JOC The Journal of Organic Chemistry

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pubs.acs.org/joc

One-Pot Synthesis of Rotationally Restricted, Conjugatable, BODIPY Derivatives from Phthalides

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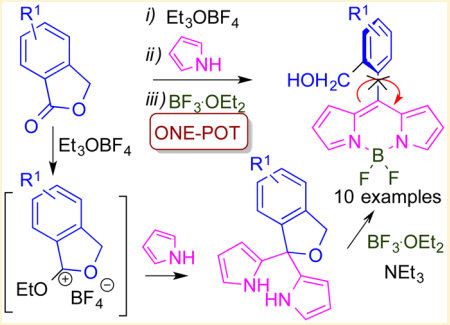
Supporting Information

ABSTRACT: *O*-Ethylation of phthalides with Meerwein's reagent followed by reaction of the ensuing salts with pyrrole, results in the formation of 5-alkoxy-5-phenyl dipyrromethane derivatives, which function as ready precursors of ortho-substituted 8-aryl BODIPY derivatives by reaction with borontrifluoride etherate, an overall process that can be carried out in a one-pot operation.



Difluoroboron dipyrromethene (4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene) or BODIPY, i.e., **1** (Figure 1), fluorescent dyes have attracted considerable interest in the past years.[1] BODIPY dyes are characterized by strong-UV−vis absorption profiles, and fluorescence quantum yields (Φ).

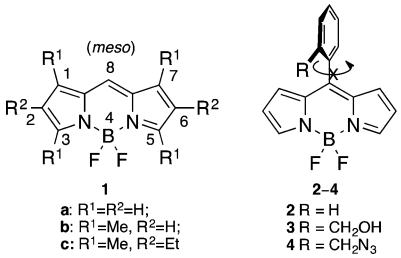


Figure 1. Structures of BODIPYs.

Moreover, they are reasonably stable under physiological conditions and their photophysical properties are relatively insensitive to solvent polarity. Owing to these features, BODIPY derivatives have found application as laser-dyes,[2] photosensitizers,[3] fluorescent labels,[4] artificial light-harvesting arrays,[5] and as components of energy transfer cassettes,[6] among others.[7]

During the course of ongoing studies, we became interested in the preparation of ortho-substituted 8-*C*-aryl BODIPY derivatives, e.g. **3**, **4**, for conjugation to biomolecules (Figure 1).[8] The ortho-substituent in these derivatives plays a key dual role, (i) it impedes the rotation of the phenyl moiety about the 8C-aryl bond, which would favor radiative relaxation, thus endowing the molecule with a much higher fluorescence quantum yield than that of the unsubstituted analogue **2**,[9] and (ii) it provides the handle for derivatization and/or conjugation to the target molecule.[10] Furthermore, the incorporation of a bulky group at the apical position has been suggested as a useful strategy to prevent aggregation, a phenomenon known to lower the quantum yield on fluorophores.[11]

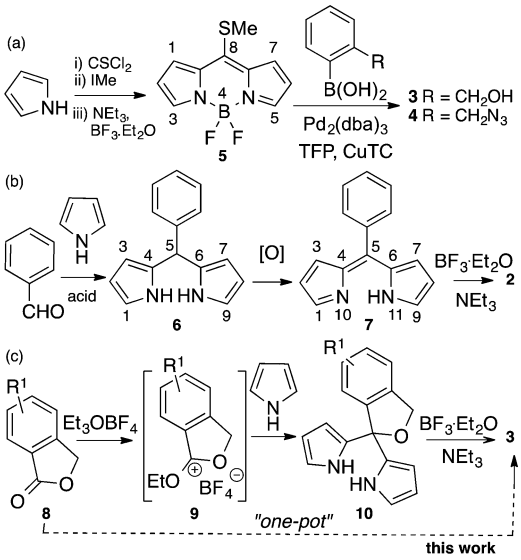
Previous synthesis of derivatives **3** and **4**, have made use of the Liebeskind-Srogl cross-coupling reaction of 8-methylthio (Biellman's) BODIPY (**6**)[12] with boronic acids, according to a methodology described by Peña-Cabrera's group (Scheme 1a).[13,14] On the other hand, the most commonly used approaches to BODIPY derivatives **2**, make use of the acid catalyzed condensation of aromatic aldehydes with pyrrole (Scheme 1b).[15] This reaction involves the intermediacy of 5-aryl dipyrromethane derivatives, e.g. **5**, which are oxidized to dipyrromethenes, e.g., **7**, and then transformed to borodipyrromethenes (**2**) by treatment with $BF_3{\cdot}Et_2O$. In this context, the reaction of pyrrole with carboxylic acid derivatives, rather than aldehydes, leads directly to dipyrromethene intermediates, thus obviating the additional oxidation step.[1,16]

In our search for a concise route to ortho-substituted 8-*C*-aryl-BODIPY derivatives we envisaged: (i) the use of phthalide(s) **8**,[17,18] as the 8-*C*-aryl ortho-substituted component(s) in the synthesis of previously undescribed 1,1-dipyrrolyl 1,3-dihydroisobenzofurans (phthalans),[18] e.g., **10**, and (ii) the usefulness of the latter as synthetic equivalents to

Received: October 5, 2016
Published: December 27, 2016

DOI: 10.1021/acs.joc.6b02426
J. Org. Chem. 2017, 82, 1240−1247

Scheme 1. Synthetic Routes to 8-Aryl BODIPYs



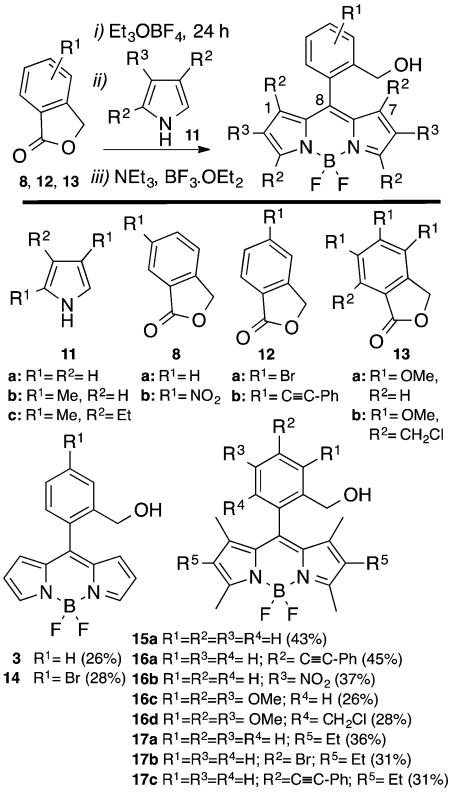
dipyrromethenes, e.g., **7** (Scheme 1c). In this article, we describe the unprecedented and mild reaction of salt **9**[19,20]—easily obtained by *O*-ethylation of phthalide (**8**) with Meerwein's reagent—with pyrrole. This process leads to 1,1-[2,2′-bis(1*H*-pyrrolyl)] 1,3-dihydroisobenzofurans (phthalans) **10**, which paves the way to a one-pot entry to rotationally restricted, conjugatable, BODIPYs related to **3**, from phthalide derivatives.

