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An efficient method of chemical modification of BODIPY core

Yuriy V. Zatsikha [a], Viktor P. Yakubovskyi [a], Mykola P. Shandura [a], Igor Ya Dubey [b], Yuriy P. Kovtun [a,*]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska Str., 02094 Kyiv, Ukraine
[b] Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, 150 Zabolotnogo Str., 03680 Kyiv, Ukraine

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ABSTRACT

A simple approach to the modification of BODIPY nucleus has been developed. The method is based on the reaction of acetaldehyde-substituted dye with primary amines followed by cyclization of enamine intermediates. This procedure allowed preparing a series of new BODIPY derivatives with functional substituents useful for various practical purposes, including bioconjugation and other biomedical applications. The synthesized BODIPYs annealed to a pyridone fragment are stable compounds and intense fluorophores with emission maximum around 615 nm. This λ_{em} may be red-shifted by the introduction of styryl substituent.

1. Introduction

Borondipyrromethene dyes (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, BODIPY, BDP) have found numerous applications, especially in biochemistry and molecular biology, owing to their excellent thermal, chemical and photochemical stability, high molar absorptivity, high fluorescence quantum yield, and low sensitivity to both solvent polarity and pH.[1] Since practical applications of the dye often require specific modification of the basic nucleus for specific tasks, the selective functionalization of the dye is one of the main challenges of borondihydromethene chemistry. Thus, approaches have been developed for the introduction of functional substituents at each position of BODIPY nucleus. Functional groups can be introduced either at early steps of syntheses using appropriately substituted pyrroles as the precursors or at later stages by functionalization of intermediate dipyrromethene or directly the BODIPY core.

For instance, electrophilic substitution reactions, such as nitration,[2] sulfonylation,[2,3] formylation[4] or palladium-catalyzed C–H functionalization,[5] are known to proceed easily at free β-positions of BODIPY nuclei. Halogenation primarily occurs at the same positions,[2,6] however polyhalogenation is possible when other unsubstituted positions are available.[7] Halogen atoms at α-(C-3 or C-5),[8] C-1 and C-7[9] position can undergo nucleophilic substitution; *S*-methyl group at C-8 (*meso*-) position may be substituted as well.[10] Alkylthio-substituted BODIPYs can enter into Liebeskind–Srogl cross-coupling,[11] and halogen derivatives into Pd-catalyzed Suzuki, Heck or Sonogashira reactions.[12] Oxidative[13a,b] or vicarious nucleophilic substitution[13c] of hydrogen atom can be performed at free α-position.

Methyl groups at α-positions provide various possibilities for the modification of BODIPY core, for example, via the Knoevenagel condensation.[14] This method was used for the synthesis of numerous derivatives, including combinatorial series.[14f,i] In addition to modification of the basic structure, an important consequence of this reaction is essential red shift for both absorption and emission bands of the products. Knoevenagel reaction can be performed also at methyl groups at C-1, C-7[15] and *meso*-position[16] that allows obtaining unusual structures with specific spectral properties. Moreover, α-CH_3 can be oxidized to aldehyde group[17] or brominated with subsequent nucleophilic substitution.[18]

We have recently found a new possibility of using the α-methyl group of BODIPY for chemical transformations. It was discovered that aldehyde function can be readily introduced at this position.[19] Reactions of acetaldehyde **1** (Scheme 1) allowed the preparation of a large number of derivatives, including some rather nontrivial structures with intense fluorescence and deep color. In particular, reaction of this aldehyde with methylamine led to the formation of BODIPY **4b** with annealed pyridone ring, stable, and highly fluorescent dye with λ_{abs}=586 nm and λ_{em}=614 nm. Although the reaction performed with heating in toluene in the presence of acetic acid was very fast, the yield of **4b** was only 40% and large amounts of side products were formed. Nevertheless, this approach has great

* Corresponding author. E-mail address: kovtun@ioch.kiev.ua (Y.P. Kovtun).

