Published in final edited form as:

J Org Chem. 2017 April 07; 82(7): 3880–3885. doi:10.1021/acs.joc.6b02981.

Enhanced Hypsochromic Shifts, Quantum Yield, and π - π Interactions, in a *meso*, β -Heteroaryl-fused BODIPY

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Abstract

We report the synthesis and investigation of an unprecedented 8-heteroaryl-fused BODIPY **4**. This compound exhibits enhanced π - π stacking in the solid state, unusually large blue-shifts in the absorbance and emission spectra, and higher quantum yield than its unfused precursor; DFT calculations suggest a small energy gap for **4**, and strong electronic communication between the 8-OPh and the BODIPY core.

Graphical Abstract

INTRODUCTION

Due to their remarkable properties,¹ boron dipyrromethenes (known as BODIPYs) are finding wide applications as fluorescent probes,² as sensitizers in photodynamic therapy,³ in dye-sensitized solar cells,⁴ and as boron delivery agents for boron neutron capture therapy.⁵ Their favorable properties include strong and narrow absorption and emission bands in the far-red or near-infrared (NIR) regions, high quantum yields, high chemical and physical stability, and high tunability that allows the design of specific targets for a particular application.

Among the functionalized BODIPYs, aryl-fused derivatives are particularly attractive due to their characteristic rigid π -conjugated systems, and the resulting high quantum yields and enhanced molecular π - π stacking in the solid state.⁶ Furthermore, aryl-fused BODIPYs with flattened structures tend to promote solid state fluorescence.⁷ As a consequence, a

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The authors declare no competing financial interest.

Supporting Information

¹H, ¹³C and ¹¹B NMR spectra for BODIPYs **2–4**, detailed optimized conditions for synthesis of BODIPY **4**, absorbance and emission spectra, partial charges of BODIPY **3–4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

significant number of benzo-[*a*]⁸ and [*b*]^{3c, 6, 9} fused, *meso*-(8)-aryl-fused¹⁰ and B,O-chelated¹¹ BODIPYs have been reported in the last decade. However, a main challenge remains in the case of 8-aryl substituted BODIPYS, due to the rotation of the *meso*-(8)-aryl group (e.g. phenyl, thienyl, furyl), even in the presence of 1,7-substituents; this increases nonradioactive decay to the ground state and lowers the quantum yields. For example, aryl-fused BODIPYs **a** and **b** (Figure 1) show quantum yields of about 0.5,^{6, 9i} while BODIPY **c** with a *meso*-2,4,6-trimethylphenyl group exhibits enhanced quantum yield because of restricted rotation of the 8-aryl group.^{9g} However in this case, the π - π interactions in the solid state are also reduced due to the bulkiness of the 2,4,6-trimethylphenyl group at the 8-position. For example, the X-ray analysis of **a** shows an interplanar distance around 3.48 Å, which is about twice the van der Waals radius of carbon (1.7 Å). On the other hand, the *meso*-2,4,6-trimethylphenyl group increases the interplanar distance in the solid state, therefore weakening the π - π interactions.⁶ Furthermore, the nearly perpendicular *meso*-8-aryl group interferes with the transmission of electronic push-pull effects,¹² which are in turn favored by a rigid aryl-fused BODIPY, as previously observed.^{9a} In addition, the reported *meso*-perylene-,^{10a} porphyrin-,^{10b} and anthracene-fused^{10c} BODIPYs also suffer from low quantum yields, and/or loss of the characteristic sharp and narrow absorption and emission spectra.

In this work, we report the synthesis of a new dye, 8-phenoxy-fused BODIPY **4**, designed to exhibit both enhanced π - π interactions and high fluorescence quantum yields. BODIPY **4** was prepared in two steps from perhalogenated BODIPY **1**,¹³ via a substitution reaction followed by a Pd(0)-catalyzed intramolecular cyclization. There are several advantages to our strategy: (1) 8-aryloxy (and alkoxy) substituted BODIPYs typically display high quantum yields;¹⁴ (2) the 8-phenoxy group allows the formation of a 6-membered fused ring; (3) the 1,7-bromo groups are more reactive than hydrogens,^{6, 9i, 15} particularly under Pd(0)-catalyzed reaction conditions; and (4) the presence of halogen groups at the pyrrolic positions allows for further functionalization of the BODIPY. BODIPY **4** features a planar backbone as evidenced by X-ray crystallography, strong π - π stacking, high quantum yields, and unusually large hypsochromic shifts in its absorption and emission spectra. DFT calculations were performed to gain insight into the observed properties.

