[11] A Nd–Rh single bond, in the sense of a σ bond, cannot be assumed here. It is conceivable that there is an interaction of the d_{z^2} orbital, which are directed orthogonal to the coordination plane, with the neodymium atom.

[12] Metal–metal distances for unbridged single bonds have not, as far as we know, been reported for the combinations Ln–M (M = Co, Rh, Ir, Ni, Pd, Pt). The Lu–Ru distance in $[Cp_2(thf)LuRuCp(CO)_2]$ is 2.955(2) Å: I. P. Beletskaya, A. Z. Voskoboynikov, E. B. Chuklanova, N. I. Kirillova, A. K. Shestakova, I. N. Parshina, A. I. Gusev, G. K.-I. Magomedov, *J. Am. Chem. Soc.* **1993**, *115*, 3156–3166. The shortest metal–metal distance in bridged systems was found for $[Cp^*_2Yb(\mu\text{-}H)(\mu\text{-}CH_3)Pt(dippe)]$[3c] and is 3.388(9) Å. Cp* = C_5Me_5, dippe = $i\text{Pr}_2P(CH_2)_2P i\text{Pr}_2$.

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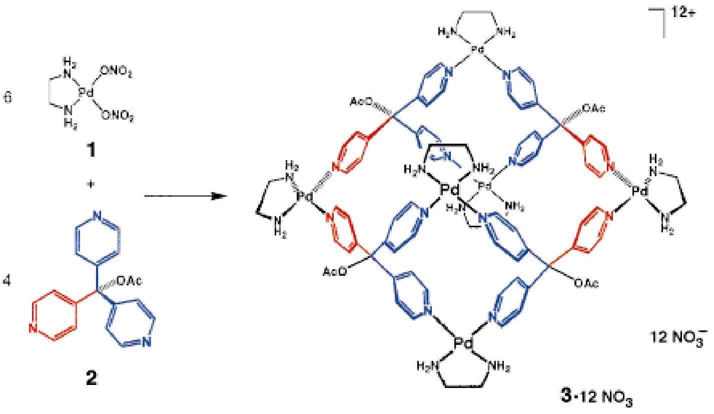
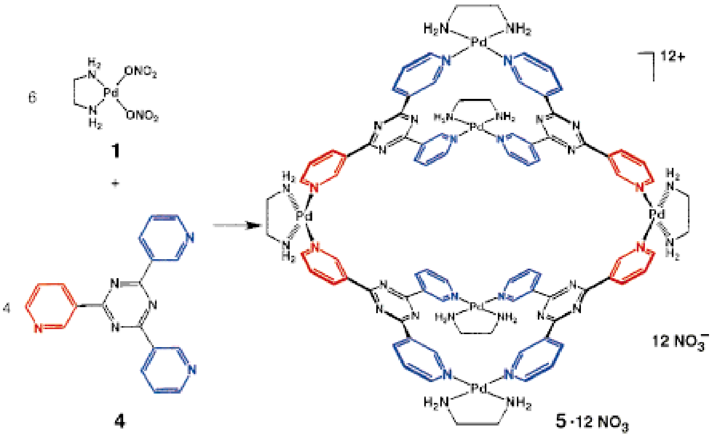
Self-Assembly of Nanometer-Sized Macrotricyclic Complexes from Ten Small Component Molecules**

Makoto Fujita,* Shu-Yan Yu, Takahiro Kusukawa, Hidenori Funaki, Katsuyuki Ogura, and Kentaro Yamaguchi

