Immobilized 1,2-Bis(guanidinoalkyl)benzenes: Potentially Useful for the Purification of Arsenic-Polluted Water

Noriyuki Suzuki,*[a] Kaito Kishimoto,[a] Kohei Yamazaki,[a] Takuya Kumamoto,[a] Tsutomu Ishikawa,*[a] Davor Margetić[b]

[a] Department of Medicinal Organic Chemistry, Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo, Chiba 260-8675, Japan
Fax +81(43)2262919; E-mail: n-suzuki@chiba-u.jp; Fax +81(43)2262944; E-mail: benti@faculty.chiba-u.jp

[b] Laboratory for Physical-Organic Chemistry, Division of Organic Chemistry and Biochemistry, Ruder Bošković Institute, Bijenicka c. 54, 10001 Zagreb, Croatia

Received: 11.09.2013; Accepted: 17.09.2013

Abstract: Guanidines can act as ligands for various organic and inorganic ions. We have previously synthesized polymer-supported aromatic bisguanidine derivatives and evaluated their potential for removing arsenic from polluted water. In this work, we designed and synthesized the corresponding aliphatic bisguanidine derivatives, and we demonstrated that they show greater affinity for arsenic acid than do the previous aromatic ligands. The newly synthesized HypoGel resin-anchored aliphatic bisguanidines might serve as useful recyclable scavengers for the removal of arsenic from polluted water.

Key words: chelates, complexes, ligands, green chemistry, polymers

Contamination of drinking water by arsenic is a serious problem in Asia, particularly in Bangladesh. The source of the arsenic is usually an inorganic acid, such as arsenic acid (H_3AsO_4).[1–4] Guanidines can act as powerful organosuperbase catalysts in organic synthesis[5,6] or as ligands capable of forming complexes with various cations or anions.[7] We are currently studying guanidine chemistry with the aim of discovering practical applications,[8] including the decontamination of water containing toxic substances.[9–13] We previously examined the roles of 1,2-diaminobenzene-based bisguanidinobenzenes (BGBs; Figure 1), such as *N*,*N*′-bis(1,3-dimethylimidazolidin-2-ylidene)benzene-1,2-diamine (**1**) and *N*″,*N*‴″-1,2-phenylenebis(*N*,*N*,*N*′,*N*′-tetramethylguanidine) (**2**) as aromatic bisguanidine-type Brønsted base ligands for arsenic acid and phosphoric acid in solution and as solids.[13] We prepared the Merrifield resin-anchored BGB **3** and the HypoGel resin-anchored BGBs **4** and **5** as polymer-supported host ligands and we investigated these immobilized BGBs as potential solid scavengers for toxic metals and for arsenic acid. The monomeric BGBs **1** and **2** acted as Brønsted base ligands for arsenic acid, which has pK_a values of 2.25, 6.77, and 11.60 at 18 °C, and for phosphoric acid, which has pK_a values of 2.12, 7.21, and 12.67 at 25 °C,[14] although the composition ratios of the base and acid components in the solution and solid states were different. Furthermore, the HypoGel resin-anchored BGBs **4** and **5** effectively coordinated metal salts ($ZnCl_2$ and $CoCl_2$), as well as arsenic acid, in aqueous media. Thus, immobilized bisguanidine base ligands might serve as useful recyclable scavengers for the removal of toxicants from polluted water. Here we describe the preparation of the HypoGel resin-anchored aliphatic bisguanidines **6** and **7** containing a 1,2-bis(aminoalkyl)benzene core, the evaluation of their relative affinities for arsenic acid, and their comparison with the commercially available bicyclic guanidine **8**.

We have previously reported that BGBs can serve as Brønsted base ligands for arsenic acid. A Job plot obtained from a ^{1}H NMR spectroscopy experiment indicated that 1:1 complexes are formed in solution; however, X-ray crystallographic analysis and solid-state ^{13}C NMR spectroscopy of the crystalline complexes indicated the formation of 1:2 complexes between the BGBs and the acid.[13] Before attempting to prepare immobilized aliphatic bisguanidines, such as the 1,2-bis(guanidinoalkyl)benzenes (BGABs) **6** and **7**, we assessed the basicity of the monomeric model bisguanidine substrates. The absolute proton affinities of aromatic BGB **1**, aliphatic–aromatic bisguanidine hybrid **9**, and aliphatic BGAB **10** (Figure 2) were calculated to be 254.3–262.8, 260.2–263.9, and 265.1–269.1 kcal/mol, respectively, suggesting that aliphatic BGAB **10** should be the strongest organosuperbase.[15] Immobilized BGABs **6** and **7** could therefore be expected to act as effective basic ligands for acids, and might be useful for purifying arsenic-polluted water.

