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Multifunctional Bacteriochlorins from Selective Palladium-Coupling Reactions

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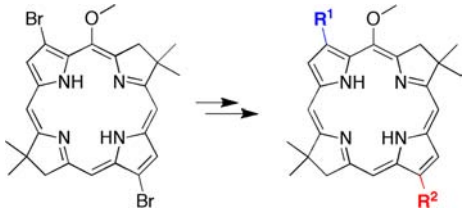
ABSTRACT



Nonsymmetrical, multifunctional bacteriochlorin derivatives possessing different substituents at the β-pyrrolic positions have been prepared by stepwise, selective functionalization of 3,13-dibromo-5-methoxybacteriochlorin via palladium-coupling reactions. The new derivatives reported here include monovalent bioconjugatable bacteriochlorin, orthogonally protected bacteriochlorin amino acid, and push−pull bacteriochlorins. Taken together, this study provides a route to previously unavailable bacteriochlorin architectures for fundamental studies and diverse applications.

There is a continuously growing interest in applications of bacteriochlorin derivatives in photomedicine because of their relatively strong absorption and emission in the near-IR spectral window. Biomedical applications of bacteriochlorins started from anticancer photodynamic therapy (PDT)[1,2] and recently have been expanded to antimicrobial PDT,[3] anticancer photothermal therapy,[4] fluorescence[5] and photoacoustic[4] in vivo imaging, as well as theranostic agents.[6] The precise tuning of physicochemical properties of bacteriochlorins, necessary for such applications, requires access to their diversely functionalized derivatives. In this regard, the ability to install different substituents selectively at the designated positions would allow precise tuning of the optical properties of bacteriochlorins and provide more flexibility in tailoring the resulting derivatives for biomedical applications (e.g., one group might work as a water solubilizing group, whereas the second as a bioconjugatable one). It also would allow the synthesis of certain classes of derivatives with potentially interesting properties; e.g., push−pull bacteriochlorins (i.e., bacteriochlorins with electron-donating and electron-withdrawing groups, located on the opposite sites of macrocycle).

In this regard, we are particularly interested in a method for selective installation of different substituents at β-positions (2, 3, 12, and 13, see Scheme 1) of the bacteriochlorin

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macrocycle. Substitution at these positions has a pronounced effect on the long-wavelength absorption Q_y band.[7] Thus, properly designed substituents would allow tuning of their optical properties, and at the same time, enable installing of desirable functional groups, thus reducing the efforts necessary to obtain derivatives with designated properties.

Among the three general strategies for synthesis of bacteriochlorin derivatives: (a) modification of the naturally occurring bacteriochlorophylls and chlorophylls;[8] (b) modification of the synthetic porphyrins;[9] and (c) de novo synthesis of bacteriochlorin macrocycle,[10−15] the latter approach seems to offer a versatile way to obtain diversely substituted derivatives. Substituents at the designated positions of bacteriochlorins can be introduced either by using prefunctionalized dihydrodipyrrins,[11−15] or by postsynthetic functionalization of the bacteriochlorin macrocycles.[15−19] The earlier approach leads to symmetrical bacteriochlorins, with the same sets of substituents at the 2,3 and 12,13 positions.[11−15] The latter method predominantly employs the corresponding bromobacteriochlorin derivatized and palladium cross-coupling reactions. Palladium-coupling reactions on 3,13-dibromobacteriochlorin lead to the inevitable formation of disubstituted products, given the equal reactivity of both positions, with formation of monosubstituted des-bromobacteriochlorins as side products in some cases.[18,20]

We have envisioned a concise method for introduction of two different substituents via selective functionalization of 3,13-dibromo-5-methoxybacteriochlorins (**1**).[12] Our reasoning was that the presence of the methoxy group in the close vicinity of the 3-position will sterically hinder the bromine at that position, making it less accessible for palladium insertion. We show that by careful choosing of the conditions the selective functionalization only at the 13-position can be achieved, and bromine at 3-position remains intact. (Formation of 3-acetyl-13-bromo-bacteriochlorin in Stille coupling of 3,13-dibromobacteriochlorins upon certain conditions has been mentioned in ref 15.) Further reaction of the resulting 3-bromo-13-substituted bacteriochlorin under harsher conditions would afford nonsymmetrically substituted derivatives. Here, we present a method for selective substitution of bromine at the 13-position via Sonogashira reaction and demonstrate the utility of the new method for synthesis of a variety of novel bacteriochlorins.