Our approach contrasts with currently employed methods to access 1,1-disubstituted phthalans, e.g., **10**,[18] that are generally based in the reaction of phthalide (**8**) with two equivalents of the appropriate Grignard reagents followed by cyclization of the resulting open-chain diols.[19,21] On the other hand, ethylphthalidinium salts **9**,[19] have been normally confronted with organometallics or alkoxides leading to either ketals or orthoesters, respectively.[22] In practice, we have shown that the overall transformation phthalide → BODIPY (e.g., **8** → **3**) can be successfully performed as a one-pot operation (Scheme 2). As a result, a variety of BODIPY derivatives can be accessed by changes in the pyrrole and the phthalide partners, in moderate to good yields. The reaction has been explored with substituted pyrroles, e.g., **11b**, **11c**, in combination with a variety of phthalides **8**, **12**, and **13**, thus paving the way to BODIPY derivatives **3**, **14**−**17** (Scheme 2). Higher yields were consistently observed when substituted pyrroles were employed, rather than when pyrrole itself was used.

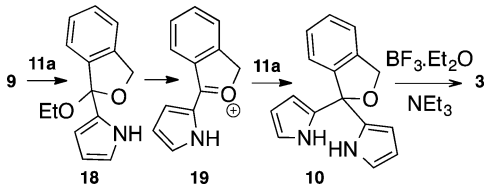
The proposed reaction pathway for the overall transformation might involve initial reaction of cation **9** with pyrrole to form an intermediate ketal **18**, which upon elimination would lead to branched oxonium ion **19**, able to react with a second pyrrole unit leading to *bis*-pyrrolyl phthalan **10**. The latter, which could be regarded as a 5-alkoxy-5-aryl dipyrromethane, is a synthetic equivalent to a dipyrromethene and upon reaction with $BF_3{\cdot}OEt_2$ leads to the desired borondipyrromethene derivatives (Scheme 3).[23] As support for the proposed mechanism, we have been able to isolate compound **10**, which upon treatment with $BF_3{\cdot}OEt_2$ led to BODIPY **3**.

In these derivatives, the presence of an ortho-functionalized aryl group attached at the meso position of the BODIPY-core hardly modifies the photophysics of the parent dyes (Table 1

Scheme 2. One-Pot Synthesis of BODIPY Derivatives



Scheme 3. Proposed Reaction Pathway



and Figure S1, where the absorption and fluorescence spectra for the representative derivatives **3**, **15a**, and **17a** bearing ortho-hydroxymethyl groups are depicted). In fact, the photophysical properties of the new derivatives seem independent of the nature of the substituent (i.e., hydroxyl or azide), as well as of the physicochemical properties of the media, in view of previously reported results for related 8-phenylBODIPYs.[24] Just a slight increase in the absorption coefficient and a slight bathochromic shift of the spectral band is promoted in all cases. On the other hand, the replacement of hydrogen atoms by methyl groups at C-1 and C-7 reinforces the steric hindrance with the ortho-substituent, thus directing the 8-aryl moiety to an orthogonal arrangement (Figure 2) and avoiding the free rotation of this substituent, which significantly increases internal conversion processes leading to a drastic reduction of the fluorescence capacity.[25] Thereby, the new derivatives are highly fluorescent with quantum yields similar to or slightly lower than those recorded for the corresponding BODIPY parent dyes (**1a**−**c**). Moreover, the subsequent *para*-functionalization (e.g., bromine atom) of the 8-ortho-substituted aryl group does not modify significantly the photophysical signatures of the resulting dyes.

The new dyes exhibit broad-line-width laser emission, with a pump threshold energy of ∼0.8 mJ, divergence of 5 mrad, and

DOI: 10.1021/acs.joc.6b02426
J. Org. Chem. 2017, 82, 1240−1247

Table 1. Photophysical[a] and Lasing Properties[b]

	λ_{ab} (nm)	ε_{max}	λ_{fl} (nm)	$\Delta\nu_{st}$ (cm^{-1})	ϕ	τ (ns)	Eff (%)	λ_{la} (nm)
1a	498.0	5.6	508.0	385	0.90	7.02	55	537
3	499.5	6.4	513.0	527	0.74	6.45	60	540
4	501.0	6.1	514.0	505	0.73	6.25	47	542
14a	501.5	6.8	515.0	523	0.67	5.74	39	546
1b	495.0	8.1	507.0	475	0.85	5.52	26	541
15a	505.5	8.4	510.0	370	0.76	5.87	19	547
15b	502.0	8.3	511.0	350	0.82	5.83	24	548
15c	502.5	8.8	513.0	410	0.85	5.77	26	550
15d	502.0	8.1	512.0	390	0.85	5.94	23	549
1c	518.0	7.4	535.0	615	0.84	6.09	48	566
17a	524.5	7.8	541.0	580	0.72	6.49	42	580
17b	526.5	8.0	537.0	370	0.71	6.62	34	571

[a]Dye concentration: 2 μM. Absorption (λ_{ab}) and fluorescence (λ_{fl}) wavelength, molar absorption (ε_{max}) (10^4 $M^{-1}cm^{-1}$), Stokes shift ($\Delta\nu_{st}$), fluorescence quantum yield (ϕ), and lifetime (τ); [b]Dye concentration 2 mM. Eff(%): Lasing efficiency, as the ratio between the energy of the laser output and the pump energy incident on the cell surface and l_{la}: Peak wavelength for the laser emission.

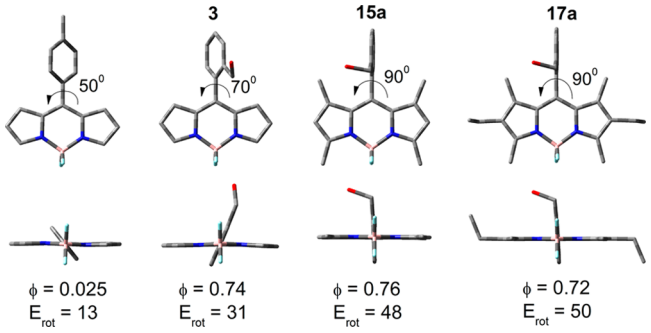


Figure 2. Ground state optimized geometries for 8-tolyl BODIPY[26] (left) and herein tested representative counterparts bearing ortho-methylhydroxyphenyl group at C-8 (meso) position in two different views. The corresponding dihedral angles, accounting for the most stable 8-aryl conformation, the rotational barrier (E_{rot} in kcal/mol), calculated from the corresponding potential energy surfaces (Figure S2 in SI), and the fluorescence quantum yields (f) are also displayed.

pulse duration of 8 ns full-width at half-maximum (fwhm) when placed in a simple plane−plane nontunable resonator cavity, and lasing efficiencies ranging from 20 to 60%, in the green spectral region (540−585 nm).