Initially, we prepared the HypoGel resin-anchored 1,2-bis(aminomethyl)benzene-derived bisguanidine **6** (Scheme 1). Reduction of 4-bromophthalic anhydride with diisobutylaluminum hydride (DIBAL-H) gave the diol **11**, which was smoothly converted into the bromide **12** by treatment with phosphoryl tribromide. Substitution with sodium azide, reduction with triphenylphosphine, and refluxing with hydrochloric acid[16] gave diamine **13**, which was characterized as its hydrochloride after treatment with hydrogen chloride in diethyl ether. Guanidinylation of diamine dihydrochloride **13** with 2-chloro-1,3-dimethylimidazolium chloride (DMC)[17] in the presence of triethylamine gave the bromobisguanidine **14** in 86% yield. Re-

SYNLETT 2013, 24, 2510–2514
Advanced online publication: 14.10.2013
DOI: 10.1055/s-0033-1338980; Art ID: ST-2013-D0872-C

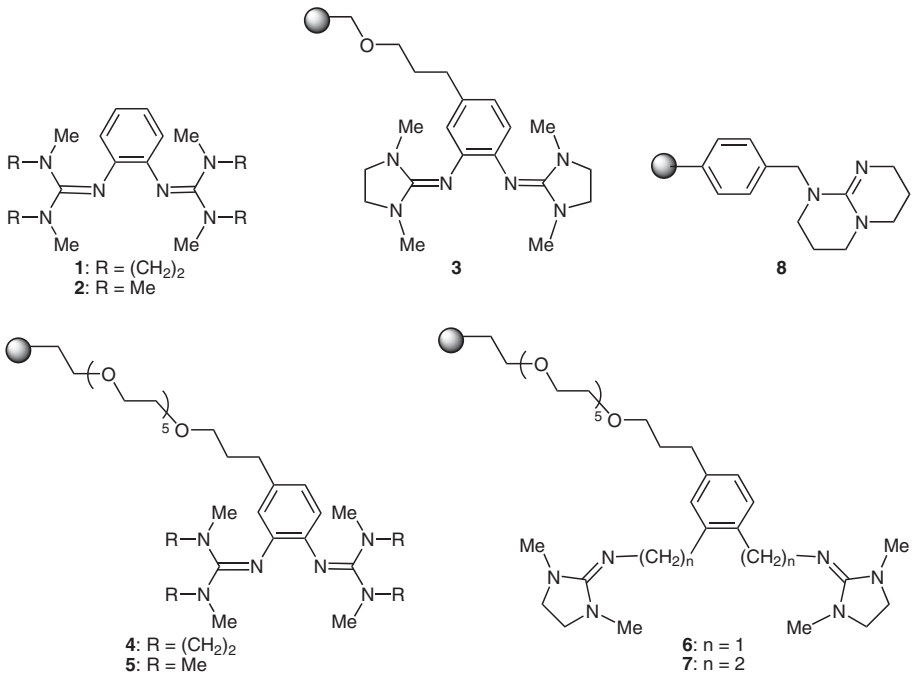


Figure 1 Structures of guanidine base ligands **1**–**8**

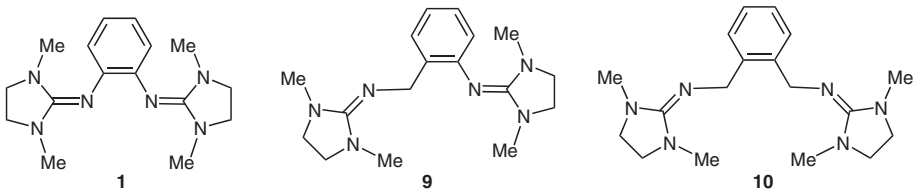


Figure 2 Structures of bisguanidine substrates **1**, **9**, and **10** used for calculating the absolute proton affinities