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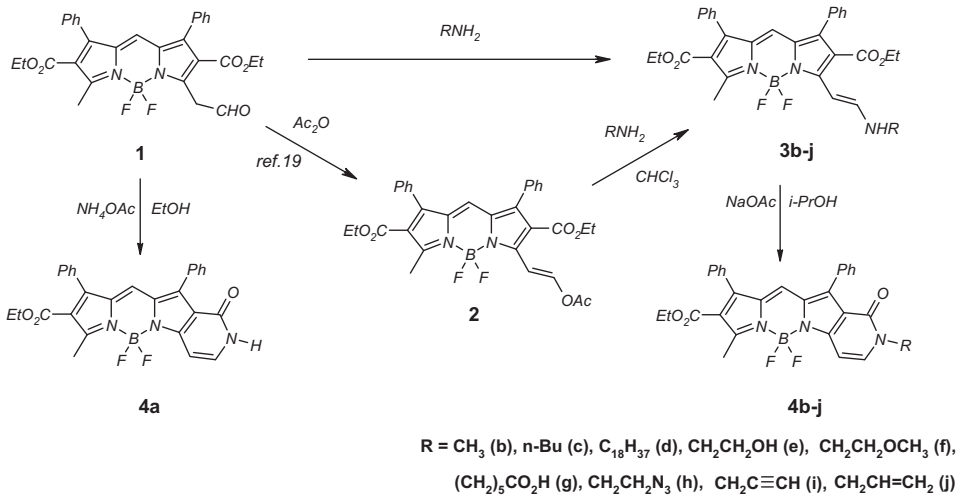


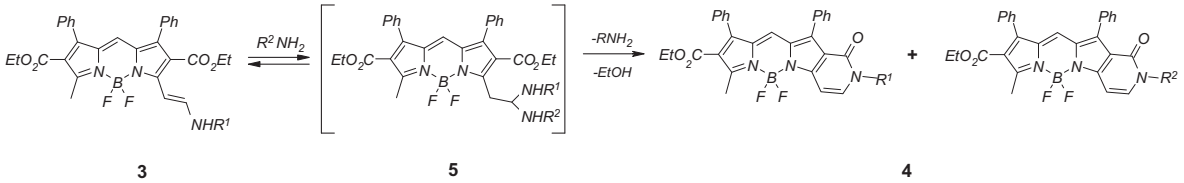
Scheme 1. Synthetic route to pyridone BODIPY dyes **4a**–**j**.

promise for specific modification of borondipyrromethene nuclei, so we decided to explore its synthetic potential. Here we describe an efficient method of BODIPY functionalization that employs the cyclization of *N*-substituted enamine intermediates.

2. Results and discussion

Upon the addition of excess aliphatic primary amine to the solution of aldehyde **1** in a neutral solvent (alcohols, chloroform, dichloromethane, toluene, DMF) the reaction is complete in few minutes. TLC analysis demonstrates the disappearance of starting compound **1** and formation of several products—blue non-fluorescent enamine **3** and larger or smaller amount of pyridone **4**, along with numerous impurities (Scheme 1).

In this mode of the reaction the isolation of pure enamines **3** is often difficult, although they are quite stable compounds in their individual state. The main reason is the presence of excess amine; the latter promotes both enamine cyclization and side reactions. Moreover, the addition of another primary amine to enamine **3** results in the formation of the mixture of two different pyridones **4**. Perhaps it can be due to the formation of an intermediate full-aminal form **5** from the semiaminal enamine form of aldehyde **3** (Scheme 2).



Scheme 2. Formation of the mixture of pyridones **4** from individual enamine **3**.

An understanding of these aspects of the reaction mechanism allowed us to make two important practical conclusions. First, for the preparation of enamine **3** from aldehyde **1** a large excess of the amine should be avoided, and the addition of acetic acid is desirable. But the best way to obtain enamines is the use of enol acetate **2**; in this case the reaction is virtually instantaneous and quantitative. Second, the presence of base is necessary to promote the cyclization of enamines **3** into pyridones **4**. It was found that this process is clean and efficient when just a catalytic amount (5–10 M %) of the base is used (triethylamine, Hunig's base, potassium carbonate, sodium acetate, etc.). This is critically important since in the presence of large quantities of the base side reactions dominate.

