$J = 8.8$ Hz), 6.74 – 6.82 (m, 2H), 6.22 (d, 1H, $J = 9.3$ Hz), 5.24 – 5.35 (m, 1H), 4.32 (dd, 1H, $J = 11.7$, 3.4 Hz), 3.97 – 4.15 (m, 2H), 4.10 (dd, 1H, $J =$ 11.7, 5.9 Hz), 2.05 – 2.16 (m, 2H), 2.05 (s, 6H). **4**: ^{1}H NMR (D_2O, 300 MHz): $\delta = 7.88$ (d, 1H, $J = 9.2$ Hz), 7.50 (d, 1H, $J = 8.5$ Hz), 6.96 – 6.91 (m, 2H), 6.23 (d, 1H, $J = 9.2$ Hz), 4.53 (m, 1H), 4.20 (m, 2H), 4.00 (m, 2H), 2.12 (m, 2H); ^{13}C NMR (D_2O/CD_3COCD_3, 75 MHz): $\delta = 164.6$, 163.2, 156.3, 146.8, 130.8, 114.6, 113.9, 112.9, 102.5, 66.0, 60.7, 58.2, 32.2; ^{31}P NMR (D_2O, 81 MHz): $\delta = 4.1$ (d, $J = 16.2$ Hz), 3.3 (d, $J = 16.2$ Hz); FAB-MS: 410 [M^+], 433 [$M + Na^+$]. All other new compounds gave satifsfactory spectral data.

All substrates and products prepared as 1 mM stock solutions in 50 % aq. acetonitrile. All reagents and buffers were prepared in deionized milliQ water. Enzymes were diluted from stock solutions (1 mg mL^{-1}) in phosphate buffer saline (PBS; 160 mM NaCl, 10 mM phosphate, pH 7.4), BSA from a stock solution (40 mg mL^{-1}) in buffer (20 mM borate, pH 8.8) or PBS. $NaIO_4$ was diluted from a freshly prepared stock solution in water (10 mM). Assays (0.1 – 0.2 mL) were followed in individual wells of round-bottom polypropylene 96-well plates (Costar) using a Cytofluor II Fluorescence Plate Reader (Perseptive Biosystems, filters $\lambda_{ex} = 360 \pm 20$, $\lambda_{em} = 460 \pm 20$ nm). Commercial enzyme preparations were purchased from Fluka or Sigma.

Received: April 20, 2000
Revised: June 19, 2000 [Z15020]

