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Synthesis of Novel α-Aminoboronate Complexes of Aminoboranes and Aminocyanoboranes

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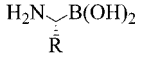
Tertiary amines activated either by borane (BH_3) or cyanoborane (BH_2CN) groups were α-C lithiated with *s*BuLi (2 equiv.) and then treated with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to produce the α-aminoboronate complexes of aminoboranes and aminocyanoboranes **2**–**7** in 70–85 % yields.

Introduction

During the last 30 years much effort has been focused in the area of pharmaceutical chemistry on the synthesis and biological activity studies of boron analogues of α-amino acids (α-aminoboronic acids **1**), in which the carboxylic acid moiety is replaced by a boronic acid moiety, as they are highly effective inhibitors of serine proteases.[1] In addition, α-aminoboronic acids have been shown to be inhibitors for proteosomes, arginase, NOS,[2] and cysteine enzymes.[3] The incorporation of a Lewis basic amine and a Lewis acidic boronic acid functionality into the same molecule is a notoriously difficult procedure, and synthetic routes to these compounds are scarce. It is known that primary and secondary derivatives of α-aminoboronic acids are not stable in their neutral form; however, they can be stabilized either by forming their hydrochloride salts or by converting the molecules into their amide derivatives.[4–6] In this context, new effective methods to prepare amino and related boron compounds will have a tremendous impact on synthetic, bioinorganic, and pharmaceutical chemistry.[7–12] The first synthesis of an α-amidoboronic ester was reported by Matteson et al.,[13] and remains the standard method for synthesis of α-aminoboronic acids; however, it is a multistep method and is time consuming.



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Deprotonation of tertiary amines can be promoted by a Lewis acid, since on forming a complex a positive charge develops on the nitrogen to inductively facilitate the removal of a proton from the α-C position. This concept of tertiary amine activation using Lewis acid activators was introduced by Kessar and co-workers in 1991. These authors used BF_3 as an activator that facilitated the α-metalation of several tertiary amine complexes.[14] Based on these results, in 1995 Ebden and co-workers applied a similar approach to aminoborane complexes, which underwent interesting metalation reactions.[15]

Trimethylaminocyanoboranes can also be easily α-deprotonated at the α-carbon and treated with various electrophiles to give more complicated aminocyanoboranes, as was recently reported by Takrouri et al.[16] The biological and pharmaceutical activities of aminocyanoboranes ($A{\cdot}BH_2CN$) and aminocarboxyboranes ($A{\cdot}BH_2COOH$) and their amide, ester, peptide, and transition metal derivatives have been investigated;[17] they have been shown to possess anticancer,[18] antiosteoporotic,[19] antiinflammatory,[20] and hypolipidemic properties.[20b,21] These molecules have also been mentioned as possible boron carriers to tumor cells for boron neutron capture therapy (BNCT).[22]

Based on the above results, we have now applied these methods with a more complex electrophile. Thus, the boron-containing electrophile 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was mainly used to give the α-aminoboronic ester attached to the cyano (BH_2CN) or borane (BH_3) groups on the same molecule. In this work, we report a novel, short, simple, and direct method to prepare novel α-aminoboronate complexes of aminoboranes and aminocyanoboranes in very good yields. Our method starts from tertiary amines that are activated either by borane or cyanoborane groups. This, in turn, leads to selective α-deprotonation. Reaction of the lithiated complexes with a boron-containing electrophile gives the title compounds.