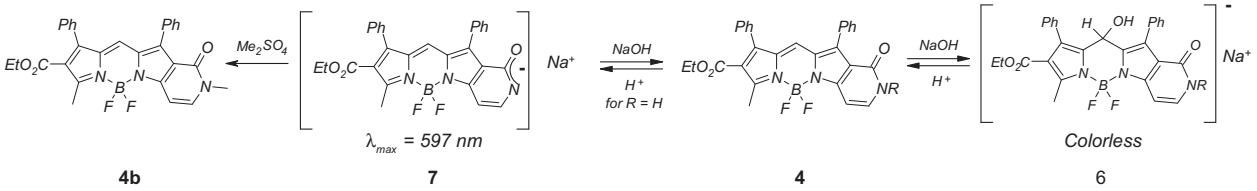
Finally, we have developed an optimized protocol for the modification of BODIPY core. Enamines **3** are readily obtained by the reaction of enol acetate **2** with corresponding amines in chloroform at room temperature. These compounds are isolated and without special purification refluxed in isopropanol with 5% mol sodium acetate. The cyclization reaction is complete in 1–1.5 h; it is faster for amines with electron-donor substituents and slower when they contain electron-withdrawing groups. Compound **4a** is a separate case: it is easily formed in ethanol in the presence of ammonium acetate, and enamine intermediate cannot be isolated.

Using this general approach, we have prepared in high yields (84–92%) a series of BODIPY derivatives **4a**–**j** containing various functional substituents. These dyes can be used in diverse applications, depending on the introduced substituent.

For example, BODIPY dye **4d** containing a hydrophobic octadecyl group is well soluble in hexane, so presumably it should be well soluble in lipid systems and thus useful for cell membrane studies. Compound **4g** is functionalized with carboxyalkyl group suitable for bioconjugation reactions, e.g., for the fluorescent labeling of peptides, proteins, and other amine-containing biomolecules via the formation of amide bond. Dyes **4h**,**i** are modified with azide and acetylene function, respectively, to be used as reagents in 'click chemistry'. Alkene fragment was introduced into compound **4j** (either for polymerization or further modification of the dye via the oxidation of ethylene bond).

The transformation of BODIPY into a colorless anionic dipyrromethane form like **6** caused by alkalies was first observed by Alfred Treibs, the founder of dipyrromethene chemistry, more than 50 years ago.[20] In case of pyridones **4** this transformation occurs instantly and without a significant excess of the base, in contrast to aldehyde **1** or its precursors. Undoubtedly, this is due to electron-acceptor action of

the pyridone ring. Dipyrromethane form **6** appeared to be quite stable. For example, even after the compound **4** was kept in aqueous alcohol alkaline solution for 6–8 h at ambient temperature, its acidification resulted in almost complete recovery of the parent pyridone form (Scheme 3).



Scheme 3. Action of bases on pyridones **4**.

BODIPY **4a** in alkaline medium behaves differently compared to other derivatives. In this case the action of the base leads to the bathochromic shift caused by the formation of deprotonated structure **7**. We had hoped to use that for N-alkylation of pyridone ring that would provide additional synthetic possibilities. However, the success of this approach was limited (Scheme 3). Indeed, upon heating of compound **4a** with dimethyl sulfate in the presence of K_2CO_3 in acetonitrile or DMF the formation of small amount of pyridone **4b** in the reaction mixture was detected by TLC. But only decomposition of starting compound was observed when less active alkylating agents (methyl tosylate, methyl iodide, propane sultone etc.) were used. Control experiments confirmed that dipyrromethene **4a** rather quickly decomposes upon heating in the presence of bases.

Intermediate enamines **3b**–**j** absorb at around 620 nm, but these compounds are virtually devoid of fluorescent properties. It is in good agreement with the view of borondipyrromethene optical properties, since free conjugated terminal amino groups as a rule lead to the fluorescence quenching.[21] Some of these intermediates were obtained as analytically pure samples (their NMR spectra are presented in Supplementary data), other enamines were used at the next step without additional purification.

Spectral characteristics of pyridones **4a**–**j** are presented in Table 1. All these compounds have close spectral parameters and are bright fluorophores. It should be noted that in addition to high fluorescence quantum yields they demonstrate good chemical and photostability: their solutions of spectral concentration have been stored for two months under diffuse daylight with no changes.

At the same time, biological applications sometimes require longer wavelength dyes emitting at the region of so-called 'phototherapeutic window' (in the range 600–900 nm). So a known approach has been employed to further deepen the color of BODIPY dyes—we have obtained styryl derivatives **8**–**10** starting from *n*-butyl pyridone **4c** (Scheme 4).

