Tetrahedron Vol. 48, No. 23, pp. 4767-4772, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Borohydride Reduction of Imidazolidino[1,2-d]dithiadiazepines+

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(*Received in USA* 18 *December* 1991)

Key Words: Imidazolidino[1,2-d]dithiazepines; 1,2-dithia-5,8-diaza-cyclodecane; borohydride reduction;by-products; reaction mechanism.

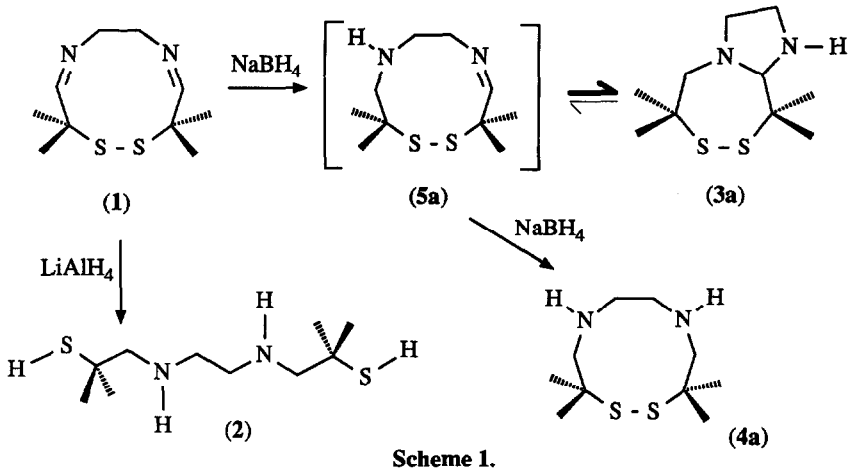
Abstract: *Imidazolidino[1,2-d]dithiadiazepines are converted to the ten-membered saturated heterocycles via borohydride reduction in acidic media or using "in situ" generated borane. Reductive alkylation in acetic or propionic acid as a solvent represents a significant side reaction. Relatively stable boron compounds are identified as intermediates which yield the saturated heterocycles upon acidic hydrolysis.*

INTRODUCTION

Diamino-dithiols have been used as ligands of ^{99m}Tc complexes in single photon emission computed tomography (SPECT). $LiAlH_4$ reduction of 3,3,10,10-tetramethyl-1,2-dithia-5,8-diaza-cyclodeca-4,8-dien (**1**) is a convenient route to prepare one of these compounds, N,N'-bis[2-mercapto-2-methylpropyl]-ethylenediamine (**2**)[1]. There is, however, no possibility for obtaining N-substituted derivatives of the ligand by this method. Specific functional groups attached to the substituents may beneficially influence the uptake and retention of the complexes in the brain allowing differential brain imaging. Brain-targeting and "lock-in" by affecting the bidirectional movement of the compounds using the chemical delivery system (CDS) approach[2,3], such as the one based on the dihydropyridine ⇌ pyridinium salt redox equilibrium[4,5], have been applied to a number of drugs. The use of this dual (redox) brain targetor function as part of the ligand may also eliminate the major drawback of the ^{99m}Tc-ligand systems prepared to date that they are either not taken up through the blood-brain-barrier or that they are poorly retained[6-8].

Reduction of **1** with $NaBH_4$ has been proposed to yield the ten-membered heterocycle[6-8] (**4a**, Scheme 1), which would be a suitable intermediate to sequentially prepare N-substituted diamino-dithiols. However, it has been found that the main product of the reaction is the bicyclic compound **3a**, and **4a** is obtained only as a by-product[9]. An equilibrium between **3a** and the monounsaturated ten-membered heterocycle (**5**) seems to exist, as shown in Scheme 1, so **3a** can be further reduced to **4a**. Nevertheless, this reaction proceeds extremely slowly, and the method would find limited preparative significance. Our aim was to develop improved procedures for the preparation of **4a** and its derivatives from imidazolidino[1,2-d]dithiadiazepines, and also to gain insight into the reaction mechanism.