The lasing behavior of the dyes shows good correlation with their photophysical properties: the longer the fluorescence wavelength, the "redder" becomes the lasing emission and the higher the fluorescence quantum yield, the higher the lasing efficiency. The Stokes shift ($\Delta\nu_{St}$) becomes key to explaining the excellent laser behavior of the BDP derivatives. In fact, a significant increase of the Stokes shift reduces the reabsorption/re-emission processes enhancing the laser action, which is particularly important when highly concentrated dye solutions are required to induce laser emission. Consequently, the lasing efficiency of the derivatives related to **1a** is similar or slightly lower than that of its parent dye in spite of the decrease in the fluorescence quantum yield, which is outweighed by the higher Stokes shift exhibited by these derivatives. On the contrary, derivatives related to **1b** and **1c**, with fluorescence quantum yield and Stokes shift lower than those of their parent dyes, exhibit the lowest laser efficiencies (20−30%).

Photostability is an important feature that defines fluorescence dyes and, in this context, we have carried out photodecomposition experiments on derivatives **15a** and **17a** as representative for this family of BODIPY derivatives. Both dyes displayed high photostability under drastic pumping conditions, with the laser emission remaining at the initial level after 60.000 pump pulses.[27]

On the other hand, it is amply documented that the spectroscopic and photophysical properties of borodipyrromethanes can be fine-tuned by synthetic postmodifications on the BODIPY core.[28] In this context, we have tested the compatibility of the C-8 "benzyl functionality" with well-established synthetic transformations on these derivatives (Figure 3). Thus, iodination of **15a** paved the way to **20a**,

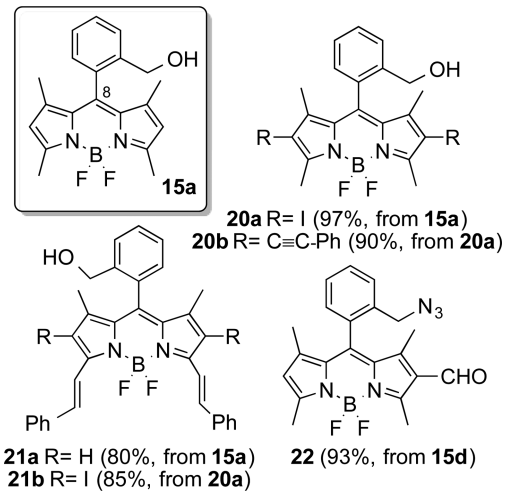


Figure 3. Synthetic postmodifications on the BODIPY core.

which could be engaged on a Sonogashira cross-coupling reaction or a Knoevenagel type condensation,[29] thus leading to **20b** or **21b**, respectively. Alternatively, Knoevenagel condensation of **15a** with benzaldehyde led to deiodinated derivative **21a**. Finally, formyl derivative **22** could be obtained from **15d** (Figure 4) by Vilsmeier−Haack formylation.[30]

Finally, synthetic modifications carried out on the pending hydroxymethyl group permit a ready entry to BODIPY derivatives with a variety of anchors, thus opening an assortment of possibilities for BODIPY conjugations. In this context, crystalline and shelf-stable, formyl, isothiocyanate, and azido derivatives **15b−d**, respectively, have been prepared from hydroxymethyl BODIPY **15a** (Figure 4). As proof of concept, (i) mild glycosylation of **15a** with D-glucose pentaacetate

DOI: 10.1021/acs.joc.6b02426
J. Org. Chem. 2017, 82, 1240−1247

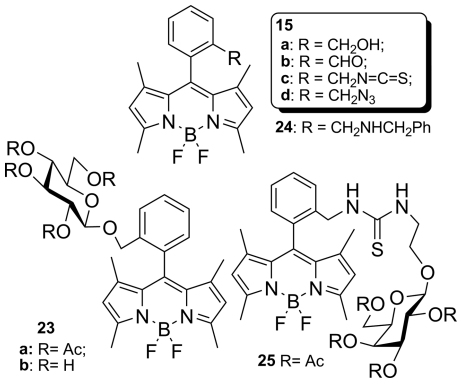


Figure 4. BODIPYs and BODIPY conjugates.

provided BODIPY β-D-glucoside **23a**, which could be uneventfully de-*O*-acetylated to **23b** (NEt_3, MeOH, 65 °C);[8] (ii) reductive amination of **15b** in the presence of benzylamine yielded amino-derivative **24**; and (iii) reaction of isothiocyanate **15c** with 2-aminoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside produced thiourea-linked glycoside **25**.

In summary, we have developed a novel, one-pot, efficient method for the generation of ortho-hydroxymethyl 8-*C*-aryl-BODIPY derivatives based on the previously unreported reaction of ethyl phthalidinium salts, e.g. **9**, with pyrrole derivatives. We have shown that the method is compatible with a variety of phthalides differing in the electronic nature of their aromatic rings, and with diverse pyrrole derivatives, thus providing easy access to a wide range of BODIPY derivatives. This method complements well-established synthesis of BODIPY derivatives by condensation of aromatic aldehydes or carboxylic acid derivatives with pyrroles,[1a] since it provides direct access to ortho-hydroxymethyl 8-*C*-aryl-BODIPY derivatives. The ensuing ortho-hydroxymethyl substituent can be engaged itself in BODIPY-conjugation, or transformed into a variety of anchoring groups that facilitate conjugation to an assortment of compounds.

EXPERIMENTAL SECTION

General Information. All solvents and reagents were obtained commercially and used as received unless stated otherwise. Residual water was removed from starting compounds by repeated coevaporation. Reactions were executed at ambient temperatures unless stated otherwise. All moisture-sensitive reactions were performed in dry flasks fitted with glass stoppers or rubber septa under a positive pressure of argon. Air- and moisture-sensitive liquids and solutions were transferred by syringe or stainless steel cannula. A 5.0 M stock solution of triethyloxonium tetrafluoroborate was prepared by dissolving 25 g (0.131 mmol) of the salt in 26.3 mL of anhydrous methylene chloride. This solution was stored on the freezer and used within one month after its preparation.

Anhydrous $MgSO_4$ or Na_2SO_4 were used to dry organic solutions during workup, and evaporation of the solvents was performed under reduced pressure using a rotary evaporator. Flash column chromatography was performed using 230−400 mesh silica gel. Thin-layer chromatography was conducted on Kieselgel 60 F254. Spots were observed first under UV irradiation (254 nm) then by charring with a solution of 20% aqueous H_2SO_4 (200 mL) in AcOH (800 mL). ^{1}H- and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300, 400, or 500 MHz and 75, 101, or 126 MHz, respectively. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.25 ppm, CD_3OD: δ 4.870 ppm). Coupling constants (J) are given in Hz. All presented ^{13}C NMR spectra are proton-decoupled. Mass spectra were recorded by direct injection with a Accurate Mass Q-TOF LC/MS spectrometer equipped with an electrospray ion source in positive mode.

