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Acid-promoted Cyclization of Tetronic Acid to Alkene; Chemical Transformation of (−)-Ircinianin to (+)-Wistarin

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The perchloric acid-promoted transformation of (−)-ircinianin (1) to (+)-wistarin (2) is described. The reaction of 1 with perchloric acid in acetonitrile gave 2 in 35% yield along with a positional isomer 4 in 35% yield. The structure of 4 was determined by two dimensional (2D) NMR studies. On the other hand, the reaction of 2-methyl-4-prenyltetronic acid (6), as a model compound for the above transformation, gave the cyclized product 8 corresponding to 2 in 58% yield and the keto-lactone 9 in 22% yield under the same conditions.

Key words marine natural product; stereospecific synthesis; 6-*endo*-trigonal cyclization; (+)-wistarin

Constitutional isomers have occasionally been found in natural products. (−)-Ircinianin (**1**) and (+)-wistarin (**2**) are constitutional isomers of marine natural products. (−)-Ircinianin (**1**) was isolated from a marine sponge, genus *Ircinia*, by Hofheinz and Schönholzer.[1] It is assumed to be formed by an intramolecular Diels-Alder reaction from the plausible furanosesterterpenetetronic acid precursor **3**, which has not been found in sponges. Takeda *et al.* demonstrated this process in an elegant synthesis of racemic **1** from racemic **3**.[2] Interestingly, **1** and **2** are the only two cyclic furanosesterterpenetetronic acids to have been isolated from this family.[3] This suggests that an asymmetric ring construction (**3** to **1**) may occur in marine organisms either chemically or enzymatically. On the other hand, (+)-wistarin **2** was isolated from *Ircinia wistarii* along with **1**.[4] Its structure was proposed by Gregson and Ouvrier[4] initially, and has recently been revised.[5] Compound **2** is believed to be produced by the intramolecular cyclization of the enol of **1** to an alkene. Despite attempts by Gregson, **1** did not cyclize to **3** in Lewis acid- or mineral acid-promoted reactions. Instead, only the decomposition of **1** was observed. After achieving the asymmetric total synthesis of **1** and **2**,[5] we re-examined the acid-promoted intramolecular cyclization of tetronic acid to alkene for (−)-ircinianin **1** and a model compound. We report here that perchloric acid is the most effective catalyst for the chemical transformation of **1** to **2**, and that a longer reaction time gives a fourth constitutional isomer **4**, with the formula $C_{25}H_{32}O_4$.

We first performed a model cyclization study. 2-Methyl-4-prenyltetronic acid (**6**) was chosen as a simple model of **1**. Compound **6** was prepared from 2-methyltetronic acid **5**.[6] Thus, a dianion of **5** generated with 2.2 eq of butyllithium was alkylated with prenyl bromide to give **6** in 63% yield. The cyclized compound **8** corresponding to (+)-wistarin was synthesized from **6** in two steps. Treatment of **6** with iodine in the presence of potassium carbonate gave a cyclic iodo ether **7** in 59% yield, and this was hydrogenated with tributyltin hydride under radical conditions in the presence of a catalytic amount of triethylborane to give **8** in 68% yield.

For the acid-promoted transformation of **6** to **8**, several Lewis acids such as $BF_3 \cdot OEt_2$, $SnCl_4$, $ZnCl_2$, and $TiCl_4$, and mineral and organic acids, such as HCl, H_2SO_4, $HClO_4$, CF_3CO_2H, and (±)-10-camphorsulfonic acid (CSA) were examined. Most of these were inactive or over-reactive. However, perchloric acid and $SnCl_4$ worked well in CH_2Cl_2 to give the desired tetrahydropyran **8**. Its structure was identified by comparison with an authentic standard prepared by the above synthesis. None of the tetrahydrofuranyl isomer **10** resulting from 5-*exo*-trigonal type cyclization was found in the NMR spectrum of the crude mixture of the reaction products, but an ambido-

