Selective Oxidation of a Keramaphidin B Model

Jean-Marc Gomez,[†] Laurent Gil,[‡] Clotilde Ferroud,*[,†] Alice Gateau-Olesker,[§] Marie-Thérèse Martin,[§] and Christian Marazano*[,§]

Laboratoire de Chimie Organique, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France, and Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

marazano@icsn.cnrs-gif.fr

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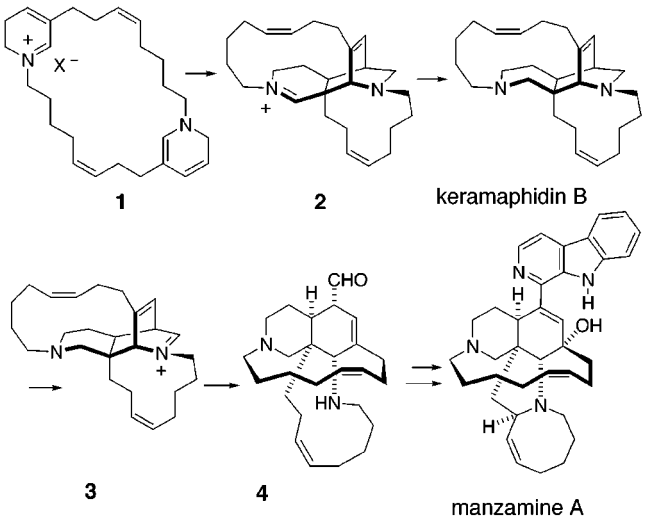
A crucial step in the Baldwin and Whitehead proposal for explaining the biogenesis of the marine alkaloid manzamine A is the selective oxidation of natural keramaphidin B to an iminium salt **3**, which is then hydrolyzed to give the aldehyde **4**. Conditions are now presented in which this selective oxidation can be performed on model compound **8**, leading to the iminium salt **16**. Although this salt can be considered as a model equivalent of the proposed aldehyde intermediate **4**, it was found to be very resistant to hydrolysis as was the corresponding amide **20**. From a synthetic point of view, the reported results illustrate the usefulness of the temporary protection of tertiary amines as aminoborane derivatives and constitute a good method for the oxidation of a sterically hindered tertiary nitrogen atom in the presence of a second nitrogen.

Introduction

An increasing number of macrocyclic alkaloids, isolated from marine sponges in the order haplosclerida, has been discovered recently.[1] In this family, manzamine A (Scheme 1) occupies a central position. Baldwin and Whitehead have suggested[2] that this alkaloid could be derived biogenetically from a hypothetical macrocyclic dihydropyridine intermediate **1**. This unstable derivative would first cyclize to give iminium salt **2**, whose reduction would give natural keramaphidin B. A selective oxidation of keramaphidin B (or direct oxido-reduction reaction of salt **2**) can then lead to the iminium salt **3**. Hydrolysis of this salt affords aldehyde **4**, which possesses the essential features of manzamine A and related alkaloids. Since then, several biogenetic proposals focusing on the chemistry of macrocyclic analogues of **1** have been invoked to explain the formation of a number of related products extracted from sponges.[3]

The chemistry depicted in Scheme 1 has been questioned experimentally. The first step, relative to the cyclization of dihydropyridine intermediates, was found to be rather efficient using bimolecular conditions, resulting in a very practical synthetic route to bicyclic analogues of keramaphidin B.[4] By contrast, the intramolecular cyclization of **1**, followed by reduction, gave keramaphidin B itself in a very low yield of 0.2−0.3%.[5] This disappointing result was the consequence of extensive and unavoidable oxido-reduction reactions of dihydropyridine intermediates. To overcome these limitations, a modified biogenetic hypothesis was recently proposed that gave preliminary encouraging results.[6] This modified hypothesis is now under further study in our laboratory, but it is evident that all proposals have to be fully investigated experimentally for the elaboration of a

Scheme 1. Biogenetic Pathways to Keramaphidin B and Manzamine A Proposed by Baldwin and Whitehead[2]



[†] Laboratoire de Chimie Organique.

[‡] Present adress: Departamento de Química, ICEB, UFOP, Campus Morro do Cruzeiro, Ouro Preto-MG, Brazil.

[§] Institut de Chimie des Substances Naturelles.

(1) For comprehensive reviews, see: (a) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765−794. (b) Andersen, R. J.; Van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press, Elsevier Science: New York, 1996; Vol. 10, pp 301−355. (c) Crews, P.; Cheng, X.-C.; Adamczeski, M.; Rodriguez, J.; Jaspar, M.; Schmitz, F. J.; Traeger, S. C.; Pordesimo, E. O. *Tetrahedron* **1994**, *50*, 13567−13574.

(2) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059−2062.

(3) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proc. Int.* **1998**, *30*, 3−51 (see also articles in ref 1).

(4) For model reactions leading to keramaphidin B and halicyclamine A skeletons, see: (a) Baldwin, J. E.; Bischoff, L.; Claridge, T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. *Tetrahedron* **1997,** *53*, 2271−2290 and references therein. (b) Gil, L.; Baucherel, X.; Martin, M.-T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 6231−6234.

(5) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154−3161.

(6) (a) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026−8034. (b) Jakubowicz, K.; Ben Abdeljelil, K.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Almourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381−7387.