RESULTS AND DISCUSSION

Recently, our group reported the synthesis and regioselective functionalization of polyhalogenated BODIPY platforms, such as **1**.^{13, 16} The results from reactivity investigations showed the following orders of reactivity for Pd(0)-catalyzed Stille cross-coupling reactions:¹⁶ 8-Cl $\approx$ 1,7-Br > 3,5-Cl > 2,6-Cl, and for nucleophilic substitution reactions:^{5a, 16b, 16c} 8-Cl > 3,5-Cl > 2,6-Cl. Based on these studies, the perhalogenated BODIPY **1** was chosen as the starting material.¹³ Treatment of BODIPY **1** with 2 equivalents of phenol, in the presence of potassium carbonate, in refluxing CH₂Cl₂, yielded the 8-phenoxy BODIPY **2** as the major product in 53% isolated yield, along with the 3,8-diphenoxy BODIPY as a minor product. By increasing the nucleophile stoichiometry to 10 equivalents, the 3,5,8-tri-substituted BODIPY **3** was the only product isolated in high yield (89%), as shown in Scheme 1. The regioselectivity of the substitution reactions was confirmed by X-ray analysis, as shown in Figure 3 (*vide infra*).

The Pd(0)-catalyzed intramolecular cyclization of BODIPY **3** was accomplished in the presence of Pd(PPh₃)₄ and excess K₂CO₃ in refluxing toluene, providing the aryl-fused BODIPY **4** in 64%, as shown in Scheme 2. Other solvents and/or base, such as DMF, THF and TEA, were also investigated for the cyclization reaction, but these led to lower yields of the targeted BODIPY **4**, as shown in Table S1. Interestingly, less than 10 equivalents of K₂CO₃ also led to lower yields of cyclized product, maybe as a result of the low solubility of K₂CO₃ in toluene. The structures of the new BODIPYs **2–4** were established by HRMS, NMR and X-ray crystallography. BODIPYs **2** and **3** showed the characteristic phenoxy hydrogens in the ¹H NMR spectra between 7.0–7.4 ppm. On the other hand, the ¹H NMR spectrum of BODIPY **4** displays four distinct downfield-shifted hydrogens belonging to the fused phenoxy group, as shown in Figure 2. Hydrogens **a** and **d** appear as dd (doublets of doublets) due to coupling with **b** and **c**, while **b** and **c** are ddd (doublets of doublets of doublets) due to coupling with each other, in addition to **a** and **d**.

Crystals suitable for X-ray analysis were obtained from slow evaporation of CHCl₃ for BODIPYs **2**, **3**, and **4**, and the structures are shown in Figure 3. In BODIPYs **2** and **3**, the phenoxy substituent lies approximately in the plane bisecting the BODIPY, with CCOC torsion angle magnitudes 87.3° about the C8-O bond and 3.2° about the C(phenyl)-O bond for **2** and 89.7° and 6.3° respectively for **3**. These conformational parameters would be 90° and 0° for perfect mirror symmetry and are similar to those (83.9° and 8.5°) in a reported structure^{16b} with methyl groups at the 1- and 7- positions. In two similar structures lacking substituents at the 1- and 7- positions,^{14b,16c} the phenoxy group tilts away from the mirror plane, with torsion angles about C8-O 7.6° and 18.6° and about C(phenyl)-O 91.2° and 67.8°. This suggests that the presence of Br at the 1- and 7- positions in **2** and **3** causes the approximate mirror symmetry rather than an electronic effect. The C₉N₂B BODIPY cores of **2** and **3** are approximately planar with mean deviations of 0.055 and 0.037 Å, respectively. In both cases, the B atom is most out of plane, with respective deviations 0.157 and 0.140 Å. The short C8-O bond lengths of 1.359(2) and 1.40(2) Å for **2** and **3** respectively, reflect their partial double bond character. The oxygen atom lies slightly out of the plane of the BODIPY core, by 0.277 Å in **2** and 0.273 Å in **3**. Cyclization in **4** causes the 8-OPh group to rotate inward from the approximate mirror seen in **2** and **3**, as shown by torsion angles about C8-O 1.9° and about C(phenyl)-O 2.4° (average of two independent molecules), resulting in a remarkably planar extended BODIPY core, as seen in Figure 3, which deeply affects the crystal packing. The mean deviation from coplanarity of the 19 atoms of the ring system is 0.053 Å (average of two molecules). The oxygen atom lies 0.086 Å (average of two) from the 12-atom BODIPY core, considerably more co-planar with the BODIPY chromophore than in **2** and **3**. The planar *meso*, β -aryl-fused BODIPY **4** exhibits a head-on, π - π stacking arrangement, as shown in Figure 4, in which the phenyl ring of one molecule overlaps with the C₅O ring of an adjacent molecule. The stacked rings are slightly slipped by 0.65 Å, and three BODIPY carbon atoms are involved in the overlap. The interplanar distance is 3.32 Å (average of two stacks). The two independent C8-O bond lengths in **4** are 1.324(17) and 1.337(19) Å.