placement of the bromine atom in **14** with acrylate under Heck reaction conditions gave the 3,4-bis(guanidinomethyl)cinnamate **15** as its dihexafluorophosphate salt in 56% yield. We then attempted to prepare the alcohol **17** for use as a precursor of the immobilized bisguanidine **6**. Direct reduction of the cinnamate **15** with sodium borohydride in the presence of poly(ethylene glycol) 300[18] resulted in no reaction, whereas the corresponding reaction with lithium aluminum hydride gave a complex mixture. We therefore adopted a stepwise approach in which hydrogenation of cinnamate **15** over platinum oxide was followed by hydride reduction with DIBAL-H to give the required alcohol **17**. The HypoGel resin was introduced in *N*,*N*-dimethylformamide for 90 hours with sonication to give the immobilized BGAB **6**. The loading was estimated by elemental analysis to be 0.185 mmol/g.

Next, we attempted to prepare the 1,2-bis(guanidinoethyl)benzene derivative **7**, which contains a more flexible side chain, from the common dibromide precursor **12** by using the same synthetic procedure, with manipulation of the three-carbon tether for anchorage to the resin after the introduction of the guanidinyl functionality (Scheme 2). The aminoethyl functionality was added to dibromide **12** by substitution with sodium cyanide followed by hydride reduction of the dicyanide **18**. Although attempts at the direct conversion of **18** into diamine **20** with lithium aluminum hydride in the presence or absence of aluminum chloride failed, treatment with a sodium borohydride–nickel(II) chloride complex in the presence of di-*tert*-butyl dicarbonate[19] gave the *tert*-butoxycarbonyl-protected aminoethyl derivative **19** in 67% yield. The *tert*-butoxycarbonyl group was removed by stirring **19** with hydrogen chloride in diethyl ether to give diamine **20**, isolated as its dihydrochloride salt in 93% yield. Other acids, such as trifluoroacetic acid in dichloromethane, 10% sulfuric acid in 1,4-dioxane, or 20% hydrochloric acid in 1,4-dioxane gave unsatisfactory results. Diamine **20** was smoothly converted into the 1,2-bis(guanidinoethyl)benzene derivative **21** by treatment with DMC; however, the product was difficult to handle because of its high basicity. We therefore changed the synthetic route to introduce the guanidinyl groups at a later stage.

Treatment of the protected diamine **19** with methyl acrylate under Heck conditions gave the cinnamate **22** in 92% yield. Cinnamate **22** underwent successive hydrogenation and hydride reduction with lithium aluminum hydride to give the phenylpropanol derivative **24**, which could also be prepared directly from **22** by reduction with lithium aluminum hydride. Treatment of phenylpropanol **24** with

hydrogen chloride in diethyl ether gave the deprotected bis(aminoethyl) phenylpropanol **25** as its crystalline hydrochloride salt. The guanidinyl functionality was introduced into alcohol **25** by treatment with DMC to give diimine **26**, which was immobilized on HypoGel resin by treatment in *N*,*N*-dimethylformamide for 90 hours, with sonication, to give the immobilized bisguanidine **7**. The loading of **7** was estimated by elemental analysis to be 0.185 mmol/g.

The affinities of HypoGel-anchored aliphatic BGABs **6** and **7** for arsenic acid were examined by means of our previously reported method.[13] An aqueous mixture of the BGAB and arsenic acid was stirred well with a glass rod for 30 minutes. The insoluble polymer was collected by centrifugation and washed successively with water and methanol to give a pale-yellow powder, a small portion(~2 mg) of which was treated with concentrated nitric acid to elute the bound arsenic. The concentration of arsenic liberated from each polymer was estimated by inductively coupled plasma mass spectroscopy. The comparative complexation powers of PS-BGAB, HypoGel-anchored aromatic BGBs **4** and **5**, and the Merrifield resin-anchored bicyclic bisguanidine **8** are shown in Figure 3. As expected, the aliphatic BGABs **6** and **7** that were prepared in this work showed the strongest complexation abilities, and BGAB **7**, which contains a longer alkyl chain than **6**, was the most efficient ligand for arsenic.

