JOC Article

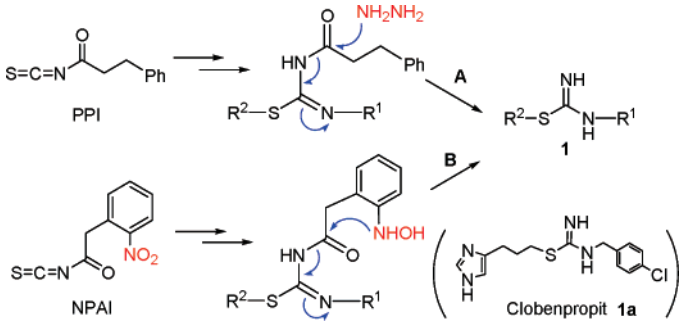
Efficient Approaches to *S*-Alkyl-*N*-alkylisothioureas: Syntheses of Histamine H_3 Antagonist Clobenpropit and Its Analogues

Hiroki Yoneyama,[†] Ayako Shimoda,[†,‡] Lisa Araki,[†] Kouta Hatano,[§] Yasuhiko Sakamoto,[‡] Takushi Kurihara,[†] Atsushi Yamatodani,[§] and Shinya Harusawa*[,†]

Osaka University of Pharmaceutical Sciences, 4-20-1, Nasahara, Takatsuki, Osaka 569-1094, Japan, Alfresa Pharma Co., 2-24-3, Sho, Ibaraki, Osaka 567-0806, Japan, and Department of Bioinformatics, Graduate School of Allied Health Sciences, Faculty of Medicine, Osaka University, Osaka 565-0871, Japan

harusawa@gly.oups.ac.jp

Received October 8, 2007



S-Alkyl-*N*-alkylisothioureas were efficiently synthesized via synthetic approach (**A**) using 3-phenylpropionyl isothiocyanate (PPI). The utility of the approach was proved by the syntheses of clobenpropit, a potent histamine H_3 antagonist, and its analogues. Alternatively, clobenpropit could be prepared via intramolecular amide cleavage (**B**) with use of 2-nitrophenylacetyl isothiocyanate (NPAI).

Introduction

S-Alkylisothioureas **1** and their salts **1**·HX are synthesized by mainly reacting thioureas with alkyl halides,[1] and other methods have been little employed so far.[2] They are crucial intermediates for the synthesis of guanidines[3] and heterocyclic systems.[4] Treatment of **1** with alkali or amine easily produces thiols,[1b] whose *S*-alkyl moieties are good leaving groups. In recent years, the isothiourea-functional group has been increasingly found in a wide range of biologically active molecules,[1c] including NO synthase inhibitors,[5] Na^+/Ca^{2+} exchanger inhibitors,[6] genotype-selective antitumor agents,[7] and anti-HIV compounds.[8]

On the other hand, the histamine H_3 receptor (H_3R) is a presynaptic autoreceptor that is mainly localized in the central nervous system (CNS) and acts to modulate the biosynthesis and release of histamine from histaminergic neurons.[9] H_3R

[†] Osaka University of Pharmaceutical Sciences.
[‡] Alfresa Pharma Co.
[§] Osaka University.

(1) (a) Sandler, R. S.; Karo, W. *Organic Functional Group Preparations*, 2nd ed.; Academic Press, Inc.: New York, 1986; pp 206−210. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; pp 495−496. (c) Denk, M. K.; Ye, X. *Tetrahedron Lett.* **2005**, *46*, 7597.

(2) (a) Hasegawa, K.; Hirooka, S.; Sasaki, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2611. (b) Iwakawa, T.; Tamura, H.; Sato, T.; Hayase, Y. *Chem. Pharm. Bull.* **1988**, *36*, 4755. (c) Takagi, K. *Chem. Lett.* **1985**, 1307. (d) Vowinkel, E.; Claussen, G. *Chem. Ber.* **1974**, *107*, 898.

(3) (a) Manimala, J. C.; Anslyn, E. V. *Eur. J. Org. Chem.* **2002**, 3909. (b) Drouin, C.; Woo, J. C. S.; MacKay, D. B.; Lavigne, R. M. A. *Tetrahedron Lett.* **2004**, *45*, 7197. (c) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913.

(4) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II, A Review of the Literature 1982−1995*; Pergamon: Oxford, UK, 1996.

(5) (a) Di Giacomo, C.; Sorrenti, V.; Salerno, L.; Cardile, V.; Guerrera, F.; Siracusa, M. A.; Avitabile, M.; Vanella, A. *Exp. Biol. Med.* **2003**, *228*, 486. (b) Garvey, E. P.; Oplinger, J. A.; Tanoury, G. J.; Sherman, P. A.; Fowler, M.; Marshall, S.; Harmon, M. F.; Paith, J. E.; Furfine, E. S. *J. Biol. Chem.* **1994**, *269*, 26669.

(6) (a) Uetani, T.; Matsubara, T.; Nomura, H.; Murohara, T.; Nakayama, S. *J. Biol. Chem.* **2003**, *278*, 47491. (b) Watano, T.; Kimura, J.; Morita, T.; Nakanishi, H. *Br. J. Pharmacol.* **1996**, *119*, 555.

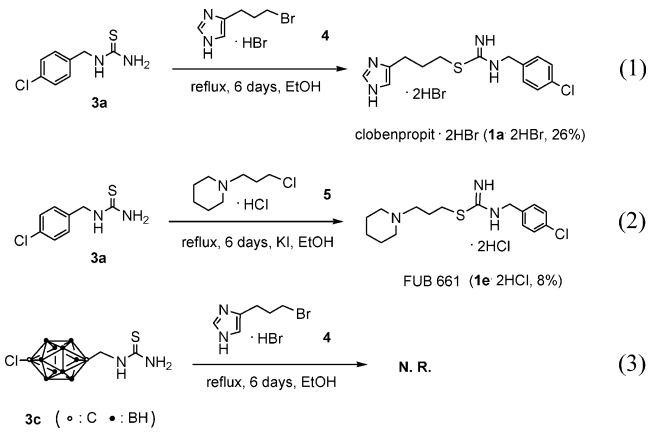
(7) Dolma, S.; Lessnick, S. L.; Hahn, W. C.; Stockwell, B. R. *Cancer Cell* **2003**, *3*, 285.

(8) Rawal, R. K; Tripathi, R.; Katti, S. B.; Pannecouque, C.; Clercq, E. D. *Bio. Med. Chem.* **2007**, *15*, 1725.

(9) Arrang, J.-M.; Gargarg, M.; Lancelot, J.-C.; Lecomte, J.-M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. *Nature* **1987**, *327*, 117.

10.1021/jo702181x CCC: $40.75
Published on Web 02/16/2008

SCHEME 1. Reaction of Thiourea with Alkyl Halide



antagonists increase central histamine levels and may therefore be useful for the treatment of a variety of CNS disorders, including eating disorder, schizophrenia, narcolepsy, epilepsy and cognitive disorders, and attention-deficit hyperactivity disorder (ADHD).[10] Among them, the *S*-imidazolylpropyl-*N*-phenylalkylisothiourea series was developed by Timmerman and co-workers, and in particular clobenpropit **1a**[11a] is widely used in pharmacology as a potent prototype of H_3R antagonists.[11b] H_3R antagonists and agonists were found to bind not only to H_3R but also to histamine H_4 receptor (H_4R), which was discovered as the fourth subtype of histamine receptor in 2000.[12] H_4R is now regarded as a new therapeutic target for inflammation.[13] Similar to the case of H_3R antagonists there are isothioureas that function as important histamine H_2 receptor (H_2R) and H_3R agonists, e.g., dimaprit[14] and imetit,[15] respectively.

In a previous work where we aimed to synthesize new H_3R ligands,[16] we noted that the formation of *S*-alkyl-*N*-alkylisothioureas is not an easy task. The reaction of thioureas with alkyl halides is often extremely sluggish with reflux and the yields quoted in the literature vary markedly (Scheme 1). The reaction of 4-chlorobenzylthiourea (**3a**) with 4(5)-(3-bromopropyl)-imidazole·HBr (**4**) gave clobenpropit·2HBr (**1a**) in only 26% yield under reflux in ethanol for 6 days (Scheme 1, eq 1).[11a] The yield of piperidine analogue FUB 661[17] was worse at 8% (eq 2). Further, the reaction of alkyl bromide **4** with novel

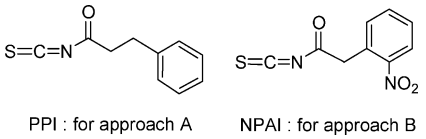


FIGURE 1. Two reagents for *S*-alkyl-*N*-alkylisothiourea syntheses.

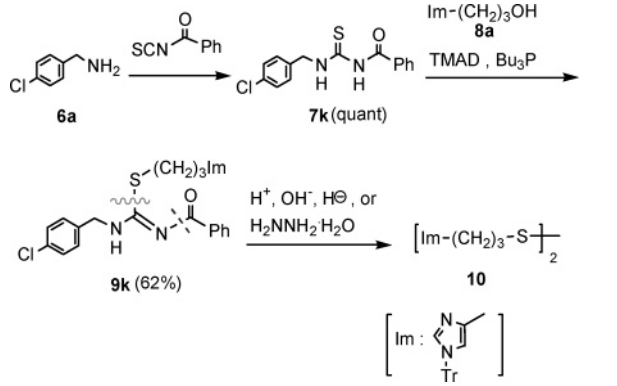
p-carborane-containing thiourea **3c** (see the preparation in Scheme 4), in which the benzene ring of thiourea **3a** was replaced with *p*-carborane, did not proceed at all (eq 3). This may be caused by an electron-withdrawing effect of the carborane framework, which is an electron-deficient cluster.[18] These results indicate that conventional methods for the *S*-alkylation of thioureas give poor yields of *S*-alkylisothioureas and their salts.

In this paper, we report two efficient synthetic approaches to *S*-alkyl-*N*-alkylisothioureas. One approach involves direct cleavage of the N−CO bond (**A**) with hydrazine hydrate starting from 3-phenylpropionyl isothiocyanate (PPI), producing clobenpropit in higher yields and in a remarkably shorter time than those of a known method.[11a] Further, clobenpropit analogues were synthesized, proving the applicability of the PPI method. In addition, an alternative approach for the synthesis of clobenpropit, which employs 2-nitrophenylacetyl isothiocyanate (NPAI) and an intramolecular amide cleavage (**B**), is described (Figure 1).