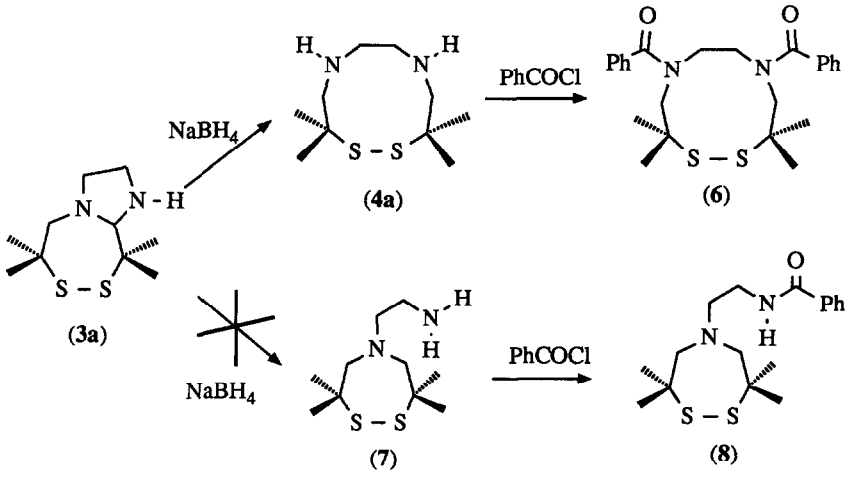
+Dedicated to Professor Gábor Fodor to his 75th birthday.



Scheme 1.

RESULTS AND DISCUSSION

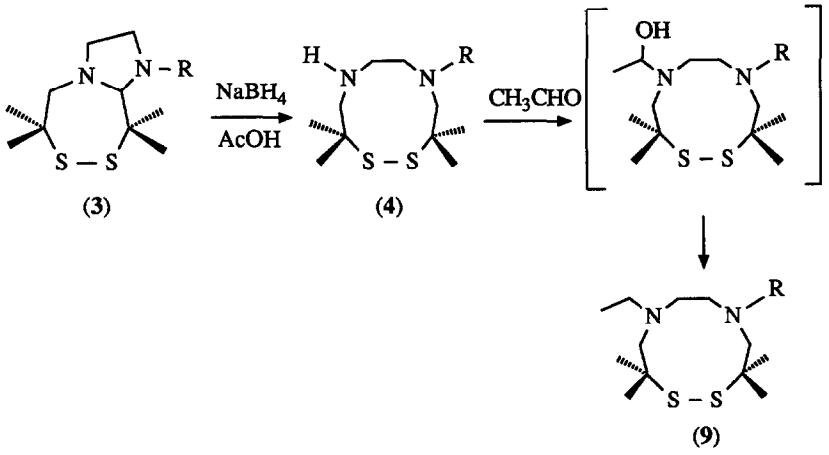
We found that $NaBH_4$ reduction of **3a**, its N-methyl (**3b**), and N-(2-hydroxyethyl) derivatives (**3c**) yields **4a-c** in acidic media such as in glacial acetic acid (Method A), respectively. Theoretically, the reduction is also possible in another way, as shown in Scheme 2 for the unsubstituted compound **3a**. However, we concluded from the subsequent acylation of the product that under the applied conditions the reaction gave solely the ten-membered saturated heterocycle (**4a**). The doubly substituted compound (**6**) is obtained from the reaction with benzoyl chloride, while **7** would yield the monoacyl compound **8.**



Scheme 2.

The reduction in acetic acid is accompanied by side reactions, so the product is contaminated with the corresponding N-ethyl derivative (**9a-c**). The yield of the by-product depends on the reaction time. The dissolution of $NaBH_4$ in the solvent takes longer when pellets are used instead of powder. As a consequence of the concomitant increase in reaction time using the pellets, the ethyl derivative (**9c**) may be obtained in as

high as 60 % yield. The probable explanation is that $NaBH_4$ is able to slowly reduce acetic acid to acetaldehyde, and the by-product is formed by reductive alkylation[10], as shown in Scheme 3. We have also carried out the reduction of **3a** in propionic acid (Method B). The N-propyl derivative (**10a**) was obtained, and it was now the main product of the reaction. This is due to the poor solubility of $NaBH_4$ in propionic acid which, similarly to the use of borohydride pellets in acetic acid, also necessitates the addition of the reducing agent to the reaction mixture over a longer period of time.



(3) (4) (9)

Scheme 3.

