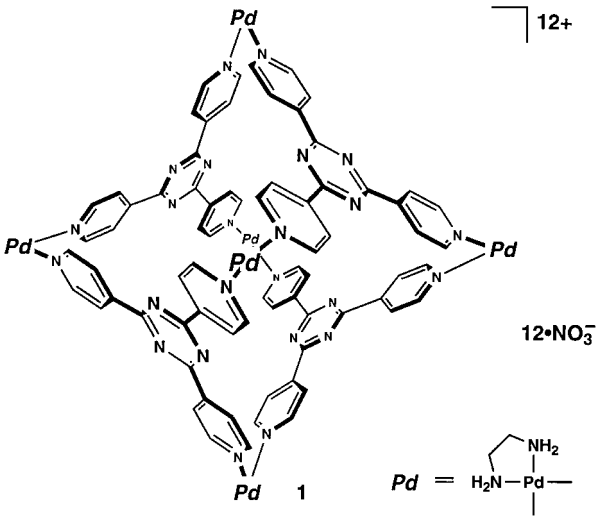
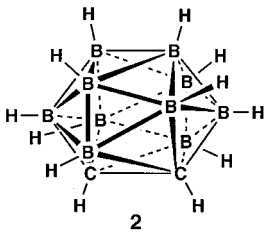
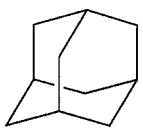
Encapsulation of Large, Neutral Molecules in a Self-Assembled Nanocage Incorporating Six Palladium(II) Ions**

Takahiro Kusukawa and Makoto Fujita*

Properties of molecules significantly change when they are encapsulated in cage compounds having functional groups in the interior space at fixed positions.[1–4] The cage compounds typically prepared by conventional covalent synthesis can encapsulate only one or two small molecules because the construction of larger cage frameworks is very difficult.[5–7] In contrast, noncovalent synthesis has been providing large cagelike structures quite efficiently. That is, hydrogen-bonded[8–11] and coordination-bonded[12] molecular capsules with large frameworks have been prepared by self-assembly. Recently, coordination cage **1** with a diameter of approximately 2 nm was constructed through transition metal mediated self-assembly from six metal ions and four ligands.[13, 14] We report herein on the remarkable ability of this complex to encapsulate large, neutral molecules.







[*] Prof. Dr. M. Fujita, Dr. T. Kusukawa
CREST, Japan Science and Technology Corporation (JST)
Coordination Chemistry Laboratories
Institute for Molecular Science
Myodaiji, Okazaki 444–8585 (Japan)
Fax: (+81) 564-555-245
E-mail: mfujita@ims.ac.jp

[**] This work was supported by the CREST (Core Research for Evolutional Science and Technology) project of the Japan Science and Technology Corporation.

We observed the remarkable ability of **1** to encapsulate large molecules in its inclusion of four molecules of *o*-carborane (**2**), an icosahedral carbon–boron cage molecule with a diameter of 8 Å.[15, 16] This large, neutral molecule is nonpolar and immiscible in water. However, when a hexane solution of **2** (10 mM, 5 mL) was stirred with a D_2O solution of **1** (5 mM, 1 mL, **2**:**1** = 10:1), four equivalents of **2** were rapidly transferred into the aqueous phase and the stoichiometric formation of $\mathbf{1}\cdot(\mathbf{2})_4$ complex was observed (Figure 1c). The