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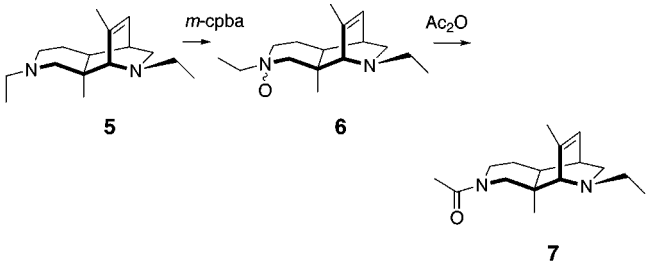
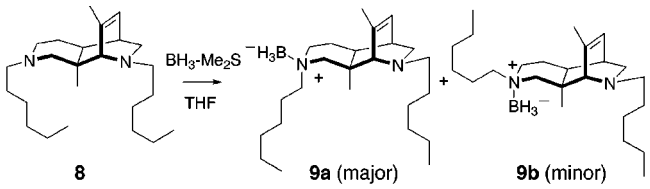
Scheme 2



Scheme 3



reasonable biogenetic scenario. Thus, to further study the experimental exploration of the biogenetic proposal depicted in Scheme 1, the second crucial step, concerning the selective oxidation of keramaphidin B to give salt **3**, followed by hydrolysis to amino aldehyde **4**, remained to be accomplished. More generally, this raised the challenging problem of the selective oxidation of a tertiary nitrogen atom to give an iminium salt in the presence of a second nitrogen.

Initial attempts toward the selective oxidation of a keramaphidin B model were reported previously (Scheme 2).[7] The *m*-CPBA oxidation of model compound **5** was regioselective at the less hindered nitrogen atom, since only diastereoisomeric *N*-oxides **6** were obtained in 75% yield. Treatment with acetic anhydride resulted in the formation of the acetamide **7** in 50% yield. Although this transformation allowed a differentiation of the two nitrogen atoms, no further work concerning the oxidation of the bridgehead nitrogen of **7** was reported to date.

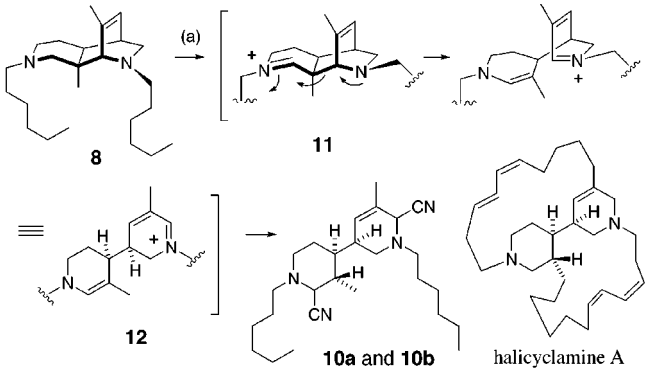
In this paper, a simple procedure allowing, on a model, a selective oxidation that mimics the transformation of keramaphidin B to the iminium salt **3**, is now reported.

Results and Discussion

In consideration of the greater reactivity toward oxidation of the less hindered piperidine tertiary nitrogen atom (see Scheme 2), temporary protection as an aminoborane was effected (Scheme 3). Thus, treatment of keramaphidin B analogue **8**[4b] with the BH_3-Me_2S complex in THF resulted in the formation of two diastereoisomeric borane derivatives **9a** and **9b** in quantitative yield and in a 77:23 ratio in favor of **9a**.[8] These diastereoisomers were easily separated over alumina and were recovered in 62 and 21% yield, respectively.

Conditions were then sought for the oxidation of the bridgehead nitrogen atom to an iminium salt using the Polonovski−Potier reaction.[9] Oxidation of derivative **9a** or **9b** to an *N*-oxide using *m*-CPBA or H_2O_2 failed completely. This result was not surprising if one considers the reducing properties of aminoborane derivatives.

Scheme 4[a]



[a] Key: (a) TPP (cat.), TMSCN (4 equiv), O_2, CH_2Cl_2, $h\nu$ ($\lambda \geq$ 495 nm), 10 min, 15% yield for **10a**,**b** (75/25 ratio).

As a consequence, the borane protection route was incompatible with this approach.

Consequently, an alternative oxidation method, compatible with the borane protection strategy, was required in order to obtain the iminium salt. The direct photochemical oxidation of tertiary amines by a single-electron-transfer (SET) process, an approach reported to be very efficient in a related example, the photoinduced oxidation of the natural alkaloid catharanthine,[10] was therefore considered.

The first attempts were conducted on the nonprotected derivative **8** (Scheme 4). The photocyanation of this model compound, proceeding by irradiation with visible light (λ > 495 nm) in the presence of a catalytic amount of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) as photosensitizer, with trimethylsilyl cyanide (TMSCN), under bubbling oxygen, resulted in the formation of a complex mixture of aminonitrile derivatives in a few minutes. From the crude reaction mixture chromatography yielded two unseparable diastereoisomeric products in 15% yield, and in an approximate 75:25 ratio. These derivatives are two of the four possible diastereoisomers corresponding to structure **10**, as determined by NMR spectroscopy.[11] The stereochemistry of the two aminonitrile functions was difficult to establish with certainty. These products can be considered as resulting from an initial oxidation to the iminium salt **11**, followed by a retro-Mannich process leading to salt **12**, a precursor of the halicyclamine A core skeleton. This result is in agreement with other observations suggesting that the iminium salts, such as **11** and **12**, are in equilibrium[4a,b] and constitutes additional evidence regarding the relationship between the marine alkaloids possessing the keramaphidin and halicyclamine A core skeletons.