Results and Discussion

Preparation of Aminoborane Derivatives

We initially focused on 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as an electrophile in our study. Treat-

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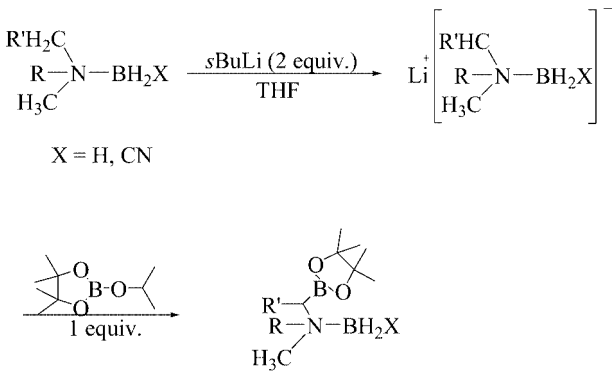
ment of the borane adduct with two equivalents of *s*BuLi in THF at –78 °C, warming to the room temperature, followed by recooling to –78 °C and addition of the electrophile gave good yields of the desired α-aminoboronic acid products **2** and **3** (Scheme 1, Table 1).



Scheme 1. Synthesis of α-aminoboronate complexes of aminoboranes and aminocyanoboranes.

Table 1. α-Aminoboronic acid derivatives **2**–**7** prepared from aminoboranes or aminocyanoboranes.

Product	X	R′	R	Yield [%][a]
2	H	Ph	CH_3	85
3	H	2-naph	CH_3	84
4	CN	H	CH_3	83
5	CN	H	C_4H_9	70
6	CN	H	C_9H_{19}	80
7	CN	H	$C_{12}H_{25}$	70

[a] Yields after column chromatography.

The use of an excess of *s*BuLi is necessary to get high yields, as using a lower amount of *s*BuLi resulted in reduced conversion to product and recovery of unreacted starting material. We suspect that this may be due to the known instability of organolithium reagents in THF.[23] It is also possible that some limited destruction of the borane complexes occurs by nucleophilic attack of *s*BuLi, resulting in partial consumption of the base. Adventitious water may also be involved.[15]

The products were stable enough to be purified on silica gel and were isolated as solids. However, these products should be stored at low temperature, otherwise they decompose slowly to give back the starting material.

Preparation of Aminocyanoborane Derivatives

In an analogous manner, trialkylaminocyanoboranes were lithiated with *s*BuLi and then treated with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give the oily alkyl α-aminoboronic acid derivatives **4**–**7**. The desired products were purified on silica gel in high yields and in high purity (Scheme 1, Table 1).

Products **2**–**7** were fully characterized by ^1H, ^{13}C, and ^{11}B NMR spectroscopy, GC/MS, FT-IR spectroscopy, and elemental analysis. In the borane products **2** and **3** a new stereogenic center is created in the benzylic position, which means that the methyl groups attached to the nitrogen become diastereotopic and peaks for each group are evident in both the ^1H and ^{13}C NMR spectra. The methyl groups on the pinacol are also diastereotopic and peaks for each of the two methyls appear in the ^1H and ^{13}C NMR spectra.

The 4,4,5,5-tetramethyl-1,3,2-dioxaborolane group causes a high-field shift of the benzylic proton in the ^1H NMR spectra in products **2** and **3** and also for the methylenic protons in products **4**–**7** in comparison with the starting materials. In the ^{13}C NMR spectra of all products typical pinacol peaks are observed at δ = 24 [C(CH_3)$_2$] and 84 ppm [C(CH$_3$)$_2$]. No peaks are observed for the carbon in the α-position to the boron due to the rapid relaxation of this boron-bound carbon.[24] Two peaks are observed in the ^{11}B NMR spectra of all the products: a positive boron chemical shift appears as a singlet at δ = 29–30 ppm, which is typical for a boron substituted with two oxygens, and a negative boron chemical shift, which is typically associated with tetracoordinate boron, appears as a quartet for products **2** and **3** at δ = –9 ppm or as a triplet for products **4**–**7** at δ = –14 ppm. These results agree with results published in the literature.[25] Typical peaks are also observed in the FT-IR spectra [2236–2407 (B–H), 2196–2199 (C≡N), 653–752 cm^{-1} (B–N)].

Conclusions

A series of novel α-aminoboronic acids **2**–**7** that also bear a borane or cyanoborane group have been prepared in a one-pot reaction in very good yields. This method involves short reaction times and is applicable to prepare diverse α-aminoboronic acids.