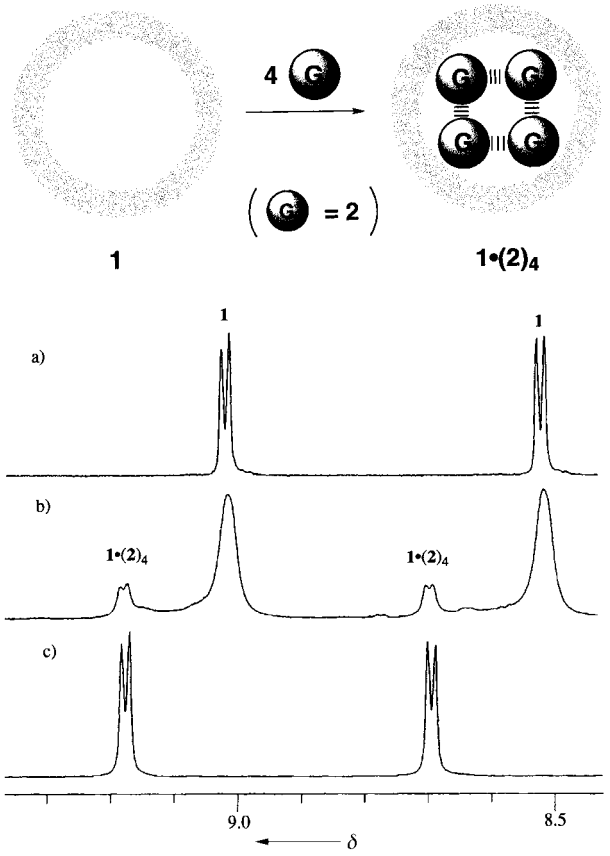


Figure 1. NMR observation of the encapsulation of *o*-carborane (**2**) in nanocage **1**. a) Empty **1**. b), c) A D_2O solution of **1** (5 mM, 1 mL) was treated with a hexane solution of **2** [10 mM; 0.5 mL (b), 5 mL (c)].

encapsulation of **2** in the cage of **1** was supported by the significant upfield shifting of δ_H signals of **2** appearing at $\delta =$ 1.3 to −0.3.[17] The 1:4 stoichiometry was confirmed by the integration ratio of signals of **1** and **2** in the ^1H NMR spectrum. Even when only one equivalent of **2** was employed (**2**: 10 mM, 0.5 mL; **1**: 5 mM, 1 mL), 82% of **2** was effectively transferred into the aqueous phase and complexed with **1** to give the $\mathbf{1}\cdot(\mathbf{2})_4$ complex in roughly 20% yield (or ca. 80% based on **2**, Figure 1b).[18] Surprisingly, a strong cooperative effect was observed in this complexation: that is, no intermediary complexes $\mathbf{1}\cdot(\mathbf{2})_n$ ($n = 1-3$) were observed.

Adamantane (**3**) was also encapsulated by **1** to form a 1:4 complex. Again, a D_2O solution of **1** (2 mM) was stirred with a saturated hexane solution of **3** at 60 °C. While the encapsulation of **2** by **1** was a rapid process, the transfer of **3** from hexane into water phase was slow (ca. 30 min until completion), and this process was clearly monitored by time-

  1433-7851/98/3722-3142 $ 17.50+.50/0

dependent NMR measurement (Figure 2). The high upfield shift of ^{1}H NMR signals of **3** ($\Delta\delta = -0.4$ to -2.2) was consistent with the encapsulation in the cavity lined by

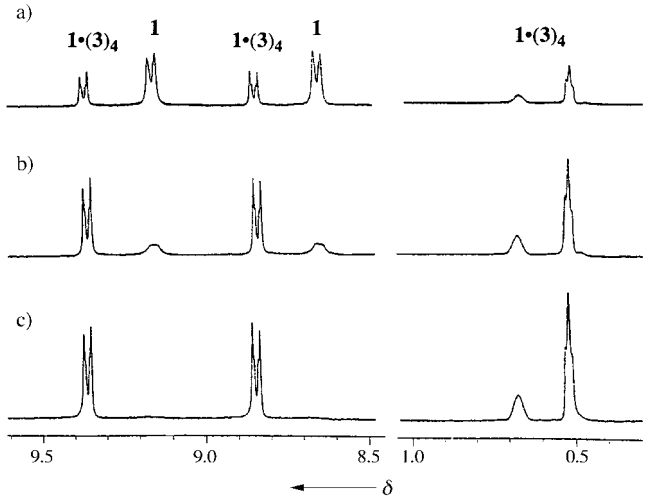


Figure 2. NMR observation of the formation of the $\mathbf{1}\cdot(\mathbf{3})_4$ complex from an aqueous solution of **1** and a saturated hexane solution of **3** at 60 °C after a) 1 min, b) 5 min, and c) 30 min.

aromatic rings. Again, intermediary complexes $\mathbf{1}\cdot(\mathbf{3})_n$ ($n = 1-3$) were not observed. More surprisingly, adamantane was transferred into the aqueous phase even in a solid–liquid two-phase system. Thus, the high-yield formation of $\mathbf{1}\cdot(\mathbf{3})_4$ (>95%) was observed when powdered **3** (excess amount) was suspended in a D_2O solution of **1** at 60 °C for four days.