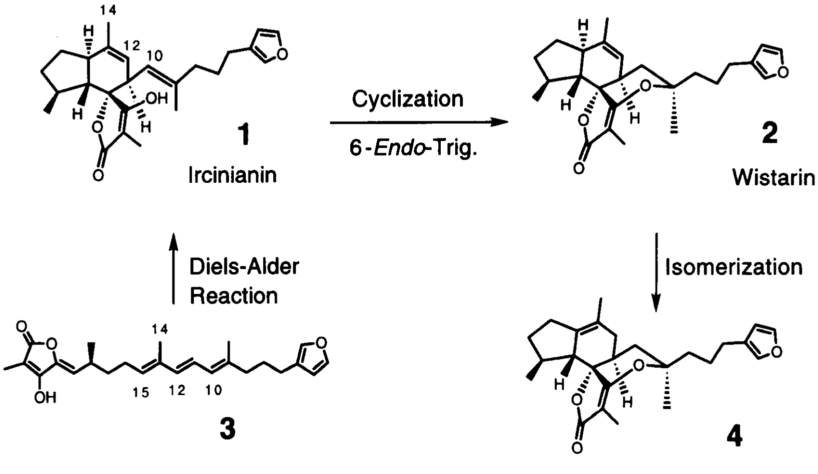

Chart 1

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isomer **9** was produced as a by-product due to cyclization of the carbon nucleophile in the above reactions. The structure of **9** was confirmed by carbon NMR, which showed the two carbons of the ketone and lactone carbonyls at 208.3 and 173.4 ppm, respectively, and also by the IR spectrum, which showed two clear adsorptions at 1750 and 1800 cm^{-1}. The best result was obtained when the reaction was conducted in a 1 : 9 mixture of 60% $HClO_4$ and CH_2Cl_2 for 30 min at room temperature, affording **8** and **9** in 58% and 22% yields, respectively. If **8** was treated again with perchloric acid under the same conditions as described above, the reaction gave a 1: 1.6 mixture of **8** and **9** after 12 h. When compound **9** was examined under the same conditions, a mixture of **8** and **9** was obtained in the same ratio. On the other hand, treatment of **6** with 60% $DClO_4$ in D_2O and CH_2Cl_2 (1 : 9) afforded a mixture of deuterated **8** and **9**. These experiments suggest that the cyclization of **6** initially gives the kinetic product **8**, which isomerizes to give the thermodynamically more stable isomer **9**. These processes are reversible and the reaction convergently reaches an equilibrium of **8** and **9**.