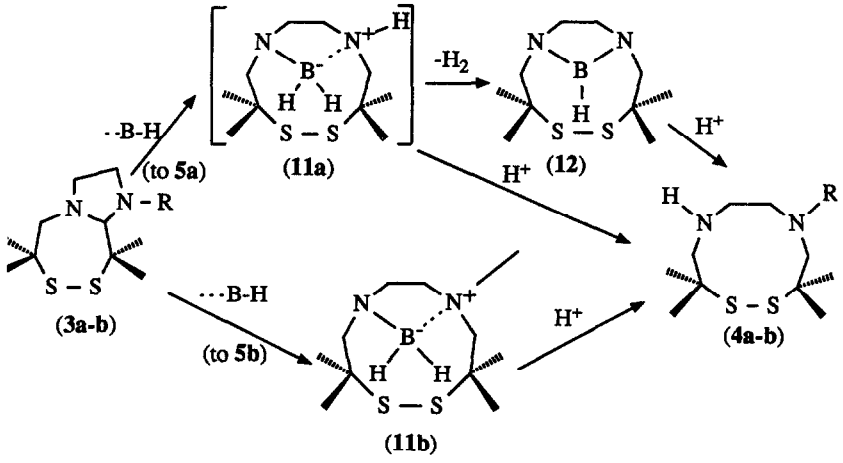
The reductive alkylation can be avoided using an acetic acid/methanol mixture (3:2, v/v) as a solvent (Method C). In this way, the yield may be as high as 90 %, and the product usually does not need chromatographic purification.

We noted that the crude reaction products also contained small amounts of unknown compounds detected by fast atom bombardment (FAB) mass spectrometry at *m/z* values 10 (for **3a**) or 12 (for **3b-c**) higher than the expected product molecular ions. These peaks diminished upon repeated treatment of the crude product with acid, thus this was an indication that relatively stable reaction intermediates were detected. The isotope pattern of the mass-separated intermediates also showed the presence of boron in the molecules. The boron has two stable isotopes (^{10}B and ^{11}B) with 20 and 80 percent natural abundance, respectively[11].

The observed acid sensitivity of the intermediates suggests that by avoiding acidic solvent compounds **4a-c** can also be obtained in a two-step reaction, provided that the "activity" of $NaBH_4$ toward **3a-c** can be increased. We employed stoichiometric amount of BF_3*Et_2O complex to generate borane as the reducing agent from $NaBH_4$ in tetrahydrofuran solution[12], and isolated the relatively stable boron compounds detected earlier by FAB mass spectrometry. These intermediates decompose in acetic acid slowly, but in the presence of hydrochloric acid the ten-membered saturated heterocycles can be obtained almost instantaneously (Method D). The N-ethyl derivatives (**9a-c**) remained as by-products, but they are now due to alkylation by the BF_3*Et_2O. Therefore, this reaction can be avoided using another complex such as BF_3*THF as a source of the boron halide. Nevertheless, this procedure has mechanistic significance in terms of detecting intermediates in the borohydride/borane reduction of the title compounds. The proposed reaction mechanism is shown in Scheme 4.

The hydride addition/transfer obviously takes place at the C=N double bond of structure **5**[13]. It is reasonable to assume that coordinative N-B bond involving the amino nitrogen is also an attribute of the structure. We obtained a bond order of 0.478 between the boron and the methyl nitrogen in compound **11b** by semi-empirical (AM1) quantum chemical calculations[14]. The existence of this bond gives a weak zwitterionic character to the compound. However, **11a** cannot be stable due to the presence of an acidic

hydrogen (N^+-H) together with a hydride (B^--H) moiety in the complex, and it is stabilized through the elimination of a hydrogen molecule resulting in a neutral boron compound **12**.



Scheme 4.

In conclusion, we have developed methods for obtaining possible intermediates of novel N-substituted or even N,N'-disubstituted diaminodithiols, which could be used as ligands for ^{99m}Tc complexes. Evidence on the mechanism of the borohydride reduction of imidazolidino[1,2-d]dithiazepines has also been reported.

EXPERIMENTAL

Instruments and Methods

Melting points were determined on a Fisher-Jones apparatus, and are reported uncorrected. Elemental (combustion) analyses were supplied by Atlantic Microlabs, Inc. (Norcross, GA). ^{1}H-NMR spectra were obtained on a Varian EM 390 (90 MHz) instrument using deuterochloroform solvent and tetramethylsilane internal standard. Electron ionization (EI, 70 eV) and FAB mass spectra were recorded on a Kratos MS80RFA instrument. Direct probe introduction was used for recording the EI mass spectra, and FAB analyses (xenon beam, 8 keV) were performed by dissolving the sample in 3-nitrobenzyl alcohol matrix.