The inclusion geometry of the guest molecules is particularly interesting. When 1- or 2-adamantanol (**4** or **5**, respectively) was employed as a guest, the formation of a stable 1:4 complex was again observed. Careful NMR analysis[19] of this complex showed that the signals of the hydrophobic moieties were shifted significantly upfield while those of the hydrophilic moiety were not (Figure 3). This result shows that the interior of host **1** is highly hydrophobic and the guest molecule is located in the cage such that the hydroxyl group is pointed outward.

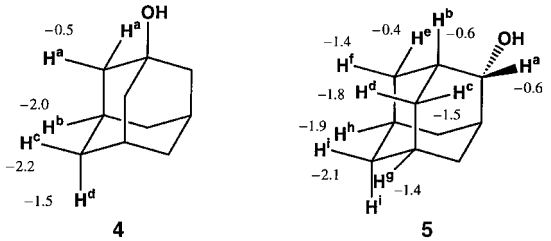
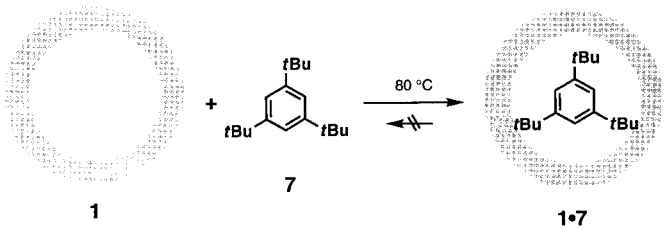


Figure 3. Change in the NMR chemical shifts of adamantanol guests **4** and **5** upon inclusion in **1**. Negative values indicate upfield shift values ($\Delta\delta$ in ppm).

Significant π-donor–acceptor interactions were observed when 1,3,5-trimethoxybenzene (**6**) was employed as a guest. Upon the addition of this aromatic guest, the solution turned yellow immediately and the 1:4 complex ($\mathbf{1}\cdot(\mathbf{6})_4$) formed quantitatively. The very large upfield shift ($\Delta\delta = -2.0$) of Ar*H* of **6** strongly supports an efficient aromatic stacking between guest **6** and the interior face of host **1**. Anisole behaved similarly as a guest, but addition of toluene, which is moderately electron-rich, did not lead to a significant color change although a 1:4 complex formed. In striking contrast, electron-deficient 1,4-dibromo-, 1,3,5-tribromo-, and perfluorobenzene were not complexed by **1** at all. These result clearly shows that the interior of the nanocage creates not only a hydrophobic but also an electrophilic microspace with properties quite different from those of the bulk phase.

It is also noteworthy that the complexation is much faster when the guest molecules are smaller. With such small guests as toluene or methoxy-substituted benzenes, the proton signals of both free **1** and the $\mathbf{1}\cdot(\mathbf{G})_4$ complex ($\mathbf{G}$ = guest) were completely averaged due to the rapid exchange on the NMR time scale.[20]

Particularly interesting is that tri-*tert*-butylbenzene (**7**), which is slightly larger than the portal of **1**,[21] is very slowly encapsulated by the cage through thermally induced slippage. Thus when a D_2O solution of **1** was stirred with a hexane



solution of **7** at 80 °C, the 1:1 complex **1**·**7** formed in approximately 40% yield after 2 h ($\Delta\delta = -1.5$ (*t*Bu), -2.5 (Ar*H*)). However, encapsulation and decapsulation become very slow at room temperature. Thus, once encapsulated, guest **7** did not escape from the cavity of **1** within two hours at room temperature even when the solution was treated with an organic solvent.