The spectroscopic properties of the new BODIPYs **2–4** were evaluated in CH₂Cl₂. The results are shown in Table 1, Figure 5 and in the Supporting Information. Compared with **1**,

BODIPYs **2** and **3** bearing an 8-phenoxy group exhibited 14 and 13 nm blue-shifted absorption bands, respectively, as previously observed due to the electron-donating character of this group, which generally increases the LUMO energy and decreases the HOMO-LUMO gap.¹⁸ The blue-shifts for the fluorescence bands are slightly larger, 19 and 16 nm, respectively, and the Stokes shifts are within the normal range for BODIPY dyes. On the other hand, surprisingly large blue-shifts in both the absorption (74 nm) and emission (68 nm) bands were observed for BODIPY **4** compared with **1**. These results are caused by the intramolecular cyclization of the 8-phenoxy group of **3**, leading to an extended BODIPY core with a nearly planar structure (Figure 3) and a more conjugated system in BODIPY **4**, with enhanced electron coupling of the phenoxy group with the BODIPY core. Indeed, the *meso*(8)- β (7)-fusion induced blue-shifts in the order of 52–61 nm in absorption and emission, compared with the unfused precursor **3**, as shown in Figure 5. The large blue-shifts observed are probably due to a favored merocyanine-like delocalized-system in BODIPY **4**, in which there is enhanced electronic interaction of the oxygen atom and the BODIPY core, compared with **3**. These results are also in agreement with the X-ray analysis, which shows the oxygen in **4** more coplanar with the BODIPY core and a shorter C8-O bond length, suggesting more double bond character, and therefore a favored merocyanine-like delocalization in this case. The fluorescence quantum yields of the polyhalogenated BODIPYs **1** and **2** are low due to the heavy atom effect, particularly the heavy bromine atoms at the 1,7-positions. Interestingly, BODIPY **3** with phenoxy groups at the 3,5,8-positions shows a dramatic increase in the quantum yield, in agreement with previous observations on 3,5,8-trisubstituted BODIPYs.^{16c,19} BODIPY **4** displays the highest quantum yield, as anticipated due to the loss of one heavy bromine atom, the rigidity induced by the intramolecular cyclization, and the stabilization of a merocyanine-like structure.