*Representative Procedure for the One-Pot Synthesis of BODIPYs **3**, **14**−**17c** from Phtalides **8**, **12**−**13**.* A solution of the corresponding lactone in anhydrous dichloromethane (1/mmol mL) under argon and in the presence of preactivated 4 Å molecular sieves (200 mg/mmol) was treated with the stock solution of triethyloxonium tetrafluoroborate (1 equiv). The resulting solution was stirred magnetically for 24 h. After cooling down to 0 °C, the appropriate pyrrole (10.0 and 3.0 equiv for **11a** and **11b**/**11c**, respectively) was added and the resulting mixture stirred under argon at room temperature (rt) for additional 3 h. The reaction flask was recooled to 0 °C, triethylamine (6.0 equiv) and borontrifluoride diethyl etherate complex (9.0 equiv) were added dropwise and stirred at rt for another 2 h. The reaction mixture was diluted with dichloromethane (150 mL), molecular sieves were filtered off, and the filtrated sequentially washed with distilled water (3 × 200 mL) and saturated sodium chloride (1 × 200 mL). The organic layer was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane−ethyl acetate 9:1) to afford the corresponding BODIPY derivative, **3**, **14**−**17**.

In some instances, the ensuing BODIPY is contaminated with unreacted phthalide since they often display very similar Rf in hexane-ethyl acetate mixtures. In these cases, chromatographic separation of the mixture becomes difficult, and we have found advantageous to perform the separation by stirring a solution of the mixture in CH_2Cl_2 in the presence of 1N NaOH aqueous solution (90 min). Under these conditions, saponification of the phthalide takes place generating the sodium salt of the corresponding acid, which becomes water-soluble. Separation of the organic layer then yields the uncontaminated BODIPY.

*2,2′-(1,3-Dihydroisobenzofuran-1,1-diyl)bis(1H-pyrrole) (**10**).* A solution of the phthalide **8a** (500 mg, 3.73 mmol) in anhydrous dichloromethane (5 mL) under argon and in the presence of preactivated 4 Å molecular sieves (500 mg) was treated with the stock solution of triethyloxonium tetrafluoroborate (1.0 equiv, 3.73 mmol, 980 μL). The resulting solution was stirred magnetically for 24 h. After cooling down to 0 °C, pyrrole **11a** (10 equiv, 37.3 mmol, 2.6 mL) was added and the resulting mixture stirred under argon at room temperature (rt) for additional 3 h. The reaction mixture was diluted with dichloromethane (100 mL), molecular sieves were filtered off, and the filtrated sequentially washed with distilled water and brine. The organic layer was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane−ethyl acetate 9:1) to give a single spot on this system containing a mixture 1:1 of 2,2′-(1,3-dihydroisobenzofuran-1,1-diyl)-bis(1*H*-pyrrole) **10**, along with unreacted phtalide **8a** (93 mg, 22%). A further chromatography of the above-mentioned material on preparative tlc (eluent: hexane−ethyl acetate = 9:1, run three times) allowed to isolate a fraction containing pure dipyrromethane **10**, δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 2H), 7.36−7.05 (m, 4H), 6.69 (m, 2H), 6.07 (m, 2H), 5.86 (m, 2H), 5.06 (s, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.7, 138.9, 133.1, 128.1, 127.6, 123.0, 121.0, 118.1, 108.3, 107.5, 85.5, 71.0. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{15}N_2O$: 251.1184; Found 251.1178.

*8-(2-Hydroxymethylphenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**3**).*[10] This compound was prepared according to the general procedure from phthalide **8a** (2.8 g, 21 mmol) and pyrrole **11a** (14 g, 210 mmol). Orange crystals (1.63 g, 26%), mp = 101−102 °C.

Alternatively, a solution of compound **10** (38 mg, 0.15 mmol) in anhydrous dichloromethane (3 mL) was cooled to 0 °C, triethylamine (126 μL, 6.0 equiv, 0.9 mmol) and borontrifluoride diethyl etherate complex (169 μL, 9.0 equiv, 1.35 mmol) were added dropwise and the mixture stirred at rt for 15 min. The reaction was then diluted with dichloromethane (10 mL), washed with water and brine. The organic layer was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane−ethyl acetate 9:1) to afford BODIPY **3** (36 mg, 82%).

*8-(4-Bromo-2-hydroxymethylphenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**14**).* This compound was prepared according to the

DOI: 10.1021/acs.joc.6b02426
J. Org. Chem. 2017, 82, 1240−1247

general procedure from 5-bromo-3H-isobenzofuranone **12a** (372 mg, 1.75 mmol) and pyrrole **11a** (1.3 mL, 17.5 mmol). Yellow crystals (184 mg, 28%), mp = 109−110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (s, 2H), 7.88 (d, J = 2.1 Hz, 1H), 7.56 (dd, J = 8.0, 2.0, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 4.3 Hz, 2H), 6.51 (d, J = 4.1 Hz, 2H), 4.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.2, 143.9, 141.4, 135.1, 131.2, 131.0, 130.7, 130.3, 130.0, 124.7, 119.0, 61.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ − 146.2 (q, J = 31.9 Hz). HRMS (ESI-QTOF) m/z: $[M+NH_4]^+$ Calcd for $C_{16}H_{16}BBrF_2N_3O$ 394.0538; Found 394.0534.

*8-(2-Hydroxymethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**15a**).* This compound was prepared according to the general procedure from phthalide **8a** (1.45 g, 10.8 mmol) and pyrrole **11b** (3.13 mL, 29.5 mmol). Orange crystals (1.64 g, 43%), mp = 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64 (dd, J = 7.9, 1.3 Hz, 1H), 7.50 (t, J = 7.6, 1.4 Hz, 1H), 7.41 (t, J = 7.5, 1.3 Hz, 1H), 7.18 (dd, J = 7.6, 1.4 Hz, 1H), 5.97 (s, 2H), 4.56 (s, 2H), 2.54 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.9, 143.0, 139.8, 138.2, 132.9, 131.0, 129.7, 128.5, 128.2, 128.1, 121.5, 62.4, 14.7, 14.0. HRMS (ESI-QTOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{21}BF_2N_2NaO$ 377.1613; Found 377.1598.

*8-(2-Hydroxymethyl-4-phenylethynyl-phenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**16a**).* This compound was prepared according to the general procedure from phthalide **12b**[31] (800 mg, 3.4 mmol) and pyrrole **11b** (1.05 mL, 10.2 mmol). Orange crystals (694 mg, 45%); mp >230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (dd, J = 1.7 Hz, 1H), 7.57 (m, 3H), 7.37 (m, 3H), 7.20 (d, J = 7.8 Hz, 1H), 5.99 (s, 2H), 4.58 (s, 2H), 2.56 (s, 6H), 1.42 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 142.9, 138.9, 138.7, 132.9, 131.8, 131.4, 131.2, 130.8, 128.8, 128.6, 128.4, 124.9, 123.0, 121.6, 90.9, 88.8, 62.1, 14.8, 14.3. API-ES positive 455.3 $(M+H)^+$; HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{26}BF_2N_2O$: 455.2106; Found 455.2115.