Results and Discussion

We first paid attention to *N*-benzoyl thiourea **7k**, which has an acidic N−H between C═O and C═S groups (Scheme 2). The reaction of 4-chlorobenzylamine **6a** with benzoyl isothiocyanate gave **7k**. *S*-Alkylation of **7k** by the Mitsunobu reaction[19] with use of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[20] and Bu_3P proceeded as expected to give *S*-alkylated isothiourea **9k**. However, selective cleavage of the N−CO bond of **9k** failed owing to the sensitivity of the C−S bond in spite of many trials (acid, base, hydride anion, or hydrazine hydrate), causing the formation of disulfide **10**.

SCHEME 2. Sensitivity of the C−S Bond of *N*-Benzoyl-*S*-alkylated Isothiourea 9k



(10) Watanabe, T.; Timmerman, H.; Yanai, K. *Histamine Research in the New Millennium*; Elsevier: New York, 2001.

(11) (a) Van der Goot, H.; Schepers, M. J. P.; Sterk, G. J.; Timmerman, H. *Eur J. Med. Chem.* **1992**, *27*, 511. (b) Barnes, J. C.; Brown, J. D.; Clarke, N. P.; Clapham, J.; Evans, D. J.; O'Shaughnessy, C. T. *Eur. J. Pharmacol.* **1993**, *250*, 147.

(12) (a) Oda, T.; Morikawa, N.; Saito, Y.; Masuho, Y.; Matsumoto, S. *J. Biol. Chem.* **2000**, *275*, 36781. (b) Nakamura, T.; Itadani, H.; Hidaka, Y.; Ohta, M.; Tanaka, K. *Biochem. Biophys. Res. Commun.* **2000**, *279*, 615. (c) Hough, L. B. *Mol. Pharmacol.* **2001**, *59*, 415 and references cited therein.

(13) de Esch, I. J. P.; Thurmond, R. L.; Jongejian, A.; Leurs, R. *Trends Phamacol. Sci.* **2005**, *26*, 462.

(14) Durant, G. J.; Ganellin, C. R.; Parsons, M. E. *Agents Actions* **1977**, *7*, 39.

(15) Garbarg, M.; Arrang, J. M.; Rouleau, A.; Ligneau, X.; Dam Trung Tuong, M.; Schwartz, J. C.; Ganellin, C. R. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304.

(16) (a) Harusawa, S.; Imazu, T.; Takashima, S.; Araki, L.; Ohishi, H.; Kurihara, T.; Yamamoto, Y.; Yamatodani, A. *Tetrahedron Lett.* **1999**, *40*, 2561. (b) Harusawa, S.; Kawamura, M.; Araki, L.; Taniguchi, R.; Yoneyama, H.; Sakamoto, Y.; Kaneko, N.; Nakao, Y.; Hatano, K.; Fujita, T.; Yamamoto, R.; Kurihara, T.; Yamatodani, A. *Chem. Pharm. Bull.* **2007**, *55*, 1245 and references cited therein. (c) Hashimoto, T.; Harusawa, S.; Araki, L.; Zuiderveld, O. P.; Smit, M. J.; Imazu, T.; Takashima, S.; Yamamoto, Y.; Sakamoto, Y.; Kurihara, T.; Leurs, R.; Bakker, R. A.; Yamatodani, A. *J. Med. Chem.* **2003**, *46*, 3162.

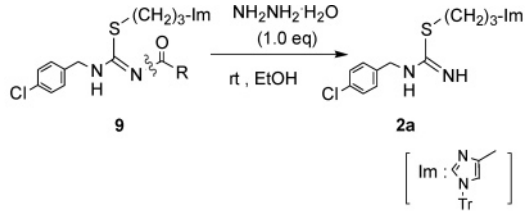
(17) Meier, G.; Apelt, J.; Reichert, U.; Grassmann, S.; Ligneau, X.; Elz, S.; Leurquin, F.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. *Eur. J. Pharm. Sci.* **2001**, *13*, 249.

(18) *Carboranes*; Grimes, R. N., Ed.; Academic: New York, 1970; pp 1−22.

(19) Nagasawa, H.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2223.

(20) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539.

TABLE 1. Treatment of *N*-Acylisothioureas with Hydrazine



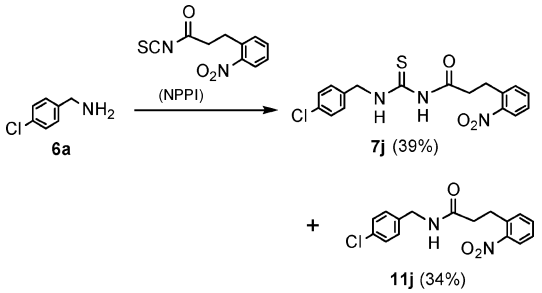
entry	R	9	time (h)	2a (%)
1	—(CH$_2$)$_2$— (PP)	9a	2	29
2			17	69
3			0.17[a]	51
4	—CH$_3$	9h	2	53
5	—CH$_2$— (NPA)	9i	2	34
6			17	53
7	—(CH$_2$)$_2$— (NPP)	9j	1	63
8			1.5[b]	71
9			1[c]	14
10	—NO$_2$	9l	2	–

[a] MW irradiation was used (see the Experimental Section). [b] The reaction was carried out in the presence of 10% Pd/C. [c] MeNH$_2$ was used as nucleophile.

Fortunately, in the case of *N*-acyl-*S*-alkylisothioureas (Table 1), we found that treatment of *N*-phenylpropionyl (PP)-protected isothiourea **9a** with hydrazine hydrate (1.0 equiv) at room temperature (rt) for 17 h afforded the desired **2a** in 69% yield with retention of the *S*-alkyl moiety (Table 1, entry 2). The reaction time could be remarkably shortened to 10 min by microwave (MW) irradiation (75 °C), giving **2a** (51% yield; entry 3). Acetyl analogue **9h** and NPA-protected **9i** similarly afforded **2a** (entries 4 and 6), while treatment of *N*-(2-nitrophenyl)propionyl (NPP) analogue **9j** with hydrazine in the presence of a catalytic amount of 10% Pd/C provided **2a** in 71% yield (entry 8). Use of methylamine (1.0 equiv) as nucleophile gave **2a** in only 14% yield, competing with the thiol elimination (entry 9). The reaction of 4-nitrobenzoyl isothiourea **9*l*** occurred with only elimination of the *S*-alkylated moiety (entry 10).

On the other hand, the first reaction of amine **6** with acyl isothiocyanate (PPI, acetyl isothiocyanate, NPAI, or NPPI) usually gives *N*-acylthiourea **7** accompanied by amide **11** as byproduct owing to the attack of amine **6** at the carbonyl group of acyl isothiocyanates. For example, as shown in Scheme 3, the reaction of amine **6a** with NPPI afforded acylthiourea **7j** (39%) and *N*-(4-chlorobenzyl)-3-(2-nitrophenyl)propionamide **11j** (34%), the structure of which was confirmed by condensation of 3-(2-nitrophenyl)propionic acid with **6a** in the presence of diethyl phosphorocyanidate (DEPC).[21] Among isothiocyanates employed, PPI most strongly suppressed the production of amide **11a**, providing **7a** in 78% yield (Table 2, entry 1). In addition, PPI itself can be easily prepared by the one-step reaction of commercially available 3-phenylpropionyl chloride with Pb(SCN)$_2$.[22] From the results of Table 1 and the suppression of amide formation in the first reaction, we adopted the

SCHEME 3. Reaction of 6a with NPPI



PPI method as the general method for the synthesis of isothioureas **1**.

Removal of the N^{im}-Tr group of thus obtained *S*-alkylisothiourea **2a** with hydrochloric acid provided clobenpropit·2HCl (**1a**·2HCl) in four steps in 51% overall yield from **6a** (Table 2, entry 1). Clobenpropit synthesis by using the PPI method requires within less than 2 days. In contrast, Timmerman et al.'s method[11a] gave only 10% overall yield of clobenpropit·2HBr (**1a**·2HBr) with the same amine **6a** and required at least one week more to complete the synthesis.

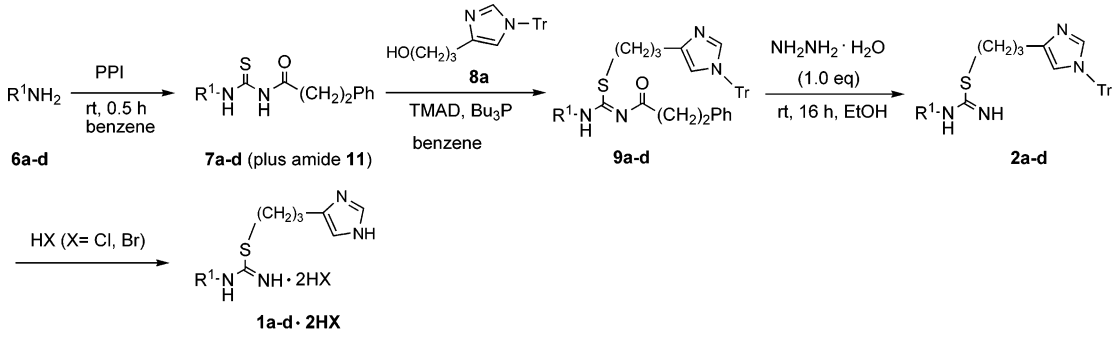
Several analogues of clobenpropit were synthesized to demonstrate the applicability of this method (Table 2). **1b**·2HBr (VUF 4598) (24% overall yield, entry 2) was synthesized from **6b**. VUF 4598 is the precursor of ^{125}I-labeled iodophenpropit, which is the first {^{125}I}-labeled selective H$_3$R antagonist having high specific activity.[23] Further, using this method we synthesized novel *p*-carborane-containing isothioureas **1c** and **1d** (26% and 46% overall yields, respectively, entries 3 and 4), although their syntheses failed with use of the conventional method (Scheme 1, eq 3). In the carborane derivative **1c**, the benzene ring of clobenpropit is replaced with *p*-carborane, because spherical carborane has similar size to adamantane and its hydrophobicity is comparable to that of hydrocarbons.[24] The starting amines, 1-aminomethyl-1,12-dicarba-*closo*-dodecaboranes **6c** and **6d**, were successfully prepared in four or five steps starting from *p*-carborane via volatile **14** and **15** under vacuum, as illustrated in Scheme 4. However, unfortunately, preliminary investigations of in vivo histamine release in rat hypothalamus measured by brain microdialysis[16a,b] showed that **1c** and **1d** were inactive against H$_3$R.