Thin layer chromatography (TLC) was performed on $60F_{254}$ Silicagel plates (Merck, Darmstadt, Germany). Chemicals, solvents and silicagel (70-230 Mesh, 60 Å, for column chromatography) were purchased from Aldrich (Milwaukee, WI).

The AM1 molecular orbital method[14] was part of the MOPAC (version 5.10) program. A Tektronix Computer Aided Chemistry (CAChe™) Worksystem run on an Apple Macintosh™ II computer was used for computation. The structural input was generated using a Macintosh interface, and all starting geometries were obtained by molecular mechanics (MM2) optimization.

Synthesis

The procedures applied for the preparation of 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacylodeca-4,8-diene[1,6], **3a**[9], and **3b**[15] were adopted from the literature.

9-(2-Hydroxyethyl)-1,1,4,4-tetramethylimidazolidino[1,2-d]dithiazepine (3c). **3a** (9.98 g, 43.0 mmol) was dissolved in ethanol (50 ml), then 3.0 g (28.3 mmol) of Na_2CO_3, 1.0 g (6.7 mmol), and 6 ml (10.38 g, 85 mmol) of bromoethanol were added. The mixture was refluxed for 16 hours. The precipitated solids were then filtered off, the solvent was evaporated, and the residue was treated with water. Extraction with

chloroform resulted in a light brown oil which was purified by column chromatography (benzene; benzene - ethyl acetate, 8:2) to yield 7.81 g (65 %) of colorless oil. FAB-MS (*m/z*, relative intensity) 277 (100, $[M+H]^+$); Anal. found (calc. for $C_{12}H_{24}N_2OS_2$) C 52.06 (52.13) %, H 8.71 (8.75) %, N 10.03 (10.13) %, S 23.27 (23.19) %; ^{1}H-NMR ($CDCl_3$) δ 1.20-1.30 (q, 12H, 4 x CH_3), 2.4-3.6 (m, 9H), 3.59 (t, 2H).

Preparation of the 1,2-Dithia-5,8-Diazacyclodecanes - Method A. The imidazolidino[1,2-d]-dithiazepine (**3**, 10 mmol) is dissolved in acetic acid (40 ml). At cold water temperature (10°C), $NaBH_4$ (1.3 g, 34 mmol) was added in portions within an hour. It was stirred for an additional 2 hours, then acetone (5 ml) and water (10 ml) were added to obtain clear solution. The solvents were evaporated under reduced pressure, and the residue was treated with water acidified with cc. HCl. The solution was concentrated, then extracted with chloroform at pH 10. After evaporation of the solvent, the residue (a colorless oil) was purified by chromatography (chloroform; chloroform-ethanol, 3:2).

*3,3,10,10-Tetramethyl-1,1-dithia-5,8-diazacyclodecane (**4a**).* This compound was obtained in 61 % yield according to Method A. M.p. 56-58°C; EI-MS (*m/z*, relative intensity) 234 (58, $M^{+\cdot}$), 85 (79), 84 (63), 71 (45), 56 (57), 55 (60), 43 (100), 41 (44); Anal. found (calc. for $C_{10}H_{22}N_2S_2$) C 51.16 (51.21) %, H 9.49 (9.43) %, N 11.93 (11.95) %, S 27.30 (27.34) %; ^{1}H-NMR ($CDCl_3$) δ 1.20-1.35 (q, 12H, 4 x CH_3), 2.10 (s, 2H), 2.75 (m, 8H).

*5-Ethyl-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane (**9a**).* This compound was obtained as the by-product of the reduction of **3a** according to method A. Yield 34 %; EI-MS (*m/z*, relative intensity) 262 (98, $M^{+\cdot}$), 204 (100), 130 (54), 84 (33), 58 (100), 56 (43), 55 (43), 42 (42), 41 (37); ^{1}H-NMR ($CDCl_3$) δ 1.10 (t, 3H), 1.20-1.30 (q, 12H, 4 x CH_3), 2.30-2.90 (m, 10H).