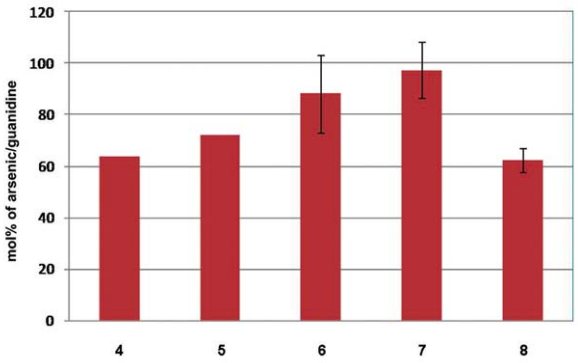
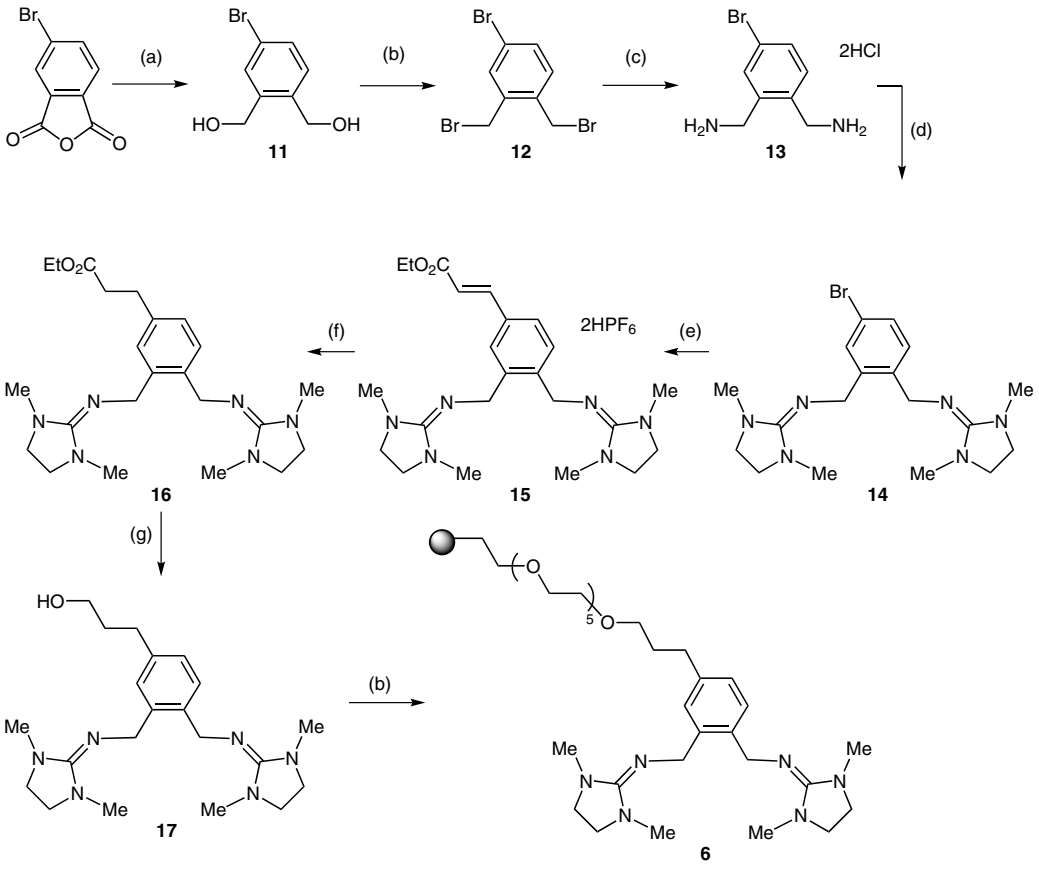
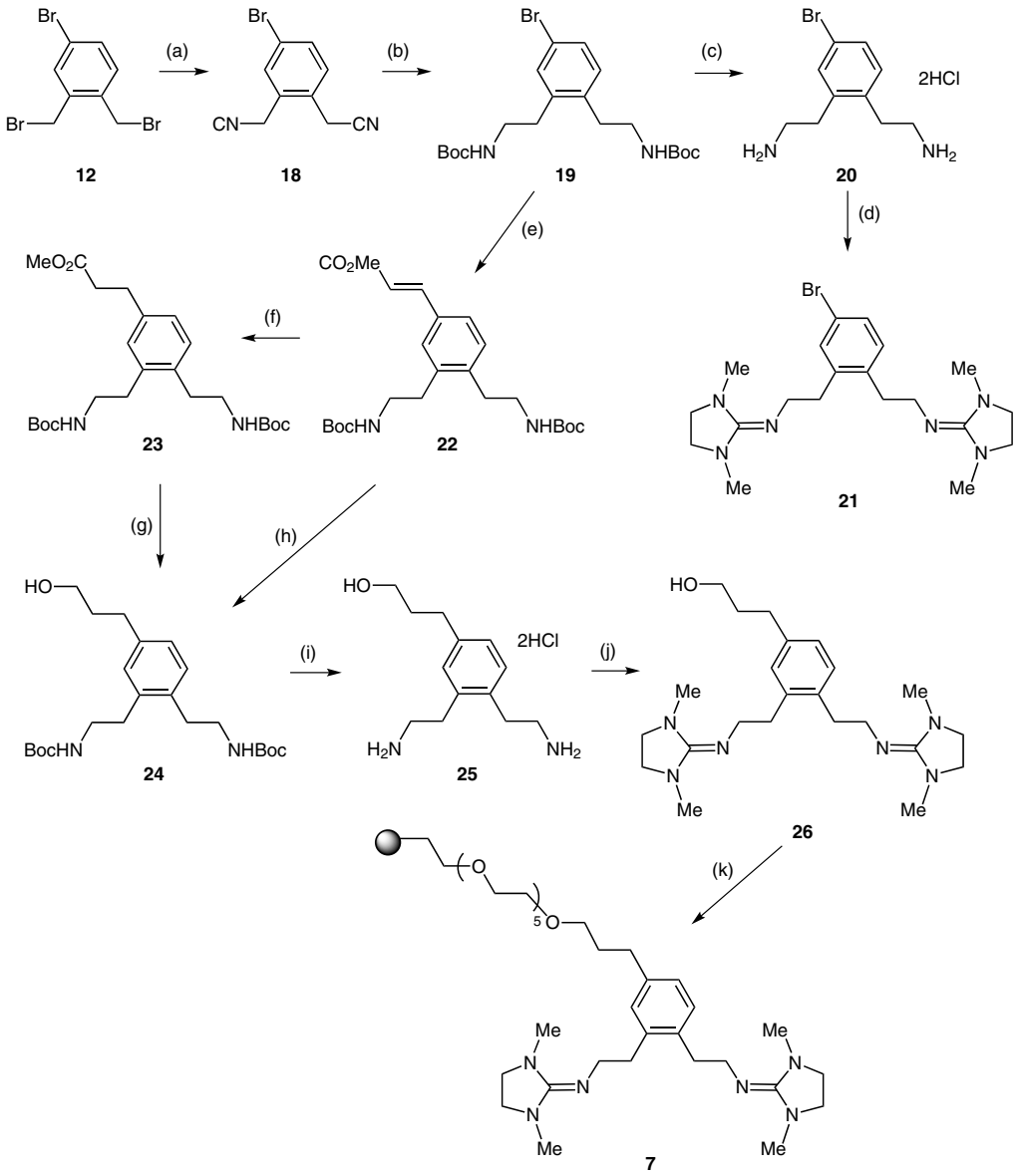