Experimental Section

Materials and Instrumentation: Solvents were dried with sodium/benzophenone and freshly distilled before use. All reactions were carried out under dry nitrogen in oven-dried glassware. Melting points were determined on a Fisher scientific melting point apparatus. Infrared spectra were run for samples as neat films for liquids and in KBr disks for solids on a Bruker Vector 22 FT-IR spectrophotometer. ^1H, ^{13}C, and ^{11}B NMR spectra were recorded with a Varian Unity spectrometer (300, 75, and 96 MHz, respectively). Elemental analysis was performed in-house at the Hebrew University Microanalysis laboratory. Chemical shifts were recorded relative to an internal standard ($SiMe_4$) for ^1H and ^{13}C NMR and an external standard ($Et_2O{\cdot}BF_3$) for ^{11}B NMR spectroscopy. Liquid chromatography was performed by column chromatography with the indicated solvent system on Merck silica gel 60 (0.040–0.063 mm).

Synthesis: All aminoboranes complexes were prepared from borane methylsulfide and the corresponding amine using the literature method.[15] Trimethylaminocyanoborane was prepared from trimethylamine hydrochloride and sodium cyanoborohydride using the literature method.[26] All other cyanoboranes were prepared analogously as in the literature.[16] The electrophile 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared using the literature method.[27] All other chemicals were obtained from Sigma–Aldrich and used as received without any further purification.

General Procedure. Synthesis of 2: A solution of *s*BuLi in cyclohexane (1.3 M, 2 mmol) was added dropwise to a solution of (dimethylbenzylamino)borane (0.149 g, 1 mmol) in THF (2.5 mL) at –78 °C. The solution was stirred for 30 min at –78 °C, then it was warmed up to room temperature for 30 min, before cooling down to –78 °C again and addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.186 g, 1 mmol) in one portion. After 2 min the cooling bath was removed, and the reaction mixture was stirred for 30 min at room temperature. A saturated $NaHCO_3$ solution (10 mL) was then added, the layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 10 mL); the combined organic layers were dried with sodium sulfate. After evaporation of all the volatiles the residue was purified by column chromatography on silica gel (2.5% EtOAc in petroleum ether) to give *N*,*N*-dimethyl-*N*-[phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]aminoborane (**2**) as a white solid, m.p. 93–95 °C, (0.235 g; yield: 85%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.22 [s, 6 H, $C(CH_3)_2$], 1.28 [s, 6 H, $C(CH_3)_2$], 2.36 (s, 3 H, NCH_3), 2.70 (s, 3 H, NCH_3), 3.83 (s, 1 H, PhC*H*), 7.35 (m, 5 H, Ph) ppm; BH could not be detected. ^{11}B NMR ($CDCl_3$, 25 °C): δ = –9.1 (q, J = 96.25 Hz), 29.4 ppm (s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = 24.7, 24.8, 47.0, 52.1, 84.3, 128.6, 129.0, 132.5, 132.9 ppm; BC could not be detected. IR (KBr): $\tilde{\nu}$ = 2363 cm^{-1} (B–H), 2321 (B–H), 2270 (B–H), 1469 (C–N) 664 (B–N) ppm. MS (EI): *m*/*z* = 275 [M$^+$], 261, 246, 231, 217, 202, 187, 172, 157, 132, 127. $C_{15}H_{27}B_2NO_2$ (275): calcd. C 65.45, H 9.81, N 5.09; found C 66.25, H 9.80, N 5.12.