Transition metals with specific coordination geometries have been employed for the rational design and construction of highly ordered supramolecular structures.[1] We have shown that the simple combination of the square-planar coordination geometry of palladium (90° bond angle) with pyridine-based bridging ligands leads to the quantitative self-assembly of nanometer-sized, discrete organic frameworks[2] such as "molecular squares"[3, 4] and an adamantanoid cages.[5] Here we report the efficient self-assembly of nanometer-sized macrotricycles from ten small components. Treatment of $[Pd(NO_3)_2(en)]$ (**1**) with the tripyridylmethane **2**[6] results in self-assembly to the nanometer-sized macrotricyclic framework **3**, in which four ligand molecules are held together by six metal ions (Scheme 1). A similar ten-component self-assembly process leads to formation of the nanoscale macrotricycle **5** from **1** and the triazine-based ligand **4** (Scheme 2). Recently, there were a few reports of the metal-directed self-assembly of nanometer-sized macrocycles.[7, 8] However, their structures have often been deduced from spectroscopic data.[8] In contrast, the structures of nanometer-sized macrotricycles **3** and **5** were unambiguously determined by X-ray crystallographic analyses.



Scheme 1. Synthesis of **3**.



Scheme 2. Synthesis of **5**.

Ligand **2** was suspended in an aqueous solution of **1** (1.5 equiv), and the mixture was heated at 70 °C.[9] After 40 min a colorless clear solution was obtained. Analysis by NMR spectroscopy of the solution obtained by carrying out the reaction in D_2O showed the quantitative self-assembly of **1** and **2** to form a single product. The addition of aqueous $NaClO_4$ (1 M) resulted in precipitation of $\mathbf{3}\cdot 12\,ClO_4$ in 85% yield. When ethanol/water was employed as the solvent, the product was obtained from the solution directly as a NO_3^- salt by cooling to about 5 °C for several days. The elemental analyses agreed with the empirical formulas of $\mathbf{3}\cdot 12\,ClO_4\cdot 8\,H_2O$ and $\mathbf{3}\cdot 12\,NO_3\cdot 12\,H_2O$. The NMR spectra of **3** contain only one acetoxyl signal (^1H NMR: $\delta = 2.24$ (Figure 1); ^{13}C

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[++] Crystal structure analysis.

[**] This work was supported by the CREST (Core Research for Evolutional Science and Technology) project of Japan Science and Technology Corporation. S.-Y.Y. thanks the Japan Society for the Promotion of Science for a JSPS postdoctoral fellowship.

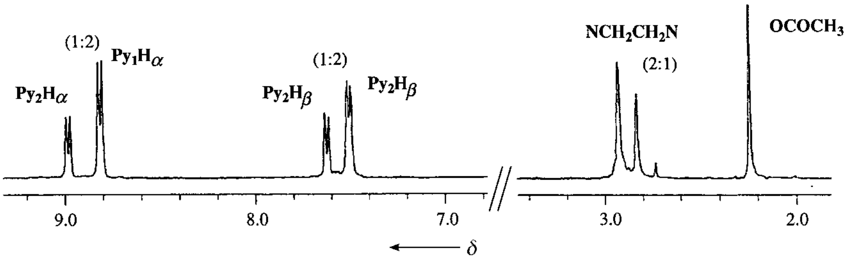


Figure 1. ^{1}H NMR spectrum of **3** (300 MHz, D_2O).

NMR: $\delta = 20.80$), although two inequivalent pyridyl groups are present in a 2:1 ratio in the self-assembled product (e.g., for PyH$_\alpha$: ^{1}H NMR: $\delta = 8.98$ and 8.81 (Figure 1); ^{13}C NMR: $\delta = 151.8$ and 151.6). Furthermore, two different Pd(en) units are present in a ratio of 2:1 (^{13}C NMR: $\delta = 46.86$ and 46.82). Therefore, the NMR data are fully consistent with the structure of **3**, that is, the pyridyl groups drawn in blue and red in Scheme 1 are inequivalent, but all acetyl groups are equivalent.