Piperidine analogue **1e**·2HCl (FUB 661)[17] of clobenpropit was previously synthesized in an attempt to replace the imidazole ring with other heterocycles, but the yield of the key reaction was only 8% (Scheme 1, eq 2). Our approach afforded FUB 661 in 38% overall yield from **6a** (Table 3, entry 1). Novel pyrrolidine and morpholine analogues **1f** and **1g** were similarly synthesized in 30% and 25% overall yields, respectively (entries 2 and 3). As brain microdialysis experiments of FUB 661 have not been reported so far, we carried out microdialysis experiments for FUB 661, plus **1f**, and **1g**. The results indicated that FUB661 and morpholino derivative **1g** increased moderately histamine release by 130−140% and 140−150%, respectively, while pyrrolidino derivative **1f** was inactive.

We next directed our interest to the alternative synthesis of clobenpropit using intramolecular amide cleavage,[25] as shown

(21) Shioiri, T.; Yokoyama, Y.; Kasai, Y.; Yamada, S. *Tetrahedron* **1976**, *32*, 2211.
(22) Lipp, M.; Dallacker, F.; Koenen, G. *Chem. Ber.* **1958**, *91*, 1660.
(23) Menge, W. M. P. B.; Van der Goot, H.; Timmerman, H.; Eersels, J. L. H.; Herscheid, J. D. M. *J. Labelled Compd. Radiopharm.* **1992**, *31*, 781.
(24) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Fukasawa, H.; Miyaura, C.; Inada, M.; Kubo, A.; Itai, A. *Chem. Biol.* **2001**, *8*, 341.
(25) Entwistle, I. D. *Tetrahedron Lett.* **1979**, 555.

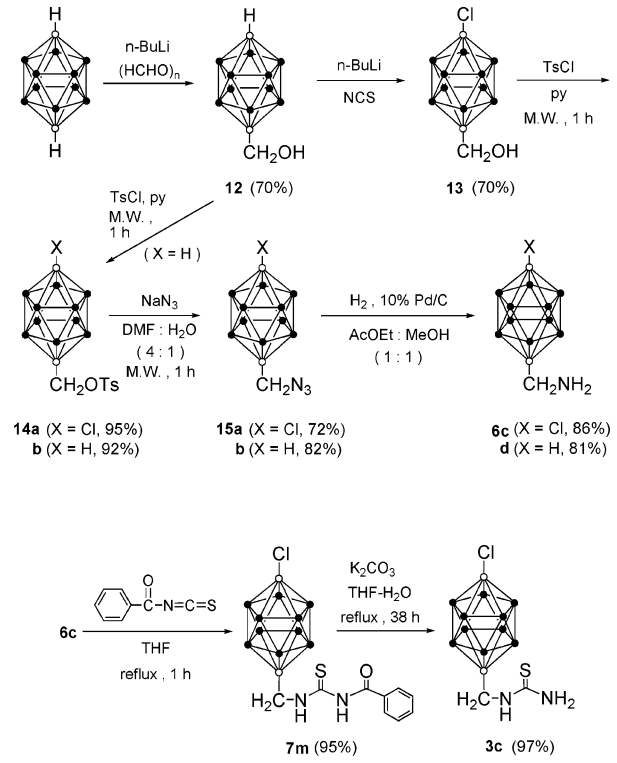
TABLE 2. Syntheses of Imidazole-Containing Isothioureas with PPI



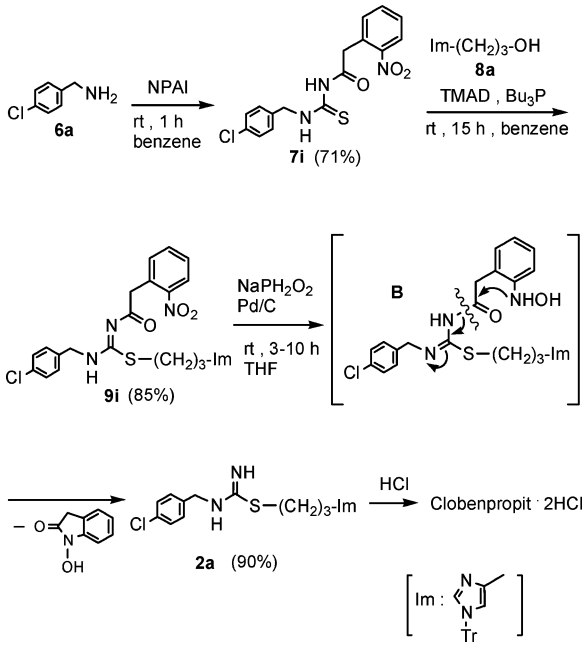
entry	6	R^1	yield (%) 7	9	2	1·2HX	total yield (%) from 6
1	6a	Cl—C$_6$H$_4$—CH$_2$—	78 (7a)	94 (9a)	69 (2a)	quant (1a·2HCl :clobenpropit·2HCl)	51
2	6b	Br—C$_6$H$_4$—(CH$_2$)$_2$—	45 (7b)	94 (9b)	57 (2b)	98 (1b·2HBr :VUF 4598)	24
3	6c	Cl—C$_2$B$_{10}$H$_{10}$—CH$_2$—	67 (7c)	84 (9c)	49 (2c)[a]	94 (1c·2HCl)	26
4	6d	H—C$_2$B$_{10}$H$_{10}$—CH$_2$—	95 (7d)	62 (9d)	88 (2d)[a]	88 (1d·2HCl)	46

[a] The reaction was carried out according to Table 1, entry 8.

SCHEME 4. Synthesis of *p*-Carborane Derivatives 6c, 6d, and 2b



SCHEME 5. Second Synthesis of Clobenpropit with NPAI

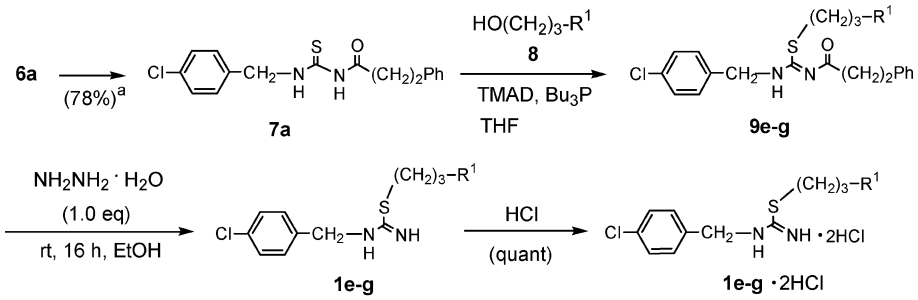


in Scheme 5. We reasoned that elimination of the acyl moiety in NPA-protected isothiourea **9i** could be realized by reductive cyclization of the NO_2 group, such as **B**. Addition of **6a** to NPAI followed by the Mitsunobu alkylation provided NPA-protected isothiourea **9i**. When **9i** was treated with sodium phosphinate and 10% Pd/C,[26] isothiourea **2a** was obtained in 90% yield with retention of chlorine and imino double bond, and removal of 1-hydroxy-2-oxindole.[27] Removal of the N^{im}-trityl group of **2a**

(26) Entwistle, I. D.; Jackson, A. E.; Johnstone, R. A. W.; Telford, R. P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 443.

(27) Somei, M.; Yamada, F.; Kurauchi, T.; Nagahama, Y.; Hasegawa, M.; Yamada, K.; Teranishi, S.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **2001**, *49*, 87.

TABLE 3. Syntheses of Cyclic-Amine-Containing Isothioureas with PPI



entry	8	R^1	yield (%) 9	yield (%) 1		total yield (%) from 6a
1	8e	N—	64 (9e)	76 (1e)[b]	(1e·2HCl : FUB 661)	38
2	8f	N—	51 (9f)	76 (1f)		30
3	8g	O N—	62 (9g)	52 (1g)		25

[a] **7a** was synthesized from **6a** in 78% yield (Table 1, entry 1). [b] Benzene was used as a solvent.

gave clobenpropit·2HCl in four steps in 54% overall yield from **6a**. NPAI was prepared in two steps from 3-(2-nitrophenyl)-acetic acid. Therefore, a second method for the synthesis of clobenpropit was established. Comparing the two methods for clobenpropit synthesis, the PPI method was found to be more convenient than the NPAI method, because in the latter method, the reductive step to **2a** from **9i** is sluggish (3−10 h) and somewhat troublesome, requiring repeated addition of aqueous (aq) saturated sodium phosphinate and monitoring by TLC until completion of the reaction.

Conclusions

We herein described two efficient synthetic approaches to *S*-alkyl-*N*-alkylisothioureas starting from PPI or NPAI. The utility of those two approaches was proved by the syntheses of clobenpropit and its analogues. The two approaches are expected to supply a variety of H_3R or H_4R ligand candidates having the isothiourea moiety by which their biological activities could be assessed.

Experimental Section

2-Nitrophenylacetyl Isothiocyanate (NPAI). A stirred solution of 2-nitrophenylacetic acid (1.81 g, 10 mmol) and thionyl chloride (1.46 mL, 20 mmol) in CH_2Cl_2 (20 mL) was refluxed for 20 h. The reaction mixture was evaporated to give crude 2-nitrophenylacetyl chloride, which was allowed to stand under reduced pressure for 2 h. Without additional purification, 2-nitrophenylacetyl chloride was added to a suspension of $Pb(SCN)_2$ (1.94 g, 6 mmol) in benzene (10 mL), and the mixture was refluxed for 3 h. After filtration through Celite, the filtrate was evaporated to give a residue. It was subsequently diluted with EtOAc and mixed with a small amount of silica gel. Evaporation of the mixture gave coated silica gel for use in column chromatography. Chromatography with EtOAc−hexane (1:9) as eluent gave **NPAI** (1.90 g, 86%) as an oil. **NPAI**: IR film ν_{max} 1340, 1518, 1720, 1940−1980 (br, NCS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (s, 2H), 7.34−7.70 (m, 3H), 8.14−8.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 46.0, 125.2, 127.6, 129.2, 133.2, 133.7, 147.3, 147.7, 164.8; HRMS (FAB) *m*/*z* calcd for $C_9H_7N_2O_3S$ 233.0177 $[M + H]^+$, found 223.0181.