Preparation of *N*,*N*-Dimethyl-*N*-[naphthalen-2-yl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]aminoborane (3): White solid, m.p. 108–110 °C, (0.275 g; yield 84%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.23 [s, 6 H, $C(CH_3)_2$], 1.30[s, 6 H, $C(CH_3)_2$], 2.42 (s, 3 H, NCH_3), 2.78 (s, 3 H, NCH_3), 4.01 (s, 1 H, PhC*H*), 7.54 (m, 4 H), 7.84 (m, 2 H), 7.95 (s, 1 H) ppm; BH could not be detected. ^{11}B NMR ($CDCl_3$, 25 °C): δ = –9.0 (q, J = 94.38 Hz), 29.1 ppm (s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = 24.5, 24.6, 46.9, 52.0, 84.1, 126.3, 126.7, 127.5, 127.9, 128.1, 129.91, 129.95, 132.4, 133.0, 133.1 ppm; BC could not be detected. IR (KBr): $\tilde{\nu}$ = 2361 cm^{-1} (B–H), 2311 (B–H), 2269 (B–H), 1468 (C–N), 632 (B–N) ppm. MS (EI): *m*/*z* = 327 [M$^+$], 313, 298, 283, 269, 254, 239, 224, 209, 184, 129, 127. $C_{19}H_{31}B_2NO_2$ (327): calcd. C 69.72, H 9.48, N 4.28; found C 70.27, H 9.37, N 4.30.

Preparation of *N*,*N*-Dimethyl-*N*-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]aminocyanoborane (4): The crude product was purified by column chromatography with 20% of EtOAc in petroleum ether as eluent to give a yellow oil (0.186 g; yield 83%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.27 {s, 12 H, $[C(CH_3)_2]_2$}, 2.68 (s, 2 H, NCH_2B), 2.79 [s, 6 H, $N(CH_3)_2$] ppm; BH could not be detected. ^{11}B NMR ($CDCl_3$, 25 °C): δ = –14.1 (t, J = 103.12 Hz), 29.6 ppm (s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = 24.6, 52.0, 84.5 ppm; BC could not be detected. IR (neat): $\tilde{\nu}$ = 2354 cm^{-1} (B–H), 2330 (B–H), 2199 (C≡N), 1470 (C–N), 752 (B–N) ppm. MS (EI): *m*/*z* = 224 [M$^+$], 209, 194, 184, 170, 155, 127. $C_{10}H_{22}B_2N_2O_2$ (224): calcd. C 53.57, H 9.82, N 12.50; found C 54.01, H 9.69, N 12.70.

Preparation of *N*-Methyl-*N*-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]butylaminocyanoborane (5): The crude product was purified by column chromatography with 20% of EtOAc in petroleum ether as eluent to give a yellow oil (0.186 g; yield 70%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.95 (t, $J_{H,H}$ = 15 Hz, 3 H, CH_2CH_3), 1.26 {s, 12 H, $[C(CH_3)_2]_2$}, 1.68 [m, 4 H, $CH_3(CH_2)_2$], 2.60 (s, 2 H, NCH_2B), 2.74 (s, 3 H, NCH_3), 2.99 (m, 2 H, NCH_2CH_2) ppm; BH could not be detected. ^{11}B NMR ($CDCl_3$, 25 °C): δ = –15.5 (t, J = 103.5 Hz), 29.5 ppm (s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = 13.7, 20.1, 24.6, 25.4, 49.9, 62.6, 84.4 ppm; BC could not be detected. IR (neat): $\tilde{\nu}$ = 2407 cm^{-1} (B–H), 2338 (B–H), 2197 (C≡N), 1467 (C–N), 653 (B–N) ppm. MS (EI): *m*/*z* = 266 [M$^+$], 251, 227, 212, 198, 184, 169, 154. $C_{13}H_{28}B_2N_2O_2$ (266): calcd. C 58.64, H 10.52, N 10.52; found C 58.75, H 10.33, N 10.32.