*5,8-Dibenzoyl-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane (**6**).* This compound was prepared by dissolving **4a** (0.85 g, 3.63 mmol) in pyridine (20 ml) and reacting with benzoyl chloride (1.2 ml, 10 mmol). The mixture was stirred overnight at room temperature, then it was poured into water (200 ml). The precipitate was filtered off and washed with water. The white solid was recrystallized from methanol (6 ml), and colorless crystals were obtained. Yield 0.67 g (42 %); M.p. 182-183°C; FAB-MS (*m/z*, relative intensity) 443 (13, $[M+H]^+$), 202 (15), 148 (12), 105 (100); Anal. found (calc. for $C_{24}H_{30}N_2O_2S_2$) C 65.19 (65.12) %, H 8.68 (8.83) %, N 6.27 (6.33) %, S 14.39 (14.48) %; ^{1}H-NMR ($CDCl_3$) δ 1.20-1.40 (q, 12H, 4 x CH_3), 3.30-4.20 (m, 8H), 7.00-7.40 (m, 10H).

*5-(2-Hydroxyethyl)-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane (**4c**).* The compound was obtained in 51 % yield according to Method A. M.p. 64-67°C; FAB-MS (*m/z*, relative intensity) 279 (100, $[M+H]^+$), 218 (13), 204 (67); Anal. found (calc. for $C_{12}H_{26}N_2OS_2$) C 51.80 (51.75) %, H 9.42 (9.41) %, N 10.00 (10.06) %, S 22.96 (23.02) %; ^{1}H-NMR ($CDCl_3$) δ 1.20-1.30 (q, 12H, 4 x CH_3), 2.30-2.90 (m, 10H), 3.55 (t, 2H).

*5-(2-Hydroxyethyl)-8-Ethyl-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane (**9c**).* This compound was obtained as a by-product (35 % yield) of the reduction of **3c** according to Method A. FAB-MS (*m/z*, relative intensity) 307 (38, $[M+H]^+$), 218 (16), 204 (19), 116 (64), 102 (100); ^{1}H-NMR ($CDCl_3$) δ 1.00 (t, 3H), 1.20-1.30 (q, 12H, 4 x CH_3), 2.30-2.90 (m, 12H), 3.50 (t, 2H).

Preparation of the 1,2-Dithia-5,8-Diazacyclodecanes - Method B. It is similar to Method A, but uses propionic acid as a solvent. The addition of $NaBH_4$ lasted more than 2 hours.

*5-Propyl-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane (**10a**).* This compound was prepared from **3a** in 77 % yield according to Method B. EI-MS (*m/z*, relative intensity) 276 (84), 204 (94), 130 (53), 84 (35), 58 (100); ^{1}H-NMR ($CDCl_3$) δ 0.85-1.25 (m, 17H), 2.30-2.90 (m, 8H).

Preparation of the 1,2-Dithia-5,8-Diazacyclodecanes - Method C. Same as Method A with the exception that a mixture of acetic acid and methanol (3:2, v/v) was used as a solvent.

*5-(2-Hydroxyethyl)-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane (**4c**).* A yield of 93 % was achieved by the reduction of **3c** according to Method C. No chromatographic purification was necessary due to the presence of trace impurities from side reactions.

Preparation of the 1,2-Dithia-5,8-Diazacyclodecanes - Method D. The imidazolidino[1,2-d]-dithiazepine (**3**, 10 mmol) was dissolved in tetrahydrofurane (40 ml), then BF_3*Et_2O (4 ml, 32 mmol) was

added. Under cooling, $NaBH_4$ was slowly admixed, and the solution was stirred overnight at room temperature. Acetone (5 ml) was then added, and the solvents were evaporated under reduced pressure. The residue contained the boron complex (**11a-c**), and/or the diaminoborane (**12**), as appropriate (See Scheme 4). (After treatment with water and adjusting the pH to slightly basic with 10 % aqueous $NaCO_3$, the relatively stable boron complex **11b** and the cyclic diaminoborane **12** could be obtained. They were recrystallized from heptane or heptane - petroleum ether.) Normally, the extraction residue was dissolved in methanol, acidified with cc. HCl, and concentrated again. The work-up procedure was the same as described under Method A.

*3,3,10,10-Tetramethyl-1,2-dithia-5,8-diazacyclodecane (**4a**).* This compound was obtained in 42 % yield from **3a** according to Method D.

*5-Ethyl-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane (**9a**).* It was the by-product (56 % yield) of the reduction of **3a** according to Method D.