[1] a) D. C. Demirjian, P. C. Shah, F. Moris-Varas, *Top. Curr. Chem.* **1999**, *200*, 1; b) M. T. Reetz, K.-E. Jaeger, *Top. Curr. Chem.* **1999**, *200*, 31.
[2] a) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885; b) A. H. Hoveyda, *Chem. Biol.* **1998**, *5*, 187; c) A. Berkessel, D. A. Hérault, *Angew. Chem.* **1999**, *111*, 99; *Angew. Chem. Int. Ed.* **1999**, *38*, 102.
[3] a) W. P. C. Stemmer, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 10747; b) J. H. Zhang, G. Dawes, W. P. Stemmer, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 4509; c) A. Merz, M. C. Yee, H Szadkowski, G. Pappenberger, A. Crameri, W. P. Stemmer, C. Yanofsky, K. Kirschner, *Biochemistry* **2000**, *39*, 880.
[4] F. Taran, P. Y. Renard, C. Créminon, A. Valleix, Y. Frobert, P. Pradelles, J. Grassi, C. Mioskowski, *Tetrahedron Lett.* **1999**, *40*, 1887; F. Taran, P. Y. Renard, C. Créminon, A. Valleix, Y. Frobert, P. Pradelles, J. Grassi, C. Mioskowski, *Tetrahedron Lett.* **1999**, *40*, 1891, and references therein.
[5] a) S. J. Taylor, J. P. Morken, *Science* **1998**, *280*, 267; b) A. Holzwarth, H.-W. Schmidt, W. F. Maier, *Angew. Chem.* **1998**, *110*, 2788; *Angew. Chem. Int. Ed.* **1998**, *37*, 2647; c) M. T. Reetz, M. H. Becker, M. Liebl, A. Fürstner, *Angew. Chem.* **2000**, *112*, 1294; *Angew. Chem. Int. Ed.* **2000**, *39*, 1236.
[6] M. T. Reetz, M. H. Becker, H.-W. Klein, D. Stöckigt, *Angew. Chem.* **1999**, *111*, 1872; *Angew. Chem. Int. Ed.* **1999**, *38*, 1758.
[7] a) L. E. Janes, R. J. Kazlauskas, *J. Org. Chem.* **1997**, *62*, 4560; b) L. E. Janes, A. C. Löwendahl, R. J. Kazlauskas, *Chem. Eur. J.* **1998**, *4*, 2324; c) G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **1999**, *121*, 4306; d) P. Geymayer, N. Bahr, J.-L. Reymond, *Chem. Eur. J.* **1999**, *5*, 1006.
[8] FRET (fluorescence resonance energy transfer) substrates: a) E. D. Matayoshi, G. T. Wang, G. A. Krafft, J. Erickson, *Science* **1990**, *247*, 954; b) G. T. Wang, E. Matayoshi, H. J. Huffaker, G. A. Krafft, *Tetrahedron Lett.* **1990**, *31*, 6493; c) A. Berkessel, R. Riedl, *Angew. Chem.* **1997**, *109*, 1518; *Angew. Chem. Int. Ed. Engl.* **1997**, *109*, 1481; d) A. Jenne, W. Gmelin, N. Raffler, M. Famulok, *Angew. Chem.* **1999**, *111*, 1383; *Angew. Chem. Int. Ed.* **1999**, *38*, 1300.
[9] G. Klein, J.-L. Reymond, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1113.
[10] Related assay for aldolases: a) N. Jourdain, R. Pérez Carlón, J.-L. Reymond, *Tetrahedron Lett.* **1998**, *39*, 9415; b) R. Pérez Carlón, N. Jourdain, J.-L. Reymond, *Chem. Eur. J.*, in press.
[11] J. Fatiadi, *Synthesis* **1974**, 229.
[12] Assays for lipases: a) F. Beisson, A. Tiss, C. Rivière, R. Verger, *Eur. J. Lipid Sci. Technol.* **2000**, 133; b) F. Beisson, N. Ferté, J. Nari, G. Noat, V. Arondel, R. Verger, *J. Lipid Res.* **1999**, *40*, 2313.
[13] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[14] H. C. Kolb, K. B. Sharpless, *Tetrahedron* **1992**, *48*, 10515.
[15] M. Chini, P. Crotti, L. Favero, F. Macchia, M. Pineschi, *Tetrahedron Lett.* **1994**, *35*, 433.
[16] X-J. Chen, A. Archelas, R. Furstoss, *J. Org. Chem.* **1993**, *58*, 5528.
[17] C. A. G. M. Weijers, A. L. Botes, M. S. van Dyk, J. A. M. de Bont, *Tetrahedron: Asymmetry* **1998**, *9*, 467.
[18] Heat deactivation was tested with five of the most active lipases from *Pseudomonas* sp. type B, *Pseudomonas fluorescens*, *Chromobacterium viscosum*, *Aspergillus niger*, and pig pancreas. In all cases, there was no residual activity, as revealed by the assay with a racemic mixture of substrate **2b** after heat treatment (85 – 90 °C, 1 h).
[19] Nitrophenyl esters and other aryl esters can be hydrolyzed by heat-deactivated lipases and even by noncatalytic lipases fragments; see J. D. De Caro, P. Rouimi, M. Rovery, *Eur. J. Biochem.* **1986**, *158*, 601 and also ref. [7].
[20] The stability of our substrates in the presence of BSA (2 mg mL^{-1}) illustrates their resistance to nonspecific catalysis. Amide **1** and phosphate **4** show no detectable hydrolysis upon heat treatment (80 °C, 10 min. in aq. phosphate (20 mM, pH 7.2) or aq. borate buffers (20 mM, pH 8.8)). Under the same conditions, the hydrolysis to **5** is 0 % (pH 7.2) and 3 % (pH 8.8) for diacetate **2a**, 3 % (pH 7.2) and 24 % (pH 8.8) for mono-acetate **2b**, and 9 % (pH 7.2) and 7 % (pH 8.8) for epoxide **3**.
[21] G. Klein, J.-L. Reymond, *Helv. Chim. Acta* **1999**, *82*, 400.