3-Phenylpropionyl Isothiocyanate (PPI). Known PPI was prepared according to Koenen et al.'s procedure.[22] A mixture of 3-phenylpropionyl chloride (1.52 mL, 10 mmol) and $Pb(SCN)_2$ (1.94 g, 6 mmol) in dry benzene (3 mL) was refluxed for 3 h to give a crude oil, which was subsequently purified by column chromatography with 20% EtOAc in hexane as eluent to give PPI (1.49 g, 79%). **PPI**: orange oil; bp 95−98 °C (0.5 mmHg) [(lit.[22] bp 93−95 °C (0.5 mmHg)]; IR (film) ν_{max} 1720, 1940−2000 (br, NCS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85−3.05 (m, 4H), 7.10−7.30 (m, 5H).

3-(2-Nitrophenyl)propionyl Isothiocyanate (NPPI). NPPI (13.2 g, 80%) was prepared from 3-(2-nitrophenyl)propionic acid[28] (1.44 g 7.4 mmol) by using the same procedure as that for the preparation of NPAI. **NPPI**: yellow solid; IR (film) ν_{max} 1340, 1510, 1710, 1950−2000 (br, NCS) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (2H, t, J = 7.3 Hz), 3.25 (2H, t, J = 7.3 Hz), 7.38−7.45 (m, 2H), 7.57 (1H, td, J = 7.7, 1.4 Hz), 7.99 (1H, dd, J = 8.5, 1.4 Hz); HRMS (FAB) *m*/*z* calcd for $C_{10}H_9N_2O_3S$ 237.0334 $[M + H]^+$, found 237.0331.

***N*-(4-Chlorobenzyl)-3-(2-nitrophenyl)propionamide (11j).** To a solution of 3-(2-nitrophenyl)propionic acid (482 mg, 2.47 mmol) in DMF (10 mL) were added **6a** (0.3 mL, 2.47 mmol), 90% DEPC[21] (0.55 mL, 3.71 mmol), and Et_3N (1.03 mL, 7.42 mmol) in that order. The resulting mixture was stirred at rt for 4 h, and then diluted with EtOAc−hexane (1:1) and water. The organic layer was washed with water, aq saturated $NaHCO_3$, and brine, then dried and evaporated to give a residue. Chromatography with EtOAc−hexane (3:10 to 1:1) as eluent gave **11j** (78 mg, 10%). **11j**: cotton-like fibers; IR (Nujol) ν_{max} 1340, 1510, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (2H, t, J = 6.3 Hz), 3.16 (2H, t, J = 6.3 Hz), 4.28 (2H, d, J = 4.6 Hz), 5.95 (1H, br s), 7.00−7.50 (7H, m), 7.80−7.90 (1H, m); ^{13}C NMR ($CDCl_3$) δ 29.6, 37.4, 43.0, 124.5, 127.2, 128.3,

(28) Lin, B.; Hu, L. *Bioorg. Med. Chem.* **2003**, *11*, 3889.

128.5, 132.1, 132.7, 132.9, 135.3, 136.2, 148.4, 170.7; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{16}{}^{35}ClN_2O_3$ $[M + H]^+$ 319.0849, found 319.0847.

Synthetic Approach (A) to Clobenpropit with Use of PPI (General Procedures to Obtain *S*-alkyl-*N*-alkylisothioureas): *N*-(4-Chlorobenzyl)-*N′*-(3-phenylpropionyl)thiourea (7a). PPI (955 mg, 5.0 mmol) was added to 4-chlorobenzylamine **6a** (0.61 mL, 5.0 mmol) in dry benzene (10 mL). The resulting mixture was stirred for 0.5 h and evaporated to give a crude yellow solid, which was subsequently purified by column chromatography with 20% EtOAc in hexane as eluent to give **7a** (1.30 g, 78%) and *N*-(4-chlorobenzyl)-3-phenylpropionamide (**11a**)[29] (219 mg, 16%) in that order, using the coated silica gel technique described in the purification of NPAI. **7a**: yellow needles (EtOAc); mp 135−141 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 2.78−3.00 (4H, m), 2.88 (2H, d, J = 6.0 Hz), 7.15−7.50 (9H, m), 10.15 (1/2H, br s), 11.00 ($^1/_2$H, br s); ^{13}C NMR ($CDCl_3$) δ 31.1, 38.6, 48.2, 126.3, 128.4, 128.5, 128.6, 129.6, 132.7, 135.9, 140.6, 173.6, 180.8; HRMS (EI) *m*/*z* calcd for $C_{17}H_{17}{}^{35}ClN_2OS$ $(M)^+$ 332.0750, found 332.0748. **11a**:[29] cotton-like fibers; ^{1}H NMR ($CDCl_3$) δ 2.72 (2H, t, J = 7.2 Hz), 2.96 (2H, t, J = 7.2 Hz), 4.32 (2H, d, J = 5.8 Hz), 5.72 (1H, br s), 7.00−7.35 (9H, m).

***N*-(4-Chlorobenzyl)-*N′*-(3-phenylpropionyl)-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}isothiourea (9a).** To a solution of 3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanol (**8a**)[30] (405 mg, 1.1 mmol) in dry benzene (10 mL) were added **7a** (333 mg, 1.0 mmol) and Bu_3P (0.37 mL, 1.5 mmol) in dry benzene (10 mL) at rt. Then, TMAD (258 mg, 1.5 mmol) was added rapidly and the mixture was stirred continuously for 15 h. The insoluble material was removed by filtration and the filtrate was evaporated to give a residue, which was purified by chromatography with EtOAc−hexane (1:1) as eluent by using the coated silica gel technique to yield **9a** (640 mg, 94%). **9a**: oil; ^{1}H NMR ($CDCl_3$) δ 1.93 (2H, quint, J = 6.8 Hz), 2.50−2.70 (4H, m), 2.87 (2H, t, J = 7.5 Hz), 3.04 (2H, t, J = 6.8 Hz), 4.37 (2H, s), 6.45 (1H, s), 6.90−7.40 (25H, m), 11.15 ($^1/_4$H, br s); ^{13}C NMR ($CDCl_3$) δ 27.6, 28.5, 29.3, 30.9, 32.1, 42.7, 47.1, 75.1, 117.8, 125.4, 127.6, 127.9, 128.1, 128.3, 128.5, 129.3, 137.9, 139.9, 141.2, 141.9, 172.3, 184.4; HRMS (FAB) *m*/*z* calcd for $C_{42}H_{40}{}^{35}ClN_4OS$ $[M + H]^+$ 683.2612;, found 683.2615.

***N*-(4-Chlorobenzyl)-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]-propyl}isothiourea (2a).** A mixture of **9a** (137 mmol, 0.20 mmol) and 80% hydrazine hydrate (12 μL) in EtOH (2 mL) was stirred at rt (16 h). A heaping microspatula of 10% Pd/C was added and the resulting mixture was stirred for 30 min. After filtration through Celite, the filtrate was evaporated to give a residue, which was purified by column chromatography with MeOH−EtOAc (0:100, 20:80, to 50:50) as eluent to give the eliminated 3-phenylpropionyl hydrazide (22 mg, 61%) and **2a** (76 mg, 69%) in that order. **2a**: oil; ^{1}H NMR ($CDCl_3$) δ 2.04 (2H, quint, J = 7.2 Hz), 2.62 (2H, t, J = 7.2 Hz), 3.20 (2H, t, J = 7.2 Hz), 4.42 (2H, s), 6.54 (1H, s), 7.05−7.40 (20H, m); ^{13}C NMR ($CDCl_3$) δ 25.2, 28.6, 30.1, 47.0, 75.3, 117.9, 127.6, 128.3, 128.4, 129.2, 133.0, 134.5, 137.7, 138.4, 141.7, 168.9; HRMS (FAB) *m*/*z* calcd for $C_{33}H_{32}{}^{35}ClN_4S$ $[M + H]^+$ 551.2036, found 551.2032. **3-Phenylpropionyl hydrazide**: white powder; IR (film) ν_{max} 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (2H, t, J = 7.6 Hz), 2.97 (2H, t, J = 7.6 Hz), 3.54 (2H, br s), 6.84 (1H, br s), 7.05−7.40 (5H, m).

Synthesis of 2a by MW Irradiation. In a 5 mL Teflon MW reaction vessel were dissolved **9a** (68 mg, 0.1 mmol) and 80% hydrazine hydrate (6 μL, 0.1 mmol) in EtOH (1.0 mL). The vessel was sealed, heated in the MW reactor to 75 °C for 10 min, and cooled thereafter. The same workup as that for the previous **2a** gave 3-phenylpropionyl hydrazide (12 mg, 67%) and **2a** (28 mg, 51%).

***N*-(4-Chlorobenzyl)-*S*-{3-[4(5)-imidazolyl]propyl}isothiourea Dihydrochloride [Clobenpropit·2HCl (1a·2HCl)].** A solution of **2a** (277 mg, 0.50 mmol) in aq 2 N HCl (0.5 mL)−EtOH (5 mL) was refluxed for 30 min and the reaction mixture was evaporated to give a residue, which was partitioned between benzene and water. The aq solution was evaporated as a benzene azeotrope to give **1a**·2HCl (195 mg, quant). **1a**·2HCl: white powder; ^{1}H NMR (CD_3OD) δ 2.00−2.20 (2H, br m), 2.85−3.95 (2H, br m), 3.25−3.35 (2H, br m), 4.62 (2H, s), 7.32−7.42 (5H, m), 8.84 (1H, s); ^{13}C NMR (CD_3OD) δ 24.2, 29.1, 31.7, 47.8, 116.8, 129.2, 129.4, 130.0, 133.2, 134.0, 134.2, 134.5, 167.8.