*3,3,5,10,10-Pentamethyl-1,2-dithia-5,8-diazacyclodecane (**4b**).* This compound was prepared in 28 % yield according to Method D. M.p. 168-170°C; EI-MS (*m/z*, relative int.) 248 (63, $M^{+\cdot}$), 204 (100), 130 (55), 107 (51), 55 (48), 44 (93), 42 (40), 41 (46); ^{1}H-NMR ($CDCl_3$) δ 1.20-1.30 (q, 4 x CH_3), 2.30-2.90 (m, 11H).

*5-(2-Hydroxyethyl)-3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodeca ne (**4c**).* From the reduction of **3c** according to Method D, this compound was obtained in 44 % yield after column chromatography.

*5-(2-Hydroxyethyl)-8-Ethyl-3,3,10,10-tetramethyl-1,2-dithia-5,8-cyclodecane (**9c**).* It was separated as the by-product (28 % yield) of the reduction of **3c** according to Method D.

*Amine(N-B)-Aminoborane internal complex of 3,3,5,10,10-Pentamethyl-1,2-dithia-5,8-diazacyclodecane (**11b**).* This complex was isolated as an intermediate of the reduction of **3b** according to Method D. M.p. 75-76°C; FAB-MS (*m/z*, relative intensity) 261 (100, $[M+H]^+$ for ^{11}B), 260 (23, $[M+H]^+$for ^{10}B); Anal. found (calc. for $C_{11}H_{25}BN_2S_2$) C 50.38 (50.76) %, H 10.33 (9.68) %, N 10.70 (10.77) %, S 24.39 (24.64) %.

*3,3,10,10-Tetramethyl-1,2-dithia-5,8-diaza-11-borabicyclo[6,2,1]undecane (**12**).* This cyclic diaminoborane was isolated as an intermediate of the reduction of **3a** according to Method D. M.p. 52-54°C; FAB-MS (*m/z*, relative intensity) 245 (100, $[M+H]^+$ for ^{11}B), 244 (30, $[M+H]^+$ for ^{10}B).

REFERENCES AND NOTES

1. Corbin, J.L.; Work, D.E. *J. Org. Chem.* **1976**, *41*, 489-.
2. Bodor, N. In *Advances in Drug Research*, Vol. 13, Academic Press, London, 1984, pp. 255-331.
3. Bodor, N.; Elkoussi, A.; Kano, M.; Nakamura, T. *J. Med. Chem.* **1988**, *31*, 100-106.
4. Bodor, N.; Simpkins, J.W. *Science* **1983**, *221*, 65-67.
5. Pop, E.; Wu, W.M.; Shek, E.; Bodor, N. *J. Med. Chem.* **1989**, *32*, 1774-1781.
6. Kung, H.F.; Molnar, M.; Billings, J.; Wicks, R.; Blau, M. *J. Nucl. Med.* **1984**, *25*, 326-332.
7. Lever, S.Z.; Burns, M.D.; Kervitski, T.M.; Goldfarb, H.V.; Woo, D.V.; Wong, D.F.; Epps, L.A.; Kramer, A.Y.; Wagner, H.N., Jr. *J. Nucl. Med.* **1985**, *26*, 1287-1294.
8. Scheffel, U.; Goldfarb, H.W.; Lever, S.Z.; Gugnon, R.L.; Burns, H.D.; Wagner, H.N., Jr. *J. Nucl. Med.* **1988**, *29*, 73-82.
9. Joshua, A.V.; Scott, J.R.; Sondhi, S.M.; Ball, R.G.; Lown, J.W. *J. Org. Chem.* **1987**, *52*, 2447-2451.
10. Grible, G.W.; Lord, P.D.; Skotnicki, J.; Dietz, S.E.; Eaton, J.T.; Johnson, J.L. *J. Am. Chem. Soc.* **1974**, *96*, 7812-7814.
11. Emsley, J. *The Elements*, Oxford University Press, Oxford, 1989, pp. 32-33.
12. Brown, H.C.; Murray, K.J.; Murray, L.J.; Snover, J.A.; Zweifel, G. *J. Am. Chem. Soc.* **1960**, *82*, 4233-4241.
13. Yamada, S.; Ikegami, S. *Chem. Pharm. Bull.* **1966**, *14*, 1389-1399.
14. The AM1 molecular orbital method: (a) Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909. Parametrization for boron: (b) Dewar, M.J.S.; Jie, C.; Zoebisch, E.G. *Organometallics* **1988**, *7*, 513-521.
15. Baido, K.E.; Lever, S.Z. *Bioconjugate Chem.* **1990**, *1*, 132-137.