To further evaluate the unusually large blue-shifts observed for **4** relative to **3**, DFT calculations were carried out using the Gaussian 09 software package.²⁰ The ground state geometries and ESP partial charges of the 8-aryl fused BODIPY **4** and its unfused precursor **3** were optimized by the DFT method with the B3LYP functional and 6–31G (d,p) basis sets, the results are summarized in Figures 6 and S2–S3. The optimized ground state geometries show a drastic decrease in the dihedral angle between the 8-phenyl ring and the BODIPY core upon cyclization, from nearly 90° to about 0°, in agreement with the X-ray crystallographic results. The MO coefficient distribution greatly changed after the intramolecular cyclization, as shown Figure 5. The HOMO and LUMO of the cyclized BODIPY **4** display significant MO coefficients on the 8-OPh compared with the unfused analogue **3**. Furthermore, BODIPY **4** shows lower ESP partial charge (–0.379414) on the oxygen atom, and shorter C8-O bond (1.343 Å) compared with BODIPY **3** (–0.394504 and 1.359 Å, respectively) (see ESI). These results indicate a much stronger electron-donating effect of the 8-OPh group in BODIPY **4** than in **3**. The 8-position displays the largest MO coefficient in the LUMO,^{1b} therefore the introduction of electron-donating groups at this position generally causes hypsochromic shifts. Furthermore, the DFT calculated HOMO-LUMO energy gap for the 8-fused BODIPY **4** (3.15 eV) is significantly higher than for the unfused precursor **3** (2.88 eV) (see Figure S3 in ESI), which is consistent with the large blue shifts observed in the spectroscopic studies.

CONCLUSION

In summary, regioselective substitution reactions on perhalogenated BODIPY **1** using excess phenol and potassium carbonate, gave the corresponding 8-mono- and 3,5,8-tri-substituted products **2** and **3**, respectively, in good yields. The Pd(0)-catalyzed intramolecular cyclization of the 8-phenoxy group of **3** proceeded smoothly in the presence of Pd(PPh₃)₄/K₂CO₃ affording BODIPY **4** in 64% yield. The X-ray structures of BODIPYs **2**, **3** and **4** revealed nearly 90° dihedral angles between the 8-OPh and the BODIPY core in **2** and **3**, while in **4** the angle was drastically reduced to 1.6°. DFT calculations revealed strong electronic interaction between the 8-OPh and BODIPY **4** core in the LUMO and HOMO. The nearly planar structure of **4** and strong electron-donating effect of the 8-oxygen atom in this compound, cause unusually large *hypsochromic* shifts in the absorption and emission spectra, increased Stokes shift, high quantum yield, and enhanced π - π interactions relative to the unfused derivative.

EXPERIMENTAL SECTION

General

Chemical reagents were purchased from commercial companies, and used without further purification. The reactions were monitored by TLC using silica gel plates with 254 indicator (0.2 mm, polyester backed, 60Å, precoated) and UV lamp. Preparative TLC plates (60G, f254) for liquid chromatography or silica gel for column chromatography (60Å, 230–400 mesh) were used for the purifications. All the NMR spectra were obtained on 400 or 500 MHz NMR spectrometer. Chemical shifts (δ) are provided in ppm in CDCl₃ (7.27 and 77.0 ppm for ¹H NMR and ¹³C NMR, respectively); Hz is used as the unit for the coupling constants (*J*). High-resolution mass spectra (HRMS) were collected on an ESI-TOF spectrometer in negative mode.

Spectroscopy methods

A 10 mm Quartz cuvette and solvents (ACS grade) were used for both absorption and emission spectra collections. Molar absorption coefficients (ϵ) were determined from the plots of integrated absorbance vs. concentrations. Dilute solutions with different absorbance (0.02–0.08) at the particular excitation wavelength were used for the determination of relative quantum yields. Rhodamine B (0.40 in methanol),¹⁷ rhodamine 6G (0.95 in ethanol)¹⁸ and fluorescein (0.90 in 0.1 N NaOH)¹⁸ were used as external standards for BODIPYs **2–4**. The equation below was used for the determination of the relative fluorescence quantum yields (Φ_f):²¹

$$\Phi_s = \Phi_{st} \times (\text{Grad}_x / \text{Grad}_{st}) \times (n_x^2 / n_{st}^2)$$

where Φ and n represent the fluorescence quantum yields and refractive indexes, respectively; subscripts s and x represent the standards and tested samples; Grad represents the gradient of integrated fluorescence intensity vs absorbance at the particular wavelength.