Clobenpropit 1a and Its Dihydrobromide 1a·2HBr. Thus obtained **1a**·2HCl was confirmed by conversion into dihydrobromide previously synthesized by Timmerman et al.[11a] To a MeOH solution of **1a**·2HCl (50 mg) was added a small amount of NH-silica gel, and this mixture was subsequently placed on a column (NH-silica gel). Chromatography with $CHCl_3$−MeOH−28% NH_4-OH (50:5:1) as eluent gave salt-free clobenpropit **1a** (36 mg, 74%) as a colorless oil. **1a**: ^{1}H NMR ($CDCl_3$) δ 1.97(2H, quint, J = 6.7 Hz), 2.70 (2H, t, J = 6.7 Hz), 2.90 (2H, t, J = 6.7 Hz), 4.37 (2H, s), 6.70 (1H, s), 7.16−7.28 (4H, m), 7.32 (1H, s); ^{13}C NMR (CD_3-OD) δ 25.2, 29.6, 30.2, 47.1, 117.0, 128.2, 128.3, 132.4, 134.1, 135.2, 136.6, 159.5. Aq 48% HBr solution (33 μL, 5 equiv) was added to a solution of **1a** (36 mg) in EtOH (4 mL). The mixture was stirred at rt for 20 min and evaporated to give a residue, which was subsequently washed with acetone and dried to give **1a**·2HBr[11a] (48 mg, 64%) as a white powder. ^{1}H NMR (CD_3OD) δ 1.94 (2H, quint, J = 7.4 Hz), 2.77 (2H, t, J = 7.4 Hz), 3.31 (2H, t, J = 7.4 Hz), 4.62 (2H, d, J = 5.4 Hz), 7.32−7.54 (5H, m), 9.10 (1H, s), 9.42 (2H, br d, J = 10.2 Hz), 10.12 (1H, br t, J = 5.4 Hz), 14.05 (1H, br s), 14.25 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 22.8, 27.5, 30.0, 45.7, 115.3, 127.9, 129.0, 131.2, 131.8, 133.2, 133.8, 165.1; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{18}{}^{35}ClN_4OS$ $[M + H]^+$ 309.0940, found 309.0932.

***N*-[2-(4-Bromophenyl)ethyl]-*N′*-(3-phenylpropionyl)thiourea (7b).** 4-Bromophenethylamine **6b** (0.31 mL, 2.0 mmol) and PPI (420 mg, 2.2 mmol) were reacted to yield **7b** (352 mg, 45%) according to the synthetic procedure for **7a**. **7b**: white powder; ^{1}H NMR ($CDCl_3$) δ 2.62 (2H, t, J = 7.6 Hz), 2.85−3.00 (4H, m), 3.84 (2H, td, J = 7.6, 5.6 Hz), 7.00−7.50 (9H, m), 9.00 (1H, s), 10.55 (1H, br t, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 30.8, 34.0, 38.9, 46.7 120.3, 126.3, 127.8, 128.3, 130.0, 131.3, 136.6, 138.9, 172.3, 179.0; HRMS (EI) *m*/*z* calcd for $C_{18}H_{19}{}^{81}BrN_2OS$ 392.0381 (M^+), found 392.0369.

***N*-[2-(4-Bromophenyl)ethyl]-*N′*-(3-phenylpropionyl)-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}isothiourea (9b).** Thiourea **7b** (350 mg, 0.90 mmol) was converted into **9b** (626 mg, 94%) according to the synthetic procedure for **9a**. **9b**: oil; ^{1}H NMR ($CDCl_3$) δ 1.98 (2H, quint, J = 7.2 Hz), 2.55−2.70 (4H, m), 2.82 (2H, t, J = 7.2 Hz), 2.94 (2H, t, J = 7.8 Hz), 3.10 (2H, t, J = 7.8 Hz), 3.48 (2H, t, J = 7.2 Hz), 6.54 (1H, s), 7.00−7.50 (25H, m), 11.00 (1/2H, br s); ^{13}C NMR ($CDCl_3$) δ 27.6, 29.3, 30.7, 32.1, 35.2, 42.7, 45.1, 75.0, 117.7, 120.3, 125.3, 127.6, 127.8, 128.0, 129.3, 130.0, 131.3, 136.3, 137.9, 140.0, 141.9, 172.1, 184.3; HRMS (FAB) *m*/*z* calcd for $C_{43}H_{42}{}^{79}BrN_4OS$ $[M + H]^+$ 741.2263, found 741.2263.

***N*-[2-(4-Bromophenyl)ethyl]-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}isothiourea (2b). 9b** (626 mg, 0.84 mmol) was converted into **2b** (290 mg, 57%) according to the synthetic procedure for **2a**. **2b**: oil; ^{1}H NMR ($CDCl_3$) δ 1.97 (2H, quint, J = 7.0 Hz), 2.62 (2H, t, J = 7.0 Hz), 2.75−2.90 (4H, m), 3.48 (2H, t, J = 7.0 Hz), 5.60 (1H, br s), 6.55 (1H, s), 7.00−7.50 (20H, m); ^{13}C NMR ($CDCl_3$) δ 27.0, 29.2, 30.3, 35.1, 44.3, 74.9, 117.8, 119.6, 127.5, 129.2, 130.0, 130.9, 137.7, 137.8, 139.5, 141.8, 158.9; HRMS (FAB) *m*/*z* calcd for $C_{34}H_{34}{}^{79}BrN_4S$ $[M + H]^+$ 609.1688, found 609.1695.

***N*-[2-(4-Bromophenyl)ethyl]-*S*-{3-(imidazol-4-yl)propyl}-isothiourea (1b) and Its Dihydrobromide (1b·2HBr, VUF 4598).** **2b** (275 mg, 0.45 mmol) was converted into **1b** (161 mg, 98%)

(29) Galaffu, N.; Bradley, M. *Tetrahedron Lett.* **2005**, *46*, 859.
(30) Stark, H.; Purand, K.; Hüls, A.; Ligneau, X.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1996**, *39*, 1220.

according to the synthetic procedure for **1a**. **1b**: oil; ^{1}H NMR (CD_3OD) δ 1.90 (2H, quint, J = 7.3 Hz), 2.66 (2H, t, J = 7.3 Hz), 2.75−2.90 (4H, m), 3.40 (2H, t, J = 7.3 Hz), 6.78 (1H, s), 7.08−7.14 (2H, m), 7.32−7.38 (2H, m), 7.55 (1H, s); ^{13}C NMR (CD_3OD) δ 26.6, 30.6, 30.9, 35.8, 45.5, 117.1, 120.3, 131.2, 131.7, 135.3, 136.8, 139.5, 161.5. **1b** was confirmed by conversion into the dihydrobromide (**1b**·2HBr, VUF 4598) previously synthesized by Timmerman et al.[23] according to the synthetic procedure for **1a**·2HBr. **1b**·2HBr:[23] oil; ^{1}H NMR (D_2O) δ 1.76 (2H, quint, J = 7.2 Hz), 2.71 (2H, t, J = 7.2 Hz), 2.96 (2H, t, J = 7.2 Hz), 3.03 (2H, t, J = 7.2 Hz), 3.60−3.80 (2H, overlapped with H_2O in D_2O), 7.15−7.45 (5H, m), 8.62 (1H, s).

***N*-(12-Chloro-1,12-dicarba-*closo*-dodecaboranyl)methyl-*N*′-(3-phenylpropionyl)thiourea (7c). 6c** (110 mg, 0.53 mmol) and PPI (101 mg, 0.53 mmol) were reacted to obtain **7c** (142 mg, 67%) according to the synthetic procedure for **7a**. **7c**: oil; ^{1}H NMR ($CDCl_3$) δ 1.20−3.60 (10H, br), 2.62 (2H, t, J = 7.7 Hz), 2.96 (2H, t, J = 7.7 Hz), 3.80 (2H, d, J = 5.8 Hz), 7.10−7.40 (5H, m), 9.40 (1H, br s), 10.60 (1H, br t, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 30.8, 38.7, 48.6, 72.8, 78.9, 126.2, 127.8, 128.3, 138.8, 172.7, 179.6; HRMS (EI) m/z calcd for $C_{13}H_{23}{}^{10}B_3{}^{11}B_7{}^{35}ClN_2OS$ $(M)^+$ 399.2187, found 399.2201.

***N*-(12-Chloro-1,12-dicarba-*closo*-dodecaboranyl)methyl-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}-*N*′-(3-phenylpropionyl)}-isothiourea (9c).** Thiourea **7c** (142 mg, 0.36 mmol) was converted into **9c** (227 mg, 84%) according to the synthetic procedure for **9a**. **9c**: oil; ^{1}H NMR ($CDCl_3$) δ 1.20−3.60 (10H, br), 1.97 (2H, quint, J = 7.2 Hz), 2.62 (2H, t, J = 7.2 Hz), 2.68 (2H, t, J = 8.2 Hz), 2.94 (2H, t, J = 8.2 Hz), 3.04 (2H, t, J = 7.2 Hz), 3.40 (2H, br s), 6.54 (1H, s), 7.00−7.40 (21H, m), 11.00 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 27.6, 29.1, 30.8, 31.9, 42.7, 48.0, 73.5, 75.1, 78.7, 117.8, 125.4, 126.1, 127.6, 127.9, 128.1, 129.3, 137.9, 139.8, 141.1, 141.9, 142.0, 142.1, 171.4, 184.3; HRMS (FAB) m/z calcd for $C_{38}H_{46}{}^{10}B^{11}B_9{}^{35}ClN_4OS$ $[M + H]^+$ 750.4048, found 750.4062.

***N*-(12-Chloro-1,12-dicarba-*closo*-dodecaboranyl)methyl-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}isothiourea (2c).** To a suspension of **9c** (227 mg, 0.30 mmol) and 10% Pd/C (25 mg) in EtOH (3 mL) was added 80% hydrazine hydrate (37 μL, 0.60 mmol). The reaction mixture was stirred at rt for 1 h. After filtration through Celite, the filtrate was evaporated to give a residue, which was purified by column chromatography with EtOAc as eluent by using the coated silica gel technique to give **2c** (90 mg, 49%). **2c**: oil; ^{1}H NMR ($CDCl_3$) δ 1.20−3.60 (10H, br), 1.95 (2H, quint, J = 7.3 Hz), 2.63 (2H, t, J = 7.3 Hz), 2.84 (2H, t, J = 7.3 Hz), 3.38 (2H, s), 6.55 (1H, s), 7.00−7.50 (16H, m); ^{13}C NMR ($CDCl_3$) δ 26.9, 29.4, 30.4, 47.3, 58.9, 75.1, 78.0, 83.8, 117.9, 127.6, 129.2, 137.9, 139.6, 141.8, 157.8; HRMS (FAB) m/z calcd for $C_{29}H_{38}{}^{10}B^{11}B_9{}^{37}ClN_4S$ $[M + H]^+$ 618.3472, found 618.3495.