Formation of a Giant Supramolecular Porphyrin Array by Self-Coordination**

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Methodologies for the preparation of multi-porphyrin arrays[1–5] have been exploited to successfully assemble arrays of more than ten porphyrins.[6] The formation of extremely long porphyrin arrays by supramolecular coordination[7] and by covalently linking[8] porphyrins have recently been reported. We have been trying to extend our previous methodology of self-coordination[9] and we report here a giant multi-porphyrin array formed by the accumulation of dimeric imidazolyl-substituted Zn porphyrins. These systems should have the excellent photophysical properties of a chlorophyll substitute and enable the transfer of excitation energy to be studied.

Meso-(*N*-methyl)imidazolylporphyrinatozinc compounds such as **1b** afforded quantitatively a dimer of a slipped cofacial orientation **2** by the complementary coordination of an imidazolyl group to the Zn^{II} center (Scheme 1).[9] The coordination was very strong, but the pentacoordinating Zn^{II} ion prohibited further extension of the coordination structure.

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[**] This work was supported by Grant-in-Aids for Scientific Research (Nos. 10129210 and 11133240, "Creation of Characteristic Delocalized Electronic Systems", to Y.K.) from the Ministry of Education, Science, Sports, and Culture of Japan.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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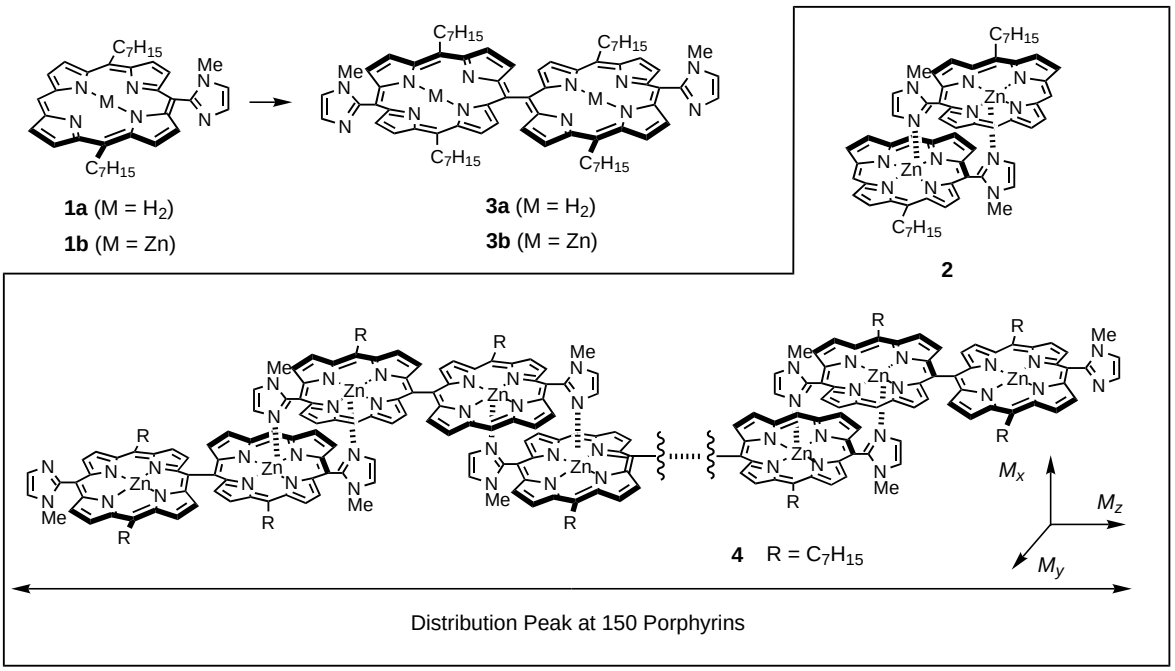

Scheme 1. Synthetic route and structures of self-assembled porphyrins. (Compounds **1b** and **3b** exist in $CHCl_3$ as **2** and **4**, respectively.)