Condensation reactions at α-methyl group have been performed by heating the compound **4c** with corresponding aldehydes in benzene in the presence of piperidine and acetic acid, i.e., under conditions most often found in the literature.[14]

As expected, the introduction of styryl substituent led to a significant bathochromic shift (50–70 nm) in both the absorption and emission spectra, but, unfortunately, fluorescence quantum yields decreased. The best brightness was achieved for *p*-methoxy substituted styryl dye **9** (Table 1, Fig. 1), which is consistent with literature data.[14]

Table 1
Photophysical properties of the dyes in dichloromethane

Dye	λ_{abs}, nm ($\varepsilon\cdot10^{-3}$, M^{-1} cm^{-1})	fwhm,[a] cm^{-1}	λ_{em}, nm (φ)
4a	578 (105)	1083	603 (0.97)
4b[19]	586 (95)	1146	614 (0.73)
4c	588 (100)	1179	618 (0.86)
4d	588 (85)	1184	618 (0.81)
	584 (83)[b]	1422	609 (0.81)[b]
4e	584 (89)	1303	614 (0.84)
4f	586 (118)	1194	617 (0.95)
4g	588 (80)	1185	617 (0.88)
4h	582 (88)	1152	612 (0.91)
4i	579 (91)	1147	607 (0.82)
4j	584 (98)	1150	612 (0.80)
8	642 (90)	1040	665 (0.41)
9	656 (113)	1104	686 (0.36)
10	660 (86)	1469	683 (0.28)

[a] fwhm=full width at half-maximum height.
[b] In hexane.

3. Conclusions

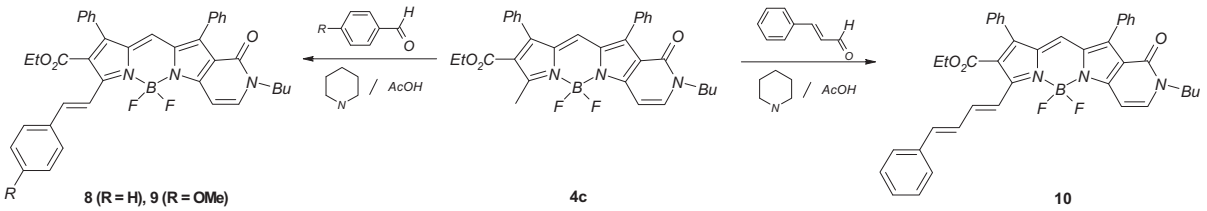
In summary, we have developed a very simple synthetic procedure that allows an efficient introduction of functional substituents into BODIPY core using aliphatic amines. Functionalized dyes containing alkyl, carboxyalkyl, azide, acetylene, and other groups have been obtained. The prepared stable dyes are intense fluorophores with emission maximum in the region of 610–615 nm, which may be further red-shifted by the transition to styryl derivatives. These dyes can be used, e.g., in biomedical research for the fluorescent labeling of biomolecules via the amide bond formation or click reactions, membrane studies, etc. It should be especially noted that the above described general method allows the preparation of unsymmetrical BODIPY derivatives with different substituents at two α-positions. We believe that this approach lays the foundation for a new combinatorial strategy in the family of BODIPY dyes, which is now considered to be of great importance in fluorescent probe development.[22]

4. Experimental section

4.1. General

Absorption spectra were recorded on a Shimadzu UV-3100 spectrophotometer. ^{1}H NMR (500 MHz, $CDCl_3$, TMS as internal standard) and ^{13}C NMR (125 MHz, DMSO-d_6) spectra were obtained at 25 °C on a Bruker Avance 500 instrument. Chemical shifts are given in parts per million. Chromato-mass spectrometry measurements were performed with LC/MS system consisting of Agilent 1100 Series HPLC instrument equipped with a diode matrix detector, and Agilent LC/MSD SL mass detector. APCI (Atmospheric Pressure Chemical Ionization) technique with detection of positive ions was used. Column chromatography was performed using Silica gel 100 (Fluka, 0.063–0.200 mm). Fluorescence spectra were recorded on a Solar CM 2203 fluorescence spectrophotometer. The relative fluorescence quantum yields (φ) were determined using Nile Blue (φ=0.27, EtOH) as the reference.

*4.1.1. 2-Carbethoxy-3-methyl-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (**4a**).* A mixture of aldehyde **1** (544 mg, 1.0 mmol) and ammonium acetate (308 mg,



Scheme 4. Synthesis of styryls **8**–**10**.