Attention was then turned to the SET oxidation of the aminoborane derivative **9a** (Scheme 5). Albeit slower (3 h), this oxidation proceeded to afford, quantitatively, a mixture of the two aminonitriles **13a** and **13b**[11] in an 82:18 ratio, respectively. The major isomer **13a** was isolated in 64% yield after chromatography over alumina. ^1H NMR spectroscopic analysis revealed several characteristic NOEs effects (see Supporting Information). The minor isomer **13b** was unstable, and its structure was deduced from an NMR study of an enriched fraction.

(7) Baldwin, J. E.; Claridge, T. D. W.; Heupel, F. A.; Whitehead, R. C. *Tetrahedron Lett.* **1994**, *35*, 7829−7832.

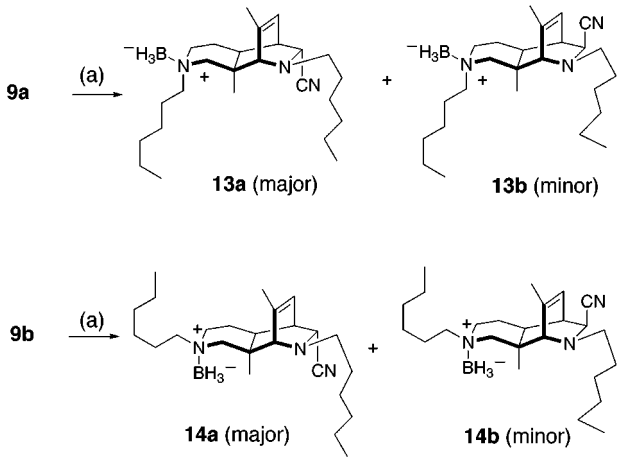
(8) For tentative attribution based on the observation of NOEs effects on **13a** and **14a**, see Scheme 6.

(9) Grierson, D. S. *Org. React.* **1990**, *39*, 85−295.

(10) Cocquet, G.; Rool, P.; Ferroud, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2277−2281.

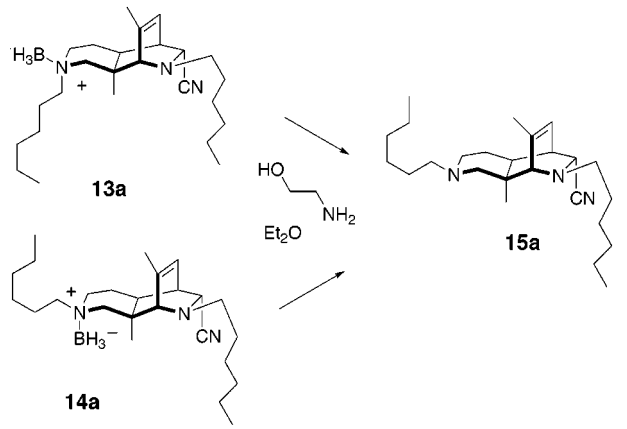
(11) All complex structures were resolved by intensive NMR-spectroscopic studies including 1D and 2D NMR experiments (COSY 90, NOESY, HMQC, HMBC).

Scheme 5[a]



[a] Key: (a) TPP (cat.), TMSCN (4 equiv), O_2, CH_2Cl_2, $h\nu$ ($\lambda \geq$ 495 nm), 3 h for **9a**, 0.25 h for **9b**.

Scheme 6

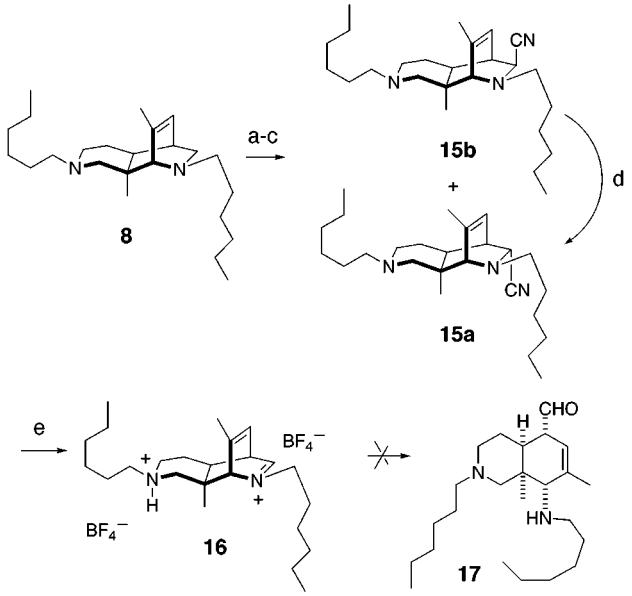


Irradiation of the amineborane **9b** under the same conditions resulted in the formation of two diastereoisomeric aminonitrile derivatives **14a** and **14b** in a 50:50 ratio and in quantitative yield. Filtration over alumina allowed the isolation of isomer **14a**, which was recovered in 53% yield. Isomer **14b** was too unstable to be isolated. Instability of the aminonitriles **13b** and **14b** is very probably due to the steric interactions of the nitrile group with the aliphatic chain at bridgehead nitrogen. The stereochemistry of this aliphatic substituent is normally as depicted in Scheme 5, since the nitrogen substituent of unsaturated isoquinuclidines is well-known to lie preferentially in a syn relationship with respect to the double bond.[12]

Removal of the borane protection from **13a** or **14a** using alcoholic solvents was accompanied by extensive reduction of the aminonitrile function by the liberated borane to give back starting product **8**. In contrast, the use of ethanolamine, which acts very probably as a strong boron complexant, resulted in quantitative formation of the desired derivative **15a** (Scheme 6).