This somewhat unusual M_6L_4 structure was confirmed by an X-ray crystallographic analysis. A single crystal suitable for X-ray analysis was obtained by allowing a solution of **3** in ethanol/water to stand at ambient temperature for ten days. The ball-and-stick representation of the crystal structure (Figure 2) corresponds to our proposed structure. The most significant aspect is that the compound has nanometer dimensions in spite of the small size of the component molecules. The molecular dimensions of **3** are approximately 30 × 23 × 22 Å, and the longest Pd–Pd distance is 19.2 Å. From the top view of **3**, a roughly elliptical cavity (14 × 5 Å) can be seen (Figure 3, top). Viewed from the side, a macrocyclic dinuclear structure with a Pd–Pd distance of 9.2 Å is evident (Figure 3, bottom).

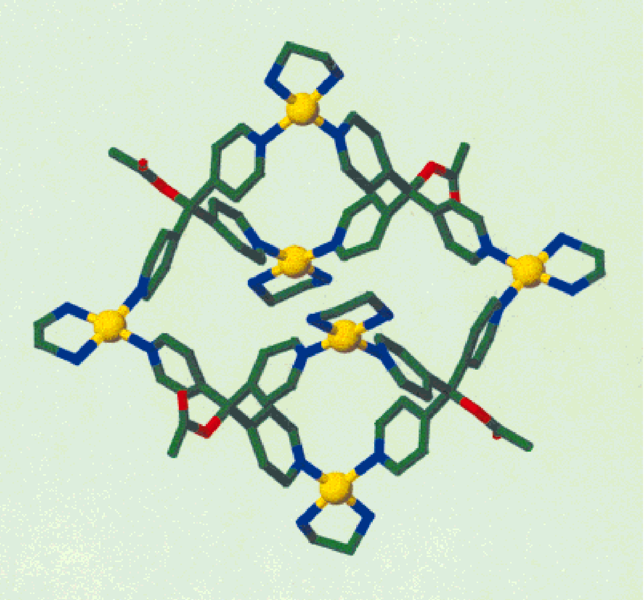


Figure 2. The X-ray crystal structure of **3**.

The nanometer-sized macrotricycle **5** was also formed by self-assembly (Scheme 2). The ligand **4** was treated with **1** (1.5 equiv) in water at 70 °C.[9] The product was recrystallized from water/methanol to give pure **5**·12NO$_3$ in 81% yield. Spectroscopic data fully supported the nanometer-sized macrotricyclic structure of **5**, which was confirmed by X-ray structure analysis (Figure 4). The macrotricycle **5** has the same topology as **3**, but a different molecular shape; that is, **5** has a bowl-shaped structure with the approximate dimensions 27 × 24 × 14 Å and a longest Pd–Pd distance of 19.1 Å.

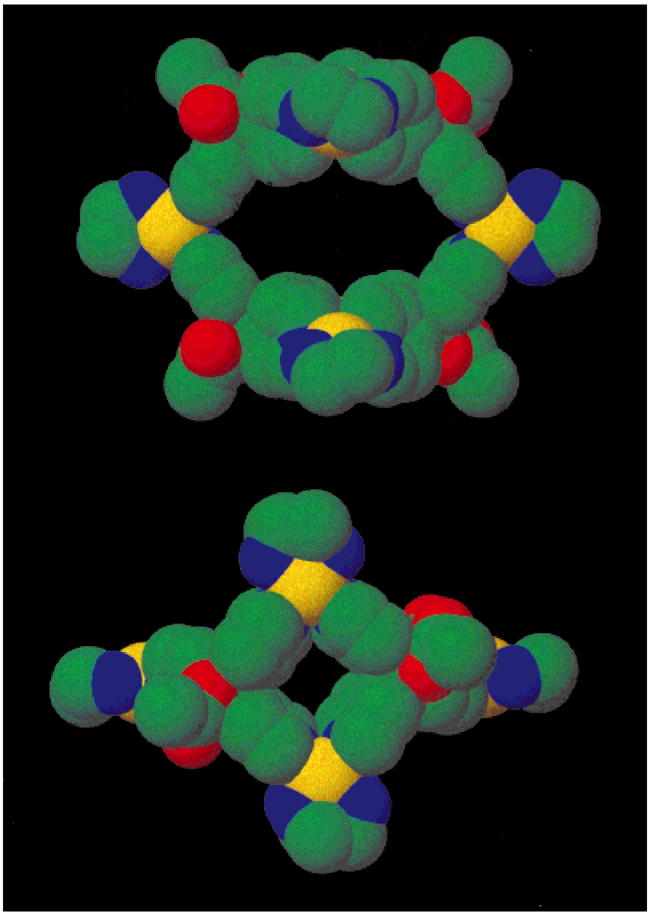
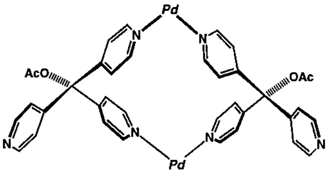
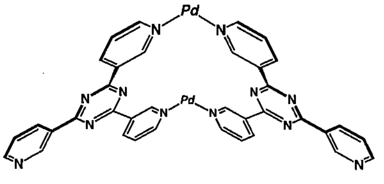