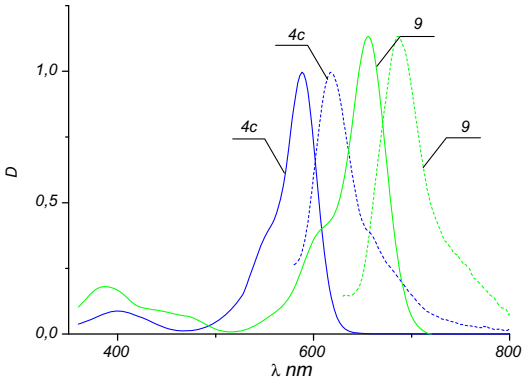


Fig. 1. Absorption (C=1×10^{-5} M, solid line) and normalized fluorescence (dashed line) spectra of compounds **4c** and **9** in CH_2Cl_2.

4 mmol) in ethanol (15 mL) was refluxed for 5 min. After cooling to room temperature, the precipitate was filtered. Yield (420 mg, 84%), green solid, mp >250 °C; [found: C, 67.85; H, 4.35; N, 8.25. $C_{28}H_{22}BF_2N_3O_3$ requires C, 67.63; H, 4.46; N, 8.45%]; R_f (10% MeOH/$CHCl_3$) 0.82; ν_{max} (KBr) 3170, 1720, 1680, 1590, 1430, 1390, 1260, 1150, 1000, 920, 750, 690, 640, 585, 560 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.43 (1H, s, N*H*), 7.55–7.54 (2H, m, Ph), 7.41–7.39 (6H, m, Ph), 7.32–7.31 (2H, m, Ph), 7.18–7.14 (2H, m, *meso*-C*H*+C*H*), 6.77 (1H, d, *J* 8.0 Hz, C*H*), 4.12 (2H, q, *J* 7.2 Hz, OC*H*$_2$Me), 2.96 (3H, s, C*Me*), 1.09 (3H, t, *J* 7.2 Hz, CH$_2$*Me*), δ_C (125 MHz, DMSO-d_6) 163.1, 160.7, 159.7, 153.7, 147.8, 145.2, 138.9, 135.4, 135.3, 131.6, 131.4, 130.8, 130.6, 130.1, 129.9, 129.6, 128.4, 128.3, 121.2, 118.3, 107.3, 95.8, 60.6, 15.1, 14.1. LC–MS: m/z MH$^+$, found 498. $C_{28}H_{22}BF_2N_3O_3$ requires 497.31.

4.2. General procedure for the synthesis of dyes 4b–j

1.1 mmol of appropriate primary amine was added to the solution of 586 mg (1 mmol) of enol acetate **2**[19] in 50 mL of $CHCl_3$ at room temperature. In 1 h the solution was washed with water, 5% aqueous acetic acid and aqueous sodium bicarbonate, dried (Na_2SO_4), and then evaporated to dryness. The residue and 10 mg (0.05 mmol) of sodium acetate were refluxed for 1 h in 50 mL of *i*-PrOH. After cooling to room temperature a mixture was diluted with water, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by silica gel column chromatography (25% EtOAc/hexane).

*4.2.1. 2-Carbethoxy-3,7-dimethyl-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]-fluoren-8-on (**4b**).* Methanolic solution of methylamine was used. After cooling to room temperature the precipitate was filtered and washed with hexane, yield 92%. All characteristics were identical to sample from Ref. 19.

*4.2.2. 2-Carbethoxy-3-methyl-7-butul-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]-fluoren-8-on (**4c**).* After cooling to room temperature the precipitate was filtered and washed with hexane. Yield (490 mg, 88%), green solid, mp 250–251 °C; [found: C, 69.84; H, 5.33; N, 7.40. $C_{32}H_{30}BF_2N_3O_3$ requires C, 69.45; H, 5.46; N, 7.59%]; R_f (25% EtOAc/hexane) 0.55; ν_{max} (KBr) 2970, 1720, 1680, 1590, 1530, 1440, 1390, 1270, 1230, 1140, 1090, 1000, 920, 805, 755, 690, 585 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.51 (2H, m, Ph), 7.41–7.38 (6H, m, Ph), 7.31–7.27 (3H, m, Ph+C*H*), 7.14 (1H, s, *meso*-C*H*), 6.75 (1H, d, *J* 7.6 Hz, C*H*), 4.15 (2H, q, *J* 7.2 Hz, OC*H*$_2$Me), 3.88 (2H, t, *J* 7.2 Hz, C*H*$_2$(CH$_2$)$_2$Me), 2.95 (3H, s, C*Me*), 1.69–1.66 (2H, m, CH$_2$C*H*$_2$CH$_2$Me), 1.37–1.32 (2H, m, (CH$_2$)$_2$C*H*$_2$Me), 1.08 (3H, t, *J* 7.2 Hz, OCH$_2$*Me*), 0.91 (3H, t, *J* 7.2 Hz (CH$_2$)$_3$*Me*); δ_C (125 MHz, DMSO-d_6) 163.0, 161.6, 158.7, 152.6, 148.1, 142.5, 135.7, 135.5, 131.5, 131.4, 130.9, 130.6, 130.2, 129.8, 129.6, 128.4, 128.2, 121.4, 95.9, 60.6, 47.9, 31.4, 19.8, 15.1, 14.0; LC–MS: m/z MH$^+$, found 554. $C_{32}H_{30}BF_2N_3O_3$ requires 553.42.