***N*-(12-Chloro-1,12-dicarba-*closo*-dodecaboranyl)methyl-*S*-{3-[4(5)-imidazolyl]propyl}isothiourea (1c) and Its Dihydrochloride 1c·2HCl. 2c** (165 mg, 0.27 mmol) was converted into **1c** (95 mg, 94%) according to the synthetic procedure for **1a**. **1c**: oil; ^{1}H NMR ($CDCl_3$) δ 1.20−3.60 (10H, br), 1.96 (2H, quint, J = 6.3 Hz), 2.72 (2H, t, J = 6.3 Hz), 2.86 (2H, t, J = 6.3 Hz), 3.32 (2H, s), 6.79 (1H, s), 7.53 (1H, s); ^{13}C NMR ($CDCl_3$) δ 25.6, 29.6, 30.3, 48.7, 78.2, 83.7, 116.4, 127.4, 129.1, 157.2. HRMS (FAB) m/z calcd for $C_{10}H_{24}{}^{10}B^{11}B_9{}^{35}ClN_4S$ $[M + H]^+$ 376.2377, found 376.2393. **1c** was converted into **1c**·2HCl according to the synthetic procedure for **1a**·2HCl. **1c**·2HCl: amorphous product; ^{1}H NMR (CD_3OD) δ 1.20−3.60 (10H, br), 2.00−2.20 (2H, br m), 2.86−2.96 (2H, br m), 3.24−3.36 (2H, m), 3.62 (2H, br s), 7.42 (1H, s), 8.86 (1H, s); ^{13}C NMR (D_2O) δ 24.2, 29.0, 31.7, 46.9, 80.0, 82.0, 116.8, 128.2, 130.0, 169.1.

***N*-(1,12-Dicarba-*closo*-dodecaboranyl)methyl-*N*′-3-phenylpropionylthiourea (7d). 6d** (302 mg, 1.75 mmol) and PPI (333 mg, 1.75 mmol) were reacted to yield **7d** (603 mg, 95%) according to the synthetic procedure for **7a**. **7d**: white powder; ^{1}H NMR ($CDCl_3$) δ 1.20−3.30 (10H, br), 2.62 (2H, t, J = 7.3 Hz), 2.72 (1H, br s), 2.94 (2H, t, J = 7.3 Hz), 3.80 (2H, d, J = 5.0 Hz), 7.10−7.35 (5H, m), 9.62 (1H, br s), 10.66 (1H, br t, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 30.7, 38.6, 50.3, 59.5, 80.6, 126.1, 127.8, 128.1, 138.8, 172.7, 179.1; HRMS (EI) m/z calcd for $C_{13}H_{24}{}^{10}B_2{}^{11}B_8N_2OS$ $(M)^+$ 364.2613, found 364.2616.

***N*-(1,12-Dicarba-*closo*-dodecaboranyl)methyl-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}-*N*′-3-phenylpropionylisothiourea (9d).** Thiourea **7d** (600 mg, 1.65 mmol) was converted into **9d** (732 mg, 62%) according to the synthetic procedure for **9a**. **9d**: oil; ^{1}H NMR ($CDCl_3$) δ 1.20−3.20 (11H, br), 1.97 (2H, quint, J = 6.8 Hz), 2.63 (2H, t, J = 6.8 Hz), 2.69 (2H, t, J = 8.5 Hz), 2.94 (2H, t, J = 8.5 Hz), 3.06 (2H, t, J = 6.8 Hz), 3.40 (2H, br s), 6.54 (1H, s), 7.05−7.50 (21H, m), 11.00 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 27.4, 29.0, 30.8, 31.9, 42.6, 49.4, 59.3, 75.0, 81.2, 117.7, 125.3, 126.0, 127.2, 127.5, 127.8, 128.8, 129.0, 129.2, 137.8, 139.6, 141.1, 141.8, 171.4, 184.4; HRMS (FAB) m/z calcd for $C_{38}H_{47}{}^{10}B_2{}^{11}B_8N_4OS$ $[M + H]^+$ 715.4474, found 715.4479.

***N*-(1,12-Dicarba-*closo*-dodecaboranyl)methyl-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}isothiourea (2d). 9d** (65 mg, 0.09 mmol) was converted into **2d** (46 mg, 88%) according to the synthetic procedure for **2a**. **2d**: oil; ^{1}H NMR ($CDCl_3$) δ 1.20−3.20 (11H, br), 1.97 (2H, quint, J = 6.3 Hz), 2.66 (2H, t, J = 6.3 Hz), 2.88 (2H, t, J = 6.3 Hz), 3.38 (2H, br s), 6.20 (^{1}/$_2$H, br s), 6.56 (1H, s), 7.05−7.50 (16H, m); ^{13}C NMR ($CDCl_3$) δ 26.8, 29.2, 30.4, 49.0, 58.9, 75.1, 83.8, 117.8, 126.6, 126.9, 127.1, 127.5, 127.8, 128.9, 129.2, 137.9, 139.5, 141.8, 159.0; HRMS (FAB) m/z calcd for $C_{29}H_{39}{}^{10}B_2{}^{11}B_8N_4S$ $[M + H]^+$ 583.3899, found 583.3904.

***N*-(1,12-Dicarba-*closo*-dodecaboranyl)-*S*-{3-[4(5)-imidazolyl]-propyl}isothiourea (1d). 1d·2HCl, and 1d·2HBr. 2d** (292 mg, 0.50 mmol) afforded **1d** (150 mg, 88%) according to the synthetic procedure for **1a**. **1d**: oil (150 mg, 88%); IR (film) ν_{max} 1600, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20−3.20 (11H, br), 1.98 (2H, quint, J = 6.3 Hz), 2.72 (2H, t, J = 6.3 Hz), 2.87 (2H, t, J = 6.3 Hz), 3.35 (2H, s), 6.78 (1H, s), 7.53 (1H, s). ^{13}C NMR ($CDCl_3$) δ 25.5, 29.5, 30.2, 49.6, 58.9, 83.8, 116.6, 134.2, 135.5, 157.7. HRMS (FAB) m/z calcd for $C_{10}H_{25}{}^{10}B_2{}^{11}B_8N_4S$ $[M + H]^+$ 341.2803, found 341.2802. **1d** was converted into **1d**·2HCl and **1d**·2HBr according to the synthetic procedure for **1a**·2HCl and **1a**·2HBr. **1d**·2HCl: amorphous product; ^{1}H NMR (CD_3OD) δ 1.20−3.20 (11H, br), 2.00−2.20 (2H, br m), 2.92 (2H, t, J = 7.0 Hz), 3.20−3.40 (2H, overlapped with H_2O), 3.64 (2H, s), 7.40 (1H, s), 8.82 (1H, s). **1d**·2HBr: ^{1}H NMR (CD_3OD) δ 1.20−3.20 (11H, br), 2.10 (2H, quint, J = 7.2 Hz), 2.92 (2H, t, J = 7.2 Hz), 3.24−3.38 (2H, m), 3.62 (2H, br s), 7.42 (1H, s), 8.85 (1H, d, J = 1.6 Hz); ^{13}C NMR (D_2O) δ 25.0, 29.6, 33.0, 49.7, 62.8, 82.2, 117.7, 133.9, 134.9, 169.8. Further, **1d** was converted into the dipicrate form for analysis. Picric acid (127 mg) in benzene (4 mL) was added to **1d** (92 mg, 0.27 mmol) in benzene (2 mL). Picrate was immediately precipitated, filtered, and dried under vacuum to give **1d**·dipicrate (197 mg). **1d**·dipicrate: yellow prisms; mp 219−221 °C (MeOH); ^{1}H NMR [$(CD_3)_2CO$] δ 1.20−3.20 (10H, br), 2.34 (2H, br m), 3.08 (2H, br m), 3.40 (1H, br s), 3.53 (2H, br m), 3.72 (2H, br s), 7.54 (1H, s), 8.72−8.78 (4H, m), 8.89 (1H, s). Anal. Calcd for $C_{22}H_{30}B_{10}N_{10}O_{14}S$: C, 33.08; H, 3.79; N, 17.54. Found: C, 32.94; H, 3.70; N, 17.57.

***N*-(4-Chlorobenzyl)-*N*′-(3-phenylpropionyl)-*S*-(3-piperidinopropyl)isothiourea (9e).** Acyl thiourea **7a** (135 mg, 0.41 mmol) was converted into **9e** (120 mg, 64%) according to the synthetic procedure for **9a**. **9e**: oil; ^{1}H NMR ($CDCl_3$) δ 1.30−1.70 (6H, m), 1.86 (2H, quint, J = 6.7 Hz), 2.30−2.50 (6H, m), 2.72 (2H, t, J = 8.0 Hz), 2.98 (2H, t, J = 8.0 Hz), 3.11 (2H, t, J = 6.7 Hz), 4.46 (2H, s), 7.10−7.40 (9H, m), 11.20 (^{1}/$_2$H, br s); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.5, 26.0, 29.3, 38.4, 42.5, 46.9, 54.4, 57.8, 125.2, 127.7, 128.1, 128.3, 133.0, 134.2, 141.0, 172.1, 184.2; HRMS (FAB) m/z calcd for $C_{25}H_{33}{}^{35}ClN_3OS$ $[M + H]^+$ 458.2033, found 458.2038.

***N*-(4-Chlorobenzyl)-*S*-(3-piperidinopropyl)isothiourea (1e). 9e** (120 mg, 0.26 mmol) was converted into **2e** (65 mg, 76%) according to the synthetic procedure for **2a**. **1e**: oil; ^{1}H NMR ($CDCl_3$) δ 1.40−1.70 (6H, m), 1.82 (2H, quint, J = 6.8 Hz), 2.32 (4H, br s), 2.43 (2H, t, J = 6.8 Hz), 2.94 (2H, t, J = 6.8 Hz), 4.44 (2H, s),

7.20−7.40 (4H, m). **1e** was confirmed by conversion into a dihydrochloride (FUB 661) previously synthesized by Schunack et al.[17a]

***N*-(4-Chlorobenzyl)-*N′*-(3-phenylpropionyl)-*S*-(3-pyrrolidinopropyl)isothiourea (9f).** Thiourea **7a** (166 mg, 0.50 mmol) was converted into **9f** (112 mg, 51%) in THF (5 mL) according to the synthetic procedure for **9a**. **9f**: oil; ^{1}H NMR ($CDCl_3$) δ 1.74 (4H, br m), 1.88 (2H, quint, J = 7.4 Hz), 2.40−2.60 (6H, br), 2.72 (2H, t, J = 7.4 Hz), 2.97 (2H, t, J = 7.4 Hz), 3.10−3.20 (2H, br), 4.46 (2H, s), 7.10−7.40 (9H, m), 11.20 ($^1/_2$H, br s); ^{13}C NMR ($CDCl_3$) δ 23.7, 29.3, 29.4, 32.0, 42.6, 47.1, 55.2, 125.3, 127.7, 127.8, 128.2, 128.3, 128.5, 133.1, 134.3, 141.2, 172.3, 184.2; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{31}{}^{35}ClN_3OS$ [M + H]$^+$ 444.1876, found 444.1870. Caution: Use of THF as solvent improved the yield of **9f** (51%) compared to that (39%) when benzene was used.