Figure 3. Space-filling (CPK) representation of the crystal structure of **3**. Top: top view, bottom: side view.

A proposed pathway leading to **3** or **5** involves a two-step self-assembly. First, two pyridyl groups of the ligand **2** or **4** are involved in the formation of the dinuclear macrocycle **7** or **8a**,



7: *Pd* = {Pd(en)}



8a: *Pd* = {Pd(en)}
8b: *Pd* = {Pd(bpy)}

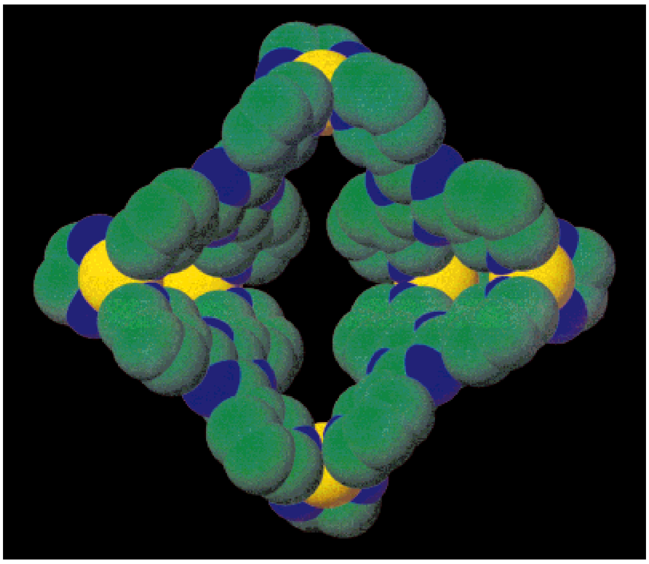
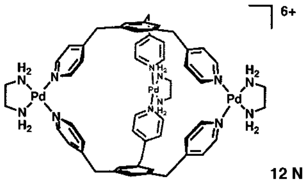


Figure 4. Space-filling (CPK) representation of the X-ray crystal structure of **5**.

respectively, in which two pyridyl groups are uncoordinated. In the second step, these pyridyl groups are intermolecularly linked together by Pd(en) units to give a large M_6L_4 macrotricyclic structure. This pathway appears reasonable because bis(4-pyridyl)methane, which has the partial framework of **3**, gives a dinuclear macrocycle corresponding to **7**.[10] Furthermore, when the en ligands were replaced by 2,2′-bipyridine (bpy), the dinuclear intermediate **8b** was obtained. This complex was isolated as single crystals from the crude reaction solution upon treatment of $[Pd(bpy)(NO_3)_2]$ (**6**) with **4** and characterized by X-ray analysis (Figure 5).[11]

Figure 5. The X-ray crystal structure of **8b**.