In order to extend this methodology to obtain higher supramolecules we have prepared mono(*N*-methylimidazolyl)-bis(*n*-heptyl)porphyrin (**1a**) and its Zn complex (**1b**) having one unsubstituted *meso* carbon atom. The coupling of **1b**, which exists as **2** in solution, at the *meso* position afforded the interconnected porphyrinatozinc(II) compound **3b**. Linear multi-porphyrin array **4** was thus obtained by independent complementary coordination at each imidazolylporphyrin unit, with an orthogonal orientation of the π-orbital planes of **3b**.[10]

Molecular weights of the resulting supramolecular porphyrin complexes were analyzed by using gel-permeation chromatography (GPC; Figure 1). The exclusion limit of the column was 5×10^5 daltons. Elution of **4** started at 8.4 min and the peak maximum appeared at 11.6 min. The molecular weights at these two points were determined as 5×10^5 and 1×10^5, respectively, by using polystyrene standards to give a rough estimate. These masses correspond to the link of about 400 and 80 bis(imidazolylporphyrin) units ($M_r = 1298$) through imidazolyl–Zn coordination bonds. The molecular length of the repeating unit has been estimated as 1.43 nm by molecular mechanics calculation using the Cerius 2 program, and hence the length of the porphyrin array reaches 550 nm and 110 nm for the longest and the most abundant species, respectively. It is noteworthy that multi-porphyrin arrays of such huge molecular weights are soluble in chloroform.

Figure 2 compares the absorption spectrum of **4** (7.7×10^{-7} M as **3b**) with those of free base **3a** and Zn complex **2**

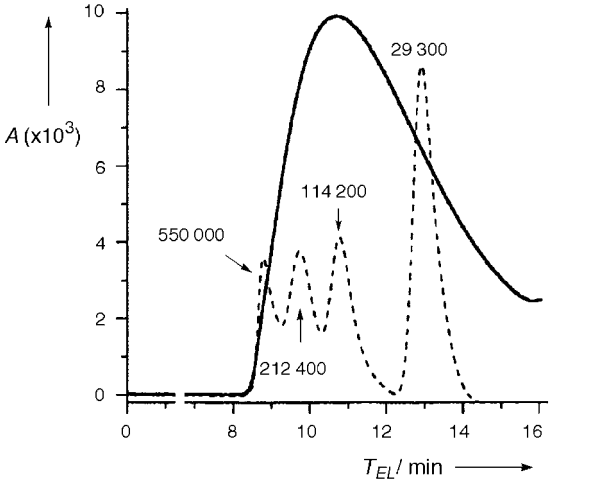

Figure 1. Gel-permeation chromatograms of **4** (bold line) and standard polystyrene mixtures (dotted line, the numbers indicate molecular weights) with a column of exclusion limit 5×10^5 daltons. The eluent is EtOH-free $CHCl_3$. T_{EL} = elution time.

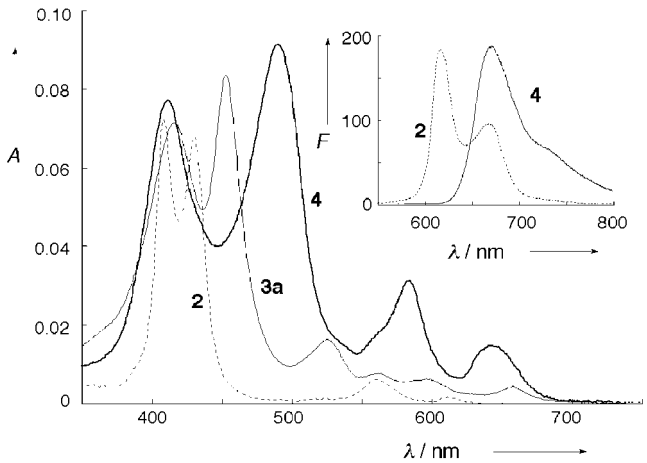

Figure 2. Absorption and fluorescence (inset) spectra in chroloform of imidazolylporphyrinatozinc **2** (dashed line), bis(imidazolylporphyrin) **3a** (thin line), and bis(imidazolylporphyrinatozinc) array **4** (bold line, 7.7×10^{-7} M as **3b**).