1.3 X-ray methods

X-ray diffraction data for **2**, **3**, and **4** were collected at T=90K on a diffractometer using either MoK α (for **2**) radiation or CuK α radiation (**3** and **4**) from a microfocus source. Crystals for **3** and **4** were extremely small and weakly scattering. In addition, crystals of **4** were twinned and had two independent molecules, and restraints were necessary to produce reasonably-shaped ellipsoids. Refinement was by SHELXL97 for **2** and SHELXL2014 for **3** and **4**, and all unique reflections were used in the refinements. H atoms were placed in calculated positions. Crystal Data: **2**, C₁₅H₅BBr₂Cl₄F₂N₂O, triclinic, $a = 10.0033(9)$, $b = 10.2945(9)$, $c = 10.8914(10)$ Å, $\alpha = 115.154(2)$, $\beta = 111.867(2)$, $\gamma = 93.784(2)^\circ$, space group $P-1$, $Z = 2$, 10782 reflections measured, $\theta_{\max} = 30.4^\circ$, 5019 unique ($R_{\text{int}} = 0.018$), final $R = 0.028$ (4262 $I > 2\sigma(I)$ data), $wR(F^2) = 0.075$ (all data), CCDC 1507957; **3**, C₂₇H₁₅BBr₂Cl₂F₂N₂O₃, monoclinic, $a = 14.0387(10)$, $b = 5.7510(4)$, $c = 16.2336(11)$ Å, $\beta = 98.473(5)^\circ$, space group $P2_1$, $Z = 2$, 7138 reflections measured, $\theta_{\max} = 68.2^\circ$ (Cu), 3433 unique ($R_{\text{int}} = 0.059$), final $R = 0.100$ (2753 $I > 2\sigma(I)$ data), $wR(F^2) = 0.269$ (all data), CCDC 1507958; **4**, C₂₇H₁₄BBrCl₂F₂N₂O₃, monoclinic, $a = 29.7825(16)$, $b = 7.1461(3)$, $c = 24.4714(13)$ Å, $\beta = 114.340(3)^\circ$, space group Cc , $Z = 8$, 19426 reflections measured, $\theta_{\max} = 69.3^\circ$ (Cu), 5176 unique ($R_{\text{int}} = 0.056$), final $R = 0.058$ (4260 $I > 2\sigma(I)$ data), $wR(F^2) = 0.141$ (all data), CCDC 1507959.

1.4 Computational methods

Calculations were carried out using the Gaussian 09 software package.²⁰ The ground state geometries of the BODIPYs were optimized by the DFT method with the B3LYP functional and 6-31G (d,p) basis sets. The ESP electrostatic potential were calculated according to the Merz-Singh-Kollman scheme.²²

1.5 Synthesis and characterization of BODIPYs

BODIPY 1 was prepared using our previously published procedure.¹³

General procedure for BODIPYs 2–3

Into a reaction vial were added BODIPY **1** (15.7 mg, 0.03 mmol), K₂CO₃ (41.4 mg, 0.3 mmol), phenol (2 equiv for **2** and 10 equiv for **3**) and dichloromethane (1 mL). The reaction mixture was stirred and refluxed in CH₂Cl₂. The reaction was stopped when the starting materials were consumed according to TLC. K₂CO₃ was removed by filtration using CH₂Cl₂ as eluent. The residue was further purified by prep-TLC (CH₂Cl₂/hexanes 1:1 as eluent) to provide the desired product.

BODIPY 2: Yield: 9.2 mg (as a red solid), 53%; mp. decomposed $> 215^\circ\text{C}$; ¹H NMR (500 MHz, CDCl₃) δ 7.36–7.39 (m, 2H), 7.14–7.17 (m, 1H), 6.97–6.99 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 157.9, 151.6, 141.9, 130.2, 125.6, 124.0, 123.9, 116.8, 114.9; ¹¹B NMR (128 MHz, CDCl₃) δ -0.170 (t, $J = 26.4$ Hz); HRMS (ESI-TOF) m/z 574.7640 [M]⁺; calculated for C₁₅H₅BBr₂Cl₄F₂N₂O: 574.7626.

BODIPY 3: Yield: 18.5 mg (as a red solid), 89%; mp. decomposed $> 215^\circ\text{C}$; ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.41 (m, 6H), 7.12–7.21 (m, 7H), 7.05–7.07 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 158.2, 155.3, 154.9, 149.9, 130.0, 129.8, 125.1, 123.5, 119.8, 117.9, 116.9,

115.0, 112.8; ^{11}B NMR (128 MHz, CDCl_3) δ -0.240 (t, J = 26.1 Hz); HRMS (ESI-TOF) m/z 690.8908 $[\text{M}]^-$; calculated for $\text{C}_{27}\text{H}_{15}\text{BBr}_2\text{Cl}_2\text{F}_2\text{N}_2\text{O}_3$: 690.8929.