For synthetic purposes, this last product was efficiently obtained in high yield without isolation of any intermediate. Thus, the three-step sequence depicted in Scheme 7

Scheme 7[a]



[a] Key: (a) BH_3·Me_2S, THF, rt, 1 h; (b) TPP (cat.), TMSCN (4 equiv), O_2, CH_2Cl_2, $h\nu$ ($\lambda \geq$ 495 nm), 10 min; (c) $H_2NCH_2CH_2OH$, Et_2O, rt, 12 h (**15a**/**15b**: 76/24 ratio, 88% yield from **8**); (d) $CDCl_3$, 2 days; (e) HBF_4, CH_3CN-H_2O.

gave a mixture of aminonitriles **15a** and **15b** in a 76/24 ratio (88% overall yield from **8**). By ^1H NMR spectroscopy it was observed that the minor isomer **15b** slowly and cleanly equilibrated to the major isomer **15a** in $CDCl_3$.

The elimination of the nitrile group was found to proceed instantaneously after the addition of fluoroboric acid to afford salt **16**. This rather unstable intermediate could be well-characterized by NMR spectroscopy but hydrolysis of this salt under acidic or basic conditions failed to give aldehyde **17**. All efforts to obtain this aldehyde from aminonitrile **15a** under a variety of conditions ($AgNO_3$, THF/H_2O; $CuSO_4$, MeOH; HCl, MeOH; oxalic acid, THF/H_2O; etc.) were also unsuccessful.

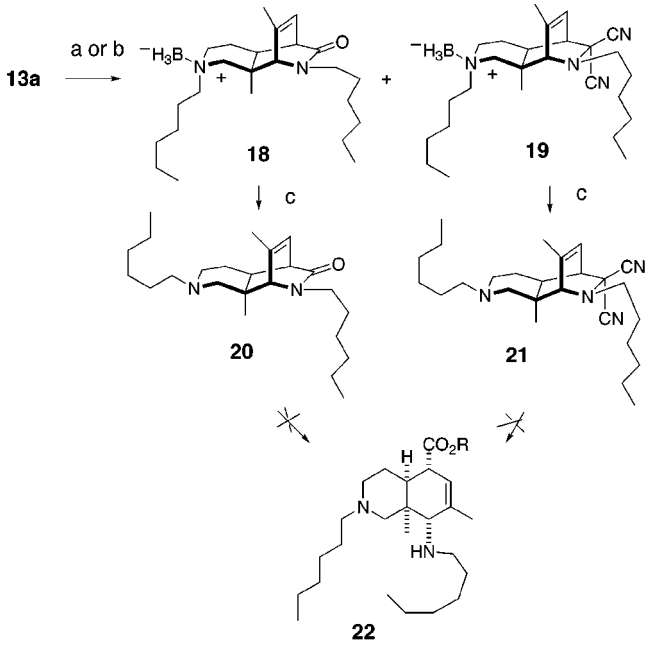
Considering these negative results, attention was turned to the synthesis and hydrolysis of the corresponding amide **20**. Photooxidation of compound **13a** (Scheme 8) in a mixture of CH_3CN/H_2O, in the presence of TMSCN and β-lapachone as a sensitizer, resulted in the formation of two compounds, the desired borane amide **18** and the *gem*-dicyano borane derivative **19**, in a 59:41 ratio. These products were recovered in 30% and 19% yield, respectively, after chromatography over alumina. When the photooxidation reaction was performed in MeOH, the ratio of oxidized derivatives **18** and **19** was found to be 37: 63, while borane amide **18** was obtained exclusively in the absence of TMSCN (51% isolated yield). Removal of borane protection proceeded smoothly using ethanolamine to afford amide **20** or *gem*-dicyanoadduct **21** in essentially quantitative yield. Amide **20** was also found to be particularly resistant to hydrolysis, and did not afford manzamine-like ester **22**. Thus amide **20** was recovered unchanged after reflux in HCl 6N during 4 days or EtOK-DMF at 140 °C. Efforts to hydrolyze the *gem*-dicyanoadduct **21** were similarly unsuccessful.

Conclusion

An efficient process mimicking the oxidation of keramaphidin B to the corresponding iminium salt **3**, a crucial

(12) Mehmandoust, M.; Marazano, C.; Singh, R.; Gillet, B.; Cesario, M.; Fourrey, J.-L.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4423−4426. Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332. Morishima, I.; Yoshikawa, K. *J. Am. Chem. Soc.* **1975**, *97*, 2950.

Scheme 8[a]



[a] Key: (a) β-lapachone, TMSCN, $h\nu$ (λ > 400 nm), 20 °C, CH_3CN/H_2O (**18**/**19**: 59/41 ratio) or MeOH (**18**/**19**: 37/63 ratio); (b) β-lapachone, $h\nu$ (λ > 400 nm), 20 °C, CH_3CN/H_2O (**18**/**19**: 100/0 ratio, 51% yield for **18**); (c) $H_2NCH_2CH_2OH$, Et_2O, rt, 12 h.

step in the biogenetic proposal summarized in Scheme 1, was achieved in high yield and with very high selectivity. Albeit disappointing from a synthetic point of view in term of access to the manzamine skeleton, the failure of the hydrolysis of the iminium salt **16** or the amide **20** does not signify that this process cannot be accomplished on iminium salt **3** itself. This last intermediate is probably more congested due to the influence of the two additional macrocyclic rings. Clearly the selective oxidation of keramaphidin B itself remains thus to be accomplished.

