*endo-endo*-6,7-dicarboxylate (11).** A mixture of **10** (68 mg, 0.3 mmol) and Pd-black (27 mg) in MeOH (5 mL) was stirred under $H_2$ for 48 h and, after addition of Pd-black (20 mg), for 48 h. Pd-black was filtered off through Celite and the solvent was evaporated. The residue was chromatographed on silica gel and elution by $CH_2Cl_2$ gave **11** (35 mg, 51%): mp 80—82 °C; MS *m/z* 290 ($M^+$, 22), 258 (100); IR (Nujol): 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=3.64 (s, 6H), 3.08 (br s, 2H), 2.45—2.83 (m, 2H), 1.57—2.27 (m, 4H), 0.63—1.53 (m, 8H); $^{13}C$ NMR ($CDCl_3$) $\delta$=174.1 (s), 51.3 (q), 44.5 (d), 32.9 (t), 32.0 (d), 29.2 (t), 27.8 (d), 19.4 (d), 18.3 (d), 10.6 (d). Found: C, 69.93; H, 7.69%. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64%.

**Competitive Reaction of 4 and Norbornadiene (12) with Maleic Anhydride.** A mixture of **4** (73 mg, 0.5 mmol), **12** (46 mg, 0.5 mmol), maleic anhydride (49 mg, 0.5 mmol), and a small amount of hydroquinone in *o*-dichlorobenzene (3 mL) was heated at 180 °C in a sealed tube for 5 h. The similar work-up to the above gave a mixture of **7** and **13** (46 mg) in a ratio of 67 : 33 (by $^1H$ NMR). The endo : exo ratio of **13** was determined to be 67 : 33 by $^1H$ NMR.

**Pentacyclo[7.3.1.$0^{2,4}$.$0^{3,8}$.$0^{5,11}$]tridec-6-ene (14).** To dry pyridine (11 mL) saturated with $O_2$ was added **8** (733 mg, 2.8 mmol) and $Pb(OAc)_4$ (1880 mg, 4.2 mmol). The mixture was heated at 65—70 °C in a preheated oil bath for 3 min and immediately cooled to room temperature in an ice bath. The reaction mixture was poured into 10% aqueous $HNO_3$ and extracted with diethyl ether. The ether solution was washed with saturated $NaHCO_3$ and brine, and dried ($Na_2SO_4$). The solvent was evaporated and the residue was chromatographed on silica gel. Elution by pentane gave **14** (322 mg, 67%) and further elution by $CH_2Cl_2$ gave **7** (66 mg, 10%). **14**: mp 205 °C (decomp); MS *m/z* (%) 172 ($M^+$, 70), 129 (72), 91 (100); IR (Nujol): 1465 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=6.17 (dd, 2H, *J*=2, 5 Hz), 2.57—2.90 (m, 2H), 1.97—2.27 (m, 1H), 1.06—1.77 (m, 8H), 0.63—1.03 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$=135.4 (d), 32.8 (t), 31.5 (d), 30.9 (t), 24.3 (d), 23.7 (d), 19.2 (d), 15.8 (d). Found: C, 90.62; H, 9.51%. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36%.

**Pentacyclo[7.3.1.$0^{2,4}$.$0^{3,8}$.$0^{5,11}$]tridecane (6).** A mixture of **14** (76 mg, 0.44 mmol) and Pd-black (7.6 mg) in MeOH (4 mL) was stirred under $H_2$ for 2h. The catalysts were removed by filtration through Celite and the solvent was evaporated. The residue was chromatographed on silica gel and elution by pentane gave **6** (75 mg, 97%): mp 207 °C (decomp); MS *m/z* (%) 174 ($M^+$, 100); $^1H$ NMR ($CDCl_3$) $\delta$=0.50—2.50 (m, 18H); $^{13}C$ NMR ($CDCl_3$) $\delta$=33.5 (t), 31.9 (t), 30.4 (d), 27.5 (d), 24.1 (t), 19.8 (d), 14.9 (d), 8.8 (d). Found: C, 89.30; H, 10.64%. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41%.

**Hexacyclo[7.3.1.$0^{2,7}$.$0^{3,5}$.$0^{4,11}$.$0^{6,8}$]tridecane (15).** A solution of **14** (228 mg, 1.3 mmol) in diethyl ether (15 mL) was irradiated through quartz filter under Ar by medium-pressure mercury lamp for 12h. The solvent was evaporated and the residue was chromatographed on silica gel. Elution by pentane gave a mixture of **15** and **14** (198 mg) in a ratio of 73 : 27 (by GLC). Pure **15** was isolated by preparative GLC. **15**: mp 199 °C (decomp); MS *m/z* 172 ($M^+$, 29), 91 (100); $^1H$ NMR ($CDCl_3$) $\delta$=0.60—3.00 (m, 16H); $^{13}C$ NMR ($CDCl_3$) $\delta$=35.6 (d), 35.5 (t), 33.8 (d), 33.3 (d), 32.4 (t), 27.1 (d), 26.7 (d), 22.5 (d). Found: C, 90.47; H, 9.50%. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36%.

**Tetracyclo[6.3.1.$1^{2,7}$.$0^{4,10}$]tridecane (5).** A mixture of **15** (70 mg, 0.41 mmol) and Pd-black (7 mg) in MeOH (5 mL) was stirred under $H_2$ for 6 h. The catalysts were removed by filtration through Celite and the residue was chromatographed on silica gel. Elution by pentane gave a mixture of **5**, **6**, and an additional product (57 mg) in a ratio of 2 : 2 : 1 (by GLC). Pure **5** was isolated by preparative GLC. **5**: mp 176 °C; MS *m/z* (%) 176 ($M^+$, 100); $^1H$ NMR ($CDCl_3$)

$\delta$=0.65—2.70 (m, 20H); $^{13}$C NMR (CDCl$_3$) $\delta$=35.0 (t), 34.2 (t and d), 32.8 (t), 31.7 (d), 30.7 (t), 30.2 (d), 26.4 (d). Found: C, 88.72; H, 11.72%. Calcd for $C_{13}H_{20}$: C, 88.57; H, 11.43%.

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