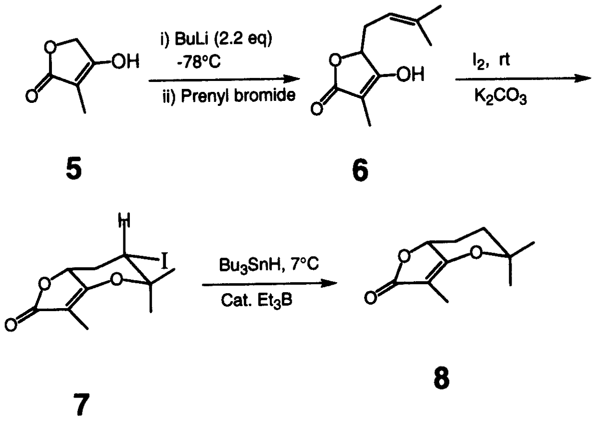

Chart 2

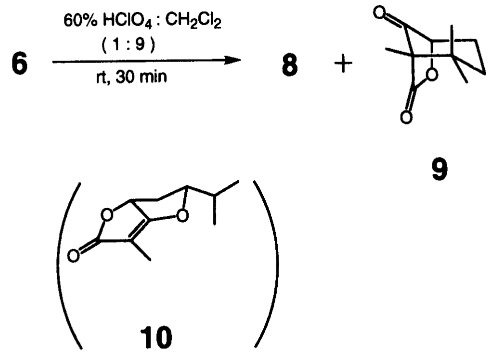

Chart 3

Next, ircinianin was subjected to acidic cyclization. When the reaction of **1** was carried out in CH_2Cl_2 using $SnCl_4$ and other Lewis acids, the reaction was sluggish and gave **2** in a poor yield. However, when cyclization was conducted in a mixture of 60% $HClO_4$ and CH_3CN (1 : 9) for 3 h, the desired cyclization occurred relatively cleanly to give **2** in 35% yield along with a by-product **4** in 35% yield. The reaction proceeded stereoselectively to form a new chiral center at C-8, and none of the ambido-isomer, corresponding to **9** in the model studies, was produced. This type of cyclization by enzyme was reported in the literature,[7] in which *tocopherol cyclase* catalyzed the transformation of phytyl hydroquinone to γ-tocopherol. The structure of **4** was determined by spectroscopic analyses. The high-resolution mass spectrum of **4** indicated that it was a constitutional isomer, based on its formula $C_{25}H_{32}O_4$. The similarity of the proton and carbon NMR spectra to those of **4** suggested that it was an isomer of **2**. In particular, the ^{13}C-NMR spectrum closely resembled that of **2**, except for the appearance of a new quaternary carbon at 132.1 ppm and a new CH_2 carbon at 34.1 ppm, instead of two CH carbons at 121.2 and 42.0 ppm, which were identified as the C-15 and C-12 carbons. The structure was eventually assigned as **4** based on careful heteronuclear multiple bond connectivity (HMBC) and proton correlation spectroscopy (COSY) experiments, as shown in Fig. 1.[8] This clearly shows the

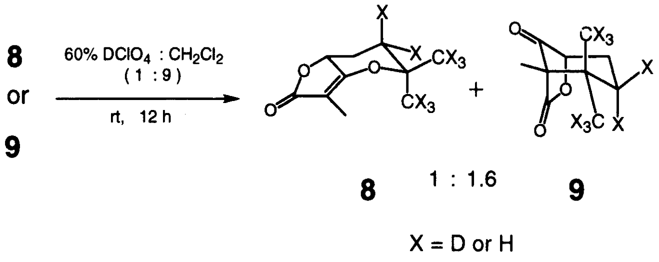

Chart 4

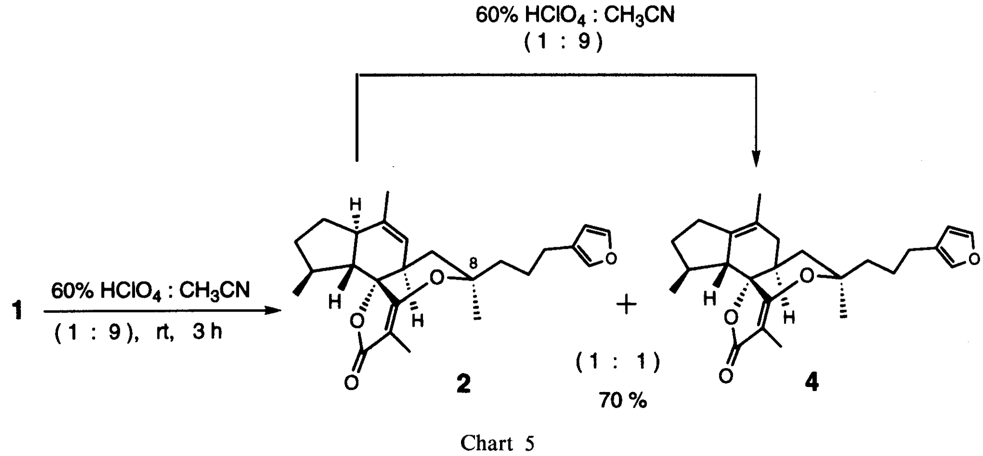

Chart 5

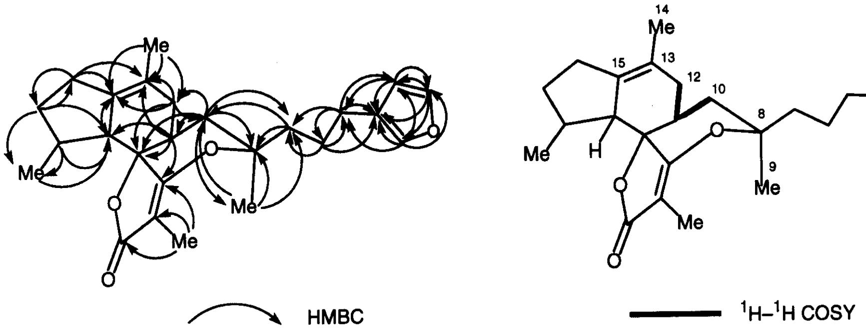

Fig. 1. HMBC and ^{1}H–^{1}H COSY Correlations of **4**

correlation of the C-12 to C-15 and C-10 to C-12 carbon chain systems, in which the double bond between the C-12 and C-13 in **2** has simply moved to the next bridgehead position.