From a synthetic point of view, the reported results illustrate the utility of borane protection of tertiary amines and afforded a convenient method for the selective oxidation of a sterically hindered tertiary amine. This transformation may find other applications in the field of alkaloid synthesis.

Experimental Section

Aminoborane Derivatives 9a and 9b. To a solution of keramaphidin A analogue **8** (451 mg, 1.25 mmol) in THF (20 mL) was added a 2 M solution of BH_3-Me_2S (0.75 mL, 1.5 mmol). After 1 h, the solvent was evaporated under reduced pressure. The resulting oily residue was dissolved in CH_2Cl_2 (20 mL) and washed two times with 5% aqueous NH_4OH. Removal of solvent left a mixture of **9a** and **9b** (460 mg, 100% yield) in a 77:23 ratio, respectively, as measured by integration of signals in the ^1H NMR spectrum. These derivatives can be used without further purification for SET oxidation. Chromatography over alumina (CH_2Cl_2/cyclohexane, gradient from 20:80 to 100:0) allowed separation of the two isomers for spectroscopic characterization. Major isomer **9a** (290 mg, 0.78 mmol, 62% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (m, 6 H), 1.30 (m, 15 H), 1.40 (s, 3 H), 1.55 (m, 2 H), 1.73 (dd, J = 9.6, 2.9 Hz, 1 H), 1.81 (d, J = 1.5 Hz, 3 H), 1.84 (m, 2 H), 2.12 (m, 1 H), 2.23 (m, 1 H), 2.38 (m, 1 H), 2.46 (d, J = 1.8 Hz, 1 H), 2.49 (d, J = 14.3 Hz, 1 H), 2.56 (m, 1 H), 2.64 (d, J = 14.3 Hz, 1 H), 2.89 (m, 2 H), 2.92 (dd, J = 9.6, 1.8 Hz, 1 H), 3.09 (dm, J = 11.8 Hz, 1 H), 5.88 (d, J = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 14.1, 22.6, 22.7, 23.1, 24.0, 25.5, 26.9, 27.2, 28.4, 28.9, 31.5, 31.7, 37.48, 41.9, 54.8, 57.4, 57.9, 60.9, 64.6, 66.5, 121.3, 139.6; MS (EI) m/z (rel intensity) 360 (3), 247 (5), 180 (21), 178 (100), 94 (7); MS (FAB, thioglycerol) m/z (rel intensity) 374 ($M^{\bullet+}$, 33), 373 (86), 361 (53), 359 (31), 180 (61), 178 (100). Anal. Calcd for $C_{24}H_{47}N_2B$: C, 76.98; H, 12.65; N, 7.48. Found: C, 77.06; H, 12.72; N, 7.35. Minor isomer **9b** (98 mg, 0.26 mmol, 21% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (m, 6 H), 1.29 (m, 16 H), 1.55, s, 3 H), 1.61 (m, 2H), 1.72 (dd, J = 9.6, 2.6 Hz), 1.80 (d, J = 1.5 Hz, 3 H), 1.85 (m, 1 H), 2.11 (m, 1 H), 2.23 (m, 1 H), 2.27 (d, J = 12.5 Hz, 1 H), 2.38 (m, 1 H), 2.48 (d, J = 1.5 Hz, 1 H), 2.55 (m, 1 H), 2.65 (m, 1 H), 2.74 (m, 2 H), 2.95 (m, 1 H), 3.02 (m, 1 H), 5.90 (d, J = 6.3 Hz, 1 H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 14.1, 22.5, 22.7, 23.3, 24.2, 25.0, 26.8, 27.2, 28.4, 29.8, 31.4, 31.7, 37.7, 41.3, 41.6, 54.7, 56.1, 58.0, 63.1, 67.1, 67.6, 121.6, 140.2; MS (EI) m/z (rel intensity) 360 (3), 180 (19), 178 (100), 110 (5), 94 (9); MS (FAB, thioglycerol)) m/z (rel intensity) 374 ($M^{\bullet+}$,10), 373 (26), 361 (20), 359 (27), 180 (80), 178 (100). Anal. Calcd for $C_{24}H_{47}N_2B$: C, 76.98; H, 12.65; N, 7.48. Found: C, 76.85; H, 12.72; N, 7.52.

Photocyanation of Model 8 with TPP. To a solution of **8** (153 mg, 0.43 mmol) in CH_2Cl_2 (60 mL) were added TMSCN (0.3 mL, 2.25 mmol) and a catalytic amount of TPP (0.02 mmol). The mixture was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cutoff glass filter (λ > 495 nm) at 20 °C during 10 min. After reaction, monitored by TLC, the mixture was extracted by 5% aqueous NH_4OH. The combined organic layers (CH_2Cl_2) were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting cyano product, obtained as a red oil, was filtered over alumina (CH_2Cl_2). Removal of solvent left of a pinkish oil (140 mg). A mixture of diastereoisomers **10** (26 mg, 0.06 mmol, 15% yield) was obtained after preparative layer chromatography (Al_2O_3, cyclohexane/AcOEt 95/5) as a colorless oil in a 75:25 ratio. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (m, 6H), 1.12 (d, J = 7.0 Hz, 3H), 1.25−1.90 (m, 23H), 2.31 (m, 2H), 2.44 (t, J = 7.3 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 2.63 (m, 1H), 2.73 (m, 1H), 2.83 (m, 1H), 3.78 (d, J = 4,1 Hz, 1H), 3.92 (s, 1H), 5.42 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 15.9, 20.3, 22.6, 22.6, 25.5, 26.9, 27.0, 27.1, 31.6, 34.9, 35.6, 41.1, 45.9, 49.2, 55.6, 55.7, 56.0, 60.7, 115.4, 115.9, 128.7, 128.8; MS (CI, isobutane) m/z (rel intensity) 413 (MH^+, 14), 386 (100), 359 (74); IR cm^{-1} (film, $CHCl_3$) 2220 (CN).