Experimental Section

Typical procedure: A hexane solution of *o*-carborane **2** (10.6 mM, 1 mL) was stirred with a D_2O solution of **1** (42.4 mM, 1 mL) for 3 h. The NMR spectrum of the aqueous phase showed the stoichiometric formation of the $\mathbf{1}\cdot(\mathbf{2})_4$ complex. $\mathbf{1}\cdot(\mathbf{2})_4$: ^{1}H NMR (500 MHz, D_2O): $\delta = 9.18$ (d, $J = 6.6$ Hz, 24H, Py Hα), 8.69 (d, $J = 6.6$ Hz, 24H, Py Hβ), 3.43 (s, 8H, carborane CH), 2.85 (s, 24H, -NCH_2CH_2N-), 1.3 to −0.3 (m, 40H, carborane BH); ^{13}C NMR (125 MHz, D_2O): $\delta = 170.1$ (Cq), 153.1 (CH), 145.6 (Cq), 126.6 (CH), 55.7 (carborane CH), 47.7 (CH_2).

$\mathbf{1}\cdot(\mathbf{3})_4$: ^{1}H NMR (500 MHz, D_2O): $\delta = 9.28$ (d, $J = 6.6$ Hz, 24H, Py Hα), 8.75 (d, $J = 6.6$ Hz, 24H, Py Hβ), 2.91 (s, 24H, -NCH_2CH_2N-), 0.59 (br s, 16H, adamantane CH) 0.44 (br s, 48H, adamantane CH_2); ^{13}C NMR (125 MHz, D_2O): $\delta = 170.0$ (Cq), 153.3 (CH), 145.3 (Cq), 126.0 (CH), 47.7 (CH_2), 37.3 (adamantane CH_2), 28.1 (adamantane CH).

$\mathbf{1}\cdot(\mathbf{4})_4$: ^{1}H NMR (500 MHz, D_2O): $\delta = 9.38$ (d, $J = 6.9$ Hz, 24H, Py Hα), 8.87 (d, $J = 6.9$ Hz, 24H, Py Hβ), 2.99 (s, 24H, -NCH_2CH_2N-), 1.24 (s, 24H, 1-adamantanol CH_2), 0.18 (s, 12H, 1-adamantanol CH), 0.12 (d, 12H, 1-adamantanol CH_2), −0.56 (d, 12H, 1-adamantanol CH_2); ^{13}C NMR (125 MHz, D_2O): $\delta = 170.2$ (Cq), 153.5 (CH), 145.2 (Cq), 126.1 (CH), 47.8 (CH_2), 44.5 (1-adamantanol CH_2), 35.8 (1-adamantanol CH_2), 30.5 (1-adamantanol CH).

$\mathbf{1}\cdot(\mathbf{5})_4$: ^{1}H NMR (500 MHz, D_2O): $\delta = 9.36$ (d, $J = 6.9$ Hz, 24H, Py Hα), 8.81 (d, $J = 6.9$ Hz, 24H, Py Hβ), 3.23 (s, 4H, 2-adamantanol CH), 2.99 (s, 24H, -NCH_2CH_2N-), 1.64 (d, 8H, $J = 12.5$ Hz, 2-adamantanol CH_2), 1.33 (s,

  1433-7851/98/3722-3143 $ 17.50+.50/0

8H, 2-adamantanol CH), 0.45 (s, 4H, 2-adamantanol CH), 0.24 (d, 8H, J = 12.5 Hz, 2-adamantanol CH_2), 0.10 (d, 8H, J = 12.5 Hz, 2-adamantanol CH_2), 0.06 (d, 8H, J = 12.5 Hz, 2-adamantanol CH_2), −0.10 (s, 4H, 2-adamantanol CH), −0.43 (s, 8H, 2-adamantanol CH_2); ^{13}C NMR (125 MHz, D_2O): δ = 170.1 (Cq), 153.4 (CH), 145.2 (Cq), 126.0 (CH), 74.0 (2-adamantanol CH), 47.8 (CH_2), 37.2 (2-adamantanol CH_2), 36.1 (2-adamantanol CH_2), 31.0 (2-adamantanol CH_2), 27.3 (2-adamantanol CH), 26.8 (2-adamantanol CH).

1·(**6**)$_4$: ^{1}H NMR (500 MHz, D_2O): δ = 9.29 (d, J = 6.6 Hz, 24H, Py Hα), 8.65 (d, J = 6.6 Hz, 24H, Py Hβ), 4.09 (s, 12H, trimethoxybenzene CH), 2.98 (s, 24H, -NCH_2CH_2N-), 2.43 (br s, 36H, CH_3O); ^{13}C NMR (125 MHz, D_2O): δ = 169.9 (Cq), 160.6 (trimethoxybenzene Cq), 153.3 (CH) 145.9 (Cq), 126.2 (CH), 92.0 (trimethoxybenzene CH), 54.5 (CH_3O) 47.8 (-NCH_2CH_2N-).