To elucidate the stability of **2** and **4**, molecular mechanics and molecular orbital calculations were performed. According to the molecular mechanics calculations using MacroModel and Conflex, the steric energy of **4** was found to be 0.9 to 1.1 kcal/mol lower than that of **2**.[9] In addition, the heat of formation for **4**, calculated by MOPAC, was found to be less than that for **2**.[10] These results suggest that acidic isomerization of **2** would take place quite easily at room temperature to give **4**. In fact, when the reaction of **1** was continued for an additional two hours, **1** and **2** were consumed and finally converted to **4**. Under the same conditions, wistarin **2** also independently isomerized to **4**. Thus, including natural **1** and **2**, we have synthesized three optically pure isomers, **1**, **2**, and **4**, but not **3**. Compounds **3** and **4** have not yet been found in nature. Since compound **3** could easily be converted to **1** in sponges, it is unlikely to be isolated in the future. On the other hand, compound **4** is probably the most stable isomer among the four, and is generated quite easily from **2**. It is predicted to exist in nature, specifically in sponges.

In conclusion, we have succeeded in the biomimetic transformation of **1** to **2** by perchloric acid-promoted cyclization. Under the same acidic conditions, compound **4** was obtained from **1** and/or **2**.

Experimental

Melting points were taken on a Yanaco MP-3 melting point apparatus and are not corrected. ^{1}H-NMR spectra were recorded on JEOL GSX (400 MHz) and Varian Gemini-300 (300 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were obtained on a JMS-MS700 instrument. IR spectra were recorded on a JASCO FT/IR-230 instrument. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an Ar atmosphere. Tetrahydrofuran (THF) and benzene were distilled freshly over sodium/benzophenone ketyl under a nitrogen atmosphere, and other solvents were simply distilled before use. Thin layer chromatography (TLC) was performed with Merck $60F_{254}$ precoated silica gel plates. Column chromatography was carried out using Merck Silica gel 60 (70—230 mesh) for gravity columns, or Wako neutral aluminum oxide (200 mesh).

2-Methyl-4-prenyltetronic Acid (6) Butyllithium (7.5 ml, in 1.56 M hexane solution) was added dropwise to a stirred solution of 2-methyltetronic acid (600 mg, 5.26 mmol) in anhydrous THF (15 ml) and HMPA (3 ml) at −78°C. The mixture was stirred for 30 min at the same temperature, then prenyl bromide (0.66 ml, 5.79 mmol) was added and the whole was stirred for 15 min at 0°C. It was then acidified with dilute hydrochloric acid until the pH became 5. EtOAc (120 ml) was added. The organic layer was washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residual oil was purified by column chromatography on silica gel, eluted with 60% EtOAc in hexane. The solid product was recrystallized from 10% benzene in hexane to give **6** (600 mg) in 63% yield as colorless needles; mp 88.0—89.5 °C. *Rf*=0.37 (EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.64 (3H, br s), 1.71 (3H, br s), 1.72 (3H, d, J=0.8 Hz), 2.41 (1H, m), 2.66 (1H, m), 4.73 (1H, t, J=5.4 Hz), 5.12 (1H, t, J=7.4 Hz), 8.82 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 5.7, 17.9, 25.8, 30.2, 79.0, 97.1, 116.4, 136.3, 176.0, 178.2. EI-MS *m/z* (rel. int. %): 182 (M^+, 36), 114 (11), 69 (base). HR-EI-MS *m/z*: 182.0918 (Calcd for $C_{10}H_{14}O_3$: 182.0943). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.75; H, 7.46.