Figure 3 Comparison of the complexation abilities of PS-anchored guanidine ligands for arsenic acid

In conclusion, aliphatic BGAB derivatives were designed as more-effective ligands for arsenic acid, based on their calculated basicities. HypoGel resin-anchored BABG derivatives were prepared and their abilities to complex arsenic acid in aqueous medium were evaluated. Aliphatic



Scheme 1 Preparation of 1,2-bis(aminomethyl)benzene-derived bisguanidine **6**. *Reagents and conditions:* (a) DIBAL-H, toluene, r.t., 1.5 h (88%); (b) PBr_3, Et_2O, reflux, 7 h (95%); (c) (i) NaN_3, 4:3:1 THF–EtOH–H_2O, reflux, 1.5 h, (ii) PPh_3, reflux, 0.5 h, (iii) concd aq HCl, reflux, 2 h, (iv) HCl, Et_2O (88%), (d) DMC, Et_3N, CH_2Cl_2, r.t., 8 h (86%); (e) (i) ethyl acrylate, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 110 °C, 14 h, (ii) NH_4PF_6 (56%); (f) H_2, 10% Pd/C, MeOH, r.t., 12 h (95%); (g) DIBAL-H, toluene–CH_2Cl_2, –40 °C, 12 h (65%); (h) NaH, HypoGel, DMF, r.t., 90 h, sonication.