*8-(2-Hydroxymethyl-6-nitro-phenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**16b**).* This compound was prepared according to the general procedure from phthalide **8b** (300 mg, 1.7 mmol) and pyrrole **11b** (523 μL, 5.1 mmol). Orange oil (250 mg, 37%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, J = 8.6, 2.4 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 6.01 (s, 2H), 4.70 (s, 2H), 2.56 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 147.7, 146.3, 142.3, 136.0, 133.9, 130.4, 128.6, 124.6, 123.6, 122.1, 61.5, 14.8, 14.5. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}BF_2N_3O_3$: 400.1644; Found 400.1657.

*8-(2-Hydroxymethyl-3,4,5-trimethoxy-phenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**16c**).* This compound was prepared according to the general procedure from phthalide **13a**[32] (250 mg, 1.1 mmol) and pyrrole **11b** (338 μL, 3.3 mmol). Orange oil (127 mg, 26%); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.54 (s, 1H), 5.99 (s, 2H), 4.50 (bs, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.55 (s, 6H), 1.50 (s, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ − 147.62 (dq, J_{F-F} = 110.0, J_{B-F} = 33.0 Hz, 1F), −146.87 (dq, J_{F-F} = 110.0, J_{B-F} = 33.0 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 151.9, 150.9, 140.4, 140.3, 136.4, 128.7, 126.7, 122.1, 118.8, 104.1, 59.1, 58.7, 56.1, 53.7, 12.0, 11.3. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{28}BF_2N_2O_4$: 445.2110; Found 445.2109.

*8-(2-Hydroxymethyl-3,4,5-trimethoxy-6-chloromethyl-phenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**16d**).* This compound was prepared according to the general procedure from phthalide **13b**[32,33] (150 mg, 0.36 mmol) and pyrrole **11b** (118.2 μL, 1.10 mmol). Orange oil (49 mg, 28%); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): δ 5.99 (s, 2H), 4.49 (d, J = 4.7 Hz, 2H), 4.48 (s, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 3.97 (s, 3H), 2.56 (s, 6H), 1.48 (s, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ − 146.33 (dq, J_{F-F} = 109.4, J_{B-F} = 32.4 Hz, 1F), −145.92 (dq, J_{F-F} = 109.5, J_{B-F} = 32.6 Hz, 1F) ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 154.6, 154.2, 147.1, 142.9, 135.2, 131.1, 130.9, 129.6, 128.8, 127.4, 124.0, 121.6, 121.6, 61.8, 61.8, 61.1, 58.5, 38.6, 14.7, 13.9. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{29}BClF_2N_2O_4$: 493.1877; Found 493.1870.

*8-(2-Hydroxymethyl)-2,6-diethyl-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**17a**).* This compound was prepared according to the general procedure from phthalide **8a** (520 mg, 3.9 mmol) and 3-ethyl-2,4-dimethylpyrrole **11c** (1.4 mL, 10.6 mmol). Pink crystals (576 mg, 36%), mp = 92−94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5, 1.4 Hz, 1H), 7.41 (td, J = 7.5, 1.2 Hz, 1H), 7.20 (dd, J = 7.5, 1.3 Hz, 1H), 4.59 (dd, J = 3.4, 1.6 Hz, 2H), 2.53 (s, 6H) 2.29 (q, J = 7.5 Hz, 4H), 1.26 (s, 6H), 0.98 (t, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$,) δ 154.3, 138.1, 134.2, 133.9, 133.2, 130.5, 129.6, 129.3, 128.6, 128.5, 128.2, 62.8, 17.3, 14.8, 12.8, 11.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ − 146.06 (q, J = 32.8 Hz), − 146.24 (d, J = 33.0 Hz). API-ES positive 411.3 $(M+H)^+$; HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{30}BF_2N_2O$: 411.2419; Found 411.2397.

*8-(4-Bromo-2-hydroxymethylphenyl)- 2,6-diethyl-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**17b**).* This compound was prepared according to the general procedure from 5-bromo-3H-isobenzofuranone **12a** (472 mg, 2.22 mmol) and pyrrole **11c** (0.8 mL, 6.05 mmol). Pink crystals (335 mg, 31%), mp = 112−113 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 8.1, 2.0 Hz, 2H), 7.08 (d, J = 8.1 Hz, 1H), 4.57 (s, 2H), 2.52 (s, 6H), 2.29 (q, J = 7.6 Hz, 4H), 1.30 (s, 6H), 0.98 (t, J = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.7, 140.9, 138.0, 136.5, 133.4, 132.5, 131.5, 131.0, 130.3, 130.1, 123.8, 62.1, 17.3 (x2), 14.8 (x2), 12.8 (x2), 11.7 (x 2); ^{19}F NMR ($CDCl_3$, 376 MHz): δ − 146.2 (q, J_{F-B} = 31.9 Hz). HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{29}BBrF_2N_2O$: 489.1524; Found 489.1518.

*8-(2-Hydroxymethyl-4-phenylethynyl-phenyl)-2,6-diethyl-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**17c**).* This compound was prepared according to the general procedure from phthalide **12b** (800 mg, 3.4 mmol) and pyrrole **11c** (1.38 mL, 10.2 mmol). Pink crystals (590 mg, 34%), mp = 216−218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.66−7.51 (m, 3H), 7.37 (d, J = 4.8 Hz, 3H), 7.21 (d, J = 7.8 Hz, 1H), 4.60 (s, 2H), 2.54 (s, 6H), 2.30 (q, J = 7.6 Hz, 4H), 1.33 (s, 6H), 0.99 (t, J = 7.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 142.9, 138.9, 138.7, 132.9, 131.8, 131.4, 131.2, 130.8, 128.8, 128.6, 128.4, 124.9, 123.0, 121.6, 90.9, 88.8, 62.1, 14.8, 14.3. API-ES positive 533.3 $(M+Na)^+$; HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{34}BF_2N_2O$: 511.2732; Found 511.2734.

*2,6-Diiodo-8-(2-hydroxymethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**20a**).* To a stirred solution of 1,3,5,7-tetramethyl-BODIPY **15a** (300 mg, 0.84 mmol) in CH_2Cl_2 (20 mL), *N*-iodosuccinimide (NIS) (419 mg, 1.86 mmol) was added at rt. The reaction mixture was then stirred for 30 min and then partitioned between aqueous sodium thiosulfate and CH_2Cl_2. After washing with water and brine, the combined extracts were dried over anhydrous Na_2SO_4, and evaporated. The residue was then chromatographed over silica gel flash column (eluent: hexane−ethyl acetate = 8:2) to give the product **20a** (493 mg, 97%) as a red waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.7, 1.4 Hz, 1H), 7.57 (td, J = 7.6, 1.4 Hz, 1H), 7.45 (td, J = 7.5, 1.3 Hz, 1H), 7.16 (dd, J = 7.5, 1.3 Hz, 1H), 4.57 (s, 2H), 2.64 (t, J = 1.1 Hz, 6H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 145.3, 139.7, 138.2, 132.9, 131.1, 130.4, 128.9, 128.6, 128.1, 62.5, 16.7, 16.3, 16.3. HRMS (ESI-QTOF) m/z: $[M+NH_4]^+$ Calcd for $C_{20}H_{23}BF_2I_2N_3O$: 623.9992; Found 623.9979.