Initially, we examined Sonogashira coupling of **1**[12] with methyl 4-ethynylbenzoate.[21] We have chosen the Sonogashira reaction since arylethynyl groups installed in that way allow extensive modulation of electronic and optical properties of tetrapyrrolic macrocycles,[7,22] and it appears to be a convenient way to install a variety of functional groups as well. The Sonogashira cross-coupling of **1** with methyl 4-ethynylbenzoate (1.1 equiv) was carried out using $Pd(PPh_3)_4$ (10 mol % versus bacteriochlorin) and K_2CO_3 (10 equiv) in DMF at 80 °C. The reaction afforded the product of monosubstitution **2a** (~50% yield) together with corresponding product of disubstitution (16%), unreacted starting material, and traces of minor, unidentified byproducts. The product of monosubstitution at the 3-position was not detected in this reaction. The use of Et_3N as a base afforded a substantial amount of debrominated starting material. Other conditions or catalysts examined [$(PPh_3)_2PdCl_2$ or $Pd_2(dba)_3$] did not improve the yield of **2a**. The Sonogashira cross-coupling reaction of **1** with 4-dimethylaminophenylacetylene showed a similar result and afforded monosubstituted product **2b** in 54% yield. Both products **2a** and **2b** were easily purified by column chromatography.

Initially, we attempted to establish the position of phenylacetylene substituents (3 vs 13) by analyzing the NMR spectra of **2a** and **2b**. 2D NOESY spectra of **2a** and **2b** do not show any correlation signal between protons from the corresponding phenylacetylene substituents and protons from the methoxy substituents at the 5-position of bacteriochlorin (which is consistent with substitution at

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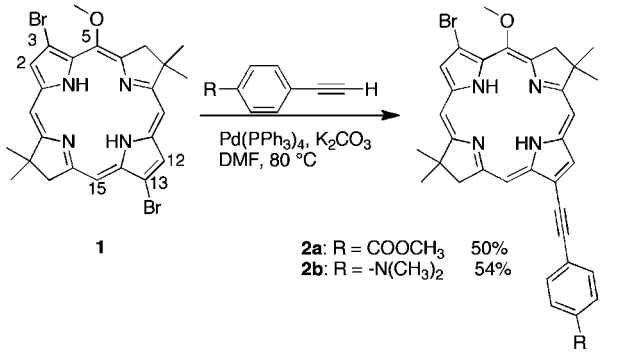
Scheme 1. Selective Monofunctionalization of **1**



13-position). However, we did not see any correlation cross-peaks between phenylacetylene protons and protons from the 15- or 12-positions of bacteriochlorins (presumably due to the distance of about 3.54 Å, obtained from molecular modeling, not shown here). The spectra therefore did not provide the ultimate evidence for the final structures at this point. The position of substituents was finally unambiguously established based on the spectroscopic analysis of the products of further derivatization of **2a** and **2b** (vide infra).

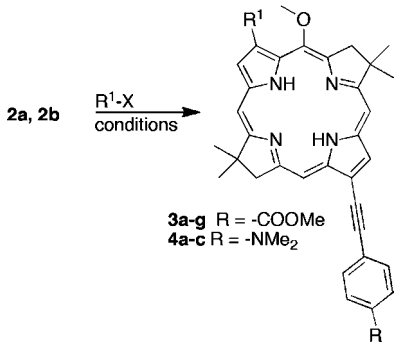
The resulting monosubstituted bacteriochlorins **2a** and **2b** can be further derivatized using a variety of palladium cross-coupling reactions to afford nonsymmetrically substituted derivatives (Table 1). Here we used the Sonogashira and Stille coupling reactions (Table 1). For the Sonogashira reaction, we initially employed conditions previously described for hydroporphyrins [$Pd_2(dba)_3$, (o-tol)$_3$P, toluene/Et_3N),[17,23] but we found difficulties in purification of obtained products from dba contamination. Therefore, we examined different copper-free conditions and found that $(PPh_3)_2PdCl_2$ in DMF/Et_3N mixture provides expected products in most cases in good yields (44−90%).

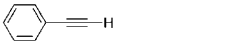
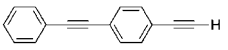
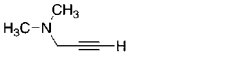
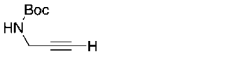
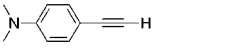
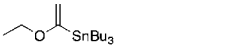
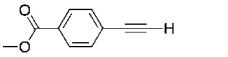
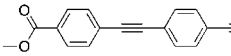
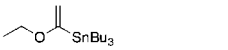
In some of the Sonogashira reactions, we observed formation of a side product that was putatively assigned as an enyne product (structure S-1).[24] While under the reaction conditions listed in Table 1 we observed the enyne product as a minor side product, we were able to optimize the conditions to obtain it in good yield as a major product (see the Supporting Information for details).

For Stille coupling, we employed conditions previously reported for hydroporphyrinic compounds,[17,23] and the target compounds were obtained in very good yields (> 85%).