It is noteworthy that complexes **3** and **5** can bind dicarboxylate dianions. A significant upfield shift was observed for the aromatic protons of the dianion of 1,4-phenylenediacetic acid in D_2O upon complexation with an equimolar amount of **3** or **5** ($\Delta\delta = -0.29$ and -1.60, respectively). Another dicarboxylate, sodium terephthalate, was also bound in the cavity ($\Delta\delta = -0.13$ and -0.44 in **3** and **5**, respectively). For host **3**, the complexation is probably due to two-point electrostatic attraction between negative (COO^-) and positive charges (Pd^{2+}), since a simple monocarboxylate such as *p*-methoxyphenylacetate was hardly complexed by **3**. In contrast, host **5** also bound *p*-methoxyphenylacetate ($\Delta\delta = -1.20$ and -1.35 for the aromatic protons). Thus, the large, bowl-shaped framework of **5**, which is formed by sixteen aromatic rings, is a very effective cavity for molecular recognition. The self-assembly of **3** and **5** depends on a delicate thermodynamic balance, since their structures are quite different from the previously reported three-dimensional cage structutes of **9**[12] and **10**,[5a] although their ligands are very similar to those used here.



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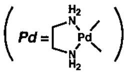

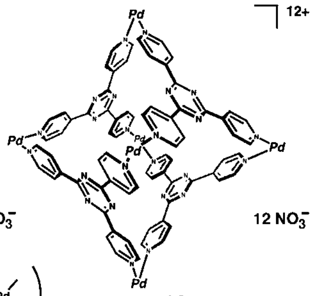

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Experimental Section

Self-assembly of **3**: Compound **2** (0.1 mmol) was suspended in an aqueous solution (1.5 mL) of **1** (0.15 mmol), and the mixture was heated to 70 °C for 40 min. A very small amount of insoluble product was removed by filtration, and an aqueous solution of $NaClO_4$ (1 M, 1.5 mL) was added to the filtrate. A colorless powder precipitated immediately and was collected by filtration and dried under reduced pressure to give pure $\mathbf{3}\cdot 12\,ClO_4$ in 85 % yield. Colorless powder; m.p. > 300 °C; ^1H NMR (300 MHz, D_2O, 25 °C, TMS): $\delta = 8.94$ (d, $J = 6.8$ Hz, 8 H, PyH_α), 8.80 (d, $J = 6.8$ Hz, 16 H, PyH_α), 7.60 (d, $J = 6.8$ Hz, 8 H, PyH_β), 7.49 (d, $J = 6.8$ Hz, 16 H, PyH_β), 2.95 (s, 16 H, NCH_2CH_2N), 2.83 (s, 16 H, NCH_2CH_2N), 2.24 (s, 12 H, $OCOCH_3$); ^{13}C NMR (125 MHz, D_2O, 25 °C, TMS): $\delta = 171.1$ (Cq), 152.4 (Cq), 151.8 (CH), 151.6 (CH), 149.0 (CH), 128.7 (CH), 124.7 (CH), 83.80 (Cq), 46.86 (CH_2), 46.82 (CH_2), 20.80 (CH_3); IR (KBr): $\tilde{\nu} = 3450, 2940, 1652, 1123, 668, 622\ cm^{-1}$; elemental analysis calcd for $C_{84}H_{108}N_{24}O_{56}Cl_{12}Pd_6 \cdot 8\,H_2O$: C 28.36, H 3.51, N 9.45; found: C 28.35, H 3.32, N 9.24.