*2,6-Bis(phenylethynyl)-8-(2-hydroxymethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**20b**).* A solution of BODIPY **20a** (30 mg, 0.047 mmol) in anhydrous THF (5 mL) was treated with $(i\text{-}Pr)_2NH$ (0.5 mL) and phenylacetylene (82 μL, 3 equiv, 0.14 mmol). The mixture was purged with argon for 5 min, and then $Pd(PPh_3)_2Cl_2$ (4.71 mg, 0.0067 mmol) and CuI (2.13 mg, 0.0112 mmol) were added. The reaction mixture was heated at 60 °C for 12 h and then evaporated under reduced pressure. The residue was then chromatographed over silica gel flash column (eluent: hexane−ethyl acetate = 9:1) to give the product **20b** (23 mg, 90%) as a blue waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 7.9 Hz, 1H), 7.58 (td, J = 7.5, 1.5 Hz, 1H), 7.46−7.28 (m, 11H), 7.23 (dd, J = 7.5, 1.4 Hz, 1H), 4.62 (s, 2H), 2.73 (s, 6H), 1.53 (s, 6H); ^{13}C NMR (75 MHz,

DOI: 10.1021/acs.joc.6b02426
J. Org. Chem. 2017, 82, 1240−1247

$CDCl_3$) δ 158.9, 143.8, 140.6, 138.1, 132.5, 131.5, 130.9, 130.2, 128.8, 128.5, 128.3, 128.0, 123.4, 116.5, 96.8, 81.5, 62.5, 13.9, 13.1. API-ES positive 577.4 $(M+Na)^+$; HRMS (ESI-QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{36}H_{30}BF_2N_2O$: 555.2419; Found 555.2436.

*8-(2-Hydroxymethylphenyl)-1,7-dimethyl-3,5-distyryl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**21a**).* BODIPY **15a** (50 mg, 0.14 mmol) and benzaldehyde (1.12 mmol, 8 equiv, 114 μL) were dissolved in dry DMF (2.5 mL) and to this solution were added piperidine (0.4 mL) and acetic acid (0.4 mL). The condensation reaction was performed under microwave irradiation for 10 min at 150 °C. The resulting crude mixture was then partitioned between CH_2Cl_2 and water, and the aqueous layer was re-extracted. The combined extracts were dried and evaporated. The residue was then chromatographed over silica gel flash column (eluent: hexane−ethyl acetate = 9:1) to give **21a** (59 mg, 80%), as a purple waxy solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.17 (m, 18H), 6.65 (s, 2H), 4.64 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 146.0, 140.0, 138.5, 136.7, 133.2, 132.6, 130.4, 129.5, 129.0, 128.9, 128.5, 128.4, 127.9, 118.8, 62.5, 17.2. API-ES positive 531.4 $(M+H)^+$; HRMS (ESI-QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{30}BF_2N_2O$: 531.2419; Found 531.2446.

*2,6-Di-iodo-8-(2-hydroxymethylphenyl)-1,7-dimethyl-3,5-distyryl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**21b**).* BODIPY **20a** (50 mg, 0.08 mmol) and benzaldehyde (0.49 mmol, 4 equiv, 50 μL) were dissolved in dry DMF (2.5 mL) and to this solution were added piperidine (0.4 mL) and acetic acid (0.4 mL). The condensation reaction was performed at rt overnight. The resulting crude mixture was then partitioned between CH_2Cl_2 and water, and the aqueous layer was re-extracted. The combined extracts were dried and evaporated. The residue was then chromatographed over silica gel flash column (eluent: hexane−ethyl acetate = 9:1) to give the product **21b** (53 mg, 85%) as a purple waxy solid. ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 16.7 Hz, 2H), 8.12−7.95 (m, 16H), 4.58 (s, 2H), 4.51 (s, 1H), 1.46 (6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.0, 142.1, 138.5, 137.0, 136.7, 133.1, 133.0, 129.8, 129.2, 129.0, 128.9, 128.6, 128.5, 128.2, 127.7, 126.9, 126.8, 119.3, 119.3, 118.1, 62.6, 14.4. HRMS (ESI-QTOF) *m/z*: $[M+Na]^+$ Calcd for $C_{34}H_{27}BF_2I_2N_2O$: 805.0172; Found 805.0186.

*8-(2-Azidomethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**15d**).* A solution of BODIPY **15a** (1.72 mmol, 608 mg) in anhydrous CH_2Cl_2 (5 mL) under argon, was cooled to 0 °C and treated with Et_3N (2.06 mmol, 1.2 equiv, 0.29 mL) and mesyl chloride (1.89 mmol, 1.1 equiv, 0.15 mL). The mixture was allowed to react at that temperature for 30 min and then washed with water. The organic layer was dried, evaporated under reduced pressure, and the intermediate *O*-mesyl derivative used in the next step without further purification.

To a solution of the previously obtained residue in anhydrous DMF (7 mL), sodium azide (3.52 mmol, 2 equiv, 230 mg) was added under argon at rt. The reaction mixture was stirred overnight and partitioned between water and ethyl acetate. After re-extracting and washing with water and brine, the combined organic extracts were dried and evaporated. The residue was then chromatographed over silica gel flash column (eluent: hexane−ethyl acetate = 8:2) to give **15d** (493 mg, 90%) as a red solid. mp = 98−100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.53 (m, 2H), 7.46 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.43−7.38 (m, 1H), 6.00 (s, 2H), 4.34 (s, 2H), 2.56 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 142.9, 138.9, 133.9, 133.8, 131.0, 129.9, 129.1, 128.9, 128.7, 121.6, 52.1, 14.8, 14.1. API−ES positive 577.4 $(M+Na)^+$; HRMS (ESI-QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{21}BF_2N_5$: 380.1858; Found 380.1874.