BODIPY 4: Into the reaction flask were added BODIPY 3 (5 mg, 0.0072 mmol), K_2CO_3 (50 mg, 0.36 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (0.832 mg, 10% mol). The flask was evacuated and refilled with N_2 four times. Anhydrous toluene (3 mL) was added to the flask. The reaction mixture was stirred at 110 °C for 24 hours. TLC was used to monitor the reaction. The reaction was stopped when the starting material was consumed according to TLC. Toluene was removed under reduced pressure, K_2CO_3 was removed by filtration using CH_2Cl_2 as eluent. The residue was subjected to prep-TLC (CH_2Cl_2 /hexanes 1:1 as eluent) to provide the desired product **4** (2.8 mg) as a yellow solid, in 64% isolated yield. mp. decomposed > 255 °C; ^1H NMR (500 MHz, CDCl_3 , at 315K) δ 8.51–8.52 (dd, J = 8.0, 1.4 Hz, 1H), 7.86–7.88 (dd, J = 8.5, 0.9 Hz, 1H), 7.70–7.73 (m, 1H), 7.59–7.62 (m, 1H), 7.31–7.37 (m, 4H), 7.08–7.20 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3 at 320K) δ 156.6, 156.2, 155.7, 151.3, 149.9, 146.8, 130.6, 129.7, 129.6, 127.0, 126.8, 124.7, 124.5, 124.0, 118.8, 118.0, 117.6, 117.0, 116.3, 113.5, 109.4, 108.9, 99.7; ^{11}B NMR (128 MHz, CDCl_3) δ -0.126 (t, J = 25.9 Hz); HRMS (ESI-TOF) m/z 610.9654 $[\text{M}]^-$; calculated for $\text{C}_{27}\text{H}_{14}\text{BBrCl}_2\text{F}_2\text{N}_2\text{O}_3$: 610.9668.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the NIH (R01 CA179902), and the NSF (CHE 1362641).

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Figure 1.
Structures of several aryl-fused BODIPYs.

Figure 2.
 ^1H NMR spectrum (500 MHz) of **4** in CDCl_3 at 315K.

Figure 3.
X-ray crystal structures of **2–4**; top view (top) and side view (bottom) with 50% ellipsoids.

Figure 4.
Top view (top) and side view (bottom) showing the π - π stacking in BODIPY **4**.

Figure 5.

Normalized absorption (a) and emission spectra (b) of BODIPYs **3** (red) and **4** (green) in dichloromethane. Inserts show photographs of **3** and **4** under ambient light (left, top) and UV light (right, top) ($\lambda_{\text{ex}} = 365 \text{ nm}$) in CH₂Cl₂.

Figure 6.

DFT-calculated frontier MO coefficient distributions (top) and the MO energies (bottom) of BODIPY 3 and 4. Small black squares denote occupied MOs. Black and gray line are used to denote LUMO/HOMO and LUMO+1/HOMO-1 MOs, respectively. The HOMO-LUMO gaps are plotted against a secondary axis and are denoted by red triangles.

Scheme 1.
Substitution reactions of BODIPY **1**.

Scheme 2.

Pd(0)-catalyzed intramolecular cyclization of BODIPY **3**.

Table 1Spectroscopic properties of BODIPYs **1–4** at room temperature in CH₂Cl₂.

	λ_{abs} (nm)	Log ϵ	λ_{em} (nm)	Φ_{fl}^a	SS ^b
1	546	4.87	560	0.18	14
2	532	4.69	541	0.05	9
3	533	5.10	544	0.68	11
4	472	4.48	492	0.99	20

^a Rhodamine B (0.40 in methanol)¹⁷ for **1**; rhodamine 6G (0.95 in ethanol)¹⁸ for **2** and **3**; fluorescein (0.90 in 0.1 N NaOH)¹⁸ for **4**.^b Stokes shift.