Aminonitrile 13a. To a solution of the major aminoborane derivative **9a** (250 mg, 0.67 mmol) in CH_2Cl_2 (80 mL), were added TMSCN (0.4 mL, 3.01 mmol) and a catalytic amount of TPP (0.02 mmol). The mixture was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cutoff glass filter (λ > 495 nm) at 20 °C during 3 h. After reaction, monitored by TLC, the mixture was extracted by 5% aqueous NH_4OH. The combined organic layers (CH_2Cl_2) were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting cyano product, obtained as a red oil, was dissolved in MeOH and filtered over cotton in order to eliminate precipitated TPP. Removal of solvent left a pinkish oil as a mixture of two stereoisomers **13a** and **13b** (270 mg, 100% yield) in a 82:18 ratio respectively, as measured by integration of signals in the ^1H NMR spectrum. A flash chromatography (Al_2O_3, cyclohexane/CH_2Cl_2 60/40) allowed separation of the two isomers and the major cyanated product **13a** was obtained as a colorless oil (172 mg, 0.43 mmol, 64% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (m, 6H), 1.20−1.50 (m, 14H), 1.51 (s, 3H), 1.62 (m, 2H), 1.81 (m, 3H), 1.86 (d, J = 1.5 Hz, 3H), 2.29 (m, 1H), 2.47 (m, 1H), 2.56 (m, 4H), 2.65 (m, 1H), 2.80 (d, J = 2.6 Hz, 1H), 2.90 (t, J = 8.5 Hz, 2H), 3.14 (dm, J = 11.4 Hz, 1H), 5.91 (d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 14.0, 22.6, 22.6, 22.8, 24.0, 25.0, 26.6, 27.1, 28.0, 28.3, 31.5, 31.5, 37.5, 39.8, 41.7, 55.6, 57.1, 57.7, 60.4, 64.8, 66.0, 120.2, 120.2, 142.5; MS (EI) m/z (rel intensity) 399 ($M^{\bullet+}$, 7), 398 (16), 385 (36), 373 (42), 360 (18), 314 (28), 303 (32), 204 (64), 180 (68), 178 (100), 94 (30); MS (FAB, thioglycerol) m/z (rel intensity) 399 ($M^{+\cdot}$, 19), 398 (43), 384 (27), 359 (36), 178 (100); IR cm^{-1} (film, $CHCl_3$) 2360 (BH_3), 1460.

Aminonitrile 14a. To a solution of the minor amino-borane derivative **9b** (82 mg, 0.22 mmol) in CH_2Cl_2 (25 mL), were added TMSCN (0.15 mL, 1.12 mmol) and a catalytic amount of TPP (0.02 mmol). The mixture was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cutoff glass filter (λ > 495 nm) at 20 °C during 15 min. After reaction, monitored by TLC, the mixture was extracted by 5% aqueous NH_4OH. The combined organic layers (CH_2Cl_2) were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting cyano product, obtained as a red oil, was dissolved in MeOH and filtered over cotton in order to eliminate precipitated TPP. Removal of solvent left a pinkish oil as a mixture of two stereoisomers **14a** and **14b** (87 mg, 100% yield) in a 50:50 ratio respectively, as measured by integration of signals in the ^{1}H NMR spectrum. A flash chromatography (Al_2O_3, cyclohexane/CH_2Cl_2 60/40) allowed separation of the two isomers and the major cyanated product **14a** was obtained as a colorless oil (46 mg, 0.12 mmol, 53% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (m, 6H), 1.10−1.65 (m, 16H), 1.68 (s, 3H), 1.75 (m, 1H), 1.85 (d, J = 1.8 Hz, 3H), 1.88 (m, 2H), 2.20 (d, J = 12.1 Hz, 1H), 2.28 (m, 1H), 2.48 (m, 1H), 2.56 (m, 2H), 2.60 (d, J = 1.5 Hz, 1H), 2.67 (m, 1H), 2.79 (m, 3H), 3.09 (m, 1H), 5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 14.1, 22.5, 22.6, 23.0, 24.2, 24.4, 26.57, 27.1, 28.0, 29.2, 31.4, 31.5, 36.9, 40.1, 41.5, 55.7, 55.7, 57.8, 62.7, 66.6, 67.7, 120.1, 120.5, 143.1; MS (CI, NH_3) m/z (rel intensity) 400 (MH^+, 13), 386 (100), 373 (14), 361 (66); MS (FAB, thioglycerol) m/z (rel intensity) 399 ($M^{\bullet+}$, 7), 398 (17), 386 (16), 373 (6), 359 (40), 178 (100); IR cm^{-1} (film, $CHCl_3$) 2360 (BH_3), 1460.