*2-Formyl-8-(2-azidomethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**22**).* A mixture of DMF (4 mL) and $POCl_3$ (3.7 mL) was stirred in an ice bath, under argon, for 5 min. After being warmed to room temperature, the reaction mixture was stirred for additional 30 min. To this mixture was added 1,3,5,7-tetramethyl-BODIPY **15d** (100 mg, 0.264 mmol) in anhydrous CH_2Cl_2 (20 mL), the temperature was then raised to 50 °C, and the mixture was stirred for 30 min. The reaction mixture was cooled to room temperature and slowly poured into saturated aqueous $NaHCO_3$ (100 mL) under ice-cold conditions. After being warmed to room temperature, the reaction mixture was further stirred for 30 min and washed with water (2 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated under vacuum. The resulting crude product was further purified using column chromatography (eluent: hexane−ethyl acetate = 9:1) to give formyl-BODIPY **22** (99 mg, 93%) as dark red crystals. mp = 140−142 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.62−7.56 (m, 2H), 7.51 (ddd, *J* = 7.0, 6.2, 2.5 Hz, 1H), 7.28−7.23 (m, 1H), 6.17 (s, 1H), 4.31 (s, 2H), 2.83 (s, 3H), 2.63 (s, 3H), 1.63 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.8, 162.4, 157.0, 146.9, 142.5, 140.7, 133.8, 133.6, 133.0, 130.3, 129.4, 129.4, 129.1, 128.4, 126.4, 124.4, 52.0, 15.2, 14.5, 13.0, 11.2. HRMS (ESI-QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{21}BF_2N_5O$: 408.1805; Found 408.1803.

*8-(2-Formylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**15b**).* Dess Martin periodinane (0.93 mmol, 1.1 equiv, 395 mg) was suspended in dry CH_2Cl_2. To this suspension was slowly added a solution of BODIPY **15a** (300 mg, 0.85 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C under argon. After 10 min, the ice bath was removed and the reaction mixture was left stirring at room temperature for 1 h. The reaction mixture was extracted with saturated aqueous $Na_2S_2O_3$ followed by saturated aqueous $NaHCO_3$ and brine. The combined organic solutions were dried. The solvent was evaporated, and the resulting crude mixture was purified by chromatography on silica gel (eluent: hexane−ethyl acetate = 9:1) to give formyl-BODIPY **15b** (189 mg, 64%). mp = 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.36 (s, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.79 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.68 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 5.92 (s, 2H), 2.59 (s, 3H), 1.54 (s, 6H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 190.7, 156.9, 143.2, 138.6, 137.2, 135.1, 132.1, 130.4, 129.9, 128.2, 122.3, 15.1, 14.5. HRMS (ESI-QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{20}BF_2N_2O$: 353.1637 Found 353.1634.

*8-(2-Isothiocyanatemethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**15c**).* To a solution of azido-BODIPY **15d** (150 mg, 0.4 mmol) and CS_2 (73 μL, 1.2 mmol) in anhydrous THF (4 mL) was added triphenylphosphine (211 mg, 0.8 mmol, 2 equiv). The reaction mixture was stirred at rt, under argon, for 24 h, then concentrated and the residue purified by chromatography on silica gel (eluent: hexane−ethyl acetate = 9:1) to give isothiocyanate-BODIPY **15c**. Red crystals (150 mg, 95%) mp = 140−141 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66−7.63 (m, 1H), 7.57 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.49 (dt, J = 7.6, 1.4 Hz, 1H), 7.28−7.23 (m, 1H), 6.00 (s, 2H), 4.64 (s, 2H), 2.56 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ (ppm): 156.6, 142.7, 137.9, 133.2, 132.0, 130.7, 130.3, 129.5, 128.8, 128.7, 128.2, 121.8, 46.2, 14.8, 14.0. HRMS (ESI-QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{21}BF_2N_3S$: 396.1517; Found 396.1525.

*Tetra-O-acetyl-β-D-Glucopyranosyl-BODIPY (**23a**).* A mixture of β-D-glucose pentaacetate (150 mg, 0.38 mmol) and BODIPY **15a** (103 mg, 0.29 mmol) in toluene (5 mL) was azeotroped to dryness and subsequently kept overnight under high vacuum. This mixture was dissolved in anhydrous CH_2Cl_2 under argon, and cooled to 0 °C, and then $BF_3 \cdot Et_2O$ was added (140 μL, 1.14 mmol). After stirring for 2 h at rt, the reaction was quenched by addition of aqueous $NaHCO_3$ (satd). The layers were separated, the aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried, filtered and concentrated. The residue was purified by chromatography on silica gel (eluent: hexane−ethyl acetate = 7:3) to give a single spot on this system containing a mixture of β-D-glucopyranosyl-BODIPY **23a**, along with the excess of starting β-D-glucose pentaacetate. A further chromatography of the above-mentioned fraction on silica gel (eluent: CH_2Cl_2−ethyl acetate = 95:5) yielded pure β-D-glucopyranosyl-BODIPY **23a**, as an orange oil (140 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.42 (td, *J* = 7.6, 1.5 Hz, 1H), 7.35 (td, *J* = 7.5, 1.4 Hz, 1H), 7.12 (dd, *J* = 7.5, 1.4 Hz, 1H), 5.92 (s, 2H), 5.06 (t, *J* = 9.2 Hz, 1H), 5.00 (t, *J* = 9.4 Hz, 1H), 4.97−4.92 (m, 1H), 4.70 (d, *J* = 12.8 Hz, 1H), 4.42 (d, *J* = 12.7 Hz, 1H), 4.40 (d, *J* = 7.9 Hz, 1H), 4.18 (dd, *J* = 12.4, 4.5 Hz, 1H), 3.97 (dd, *J* = 12.4, 2.4

DOI: 10.1021/acs.joc.6b02426
J. Org. Chem. 2017, 82, 1240−1247

Hz, 1H), 3.49 (ddd, J = 9.5, 4.5, 2.3 Hz, 2H), 2.49 (s, 16H), 1.97 (s, 7H), 1.94 (s, 6H), 1.92 (s, 6H), 1.89 (s, 7H), 1.27 (d, J = 3.7 Hz, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.2, 169.4, 169.2, 156.2, 155.5, 143.2, 142.5, 139.3, 135.0, 132.7, 131.1, 130.7, 129.5, 128.6, 128.3, 127.9, 121.5, 121.2, 100.4, 68.3, 68.2, 61.7, 20.7, 20.6, 20.6, 14.6, 14.6, 14.6, 13.9. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{34}H_{43}BF_2N_3O_{10}$: 702.3010; Found 702.3012.

*β-D-Glucopyranosyl-BODIPY (**23b**).* Acetylated derivative **23a** (80 mg, 0.12 mmol) was dissolved in 5 mL of a MeOH:NEt_3 (4:1) solution. The mixture was warmed at 65 °C and refluxed for 6 h and then concentrated. The residue was purified by chromatography on silica gel (eluent: hexane−ethyl acetate = 1:9) to give **23b** as an orange oil (53 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 7.2, 1.8 Hz, 1H), 7.56−7.40 (m, 2H), 7.25−7.20 (m, 1H), 6.13−5.85 (m, 2H), 4.78 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.25 (d, J = 7.6 Hz, 1H), 3.74 (m, 2H), 3.62−3.38 (m, 2H), 3.28−3.04 (m, 2H), 2.55 (s, 6H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 157.0, 156.8, 144.7, 144.4, 141.4, 137.2, 134.3, 132.4, 132.3, 132.1, 130.6, 130.1, 129.9, 129.6, 129.2, 122.3, 103.9, 78.1, 77.8, 75.2, 71.4, 68.8, 62.5, 14.6, 14.3, 14.1; ^{19}F NMR (376 MHz, CD_3OD,): δ − 147.47 (m, 2F). HRMS (ESI-QTOF) m/z: $[M+NH_4]^+$ Calcd for $C_{26}H_{35}BF_2N_3O_6$: 534.2587; Found 534.2598