in chloroform. The Soret band of the free base **1a** appeared as a single peak at 414 nm and those of the *meso*–*meso*-coupled dimer species were split into twin peaks at 415 and 453 nm for free base **3a** and 410 and 492 nm for the Zn complex **4**. Three in-plane transition moments M_x, M_y, and M_z in the monomeric porphyrin are degenerate when the *meso*-substituent effect is neglected, and show a single Soret band, which appears at 414 nm for **1a**. *Meso*–*meso* coupling to the dimeric free base **3a** induces a red shift of M_z through the interaction of parallel excitons, while no interactions are expected for M_x and M_y as a result of the orthogonality. As a result, the Soret band is split into two: 415 nm for the M_x and M_y components and 453 nm for the M_z component. Coordination to form **4** then gives a blue shift of the transition to 410 nm as a result of the face to face orientation[9] in M_x and M_y. No M_x-M_x or M_y-M_y interaction is expected because of the presence of an intervening orthogonal porphyrin plane, and therefore the blue shift is small and independent of the degree of organization. In contrast, the M_z component could interact successively with that of the neighboring porphyrin unit, depending on the degree of coordination. These interactions resulted in a splitting of the Soret band by 82 nm. The shift behavior is compatible with the observation that the longer Soret bands of the covalently linked di-, tri-, and tetramer of zinc porphyrin are red-shifted from 410 nm for the monomer in THF to 450, 480, and 490 nm, respectively.[11] The effect of concentration on the degree of organization was examined in the range 5.0×10^{-9}–2.2×10^{-4} M. The Soret band at longer wavelength, the most sensitive to the degree of organization, remained constant at 492 nm. The complementary coordination is therefore concluded to be complete at concentrations as low as 5.0×10^{-9} M. The fluorescence emission bands of **4** (shown in the inset of Figure 2) were considerably red-shifted (to 672 nm) by exciton interactions, while the band for the smallest complex **2** is observed at 613 nm. The fluorescence quantum yields of solutions of **2** and **4** in benzene were estimated as 0.043 and 0.053, respectively. It is interesting from a viewpoint of materials capable of light harvesting that the fluorescence intensity of **4** with such a long array structure is not lost at all, but is even higher than that of **2**.

The above-mentioned multi-porphyrin array having such a huge molecular weight was obtained in an EtOH-free chloroform solution. Addition of methanol to a solution of **4** in chloroform (9.9×10^{-7} M) reduced the splitting width of the Soret band as a result of a blue shift of the longer Soret band (M_z transition), which passes through a clear isosbestic point at 478 nm, and a smaller red shift of the shorter Soret band. The addition of 30 vol % of MeOH resulted in the shift almost reaching the saturation point, where the splitting of 41 nm was similar to that of **3a** and shows that the coordinate structure was completely broken. The fluorescence spectra showed similar solvent effects on both the intensity and the emission maximum. These results show that MeOH competes with the imidazolyl group for coordination to the Zn center and can control the degree of organization.

A mixture of **2** and **4** in a 1:5 molar ratio in ethanol-free chloroform was analyzed by GPC by using a column with an exclusion limit of 7×10^4 daltons to separate smaller components (Figure 3, thin line). Only two peaks, one starting at

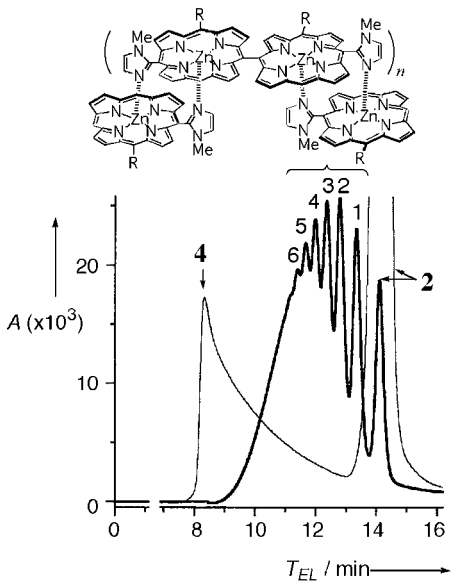

Figure 3. Gel-permeation chromatograms of a mixture of **4** and **2** in a 5:1 molar ratio (thin line) and the same sample mixture first dissolved in $CHCl_3$:MeOH (1:1), then evaporated, and re-dissolved in EtOH-free $CHCl_3$ (bold line). The exclusion limit of the column is 7×10^4 daltons (8 min). The eluent is EtOH-free $CHCl_3$. T_{EL} = elution time.