Aminonitrile 15a. The aminonitrile **15a** was obtained quantitatively either from the cyanated borane **13a** or **14a** according to the following procedure. To a solution of 208 mg (0.52 mmol) of cyanated borane **13a** in dry Et_2O (8 mL) under argon atmosphere was added ethanolamine (2 mL). The biphasic mixture was vigorously stirred at room temperature during 25 h. Then Et_2O (25 mL) was added, and the organic solution was washed by H_2O (4 × 25 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The expected cyanated product **15a** was obtained as a colorness oil (200 mg, 0.52 mmol, 100% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (m, 6H), 1.15−1.60 (m, 21H), 1.71 (m, 1H), 1.81 (d, J = 1.8 Hz, 3H), 2.16 (s, 2H), 2.25 (m, 1H), 2.47 (m, 5H), 2.58 (d, J = 1.5 Hz, 1H), 2.74 (ddd, J = 11.8, 3.7 Hz, 1H), 2.76 (d, J = 2.6 Hz, 1H), 5.80 (d, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 22.6, 22.9, 26.5, 26.6, 27.0, 27.5, 27.8, 28.1, 31.6, 31.8, 36.8, 40.5, 42.4, 49.0, 55.9, 56.0, 57.7, 59.4, 66.6, 119.9, 120.7, 142.5; MS (EI) m/z (rel intensity) 385 ($M^{\bullet+}$, 14), 314 (14), 204 (27), 180 (100), 178 (92), 110 (25), 94 (13); MS (CI, NH_3) m/z (rel intensity) 386 (MH^+, 100); MS (CI, isobutane) m/z (rel intensity) 386 (MH^+, 16), 359 (100); MS (HR) calcd for $C_{25}H_{43}N_3$ 385.3457, found 385.3459; IR cm^{-1} (film, $CHCl_3$) 2220 (CN).

Iminium 16. To a solution of the cyanated compound **15a** (99 mg, 0.26 mmol) in a mixture of CH_3CN/H_2O (5:1 ratio, 10 mL) was added 50% aqueous HBF_4 (0.5 mL). The mixture was stirred at room temperature during 4 days. The resulting green solution was concentrated under reduced pressure, and MeOH (30 mL) was added. The removal of the solvent afforded the iminium salt **16** as a green amorphous solid (140 mg, 0.26 mmol, 100% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.10 (m, 6H), 1.42 (s, 3H), 1.53 (m, 12H), 1.60−2.10 (m, 7H), 1.53 (m, 12H), 1.60−2.10 (m, 7H), 2.20 (d, J = 1.8 Hz, 3H), 3.39 (m, 2H), 3.54 (m, 2H), 3.71 (d, J = 12.9 Hz, 1H), 4.12 (m, 1H), 4.37 (dt, J = 13.2, 8.1 Hz, 1H), 4.55 (m, 1H), 5.25 (s, 1H), 6.38 (d, J = 6.3 Hz, 1H), 9.37 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 19.2, 23.7, 23.73, 23.9, 24.7, 25.7, 27.0, 27.4, 28.7, 32.5, 32.6, 39.0, 42.5, 46.7, 50.3, 55.4, 60.2, 61.6, 72.9, 123.7, 142.8, 181.2; MS (FAB, thioglycerol)) m/z (rel intensity) 359 (12), 178 (100), 114 (18); IR cm^{-1} (film, $CHCl_3$) 1670 (N^+═C).

Borane Amide 18 and gem-Dicyanoborane 19. To a solution of the cyanated compound **13a** (160 mg, 0.40 mmol) in a mixture of CH_3CN/H_2O (24:1 ratio, 25 mL) were added TMSCN (0.25 mL, 1.88 mmol) and β-lapachone (0.5 equiv., 48 mg, 0.20 mmol). The solution was degassed under argon atmosphere during 20 min. The mixture was then irradiated with a 1800 W xenon lamp through a UV cutoff glass filter (λ > 400 nm) at 20 °C during 4.5 h. After removal of solvents under reduced pressure, CH_2Cl_2 (25 mL) was added to the crude product obtained as a yellow oil. The resulting solution was then basified with an aqueous solution of 5% NH_4OH (2 × 20 mL) and the product extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was obtained as a pale yellow oil (200 mg) containing the photosensitizer and a mixture of the borane amide **18** and the *gem*-dicyanoborane **19** (59:41 ratio as determined by ^{1}H NMR spectroscopy). Pure samples of each product were obtained after flash chromatography on alumina using a cyclohexane/CH_2Cl_2 mixture (gradient from 60:40 to 50:50 and then pure CH_2Cl_2). The borane amide **18** (47 mg, 0.12 mmol, 30% yield) and the *gem*-dicyanoborane **19** (32 mg, 0.08 mmol, 19% yield) were obtained as pale yellow oils. According to the same procedure, a mixture of the borane amide **18** and the *gem*-dicyanoborane **19** (37:63 ratio) was obtained when the photooxidation was performed in MeOH. Borane amide **18**: ^{1}H NMR ($CDCl_3$, 400 MHz) 0.89 (m, 6H), 1.15−1.45 (m, 17H), 1.60−1.90 (m, 5H), 1.93 (d, J = 1.5 Hz, 3H), 2.63 (m, 3H), 2.76 (d, J = 14.0 Hz, 1H), 2.88 (t, J = 8.5 Hz, 2H), 3.19 (m, 2H), 3.25 (d, J = 2.2 Hz, 1H), 3.94 (dt, J = 14.0, 7.7 Hz, 1H), 5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.0, 20.0, 22.5, 22.5, 24.1, 25.0, 26.3, 27.1, 28.6, 28.8, 31.5, 31.6, 40.5, 43.7, 46.3, 49.6, 57.2, 60.7, 64.8, 67.5, 122.4, 142.8, 173.1; MS (EI) m/z (rel intensity) 374 (4), 303 (8), 180 (27), 178 (100), 110 (9); MS (FAB, thioglycerol) m/z (rel intensity) 388 ($M^{\bullet+}$, 20), 387 (59), 375 (100), 194 (70), 180 (88), 178 (86); IR cm^{-1} (film, $CHCl_3$) 2360 (BH_3), 1660 (C═O). *gem*-Dicyano borane **19**: ^{1}H NMR ($CDCl_3$, 400 MHz) 0.90 (m, 6H), 1.33 (m, 12H), 1.46 (s, 3H), 1.50−1.90 (m, 7H), 1.95 (d, J = 1.8 Hz, 3H), 2.56 (s, 2H), 2.66 (m, 3H), 2.80 (m, 1H), 2.89 (m, 2h), 3.02 (dd, J = 6.3, 1.8 Hz, 1H), 3.16 (dm, J = 11.8 Hz, 1H), 6.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.0, 14.1, 22.5, 22.5, 24.0, 24.7, 26.6, 27.0, 28.0, 28.6, 31.4, 31.5, 36.7, 42.3, 45.6, 54.2, 56.4, 58.1, 59.6, 64.7, 65.4, 112.5, 115.3, 119.3, 145.5; MS (FAB, thioglycerol) m/z (rel intensity) 424 ($M^{\bullet+}$, 14), 423 (49), 411 (24), 384 (45), 203 (100), 180 (38), 178 (35), 119 (70); IR cm^{-1} (film, $CHCl_3$) 2360 (BH_3), 1460. According to the same procedure, the borane amide **18** was obtained in 51% yield when the photooxidation was performed in a mixture CH_3CN/H_2O 12:1 without any addition of TMSCN.