Preparation of *N*-Methyl-*N*-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]nonylaminocyanoborane (6): The crude product was purified by column chromatography with 20% of EtOAc in petroleum ether as eluent to give a yellow oil (0.269 g, yield 80%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.87 (t, $J_{H,H}$ = 13.2 Hz, 3 H, CH_2CH_3), 1.26 {br. s, 22 H, $[C(CH_3)_2]_2$ + $(CH_2)_5$}, 1.66 (m, 4 H, $NCH_2CH_2CH_2$), 2.59 (s, 2 H, NCH_2B), 2.74 (s, 3 H, NCH_3), 2.98 (m, 2 H, NCH_2CH_2) ppm; BH could not be detected. ^{11}B NMR ($CDCl_3$, 25 °C): δ = –14.6 (t, J = 104.0 Hz), 30.2 ppm (s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = 14.0, 22.6, 23.3, 24.6, 26.8, 29.12, 29.17, 29.3, 31.7, 49.8, 62.9, 84.4 ppm; BC could not be detected. IR (neat): $\tilde{\nu}$ = 2337 cm^{-1} (B–H), 2236 (B–H), 2197 (C≡N), 1466 (C–N), 663 (B–N) ppm. MS (EI): *m*/*z* = 336 [M$^+$], 297, 282, 254, 240, 185, 170, 156, 142, 128, 114, 100, 84. $C_{18}H_{38}B_2N_2O_2$ (336): calcd. C 64.28, H 11.30, N 8.33; found C 63.55, H 11.21, N 8.37.

Preparation of *N*-Methyl-*N*-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]dodecylaminocyanoborane (7): The crude product was purified by column chromatography with 20% of EtOAc in petroleum ether to give a yellow oil (0.255 g; yield 70%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.87 (t, $J_{H,H}$ = 13.2 Hz, 3 H, CH_2CH_3), 1.26 {br. s, 28 H, $[C(CH_3)_2]_2$ + $(CH_2)_8$}, 1.72 (m, 4 H, $CH_3CH_2CH_2$), 2.59 (s, 2 H, NCH_2B), 2.74 (s, 3 H, NCH_3), 3.00 (m, 2 H, NCH_2CH_2) ppm; BH could not be detected. ^{11}B NMR ($CDCl_3$, 25 °C): δ = –15.3 (t, J = 104.23 Hz), 29.6 ppm (s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ = 14.0, 22.6, 23.3, 24.6, 26.8, 29.1, 29.2, 29.42, 29.47, 29.5, 31.8, 43.3, 49.8, 62.9, 84.4 ppm; BC could not be detected. IR (neat): $\tilde{\nu}$ = 2362 cm^{-1} (B–H), 2339 (B–H), 2196 (C≡N), 1465 (C–N), 667 (B–N) ppm. MS (EI): *m*/*z* = 378 [M$^+$], 339, 324, 310, 296, 282, 268, 254, 240, 226, 212, 198, 184, 170, 156, 141, 126, 111, 96. $C_{21}H_{44}B_2N_2O_2$ (378): calcd. C 66.66, H 11.64, N 7.40; found C 65.77, H 11.48, N 7.54.

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[1] J. C. Power, J. Harper, *Inhibitors of Serine Proteases*, Elsevier Science Publishing Co., New York, **1986**, vol. 12.
[2] C. Lebarbier, B. Carreaux, J. L. Boucher, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2573–2576.
[3] A. Urbani, E. Bianchi, F. Narjes, A. Tramontana, R. De Francesco, C. Steinkuhler, A. Pessi, *J. Biol. Chem.* **1997**, *272*, 9204–9209.
[4] D. S. Matteson, K. M. Sadhu, *Organometallics* **1984**, *3*, 614–618.
[5] P. Amiri, R. N. Lindquist, D. S. Matteson, K. M. Sadhu, *Arch. Biochem. Biophys.* **1984**, *234*, 531–536.
[6] K. Duncan, S. W. Faraci, D. S. Matteson, C. T. Walsh, *Biochemistry* **1989**, *28*, 3541.
[7] *Enzymes in Synthetic Organic Chemistry* (Eds.: C. H. Wong, G. M. Whitesides), Pergamon Publishers, New York, **1994**.
[8] C. L. M. J. Verlinde, W. G. J. Hol, *Structure* **1994**, *2*, 577–587.
[9] I. V. Kurinov, R. W. Harrison, *Nat. Struct. Biol.* **1994**, *1*, 735.
[10] M. G. Grutter, J. P. Priestle, J. Rahuel, H. Grossenbacher, H. Bode, J. Hofsteenge, S. R. Stone, *EMBO J.* **1990**, *9*, 2361–2365.
[11] T. R. Hynes, M. Randal, L. A. Kennedy, E. Eigenbrot, A. A. Kossiakoff, *Biochemistry* **1990**, *29*, 10018–10022.
[12] M. Yakamoto, R. Sawaya, S. Mohanam, V. H. Rao, J. Bruner, G. L. Nicholson, K. Ohshima, J. S. Rao, *J. Neurooncol.* **1994**, *22*, 139.