8 min (exclusion limit, **4**) and the other at 14 min (**2**), were detected a few minutes after the mixing. The same sample mixture was dissolved in a chloroform:methanol (1:1) solution, followed by evaporation. The sample was then dissolved in chloroform and subjected to GPC analysis (Figure 3, bold line). Many peaks of intermediate retention times then appeared and a significant shift of the distribution maximum to a lower molecular weight was evident. The peak at the longest retention time (14 min) corresponds to **2**, and peaks at shorter retention times (marked by number n; $n=1$–6) were assigned as a series of compounds in which n units of **3b** are inserted between **1b** terminals. The shift in the longer wavelength part of the split Soret bands was dependent on the intervening number of **3b** units, which is in full accord with progressing exciton interactions (see Supporting Information). The results clearly demonstrate that the coordination-organized supramolecules can scramble in a mixed solvent of chloroform and methanol but cannot in ethanol-free chloroform, which is in accord with the UV titration data, and more importantly that the organization can also be controlled by the addition of an appropriate terminator such as **1b**. The molecular weights of porphyrin oligomers with $n=1$–6 (Figure 3) was compared with those calibrated from retention times of polystyrene standards. The calculated molecular weights of porphyrin oligomers were about 1.3 times larger than the estimates and therefore the molecular weights of the porphyrin arrays described as a rough estimate in the earlier part of this paper were found to be even lower estimates.

The one-dimensional propagation of the multi-porphyrin array up to a few hundred nanometers in length with close inter-element distances and in which a reversible adjustment of length equilibrium can be achieved by either changing the media or the addition of a chain terminator are characteristics most desirable for forming molecular photonics and elec-

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tronics devices.[12] Applications toward artificial photosynthesis and nonlinear optics materials are under active investigation.

Received: May 29, 2000
Revised: August 22, 2000 [Z15194]

[1] D. Gust, T. A. Moore in *The Porphyrin Handbook*, *Vol. 8* (Eds.: K. Kadish, K. M. Smith, R. Guilard), Academic Press, New York, **1999**, chap. 57, p. 153.
[2] C.-T. Chen in *Comprehensive Supramolecular Chemistry*, *Vol. 5* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, New York, **1996**, chap. 4, p. 91.
[3] J. K. M. Sanders in *Comprehensive Supramolecular Chemistry*, *Vol. 9* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, New York, **1996**, chap. 4, p. 131.
[4] a) R. W. Wagner, J. S. Lindsey, *J. Am. Chem. Soc.* **1994**, *116*, 9759; b) R. W. Wagner, J. S. Lindsey, J. Seth, V. Palaniappan, D. F. Bocian, *J. Am. Chem. Soc.* **1996**, *118*, 3996.
[5] H. L. Anderson, *Chem. Commun.* **1999**, 2323.
[6] a) H. L. Anderson, S. J. Martin, D. D. C. Bradley, *Angew. Chem.* **1994**, *106*, 711; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 655; b) P. N. Taylor, H. L. Anderson, *J. Am. Chem. Soc.* **1999**, *121*, 11538; c) A. Nakano, A. Osuka, I. Yamazaki, T. Yamazaki, Y. Nishimura, *Angew. Chem.* **1998**, *110*, 3172; *Angew. Chem. Int. Ed.* **1998**, *37*, 3023; d) K. Sugiura, H. Tanaka, T. Matsumoto, T. Kawai, Y. Sakata, *Chem. Lett.* **1999**, 1193; e) C. C. Mak, N. Bampos, J. K. M. Sanders, *Chem. Commun.* **1999**, 1085; f) L. Ruhlmann, A. Schulz, A. Giraudeau, C. Messerschmidt, J.-H. Fuhrhop, *J. Am. Chem. Soc.* **1999**, *121*, 6664.
[7] U. Michelsen, C. A. Hunter, *Angew. Chem.* **2000**, *112*, 780; *Angew. Chem. Int. Ed.* **2000**, *39*, 764.
[8] N. Aratani, A. Osuka, Y. H. Kim, D. H. Jeong, D. Kim, *Angew. Chem.* **2000**, *112*, 1517; *Angew. Chem. Int. Ed.* **2000**, *39*, 1458.
[9] Y. Kobuke, H. Miyaji, *J. Am. Chem. Soc.* **1994**, *116*, 4111.
[10] The compounds numbered as **1b** and **3b** correspond essentially compounds **2** and **4**, respectively. The former numbers are used when monomer units are discussed. However, these exist as an assembled dimer for **2** and a polymer for **4** in nonpolar solvents.
[11] A. Osuka, H. Shimidzu, *Angew. Chem.* **1997**, *109*, 93; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 135.
[12] *Molecular Electronic Devices II* (Ed.: F. L. Carter), Marcel Dekker, New York, **1987**.