Dicyano Derivative 21. To a solution *gem*-dicyanated borane **19** (31 mg, 0.07 mmol) in dry Et_2O (5 mL), under an argon atmosphere, was added ethanolamine (1.25 mL). The biphasic mixture was vigorously stirred at room temperature during 12 h. Then Et_2O (10 mL) was added, and the organic solution was washed by H_2O (4 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The *gem*-dicyanated product **21** was obtained as a pale yellow oil (30 mg, 0.07 mmol, 100% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) 0.89 (m, 6H), 1.20−1.75 (m, 21H), 1.78 (m, 1H), 1.92 (d, J = 1.5 Hz, 3H), 2.07 (d, J = 11.4 Hz, 1H), 2.19 (d, J = 11.4 Hz, 1H), 2.41 (m, 3H), 2.72 (m, 4H), 2.93 (dd, J = 6.3, 1.8 Hz, 1H), 5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.0, 13.9, 22.4, 22.5, 26.4, 26.8, 27.3, 27.4, 28.5, 31.3, 31.6, 35.8, 43.0, 46.6, 48.6, 53.9, 55.6, 58.6, 59.0, 65.9, 113.0, 115.6, 119.0, 145.5; MS (EI) m/z (rel intensity) 410 ($M^{\bullet+}$, 18), 339 (19), 311 (33), 245 (31), 233 (29), 203 (43), 180 (50), 178 (100), 159 (21), 140 (21), 126 (20), 110 (19), 69 (21); MS (CI, NH_3) m/z (rel intensity) 411 (MH^+,100), 384 (24); MS (CI, isobutane) m/z (rel intensity) 411 (MH^+, 57), 384 (100), 198 (30), 203 (40); MS (HR) calcd for $C_{26}H_{42}N_4$ 410.3409, found 410.3425; IR cm^{-1} (film, $CHCl_3$) 2220 (BH_3), 1460.

Amide 20. To a solution of the borane amide **18** (43 mg, 0.11 mmol), in dry Et_2O (5 mL) under an argon atmosphere was added ethanolamine (1.25 mL). The biphasic mixture was vigorously stirred at room temperature during 15 h. Then Et_2O (10 mL) was added, and the organic solution was washed with H_2O (4 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The amide **20** was obtained as a pale yellow oil (41 mg, 0.11 mmol, 100% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) 0.88 (m, 6H), 1.17 (s, 3H), 1.28 (m, 13H), 1.41 (m, 4H), 1.50 (m, 1H), 1.58 (m, 1H), 1.87 (d, J = 1.5 Hz, 3H), 2.17 (d, J =

11.0 Hz, 1H), 2.29 (d, J = 11.0 Hz, 1H), 2.43 (t, J = 7.4 Hz, 2H), 2.50 (m, 1H), 2.72 (m, 2H), 3.09 (dd, J = 6.3, 1.8 Hz, 1H), 3.22 (d, J = 1.8 Hz, 1H), 3.91 (dt, J = 13.6, 7.7 Hz, 1H), 5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.0, 14.1, 20.0, 22.5, 22.7, 26.3, 26.5, 27.0, 27.4, 27.7, 28.8, 31.6, 31.8, 39.6, 44.4, 46.0, 48.6, 50.2, 56.1, 59.1, 68.0, 122.4, 142.5, 173.6; MS (EI) m/z (rel intensity) 374 ($M^{\bullet+}$, 3), 303 (8), 180 (26), 178 (100), 110 (10); MS (CI, NH_3) m/z (rel intensity) 375 (MH^+,100), 291 (28), 289 (26); MS (CI, isobutane) m/z (rel intensity) 375 (MH^+, 100), 194 (49), 189 (49); MS (HR) calcd for $C_{24}H_{42}N_2O$ 374.3297, found 374.3278; IR cm^{-1} (film, $CHCl_3$) 1660 (C=O).

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of derivatives **9a**,**b**, **10**, **13a**, **14a**, **15a**, **16**, and **18**−**21** with attribution of signals and schemes showing observed NOEs for compounds **13a** and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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