[13] D. S. Matteson, K. M. Sadhu, G. E. Lienhard, *J. Am. Chem. Soc.* **1981**, *103*, 5241–5242.
[14] S. V. Kessar, P. Singh, R. Vohar, N. P. Kaur, K. N. Singh, *J. Chem. Soc., Chem. Commun.* **1991**, 568–570.
[15] M. R. Ebden, N. S. Simpkins, D. N. A. Fox, *Tetrahedron* **1998**, *54*, 12923–12952.
[16] K. Takrouri, J. Katzhendler, M. Srebnik, *Organometallics* **2004**, *23*, 2817–2820.
[17] B. Györi, Z. Berente, R. Király, I. Lázár, *J. Chem. Soc., Perkin Trans. 1* **2002**, *3*, 300–303.
[18] a) B. S. Burnham, S. Y. Chen, A. Sood, B. F. Spievogel, I. H. Hall, *Pharmazie* **1995**, *50*, 779–783; b) I. H. Hall, A. Elkins, A. Sood, J. Tomasz, B. F. Spievogel, *Anticancer Res.* **1996**, *16*, 3709–3714; c) M. C. Miller III, A. Sood, B. F. Spievogel, I. H. Hall, *Anticancer Res.* **1997**, *17*, 3299.
[19] K. G. Rajendran, S. Y. Chen, A. Sood, B. F. Spievogel, I. H. Hall, *Biomed. Pharmacother.* **1995**, *49*, 131–140.
[20] a) B. F. Spievogel, A. Sood, I. H. Hall, WO Patent 9,309,123, **1993**; b) M. C. Miller III, A. Sood, B. F. Spievogel, R. P. Shrewsbury, I. H. Hall, *Met-Based Drugs* **1996**, *3*, 219–226.
[21] A. T. McPhail, B. F. Spievogel, I. H. Hall, US Patent 4,550,186, **1985**.
[22] M. Takagaki, W. Powell, A. Sood, B. F. Spievogel, N. S. Hosmane, M. Kirihata, K. Ono, S. I. Masunaga, Y. Kinashi, S. I. Miyatake, N. Hashimoto, *Radiat. Res.* **2001**, *156*, 118–122.
[23] a) H. Gilamn, B. Gaj, *J. Org. Chem.* **1957**, *22*, 1165–1168; b) A. Rembaum, S. P. Siao, N. Indictor, *J. Polym. Sci.* **1962**, *56*, S17–S19; c) A. Maercker, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 972–989.
[24] M, K. Das, S. N. Bandyopadhyay, *Inorg. Chem.* **1994**, *33*, 5358–5359.
[25] a) H. Nöth, H. Vahrenkamp, *Chem. Ber.* **1966**, *99*, 1049; b) L. H. Toporcer, R. E. Dessy, S. I. E. Green, *Inorg. Chem.* **1965**, *4*, 1649–1655.
[26] P. Wisian-Neilson, M. K. Das, B. F. Spielvogel, *Inorg. Chem.* **1978**, *17*, 2327–2329.
[27] R. Smoum, A. Rubinstein, M. Srebnik, *Bioorg. Chem.* **2003**, *31*, 464–474.

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