Preparation of Cyclic Iodo Ether 7 A chloroform solution (4.5 ml) of iodine (168 mg, 0.66 mmol) was added to a mixture of **6** (120 mg, 0.66 mmol) and anhydrous potassium carbonate (550 mg, 4 mmol) in chloroform (6 ml) at 0°C, and the mixture was stirred for 15 min at the same temperature. The mixture was directly charged on a silica gel column and eluted with 30% EtOAc in hexane to afford the iodopyran **7** (120 mg) in 59% yield. Colorless crystals; mp 94.5—95.0 °C (benzene). *Rf*=0.27 (20% EtOAc in hexane). ^{1}H-NMR (400 MHz, C_6D_6) δ: 1.02 (3H, s), 1.31 (3H, s), 1.65 (3H, d, J=1.5 Hz), 1.80 (1H, ddd, J=13.2, 12.3, 11.2 Hz), 2.24 (1H, ddd, J=12.3, 6.4, 3.6 Hz), 3.41 (1H, dd, J=13.2, 3.6 Hz), 3.68 (1H, ddd, J=11.2, 6.4, 1.3 Hz). ^{13}C-NMR (100 MHz, C_6D_6) δ: 6.0, 21.2, 26.1, 29.0, 39.0, 72.5, 84.9, 106.7, 170.0, 172.5. EI-MS *m/z* (rel. int. %): 308 (M^+, 41), 225 (12), 181 (base), 113 (48). HR-EI-MS *m/z*: 307.9923 (Calcd for $C_{10}H_{13}O_3I$: 307.9910). *Anal.* Calcd for $C_{10}H_{13}O_3I$: C, 38.98; H, 4.25. Found: C, 39.73; H, 4.23.

Synthesis of 8 A mixture of **7** (40 mg, 0.13 mmol) and tributyltin hydride (0.1 ml, 0.39 mmol) in anhydrous benzene (4 ml) was treated with triethylborane (0.13 ml, 1.0 M hexane solution) at 7 °C. The mixture was stirred for 10 min at the same temperature and water (2 ml) was added. The whole was extracted with benzene (30 ml). The organic solution was washed with water (2 ml) and brine (2 ml), dried over $MgSO_4$ and concentrated to afford a solid, which was purified by aluminum oxide column chromatography to give **8** (16 mg) in 68% yield. Colorless crystals; mp 43.8—44.2 °C (hexane). *Rf*=0.32 (30% EtOAc in hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, s), 1.49 (3H, s), 1.70 (3H, d, J=1.5 Hz), 1.76 (1H, dddd, J=12.3, 12.1, 11.7, 4.4 Hz), 1.86 (1H, ddd, J=14.3, 12.3, 3.7 Hz), 1.92 (1H, ddd, J=14.3, 4.4, 3.7 Hz), 2.31 (1H, dddd, J=12.1, 6.6, 3.7, 3.7 Hz), 4.51 (1H, ddd, J=11.7, 6.6, 1.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 5.9, 25.2, 25.4, 29.5, 33.8, 73.6, 83.0, 103.6, 172.8, 174.5. EI-MS *m/z* (rel. int. %): 182 (M^+, 53), 114 (55), 69 (69), 43 (base). HR-EI-MS *m/z*: 182.0942 (Calcd for $C_{10}H_{14}O_3$: 182.0943). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.88; H, 7.46.

Acid-Promoted Cyclization of 6 A solution of **6** (300 mg, 1.65 mmol) in methylene chloride (4.5 ml) was treated with perchloric acid (60% in water, 0.5 ml) and the resulting two layers were stirred vigorously for 30 min at room temperature. Then, water (4 ml) was added and the mixture was extracted with benzene (50 ml). The aqueous layer was re-extracted with ethyl acetate (30 ml) and this extract was combined with the benzene extract, washed with water (2 ml) and brine (2 ml), and dried over $MgSO_4$. The solvent was removed and the residual oil was purified by silica gel column chromatography eluted with 10% EtOAc in hexane to give the bicyclic lactone **9** (65 mg) in 22% yield. The fractions eluted with 15% EtOAc in hexane provided **8** (174 mg) in 58% yield. Lactone **9**, colorless crystals; 25—30 °C; *Rf*=0.50 (30% EtOAc in hexane); IR (KBr) 1800, 1750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.92 (3H, s), 1.08 (3H, s), 1.14 (3H, s), 1.51 (1H, dd, J=14.7, 6.0 Hz), 1.76 (1H, m), 2.00 (1H, m), 2.34 (1H, m), 4.63 (1H, d, $J=5.5$ Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 7.2, 20.5, 24.3, 29.1, 32.7, 44.8, 57.6, 80.5, 173.4, 208.3; EI-MS *m/z* (rel. int. %) 182 (M^+, base), 114 (80), 69 (88). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.82; H, 7.84.