Crystallographic analysis of $\mathbf{3}\cdot 12\,NO_3$: A solution of **2** (0.02 mmol) in ethanol (0.25 mL) was combined with an aqueous solution (0.25 mL) of **1** (0.030 mmol), and the clear solution was allowed to stand at ambient temperature for 10 d to give single crystals of $\mathbf{3}\cdot 12\,NO_3$. M.p. > 300 °C; IR (KBr): $\tilde{\nu} = 3451, 1617, 1383, 668, 599, 490, 456\ cm^{-1}$; elemental analysis calcd for $C_{84}H_{108}N_{36}O_{44}Pd_6 \cdot 12\,H_2O$: C 31.72, H 4.18, N 15.85; found: C 31.58, H 3.99, N 15.93. A single crystal with dimensions of $0.25 \times 0.15 \times 0.05$ mm was coated with a sealing material and mounted on a glass fiber. All measurements were made on a Rigaku RAXIS II imaging plate area detector with graphite-monochromated $Mo_{K\alpha}$ radiation. The data were collected at 173 K. The crystallographic molecule contains half a molecule of $\mathbf{3}\cdot 12\,NO_3$. Crystal data: $C_{84}H_{108}N_{36}O_{44}Pd_6 \cdot 12\,H_2O$, $M_r = 3180.57$, monoclinic, space group $P2_1/c$ (no. 14), $a = 19.450(7)$, $b = 14.586(2)$, $c = 26.40(1)$ Å, $\beta = 94.13(4)°$, $V = 7470(3)$ Å^3, $\rho_{calcd} = 1.414\ g\,cm^{-3}$, $Z = 2$, $F(000) = 3224$, $\mu(Mo_{K\alpha}) = 7.97\ cm^{-1}$, $\lambda(Mo_{K\alpha}) = 0.71070$ Å; 6703 reflections measured, 4121 observed reflections ($I > 3.50\,\sigma(I)$); number of parameters 723; $R1 = 0.131$; $wR2 = 0.161$. Owing to the high degree of disorder of the counteranions and water molecules, further refinement was unsuccessful.[13]

Self-assembly of **5**: Addition of ligand **4** (0.1 mmol) to an aqueous solution (1.5 mL) of **1** (0.15 mmol) followed by heating at 70 °C for 30 min gave a clear colorless solution, from which a yellowish microcrystalline powder was obtained by evaporation. Recrystallization from water/methanol gave colorless microcrystals of $\mathbf{5}\cdot 12\,NO_3$ in 81 % yield. M.p. > 300 °C; ^1H NMR (500 MHz, D_2O, 25 °C, TMS): $\delta = 10.56$ (d, $J = 1.5$ Hz, 8 H), 9.93 (br s, 4 H), 9.27 (d, $J = 4.9$ Hz, 8 H), 9.22–9.15 (m, 12 H), 9.12 (d, $J = 5.6$ Hz, 4 H), 7.9–7.8 (m, 12 H), 3.2-2.8 (m, 24 H, NCH_2CH_2N); ^{13}C NMR (125.65 MHz, D_2O, 25 °C, TMS): $\delta = 170.2$ (Cq), 170.0 (Cq), 155.5 (CH), 155.2 (CH), 153.3 (CH), 153.1 (CH), 141.4 (CH), 141.3 (CH), 134.7 (Cq), 134.6 (Cq), 128.1 (CH), 127.9 (CH), 47.8 (CH_2); IR (KBr): $\tilde{\nu} = 3402, 3067, 1653, 1584, 1529, 1382, 1058, 803, 698\ cm^{-1}$; elemental analysis calcd for $C_{84}H_{96}N_{48}O_{36}Pd_6 \cdot 12\,H_2O$: C 31.44, H 3.77, N 20.95; found: C 31.38, H 3.65, N 20.81.