1·**7**: ^{1}H NMR (500 MHz, D_2O): δ = 9.28 (br s, 24H, Py Hα), 8.72 (br s, 24H, Py Hβ), 4.8 (s, 3H, **7** Ar CH), 2.99 (s, 24H, -NCH_2CH_2N-), −0.12 (s, 27H, *t*Bu); ^{13}C NMR (125 MHz, D_2O): δ = 170.1 (Cq), 153.3 (CH) 149.0 (**7** Ar Cq), 146.3 (Cq), 126.0 (CH), 47.8 (-NCH_2CH_2N-), 33.8 (*t*Bu Cq), 30.4 (*t*Bu CH_3).

Received: June 2, 1998 [Z11936IE]
German version: *Angew. Chem.* **1998**, *110*, 3327 – 3329

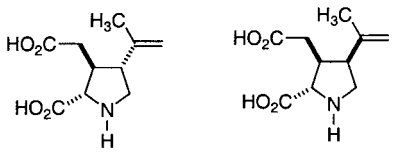
Keywords: adamantanes · boron · clusters · molecular recognition · palladium

[1] a) D. J. Cram, *Nature* **1992**, *356*, 29 – 36; b) D. J. Cram, M. T. Tanner, R. Thomas, *Angew. Chem.* **1991**, *103*, 1048 – 1051; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024 – 1027.
[2] a) R. Warmuth, *Angew. Chem.* **1997**, *109*, 1406 – 1409; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1347 – 1350; b) R. Warmuth, *J. Chem. Soc. Chem. Commun.* **1995**, 59 – 60.
[3] J. Kang, J. Rebek, Jr., *Nature* **1997**, *385*, 50 – 52.
[4] S. Watanabe, K. Goto, T. Kawashima, R. Okazaki, *J. Am. Chem. Soc.* **1997**, *119*, 3195 – 3196.
[5] a) J. Yoon, D. J. Cram, *J. Am. Chem. Soc.* **1997**, *119*, 11796 – 11806; b) J. Yoon, D. J. Cram, *Chem. Commun.* **1997**, 497 – 498; c) J. Yoon, D. J. Cram, *Chem. Commun.* **1997**, 2065 – 2066; d) R. C. Helgeson, K. Paek, C. B. Knobler, E. F. Maverick, D. J. Cram, *J. Am. Chem. Soc.* **1993**, *115*, 10111 – 10116.
[6] a) P. Timmerman, W. Verboom, F. C. J. M. van Veggel, J. P. M. van Duynhoven, D. N. Reinhoudt, *Angew. Chem.* **1994**, *106*, 2437 – 2440; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2345 – 2348; b) B.-H. Huisman, D. M. Rudkevich, F. C. M. van Veggel, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1996**, *118*, 3523 – 3524.
[7] J. R. Fraser, B. Borecka, J. Trotter, J. C. Sherman, *J. Org. Chem.* **1995**, *60*, 1207 – 1213.
[8] C. Sheu, K. N. Houk, *J. Am. Chem. Soc.* **1996**, *118*, 8056 – 8070.
[9] a) R. S. Meissner, J. Rebek, Jr., J. de Mendoza, *Science* **1995**, *270*, 1485 – 1488; b) N. Branda, R. Wyler, J. Rebek, Jr. *Science* **1994**, *263*, 1267 – 1268; c) R. Meissner, X. Garcias, S. Mecozzi, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 77 – 85; c) B. C. Hamann, K. D. Shimizu, J. Rebek, Jr., *Angew. Chem.* **1996**, *108*, 1425 – 1427; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1326 – 1329.
[10] L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469 – 472.
[11] a) J. Scheerder, R. H. Vreekamp, J. F. Engbersen, W. Verboom, J. P. M. van Duynhoven, D. N. Reinhoudt, *J. Org. Chem.* **1996**, *61*, 3476 – 3481; b) R. H. Vreekamp, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1996**, *61*, 4282 – 4288.
[12] Self-assembled cage compounds containing metals: a) R. W. Saalfrank, A. Stark, K. Peters, H. G. von Schnering, *Angew. Chem.* **1988**, *100*, 878 – 880; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 851 – 853; b) P. Baxter, J.-M. Lehn, A. DeCian, J. Fischer, *Angew. Chem.* **1993**, *105*, 92 – 95; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 69 – 72; c) S. Mann, G. Huttner, L. Zsolnai, K. Heinze, *Angew. Chem.* **1996**, *108*, 2983 – 2984; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2808 – 2809; d) P. Jacopozzi, E. Dalcanale, *Angew. Chem.* **1997**, *109*, 665 – 667; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 613 – 615; e) C. M. Hartshorn, P. J. Steel, *Chem. Commun.* **1997**, 541 – 542. f) T. Beissel, R. E. Powers, K. N. Raymond, *Angew. Chem.* **1996**, *108*, 1166 – 1168; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1084 – 1086. g) T. N. Parac, D. L. Caulder, K. N. Raymond, *J. Am. Chem. Soc.* **1998**, *120*, 8003 – 8004, and references therein.