Acid Transformation of (−)-Ircinianin to (+)-Wistarin Perchloric acid (60% in water, 0.5 ml) was added to a solution of (−)-ircinianin (37 mg, 0.093 mmol) in acetonitrile (4.5 ml), and the mixture was stirred for 3 h at room temperature. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with ether (100 ml). The extract was washed with water (2 ml) and brine (2 ml), and dried over $MgSO_4$. The solvent was removed and the residue was chromatographed on silica gel eluted with 7.5% EtOAc in hexane to give (+)-wistarin **2** (13 mg) in 35% yield, and its isomer **4** (13 mg) was isolated in 35% yield after the elution of (+)-wistarin. Isomer **4**, colorless crystals; mp 102—103 °C (methanol). *Rf*=0.23 (15% EtOAc in hexane). $[\alpha]_D^{24}$ +16.5° ($c=0.18$, $CHCl_3$). IR (KBr) 1745, 1683, 1162, 1023 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (3H, d, $J=6.3$ Hz), 1.20 (1H, m), 1.26 (3H, s), 1.52 (1H, dd, $J=14.4$, 4.4 Hz), 1.58 (3H, s), 1.71 (3H, s), 1.61—1.80 (6H, m), 1.85 (1H, m), 1.95 (1H, t, $J=13.9$ Hz), 2.15—2.28 (4H, m), 2.45—2.55 (3H, m), 6.28 (1H, br d, $J=0.6$ Hz), 7.23 (1H, br s), 7.37 (1H, t, $J=1.5$ Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 6.0 (Me), 18.9 (Me), 19.8 (Me), 24.0 (CH_2), 24.3 (Me), 24.9 (CH_2), 27.5 (CH_2), 33.3 (CH_2), 34.1 (CH), 34.1 (CH_2), 35.4 (CH), 39.6 (CH_2), 42.3 (CH_2), 48.0 (CH), 80.4, 86.3, 104.8, 110.8 (CH), 121.6, 124.5, 132.1, 138.9 (CH), 142.9 (CH), 174.6, 175.7. FAB-MS *m/z*: 397 (MH^+). HR-FAB-MS *m/z*: 397.2381 (Calcd for $C_{25}H_{33}O_4$: 397.2379). *Anal.* Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.56; H, 8.13.

Acid Transformation of (+)-Wistarin to Isomer 4 (+)-Wistarin **2** (7 mg, 0.017 mmol) was stirred in a mixture of perchloric acid (0.1 ml, 60% in water) and acetonitrile (1 ml) for 3 h at room temperature. The mixture was neutralized with 5% $NaHCO_3$, extracted with ether (20 ml), washed with water (2 ml) and brine (2 ml), and dried over $MgSO_4$. The extract was evaporated and the residue was chromatographed on silica gel eluted with 7.5% EtOAc in hexane to give **4** (5.4 mg) in 77% yield.

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8) The authors thank Dr. Himoto (JEOL) for his advice in the HMBC studies.
9) MacroModel (ver. 4.5) and Conflex (ver. 3.5) were used for the molecular mechanics calculations. The steric energies obtained with MacroModel (kcal/mol) were: **2** (23.7) and **4** (22.6), and those with Conflex (kcal/mol) were: **2** (28.6) and **4** (27.7).
10) The calculation was performed by using MOPAC (PM3, ver. 6.0). Heat of formation (kcal/mol): **2** (−118.8) and **4** (−125.8).