***N*-(4-Chlorobenzyl)-*S*-(3-pyrrolidinopropyl)isothiourea (1f).** Isothiourea **9f** (87 mg, 0.19 mmol) was converted into **1f** (45 mg, 76%) according to the synthetic procedure for **2a**. **1f**: oil; ^{1}H NMR ($CDCl_3$) δ 1.60−1.75 (4H, br), 1.81 (2H, quint, J = 6.7 Hz), 2.40−2.54 (4H, br), 2.59 (2H, t, J = 6.7 Hz), 2.98 (2H, t, J = 6.7 Hz), 4.42 (2H, s), 7.20−7.40 (4H, m); ^{13}C NMR ($CDCl_3$) δ 23.7, 28.9, 29.0, 46.9, 53.1, 53.7, 128.0, 128.1, 128.2, 131.1, 137.5, 158.8 ; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{22}{}^{35}ClN_3S$ [M + H]$^+$ 311.1222, found 311.1224.

***N*-(4-Chlorobenzyl)-*N′*-(3-phenylpropionyl)-*S*-{3-morpholinopropyl}isothiourea (9g).** Thiourea **7a** (166 mg, 0.50 mmol) was converted into **9g** (143 mg, 62%) in THF (5 mL) according to the synthetic procedure for **9a**. **9g**: oil; ^{1}H NMR ($CDCl_3$) δ 1.86 (2H, quint, J = 7.0 Hz), 2.35−2.50 (6H, m), 2.72 (2H, t, J = 7.6 Hz), 2.97 (2H, t, J = 7.6 Hz), 3.12 (2H, t, J = 7.0 Hz), 3.65−3.75 (4H, m), 4.46 (2H, s), 7.10−7.40 (9H, m), 11.30 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 27.5, 28.4, 32.0, 42.7, 47.1, 53.7, 57.5, 66.9, 125.4, 127.8, 127.9, 128.2, 128.5, 133.2, 134.2, 141.1, 172.1, 184.4; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{31}{}^{35}ClN_3O_2S$ [M + H]$^+$ 460.1825, found 460.1833. Caution: Use of benzene as solvent did not give **9g**, although the reason was unknown.

***N*-(4-Chlorobenzyl)-*S*-(3-morpholinopropyl)isothiourea (1g).** **9g** (143 mg, 0.31 mmol) was converted into **1g** (53 mg, 52%) according to the synthetic procedure for **2a**. **1g**: oil; ^{1}H NMR ($CDCl_3$) δ 1.82 (2H, quint, J = 7.0 Hz), 2.35−2.50 (6H, m), 2.94 (2H, t, J = 7.0 Hz), 3.64−3.74 (4H, m), 4.44 (2H, s), 7.20−7.30 (4H, m); ^{13}C NMR ($CDCl_3$) δ 27.4, 28.3, 46.6, 53.5, 56.2, 66.8, 128.0, 128.3, 132.1, 138.3, 158.5; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{23}{}^{35}ClN_3OS$ [M + H]$^+$ 328.1251, found 328.1251.

Alternative Synthesis (B) of Clobenpropit with Use of NPAI: *N*-(4-Chlorobenzyl)-*N′*-(2-nitrophenylacetyl)thiourea (7i). **6a** (0.37 mL, 3.0 mmol) was reacted with NPAI (666 mg, 3.0 mmol) to yield **7i** (778 mg, 71%, less polar) together with *N*-(4-chlorobenzyl)-2-(2-nitrophenyl)acetamide **11j** (266 mg, 29%, more polar) as the byproduct, according to the synthetic procedure for **7a**. **7i**: white powder; IR (Nujol) ν_{max} 1165, 1340, 1520, 1700 cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$] δ 4.32 (2H, s), 4.87 (2H, d, J = 5.7 Hz), 7.30−7.75 (7H, m), 8.05−8.15 (1H, m), 10.45 (3/4H, br s), 10.78 (3/4H, br s); ^{13}C NMR ($CDCl_3$) δ 41.7, 48.2, 125.0, 128.5, 128.9, 129.4, 129.6, 132.7, 133.8, 134.0, 136.5, 149.0, 170.8, 180.5; HRMS *m*/*z* calcd for $C_{16}H_{14}{}^{35}ClN_3O_3S$ 363.0444, found 363.0437. **N-(4-Chlorobenzyl)-2-(2-nitrophenyl)acetamide (11i):** Cotton-like fibers; IR (Nujiol) ν_{max} 1342, 1522, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (2H, s), 4.39 (2H, d, J = 6.0 Hz), 6.22 (1H, brs), 7.10−7.65 (7H, m), 8.00−8.06 (1H, m); ^{13}C NMR ($CDCl_3$) δ 41.2, 43.3, 124.8, 128.1, 128.4, 128.6, 129.8, 133.1, 133.2, 136.1, 148.3, 168.3; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{14}{}^{35}ClN_2O_3$ [M+H]$^+$, 305.0693, found 305.0697.

***N*-(4-Chlorobenzyl)-*N′*-[2-(2-nitrophenyl)acetyl]-*S*-{3-[1-(triphenylmethyl)imidazol-4-yl]propyl}isothiourea (9i).** According to the synthetic procedure for **9a**, mixing alcohol **8a**[30] (1.20 g, 3.27 mmol), **7i** (1.08 g, 2.97 mmol), Bu_3P (1.10 mL, 4.46 mmol), and TMAD (766 mg, 4.46 mmol) in dry benzene (20 mL) gave **9i** (1.81 g, 85%). **9i**: oil; ^{1}H NMR ($CDCl_3$) δ 1.76 (2H, quint, J = 7.2 Hz), 2.48 (2H, t, J = 7.2 Hz), 2.85 (2H, t, J = 7.2 Hz), 4.06 (2H, s), 4.38 (2H, s), 6.52 (1H, s), 7.00−7.50 (23H, m), 7.90−8.00 (1H, m), 11.08 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 27.5, 28.9, 30.8, 45.9, 47.2, 75.1, 117.7, 124.3, 127.1, 127.6, 128.3, 128.5, 129.3, 131.9, 132.5, 132.9, 133.9, 137.9, 139.9, 141.9, 148.7, 173.0, 180.3; HRMS (FAB) *m*/*z* calcd for $C_{41}H_{37}{}^{35}ClN_5O_3S$ [M + H]$^+$ 714.2305, found 714.2299.

Alternative Synthesis of 2a via Intramolecular Amide Cleavage. 9i (1.43 g, 2.01 mmol) in THF (15 mL) was stirred with 10% Pd/C (500 mg). To the suspension were gradually added 1 mL portions of aq saturated sodium phosphinate[26] (slight effervescence was observed between additions, and the reaction was monitored by TLC). When the volume of phosphinate added reached 14 mL after 3 h, TLC was performed to reveal no trace of **9i**. Then, the mixture was filtered and the filtrate was poured into water and extracted three times with $CHCl_3$. The combined extracts were dried and evaporated to yield the residue. Chromatography by using the coated silica gel technique with EtOAc as eluent gave 1-hydroxy-2-oxindole[27] (305 mg quant), and further elution with MeOH−EtOAc (1:1) gave **2a** (991 mg, 90%). 1-Hydroxy-2-oxindole: mp 201−204 °C (EtOAc, hot plate) (lit.[27] mp 200.5−202 °C); IR (Nujol) ν_{max} 1615, 1675 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.55 (2H, s), 7.00−7.50 (4H, m). Thus obtained **2a** was converted into **1a**·2HCl (quant) according to a previously described procedure.

Hydroxymethyl-1,12-dicarba-*closo*-dodecaborane (12). To a solution of *p*-carborane (576 mg, 4.0 mmol) in THF (3 mL) was added dropwise 1.6 M *n*-BuLi in hexane (2.50 mL, 4.0 mmol) at rt, and the mixture was stirred for 15 min at the same temperature. Paraformaldehyde (120 mg, 4.0 mmol) was added and the reaction mixture was stirred at rt for 30 min. The reaction was quenched with H_2O and THF was removed. After dissolving the residue with EtOAc, the organic layer was washed with H_2O and brine, dried, and then evaporated to give a pale yellow solid. It was again diluted with EtOAc, mixed with a small amount of silica gel, and evaporated to obtain coated silica gel for use in column chromatography. Chromatography with EtOAc−hexane (1:9) as eluent gave **12** (696 mg, 70%) as a white powder. **12**: colorless leaflets (hexane); mp 213−215 °C(lit.[31] mp 207−208 °C); ^{1}H NMR [$(CD_3)_2CO$] δ 1.1−3.1 (10H, br), 3.30 (1H, br s), 3.44 (2H, d, J = 6.6 Hz), 4.56 (1H, t, J = 7.5 Hz); HRMS (EI) *m*/*z* calcd for $C_3H_{14}{}^{11}B_{10}O$ 176.1975 (M$^+$), found 176.1977. Further chromatography with EtOAc−hexane (1:4) as eluent provided 1,12-dihydroxymethyl-1,12-dicarba-*closo*-dodecaborane (100 mg, 14%): colorless needles (20% EtOAc in hexane); mp 147−150 °C (lit.[31a] mp 152−154 °C); ^{1}H NMR [$(CD_3)_2CO$] δ 1.2−3.2 (10H, br), 3.44 (2H, d, J = 6.6 Hz), 4.56 (1H, t, J = 7.5 Hz).