Enantioselective Total Synthesis of (+)-Gelsemine: Determination of Its Absolute Configuration**

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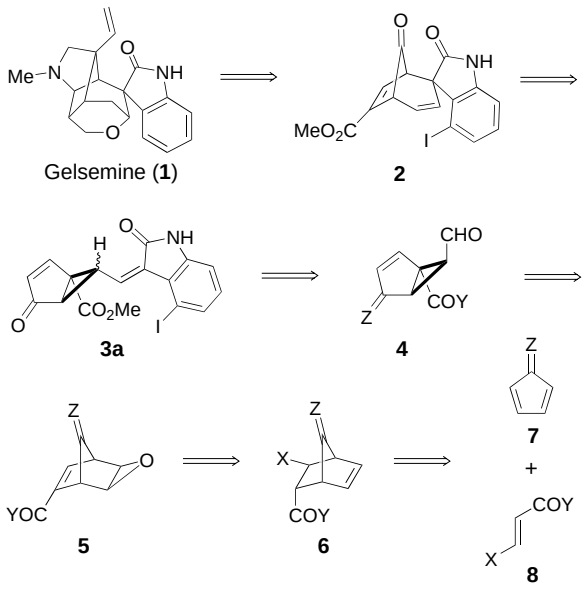
Since the structure of gelsemine (**1**) was determined in 1959, many efforts have been directed toward total synthesis of this unique hexacyclic cage-like molecule.[1] While three groups independently accomplished the total synthesis of racemic gelsemine in 1994, none of them succeeded in controlling the stereochemistry of the critical spiroindolinone system.[2] In 1996, our own approach culminated in the completely stereocontrolled total synthesis of (±)-gelsemine featuring a divinylcyclopropane rearrangement to control the stereochemistry of the spiroindolinone system.[3] Despite these intensive studies, an enantioselective total synthesis of gelsemine has not been reported to date.[4] Herein, we disclose the first enantioselective total synthesis of (+)-gelsemine.

Our retrosynthetic analysis of optically active gelsemine is illustrated in Scheme 1. According to our racemic synthesis, the stereochemistry of the spiroindolinone system could be



Scheme 1. Retrosynthesis of gelsemine.

controlled by thermal rearrangement of the key intermediate **3a**, which should be prepared easily by condensation of aldehyde **4** and 4-iodooxindole. The aldehyde **4** could in turn be derived from norbornene epoxide **5** according to the rearrangement reported by Meinwald et al.[5] It seems quite likely that **5** could be prepared from Diels–Alder adduct **6**.

Our enantioselective total synthesis of gelsemine commenced with a chiral auxiliary controlled asymmetric Diels–Alder reaction. In the presence of Et_2AlCl, the Diels–Alder reaction between dienophile **9** and 5-dimethylsilylcyclopentadiene (**10**)[6] proceeded smoothly to give adduct **11** as a single isomer (Scheme 2).[7] The relative and absolute configurations of the adduct were determined by X-ray analysis, based on the configuration of the Evans chiral auxiliary derived from L-phenylalanine.[8] The chiral auxiliary was removed by treatment with $Sm(OTf)_3$ in MeOH to afford methyl ester **12**.[9] Oxidation of the dimethylsilyl group in **12** with H_2O_2 in the presence of KF to provide alcohol **13**,[6, 10] followed by epoxidation with *t*BuOOH and $VO(acac)_2$, gave epoxide **14**.[11] After protection of the alcohol as the TES ether, dehydrochlorination by treatment with *t*BuOK furnished α,β-unsaturated ester **15**.

After extensive optimization of the acid-catalyzed rearrangement of **15**, we found that the critical rearrangement

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[**] This work was supported in part by the Ministry of Education, Sports, and Culture, Japan. S.Y. thanks the JSPS for a predoctoral fellowship.