[13] a) M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi, K. Ogura, *Nature* **1995**, *378*, 469 – 471; b) A closely related complex: P. J. Stang, B. Olenyuk, D. C. Muddiman, R. D. Smith, *Organometallics* **1997**, *119*, 3094 – 3096.
[14] Guest-templated synthesis of a stable Pt^{II} derivative of **1**: F. Ibukuro, T. Kusukawa, M. Fujita, *J. Am. Chem. Soc.* **1998**, *120*, 8561 – 8562.
[15] *o*-Carborane – azacrown ether (1:1) complex has been reported: P. D. Godfrey, W. J. Grigsby, P. J. Nichols, C. L. Raston, *J. Am. Chem. Soc.* **1997**, *119*, 9283 – 9284.
[16] R. J. Blanch, M. W. Williams, G. D. Fallon, M. G. Gardiner, R. Kaddour, C. L. Raston, *Angew. Chem.* **1997**, *109*, 520 – 522; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 504 – 505.
[17] In contrast, CH signal of carborane does not shift significantly implying the inclusion geometry with electronegative BH groups located inside and electropositive CH groups located outside. Four guest molecules are likely to reside in tetrahedral positions around the center of the cage, directed away from the octahedrally positioned Pd^{II} centers. See the X-ray structure of **1**·(**G**)$_4$ (**G** = adamantanecarboxylate) reported in ref.[13]
[18] The broadening of the signals is probably due to a slow exchange on the NMR time scale between the free and complexed host.
[19] The assignment of the signals was confirmed by H – H COSY, C – H COSY, NOESY, H – C HMBC.
[20] The 1:4 stoichiometry was estimated by the Job plot method.
[21] Force-field calculation clearly shows that tri-*tert*-butylbenzene is slightly larger than the portals of **1**.

Nickel and Palladium Catalysis in the Stereoselective Synthesis of Functionalized Pyrrolidines: Enantioselective Formal Synthesis of (+)-α-Allokainic Acid

Maxim V. Chevliakov and John Montgomery*

(+)-α-Allokainic acid and (−)-α-kainic acid are representative members of the kainoid family of neuroexcitatory amino acids whose biological activity has been attributed to their action as conformationally restricted analogues of glutamate (Scheme 1).[1] Extensive structure – activity studies have demonstrated that the C-4 isopropenyl substituent is the



(+)-α-allokainic acid (−)-α-kainic acid

Scheme 1. Kainoid natural products.

[*] Prof. J. Montgomery, M. V. Chevliakov
Department of Chemistry,
Wayne State University
Detroit, MI 48202-3489 (USA)
Fax: (+1) 313-577-1377
E-mail: jwm@chem.wayne.edu

[**] This work was supported by the National Institutes of Health. J.M. acknowledges receipt of a National Science Foundation CAREER Award, a Camille Dreyfus Teacher-Scholar Award, and a 3M Pharmaceuticals New Faculty Award. M.V.C. acknowledges receipt of a Graduate Research Assistantship Award from Wayne State University. The authors thank Hélène Fain for helpful suggestions.

  1433-7851/98/3722-3144 $ 17.50+.50/0