12-Chloro-1-hydroxymethyl-1,12-dicarba-*closo*-dodecaborane (13). To a solution of **12** (174 mg, 1.0 mmol) in THF (4 mL) was added dropwise 1.6 M *n*-BuLi in hexane (1.38 mL, 2.2 mmol) at −78 °C, and the reaction mixture was stirred for 1.5 h at the same temperature. Then, *N*-chlorosuccinimide (160 mg, 1.2 mmol) in THF (5 mL) was added slowly to produce a pale red suspension. The resulting mixture was stirred at rt for 5 h. The reaction was quenched with H_2O and THF was removed to give a residue that was partitioned between EtOAc and brine and subsequently extracted by the salting-out technique. The organic layer was dried and evaporated to give a crude material. Chromatography with EtOAc−hexane (1:9) as eluent by using the coated silica gel technique yielded **13** (145 mg, 70%) as a white powder. The chromatography provided initially fractions containing **13**, followed by fractions containing both **12** and **13**, since their R_f values on TLC were very similar. In that case, the mixture was subjected repeatedly to chromatography to obtain pure **13**. **13**: mp 125−128 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 1.2−3.4 (10H, br), 3.48 (2H, d,

(31) (a) Stanko, V. I.; Gol'tyapin, Yu. V. *Zh. Obschch. Khim.* **1971**, *41*, 2033. (b) Herzog, A.; Knobler, C. B.; Hawthorne, M. F.; Maderna, A.; Siebert, W. *J. Org. Chem.* **1999**, *64*, 1045. (c) Goto, T.; Ohta, K.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem.* **2005**, *13*, 6414.

J = 6.9 Hz), 4.70 (1H, t, J = 6.9 Hz); ^{13}C NMR [$(CD_3)_2CO$] δ 64.9, 78.4, 79.0; HRMS m/z calcd for $C_3H_{13}{}^{11}B_8{}^{10}B_2{}^{35}ClO$ (M^+) 208.1658, found 208.1655.

12-Chloro-1-(*O*-tosylmethyl)-1,12-dicarba-*closo*-dodecaborane (14a). In a 10 mL Teflon MW reaction vessel were dissolved **13** (332 mg, 1.59 mmol) and TsCl (606 mg, 3.18 mmol) in pyridine (3.0 mL). The vessel was sealed and heated in the MW reactor to 120 °C. The reaction was held at this temperature for 1 h and cooled thereafter. The contents were partitioned between EtOAc (2 mL) and 2 N HCl (2 mL). The organic layer was washed first with aq saturated $NaHCO_3$ and then with brine, dried, and evaporated to give a residue. This was subjected to the same procedure as that described for the preparation of **12** to yield **14a** (551 mg, 95%) via chromatography. **14a**: colorless plates (hexane); mp 105−106 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 1.2−3.4 (10H, br), 2.45 (3H, s), 3.98 (2H, s), 7.46 (2H, d, J = 7.2 Hz), 7.72 (2H, d, J = 7.2 Hz); ^{13}C NMR [$(CD_3)_2CO$] δ 21.6, 69.8, 72.1, 79.7, 127.9, 130.2; EIMS m/z 363 ($M^+ - 1$); HRMS (EI) m/z calcd for $C_{10}H_{19}{}^1B_9{}^{10}B^{35}ClO_3S$ (M^+) 363.1710, found 363.1733. Caution: **13a** easily sublimes under vacuum.

1-Azidomethyl-12-chloro-1,12-dicarba-*closo*-dodecaborane (15a). With use of the same MW procedure as that for the preparation of **14a**, a suspension of **14a** (576 mg, 1.58 mmol) and NaN_3 (412 mg, 6.34 mmol) in DMF (4 mL) and H_2O (1 mL) was heated in the MW reactor at 150 °C for 2 h. Filtration of the resultant precipitate followed by evaporation gave a residue, which was diluted with EtOAc−hexane (1:1). The organic layer was extracted three times by the salting-out technique. The collected organic layer was washed with brine, dried, and evaporated to give a residue. With use of the same method as that for the purification of **12**, the residue was chromatographed with hexane to give **15a** (267 mg, 72%) as a colorless oil. **15a**: positive in Beilstein's test; IR (film) ν_{max} 1280, 2100 (N_3) cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$] δ 1.2−3.5 (10H, br), 3.54 (2H, s); ^{13}C NMR [$(CD_3)_2CO$] δ 54.6, 75,0, 78.9. The mass spectrum or elementary analysis of **15a** could not be obtained owing to its volatility, but the accuracy of **15a** was guaranteed by synthesizing derivatives **6c**, **7m**, and **3c**.

1-Aminomethyl-12-chloro-1,12-dicarba-*closo*-dodecaborane (6c). A solution of **15a** (41 mg, 0.18 mmol) in a 1:1 solution of MeOH and AcOEt (3 mL) was hydrogenated over 10% Pd/C (16 mg) at 3.2 kg/cm^2 for 2 h. After filtration through Celite, a small amount of silica gel was added to the filtrate, and the mixture was subsequently evaporated to give coated silica gel. This was placed in a column for chromatography with EtOAc−hexane (1:9) as eluent to yield **6c** (31 mg, 86%). **6c**: positive in Beilstein's test; colorless needles; mp 75−78 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 1.2−3.4 (10H, br), 3.25 (2H, s); ^{13}C NMR [$(CD_3)_2CO$] δ 55.6, 77.7. Anal. Calcd for $C_3H_{15}B_{10}N$: C, 20.80; H, 8.73; N, 8.08. Found: C, 20.94; H, 8.70; N, 8.37.

1-(12-Chloro-1,12-dicarba-*closo*-dodecaboranyl)methyl-3-benzoylthiourea (7m). Amine **6c** (73.0 mg, 0.35 mmol) was added dropwise to benzoylisothiocyanate (86.4 mg, 0.53 mmol) in THF (8 mL) and the reaction mixture was refluxed for 1 h. Then, a small amount of silica gel was added. The same chromatographic procedure (hexane) as that used in the purification of **12** gave **7m** (123.0 mg, 95%). **7m**: colorless oil; positive in Beilstein's test; ^{1}H NMR ($CDCl_3$) δ 1.2−3.5 (10H, br), 3.90 (2H, d, J = 6.0 Hz), 7.48−7.55 (2H, m), 7.60−7.67 (1H, m), 7.81−7.85 (2H, m), 9.00 (1H, br s), 10.8 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 49.1, 72.9, 78.8, 127.1, 128.8, 130.9, 133.4, 166.1, 179.8; EIMS m/z 370 ($M^+ - 2$); HRMS m/z calcd for $C_{11}H_{19}{}^{11}B_8{}^{10}B_2{}^{35}ClN_2OS$ 370.1909, found 370.1898.

1-(12-Chloro-1,12-dicarba-*closo*-dodecaboranyl)methylthiourea (3c). K_2CO_3 (49 mg, 0.36 mmol) dissolved in water (2 mL) was added to a solution of **7m** (16.5 mg, 0.04 mmol) in THF (0.5 mL). The mixture was refluxed for 38 h and then THF was evaporated to give a residue that was extracted three times with EtOAc by the salting-out techniques. The organic layer was dried and evaporated to give a residue. Chromatography with EtOAc−hexane (3:7) as eluent and the coated NH-silica gel technique gave **3c** (11.4 mg, 97%) as a white wax. **3c**: positive in Beilstein's test; ^{1}H NMR ($CDCl_3$) δ 1.0−3.8 (10H, br), 3.69 (2H, br s), 5.96 (2H, br s), 6.28 (1H, br s); ^{13}C NMR (CD_3OD) δ 48.7, 77.2, 79.3, 184.7; HRMS m/z calcd for $C_4H_{15}{}^{11}B_8{}^{10}B_2{}^{35}ClN_2S$ 266.1647, found 266.1635.

1-(*O*-Tosylmethyl)-1,12-dicarba-*closo*-dodecaborane (14b). According to the synthetic procedure for **14a**, alcohol **12** (472 mg, 2.71 mmol) was converted into **14b** (819 mg, 92%). **14b**: white powder; ^{1}H NMR [$(CD_3)_2CO$] δ 1.2−3.2 (10H, br), 2.45 (3H, s), 3.40 (1H, br s), 3.92 (2H, s), 7.46 (2H, d, J = 7.9 Hz), 7.74 (2H, d, J = 7.9 Hz); ^{13}C NMR [$(CD_3)_2CO$] δ 21.6, 61.6, 71.0, 79.3, 127.9, 130.1, 132.4, 145.5; HRMS m/z calcd for $C_{10}H_{20}{}^{10}B_2{}^{11}B_8O_3S$ 328.2137, found 328.2141. Caution: **14b** easily sublimes under vacuum.

1-Azidomethyl-1,12-dicarba-*closo*-dodecaborane (15b). According to the synthetic procedure for **15a**, **14b** (1602 mg, 4.90 mmol) was converted into **15b** (795 mg, 82%). **15b**: prisms; mp 34−36 °C (hexane; hot plate); IR (film) ν_{max} 2100 (N_3) cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$] δ 1.2−3.2 (10H, br), 3.2−3.6 (3H, br); ^{13}C NMR [$(CD_3)_2CO$] δ 56.2, 60.7, 82.5. Anal. Calcd for $C_3H_{13}B_{10}N_3$: C, 18.08; H, 6.58; N, 21.09. Found: C, 18.22; H, 6.41; N, 21.31. Caution: **15b** easily sublimes under vacuum.

1-Aminomethyl-1,12-dicarba-*closo*-dodecaborane (6d). According to the synthetic procedure for **6c**, **15b** (209 mg, 1.05 mmol) was converted into **6d** (146 mg, 81%). **6d**: pillars; mp 104−107 °C (hexane; hot plate); ^{1}H NMR ($CDCl_3$) δ 1.2−3.3 (11H, br), 2.70 (2H, s); ^{13}C NMR [$(CD_3)_2CO$] δ 49.6, 58.5, 87.5. Anal. Calcd for $C_3H_{14}B_{10}ClN$: C, 17.35; H, 6.79; N, 6.74. Found: C, 17.44; H, 6.60; N, 6.81.

Acknowledgment. We are grateful to Dr. K. Minoura and Ms. M. Fujitake of this university for NMR and MS measurements, respectively. This work was supported in part by a Grant-in-Aid for Scientific Research [No.16590024 (to S.H.)] from JSPS. We also acknowledge a Grant-in-Aid for "High Technology Research Center" Project for Private Universities: matching fund subsidy from MEXT (Ministry of Education, Sciences, Sports and Culture), 2007−2009, Japan.

Supporting Information Available: General information and copies of ^{1}H and/or ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702181X