*4.2.3. 2-Carbethoxy-3-methyl-7-octadecyl-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta-[b]fluoren-8-on (**4d**).* Yield (660 mg, 88%), dark brown solid, mp 131–132 °C; [found: C, 73.97; H, 7.68; N, 5.40. $C_{46}H_{58}BF_2N_3O_3$ requires C, 73.69; H, 7.80; N, 5.60%]; R_f (25% EtOAc/hexane) 0.74; ν_{max} (KBr) 2940, 2870, 2210, 1720, 1680, 1625, 1600, 1530, 1450, 1390, 1270, 1240, 1195, 1140, 1100, 1005, 910, 805, 755, 690, 590 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.53–7.52 (2H, m, Ph), 7.40 (6H, m, Ph), 7.31–7.21 (3H, m, Ph+C*H*), 7.14 (1H, s, *meso*-C*H*), 6.75 (1H, d, *J* 7.6 Hz, C*H*), 4.13 (2H, q, *J* 7.2 Hz, OC*H*$_2$Me), 3.86 (2H, t, *J* 7.2 Hz, C*H*$_2$(CH$_2$)$_{16}$Me), 2.95 (3H, s, C*Me*), 1.68 (2H, t, *J* 6.8 Hz, CH$_2$C*H*$_2$(CH$_2$)$_{15}$Me), 1.27–1.22 (30 H, m, (CH$_2$)$_2$(C*H*$_2$)$_{15}$Me), 1.08 (3H, t, *J* 7.2 Hz, OCH$_2$*Me*), 0.85 (3H, t, *J* 7.2 Hz, (CH$_2$)$_{17}$*Me*); LC–MS: m/z MH$^+$, found 751. $C_{46}H_{58}BF_2N_3O_3$ requires 749.80.

*4.2.4. 2-Carbethoxy-3-methyl-7-(2-hydroxyethyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (**4e**).* The protocol is similar to **4c**. Yield (498 mg, 92%), brown solid, mp >250 °C; [found: C, 66.86; H, 4.80; N, 7.54. $C_{30}H_{26}BF_2N_3O_4$ requires C, 66.56; H, 4.84; N, 7.76%]; R_f (10% MeOH/$CHCl_3$) 0.50; ν_{max} (KBr) 3510, 2990, 1720, 1670, 1610, 1430, 1390, 1270, 1245, 1190, 1140, 1090, 1020, 1000, 970, 915, 800, 750, 695, 580 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.52–7.51 (2H, m, Ph), 7.41–7.40 (6H, m, Ph), 7.35–7.31 (3H, m, Ph+C*H*), 7.16 (1H, s, *meso*-C*H*), 6.78 (1H, d, *J* 8.0 Hz, C*H*), 4.15 (2H, q, *J* 7.2 Hz, OC*H*$_2$Me), 4.08–4.06 (2H, m, CH$_2$C*H*$_2$OH), 3.90–3.89 (2H, m, C*H*$_2$CH$_2$OH), 2.95 (3H, s, C*Me*), 2.31 (1H, m, (CH$_2$)$_2$O*H*),1.08 (3H, t, *J* 7.2 Hz, OCH$_2$*Me*); δ_C (125 MHz, DMSO-d_6) 163.0, 160.9, 158.8, 152.9, 147.9, 145.3, 143.7, 135.6, 135.4, 131.6, 131.4, 130.8, 130.6, 130.1, 129.8, 129.6, 128.4, 128.3, 121.3, 117.9, 95.4, 60.6, 59.4, 51.0, 15.1, 14.1; LC–MS: m/z MH$^+$, found 542. $C_{30}H_{26}BF_2N_3O_4$ requires 541.37.