*8-(2-Benzylaminomethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**24**).* To a mixture of aldehyde **15b** (20 mg, 0.057 mmol) and benzylamine (6.2 μL, 0.057 mmol, 1 equiv) in methanol (3 mL) under argon, sodium cyanoborohydride (11 mg, 0.17 mmol, 3 equiv) was added. The reaction mixture was stirred at room temperature for 24 h, then concentrated, and the residue purified by chromatography on silica gel (eluent: hexane−ethyl acetate = 85:15) to give **24** as an orange oil (22 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77−7.60 (m, 1H), 7.47 (td, J = 7.6, 1.4 Hz, 1H), 7.38 (td, J = 7.5, 1.3 Hz, 1H), 7.33−7.13 (m, 7H), 5.96 (s, 2H), 3.73 (d, J = 3.3 Hz, 4H), 2.57 (d, J = 1.4 Hz, 6H), 1.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 142.7, 140.4, 140.0, 137.8, 133.8, 131.1, 129.4, 129.0, 128.3, 128.1, 127.8, 127.8, 126.9, 121.2, 53.7, 50.4, 14.6, 14.0, 13.9. ^{19}F-NMR (376 MHz, $CDCl_3$) δ − 146.73 (m, 1F), − 147.70 (m, 1F). HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}BF_2N_3$: 444.2423; Found 444.2419.

*BODIPY-Carbohydrate (**25**).* Isothiocyanate **15c** (31 mg, 0.07 mmol) and 2-aminoethyl 2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranoside[34] (28 mg, 0.07 mmol, 1 equiv) were dissolved in anhydrous 1,4-dioxane (3 mL). The resulting solution was stirred under argon at room temperature for 24 h, and then concentrated. The ensuing residue was then purified by chromatography on silica gel (eluent: hexane−ethyl acetate =3:7) to give **25**, as an orange oil (36 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.46 (td, J = 7.6, 1.4 Hz, 1H), 7.38 (td, J = 7.5, 1.3 Hz, 1H), 7.18 (ddd, J = 7.4, 1.4, 0.5 Hz, 1H), 6.01 (s, 1H), 5.99 (s, 1H), 5.39 (dd, J = 3.4, 1.2 Hz, 1H), 5.15 (dd, J = 10.5, 7.9 Hz, 1H), 5.00 (dd, J = 10.5, 3.4 Hz, 1H), 4.79 (t, J = 6.2 Hz, 1H), 4.70 (t, J = 5.7 Hz, 1H), 4.44 (d, J = 7.9 Hz, 1H), 4.35−4.21 (m, 3H), 4.10 (d, J = 11.4, 6.2 Hz, 1H), 3.89 (td, J = 6.5, 1.2 Hz, 1H), 3.80 (dt, J = 9.9, 4.7 Hz, 1H), 3.66 (ddd, J = 10.2, 5.8, 4.5 Hz, 1H), 3.33 (q, J = 5.6 Hz, 2H), 2.56 (s, 6H), 2.15 (s, 3H), 2.02 (s, 6H), 1.99 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.1, 170.0, 169.9, 157.7, 155.8, 142.9, 140.0, 137.0, 133.2, 130.9, 129.6, 128.6, 128.1, 128.0, 121.4, 101.5, 71.0, 70.7, 70.2, 68.9, 67.1, 61.5, 41.9, 40.2, 20.8, 20.7, 20.7, 20.6, 14.6, 14.6, 14.6, 13.9. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{45}BF_2N_4NaO_{10}S$: 809.2816; Found 809.2824.

Photophysical Properties. Diluted solutions (around 2 × 10^{-6} M) were prepared by diluting a concentrated stock solution in ethanol (spectroscopic grade). UV−vis absorption and fluorescence spectra were recorded on a spectrophotometer and a spectrofluormeter, respectively. Fluorescence quantum yields (f) were obtained from corrected fluorescence spectra to avoid the sensibility of the photomultiplier with the monochromator wavelength and using the parent dyes in ethanol as reference, which means; **1a** (usually named as BDP, f^r = 0.90), **1b** (commercially known as PM546, f^r = 0.85), and **1c** PM567 (commercially known as PM567, f^r = 0.84). The values were corrected by the refractive index of the solvent. Radiative decay curves were registered with the time correlated single-photon counting technique (picosecond time-resolution). Fluorescence emission was monitored at the maximum emission wavelength after excitation at 470 nm by means of a diode laser with 150 ps full width at half-maximum (fwhm) pulses. The fluorescence lifetime (t) was obtained after the deconvolution of the instrumental response signal from the recorded decay curves by means of an iterative method. The goodness of the exponential fit was controlled by statistical parameters (chi-square and the analysis of the residuals).

Quantum Mechanical Calculations. Ground state geometries were optimized at the B3LYP theory level, using the double valence basis set with a polarization function (6-31g*), as implemented in the Gaussian 09. The geometries were considered as energy minimum when the corresponding frequency analysis did not give any negative value. The relaxed energy potential surface, and from here the rotational barrier, for the 8-phenyl twisting with regard to the BODIPY plane in the ground state was computed scanning the corresponding dihedral angle 10° and optimizing the geometry at each point. The solvent effect (ethanol) was considered in all the calculations using the polarization continuum model (PCM).

Lasing Properties. Liquid solutions of dyes were contained in 1 cm optical-path rectangular quartz cells carefully sealed to avoid solvent evaporation during the experiments. The liquid solutions were transversely pumped either at 355 nm, with 5 mJ, 8 ns fwhm pulses from the third-harmonic of a Q-switched Nd:YAG laser or at 532 nm, with 5 mJ, 6 ns fwhm pulses from a frequency-doubled Q-switched Nd:YAG laser, at a repetition rate of up to 10 Hz. The exciting pulses were line-focused onto the cell, providing pump fluences on the active medium in the range 110−180 mJ/cm^2. The oscillation cavity (2 cm length) consisted of a 90% reflectivity aluminum mirror, with the lateral face of the cell as output coupler.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02426.

Copies of ^{1}H and ^{13}C NMR spectra; photophysical studies for some of the derivatives; atomic coordinates and energies of **3**, **15a**, **17a**, and 8-tolyl-BODIPY (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Ministerio de Economia y Competitividad (MINECO, Spain) grants CTQ2015-66702-R, MAT2014-51937-C3-1-P, MAT2014-51937-C3-3-P, and MAT2015-68837-REDT, and Gobierno Vasco (IT912-16) is gratefully acknowledged. We thank Dr. Juan Ventura for performing the purification of compound **10**.

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DOI: 10.1021/acs.joc.6b02426
J. Org. Chem. 2017, 82, 1240−1247