The position of substituents for nonsymmetrical derivatives has been confirmed using 2D NOESY NMR on representative examples of derivatives from both series **3** and **4**. Thus, **3e** showed correlation between aromatic

Table 1. Synthesis of Nonsymmetrical Bacteriochlorin Derivatives



starting material	R^1-X	product	yield [%]
2a[a]		**3a**	81
2a[a]		**3b**	90
2a[a]		**3c**	44
2a[a]		**3d**	70
2a[a]		**3e**	84
2a[b]		**3f**	88
2a[c]		**3g**[d]	86
2b[a]		**4a**	70
2b[a]		**4b**	50
2b[c]		**4c**[d]	84

[a] Reaction conditions: $(PPh_3)_2PdCl_2$, DMF/Et_3N, 80 °C. [b] Reaction conditions: $(PPh_3)_2PdCl_2$, THF, reflux. [c] Reaction conditions: (1) $(PPh_3)_2PdCl_2$, THF, reflux; (2) 10% HCl. [d] R^1 = acetyl.

protons from the 4-(*N*,*N*-dimethylamino)phenylethynyl substituent and protons of the methoxy substituent at the 5-position. Similarly, we observed correlation between aromatic protons of the 4-(methoxycarbonylphenyl)ethynyl substituent and methoxy protons at the 5-position in **4a**. Compound **3g** exhibits correlation between the methyl protons from the acetyl substituent and the methoxy groups (see the Supporting Information for details). All these observations confirm that the second substituents are located at the 3-position (close to the methoxy group) and thereby also prove the identity of **2a** and **2b**.

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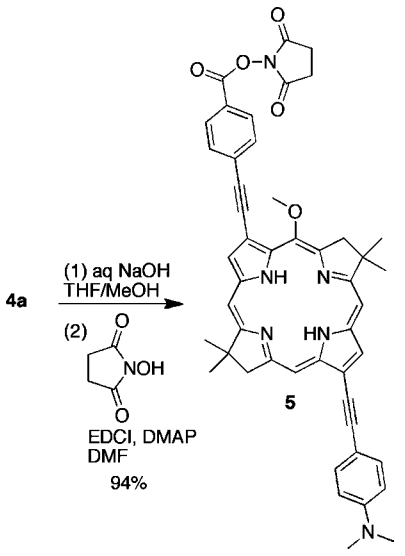
Scheme 2. Synthesis of Monovalent Bioconjugatable Bacteriochlorin



We demonstrated the utility of the new method by preparing certain classes of potentially useful, nonsymmetrically substituted bacteriochlorins. Thus, we prepared derivatives possessing two different auxochromes at the 3 and 13 positions (compounds **3f**, **3g**, and **4c**). Utilizing the nonsymmetrical derivatives **4a**, we prepared the monovalent bioconjugatable bacteriochlorin **5**, possessing an *N*-succinimide ester group (Scheme 2). We also prepared an orthogonally protected amino acid **3d**, which is a potential building block for incorporation of bacteriochlorins into more elaborated architectures. Finally, we prepared a series of push−pull chromophores **3e**, **4a**, and **4c**. Analogous push−pull porphyrin derivatives have been broadly investigated for their second-order optical properties[25] and recently have been also applied in second harmonic generation biological imaging.[26] To the best of our knowledge, the only prior push−pull bacteriochlorins are scattered examples of 3-alkyl-13-carbonyl derivatives.[8]

All new derivatives have been characterized by absorption and fluorescence emission spectroscopies (Table 2). The new derivatives exhibit typical absorption spectra for bacteriochlorins,[7] with a strong Q_y band located in the near-IR spectral window (740−762 nm), broad band

Table 2. Absorption and Emission Data for New Bacteriochlorins[a]

compd	λ_{Bx}, λ_{By} (nm)	λ_{Qx} (nm)	λ_{Qy} (nm)	λ_{em}[b] (nm)
3a	378	525	757	764
3b	377	527	761	768
3c	355, 377	522	752	758
3d	355	523	752	758
3e	374	529	762	770
3f	376	521	750	758
3g	374	516	741	750
4a	374	526	757	766
4b	373	526	759	768
4c	363	514	740	749

[a] All spectra were taken at room temperature in toluene. [b] All samples were excited at the maximum of Q_x band.

(consisting both B_x and B_y) located around 355−378 nm, and Q_x band located at 514−529 nm. All derivatives are fluorescent in toluene and show emission bands with a Stokes shift of around 6−9 nm.

In conclusion, we prepared a series of nonsymmetrical bacteriochlorin derivatives via selective derivatization of 3,13-dibromo-5-methoxybacteriochlorin. In this paper, we demonstrated the selectivity only in case of the Sonogashira reaction. We anticipate that this approach should be easily adopted for different palladium cross-coupling reactions, such as Suzuki or Stille couplings. The new protocol described here should broadly expand the palette of available bacteriochlorin architectures. The expansion of the described method to other types of palladium cross-coupling reactions, detailed characterization of optical properties of bacteriochlorins prepared herein, and application of described method for synthesis of more elaborated bacteriochlorin architectures are ongoing projects in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.