*4.2.5. 2-Carbethoxy-3-methyl-7-(2-methoxyethyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (**4f**).* As in the previous case, time of boiling in *i*-PrOH was 3 h. Yield (498 mg, 87%), dark green solid, mp 226–227 °C; [found: C, 67.35; H, 4.95; N, 7.37. $C_{31}H_{28}BF_2N_3O_4$ requires C, 67.04; H, 5.08; N, 7.57%]; R_f (50% EtOAc/hexane) 0.54; ν_{max} (KBr) 2910, 1710, 1680, 1590, 1430, 1390, 1350, 1270, 1230, 1200, 1140, 1100, 1005, 980, 915, 800, 750, 690, 650, 580 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.53–7.52 (2H, m, Ph), 7.39–7.37 (7H, m, Ph+C*H*), 7.31–7.30 (2H, m, Ph), 7.14 (1H, s, *meso*-C*H*), 6.74 (1H, d, *J* 7.6 Hz, C*H*), 4.15 (2H, q, *J* 7.2 Hz, OC*H*$_2$Me),

4.08–4.06 (2H, m, CH_2CH_2OMe), 3.61–3.59 (2H, m, CH_2CH_2OMe), 3.29 (3H, s, O*Me*), 2.95 (3H, s, C*Me*), 1.08 (3H, t, *J* 7.2 Hz, OCH_2Me); δ_C (125 MHz, DMSO-d_6) 163.0, 161.2, 158.7, 152.6, 148.1, 145.2, 143.2, 135.7, 135.4, 131.5, 130.8, 130.6, 130.2, 129.9, 129.7, 128.4, 128.3, 121.5, 117.7, 95.6, 70.2, 60.7, 58.6, 47.8, 15.2, 14.1; LC–MS: *m*/*z* MH^+, found 556. $C_{31}H_{28}BF_2N_3O_4$ requires 555.39.

*4.2.6. 2-Carbethoxy-3-methyl-7-(6-carboxyhexyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (**4g**).* Time of boiling in *i*-PrOH was 2 h. Residue was recrystallized from MeCN. Yield (550 mg, 90%), brown solid, mp 234–235 °C; [found: C, 66.98; H, 5.07; N, 6.59. $C_{34}H_{32}BF_2N_3O_5$ requires C, 66.79; H, 5.28; N, 6.87%]; R_f (10% MeOH/$CHCl_3$) 0.43; ν_{max} (KBr) 3230, 2990, 1725, 1660, 1590, 1430, 1390, 1270, 1240, 1200, 1130, 1100, 1020, 1000, 920, 800, 750, 690, 590 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.52–7.50 (2H, m, Ph), 7.41–7.38 (6H, m, Ph), 7.31–7.26 (3H, m, Ph+C*H*), 7.14 (1H, s, *meso*-C*H*), 6.76 (1H, d, *J* 7.6 Hz, C*H*), 4.17 (2H, q, *J* 7.2 Hz, OCH_2Me), 3.88 (2H, t, *J* 7.2 Hz, $CH_2(CH_2)_4COOH$), 2.95 (3H, s, C*Me*), 2.32 (2H, t, *J* 7.2 Hz, $(CH_2)_4CH_2COOH$), 1.76–1.70 (2H, m, $CH_2CH_2(CH_2)_3COOH$), 1.68–1.60 (2H, m, $(CH_2)_3CH_2CH_2COOH$), 1.41–1.34 (2H, m, $(CH_2)_2CH_2$ $(CH_2)_2COOH$), 1.08 (3H, t, *J* 7.2 Hz, OCH_2Me); δ_C (125 MHz, DMSO-d_6) 174.8, 161.8, 161.1, 160.7, 161.1, 158.8, 148.1, 142.6, 134.7, 131.5, 131.2, 130.6, 130.1, 128.8, 128.4, 128.2, 95.9, 60.7, 48.0, 34.0, 29.6, 29.1, 26.0, 24.6, 15.2, 14.4, 14.1; LC–MS: *m*/*z* MH^+, found 612. $C_{34}H_{32}BF_2N_3O_5$ requires 611.46.