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Crystallographic analysis of $\mathbf{5}\cdot 12\,NO_3$: colorless prisms of $\mathbf{5}\cdot 12\,NO_3$ were grown by diffusion of diethyl ether into a solution of the complex in water/methanol for two weeks at room temperature. A single crystal of dimensions 0.40 × 0.20 × 0.10 mm was coated with a sealing material and mounted on a glass fiber. All measurements were made on a Rigaku RAXIS II imaging plate area detector with graphite-monochromated $Mo_{K\alpha}$ radiation. The data were collected at 173 K. Crystal data for $\mathbf{5}\cdot 12\,NO_3$: $C_{84}H_{96}N_{48}O_{36}Pd_6\cdot 4\,H_2O$, $M_r = 3064.44$, triclinic, space group $P1$, $a = 20.17(1)$, $b = 22.73(1)$, $c = 19.17(1)$ Å, $\alpha = 95.68(5)$, $\beta = 98.70(2)$, $\gamma = 113.47(2)^\circ$, $V = 7845(8)$ Å^3, $\rho_{calcd} = 1.297\ g\,cm^{-3}$, $Z = 2$, $F(000) = 3080$, $\mu(Mo_{K\alpha}) = 7.51\ cm^{-1}$, $\lambda(Mo_{K\alpha}) = 0.71070$ Å; 18566 reflections measured, 15736 observed ($I > 3.50\,\sigma(I)$); number of variables 1460; $R1 = 0.133$; $wR2 = 0.179$.[13]

Received: March 24, 1998 [Z11631IE]
German version: *Angew. Chem.* **1998**, *110*, 2192–2196

Keywords: metallacycles · molecular recognition · N ligands · palladium · supramolecular chemistry

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[11] Crystal data for **8b**: yellowish prism, crystal dimensions 0.08 × 0.20 × 0.25 mm, $C_{56}H_{40}N_{16}F_{24}P_4Pd_2\cdot CH_3CN$, $M_r = 1770.75$, orthorhombic, space group $C222_1$ (no. 20), $a = 13.280(5)$, $b = 24.43(1)$, $c = 20.869(3)$ Å, $V = 6771(3)$ Å^3, $\rho_{calcd} = 1.737\ g\,cm^{-3}$, $Z = 4$, $F(000) = 3512$, $\mu(Mo_{K\alpha}) = 7.46\ cm^{-1}$, $\lambda(Mo_{K\alpha}) = 0.71070$ Å; 2802 reflections measured, 2219 observed ($I > 3.50\,\sigma(I)$); number of variables 502; $R1 = 0.083$; $wR2 = 0.098$.[13]

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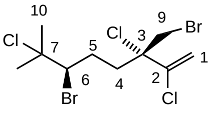
[13] Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-408575, CSD-408576, and CSD-408577.

Total Synthesis of (±)-Halomon by a Johnson–Claisen Rearrangement[**]

Thierry Schlama, Rachid Baati, Véronique Gouverneur, Alain Valleix, John R. Falck, and Charles Mioskowski*



1 halomon

The antitumor agent halomon (**1**) has generated enormous interest owing to its unique mode of action that allows it to display differential cytotoxicity against various tumor cell lines.[1] Details of its discovery and structural characterization have been reported;[2] however, further elucidation of its atypical biological activity has been hampered by the limited amount of naturally occuring halomon that can be extracted from the red alga *Portieria hornemannii* and by the synthetic challenge posed in creating such a polyhalogenated molecule. A total synthesis is, consequently, needed to establish the basis for generating a wide range of analogues to expedite the structure and activity assessment of this novel class of anticancer agents.

The clearest chemical challenge posed by a total synthesis of **1** is the fashioning of the chlorinated tertiary carbon atom C_3 bearing the α-chlorovinyl group. A further complication is the regiospecificity in the introduction of the bromine and chlorine atoms on C_6 and C7, respectively. Herein, we disclose the first total synthesis of halomon featuring as key steps two novel chemical transformations to address these synthetic problems.

Current methodologies for the construction of tertiary chlorinated carbons such as C_3 involve either β-elimination of

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[**] This work was financially supported by Rhône–Poulenc (fellowship to T.S.), National Institutes of Health (NIHGM.31278 to J.R.F.), and NATO (CRG.971096 to C.M.). We are grateful to Dr. M. Boyd of the National Cancer Institute for a generous gift of natural halomon.