Scheme 2 Preparation of the 1,2-bis(aminoethyl)benzene-derived bisguanidine **7**. *Reagents and conditions:* (a) NaCN, EtOH, reflux, 0.5 h (83%); (b) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, Boc_2O, MeOH, r.t., 8 h (95%); (c) HCl, Et_2O, r.t., 8 h (93%); (d) DMC, Et_3N, CH_2Cl_2, r.t., 1 d (85%); (e) methyl acrylate, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 110 °C, 39 h, sealed tube (92%); (f) H_2, 10% Pd/C, MeOH, r.t., 1 d (96%); (g) $LiAlH_4$, THF, r.t., 7 h (100%); (h) $LiAlH_4$, THF, r.t., 7 h (98%); (i) HCl, Et_2O, r.t., 12 h (93%); (j) DMC, Et_3N, CH_2Cl_2, r.t., 10 h (67%); (k) (i) NaH, DMF, r.t., 1 h: (ii) HypoGel, r.t., 90 h, sonication.

BGABs might serve as useful recyclable scavengers for removal of toxic arsenic from polluted water. However, the effectiveness, selectivity, and recyclability of BGAB derivatives for arsenic coordination, and their practical applicability in decontamination of toxic water remain unclear. We are currently investigating these questions and we expect to report our findings in due course.

Acknowledgment

The project was financially supported by JSPS Grants-in-Aid for Scientific Research (C) (Grant No. 23590041). We thank Ms. M. Fujinami for her experimental assistance.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) Bissen, M.; Frimmel, F. H. *Acta Hydrochim. Hydrobiol.* **2003**, *31*, 9.
(2) Bissen, M.; Frimmel, F. H. *Acta Hydrochim. Hydrobiol.* **2003**, *31*, 97.
(3) Meharg, A. *Venomous Earth: How Arsenic Caused the World's Worst Mass Poisoning*; Macmillan: Basingstoke, **2005**.
(4) Short, P. L. *Chem. Eng. News* **2007**, *85* ,17 13.
(5) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737.
(6) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines and Phosphazenes and Related Organocatalysts*; Wiley: Chichester, **2009**.

(7) (a) For anions, see: Wiskur, S. L.; Lavigne, J. J.; Metzger, A.; Tobey, S. L.; Lynch, V.; Anslyn, E. V. *Chem. Eur. J.* **2004**, *10*, 3792. (b) For metals, see: Bienemann, O.; Hoffmann, A.; Herres-Pawlis, S. *Rev. Inorg. Chem.* **2011**, *31*, 83.
(8) Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555; and references cited therein.
(9) Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *Cryst. Growth Des.* **2005**, *5*, 373.
(10) Kawahata, M.; Shikii, K.; Seki, H.; Ishikawa, T.; Yamaguchi, K. *Chem. Pharm. Bull.* **2006**, *54*, 147.
(11) Kawahata, M.; Yamaguchi, K.; Ito, T.; Ishikawa, T. *Acta Crystallogr., Sect. E* **2006**, *62*, o3301.
(12) Suda, K.; Saito, N.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ogra, Y.; Suzuki, K. T.; Ishikawa, T. *Heterocycles* **2009**, *77*, 375.
(13) Ito, T.; Suda, K.; Kumamoto, T.; Nakanishi, W.; Watanabe, T.; Ishikawa, T.; Seki, H.; Kawahata, M.; Yamaguchi, K.; Ogra, Y.; Suzuki, K. T. *Mol. Diversity* **2010**, *14*, 131.
(14) *Handbook of Chemistry and Physics*; Weast, R. C., Ed.; CRC Press: Cleveland, Ohio, **1974**, 55th ed., D-130.
(15) Obtained by the B3LYP/6-31G*+E_{vib}(B3LYP/6-31G*) method, see: Margetić, D.; Trošelj, P.; Ishikawa, T.; Kumamoto, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1055.
(16) Kawahara, S.; Uchimaru, T. *Z. Naturforsch., B* **2000**, *55*, 985.
(17) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **2001**, *99*, 7770.
(18) Pettit, G. R.; Quistorf, P. D.; Fry, J. A.; Herald, L. D.; Hamel, E.; Chapuois, J. C. J. *J. Nat. Prod.* **2009**, *72*, 876.
(19) Caddick, S.; Judd, D. B.; Lewis, A. K. K.; Reicha, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417.
(20) Zoń, J.; Miziak, P.; Amrhein, N.; Gancarz, R. *Chemistry & Biodiversity* **2005**, *2*, 1187.