*4.2.7. 2-Carbethoxy-3-methyl-7-(2-azidoethyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta-[b]fluoren-8-on (**4h**).* Yield (250 mg, 90%), brown solid, mp 231–232 °C; [found: C, 63.92; H, 4.33; N, 14.64. $C_{30}H_{25}BF_2N_6O_3$ requires C, 63.62; H, 4.45; N, 14.84%]; R_f (25% EtOAc/hexane) 0.26; ν_{max} (KBr) 2120, 1725, 1675, 1600, 1550, 1450, 1390, 1270, 1240, 1190, 1130, 1200, 915, 850, 800, 750, 690, 650, 585 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.52–7.51 (2H, m, Ph), 7.42–7.39 (6H, m, Ph), 7.31–7.29 (3H, m, Ph+C*H*), 7.16 (1H, s, *meso*-C*H*), 6.80 (1H, d, *J* 7.6 Hz, C*H*), 4.17 (2H, q, *J* 7.2 Hz, OCH_2Me), 4.01 (2H, t, *J* 5.6 Hz, $CH_2CH_2N_3$), 3.65 (2H, t, *J* 5.6 Hz, $CH_2CH_2N_3$), 2.96 (3H, s, C*Me*), 1.08 (3H, t, *J* 7.2 Hz, OCH_2Me); δ_C (125 MHz, DMSO-d_6) 163.0, 158.8, 142.5, 131.4, 131.2, 130.6, 130.1, 129.9, 129.7, 128.7, 128.4, 128.3, 117.6, 96.1, 95.9, 60.7, 49.7, 47.6, 15.2, 14.4, 14.1.

*4.2.8. 2-Carbethoxy-3-methyl-7-(1-prop-2-ynyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (**4i**).* Propargylamine was used as hydrochloride, Hunig's base (1 mmol) was added to chloroformic solution. Yield (483 mg, 90%), brown solid, mp 240–241 °C; [found: C, 69.88; H, 4.46; N, 7.63. $C_{31}H_{24}BF_2N_3O_3$ requires C, 69.55; H, 4.52; N, 7.85%]; R_f (25% EtOAc/hexane) 0.34; ν_{max} (KBr) 3290, 2110, 1720, 1670, 1600, 1440, 1385, 1270, 1235, 1200, 1140, 1085, 1005, 975, 925, 690, 585 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.57 (1H, d, *J* 7.6 Hz, C*H*), 7.53–7.51 (2H, m, Ph), 7.40–7.39 (6H, m, Ph), 7.31–7.29 (2H, m, Ph), 7.16 (1H, s, *meso*-C*H*), 6.85 (1H, d, *J* 7.6 Hz, C*H*), 4.71 (2H, d, *J* 2.4 Hz, $CH_2C{\equiv}CH$), 4.15 (2H, q, *J* 7.2 Hz, OCH_2Me), 2.96 (3H, s, C*Me*), 2.40 (1H, t, *J* 2.4 Hz, $CH_2C{\equiv}CH$), 1.08 (3H, t, *J* 7.2 Hz, CH_2Me); δ_C (125 MHz, DMSO-d_6) 162.9, 161.9, 158.1, 152.2, 148.6, 144.8, 141.0, 135.9, 135.2, 131.4, 130.7, 129.9, 129.8, 128.4, 128.3, 121.7, 117.4, 96.8, 95.9, 79.5, 76.0, 60.7, 37.0, 15.3, 14.1; LC–MS: *m*/*z* MH^+, found 536. $C_{31}H_{24}BF_2N_3O_3$ requires 535.36.

*4.2.9. 2-Carbethoxy-3-methyl-7-(1-allyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta-[b]fluoren-8-on (**4j**).* Yield (496 mg, 92%), dark brown solid, mp 238–239 °C; [found: C, 69.55; H, 4.79; N, 7.67. $C_{31}H_{26}BF_2N_3O_3$ requires C, 69.29; H, 4.88; N, 7.82%]; R_f (25% EtOAc/hexane) 0.37; ν_{max} (KBr) 3000, 1720, 1675, 1595, 1480, 1440, 1390, 1270, 1230, 1200, 1140, 1090, 1000, 970, 915, 800, 750, 690, 650, 590 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.53–7.51 (2H, m, Ph), 7.39 (6H, m, Ph), 7.31–7.25 (3H, m, Ph+C*H*), 7.15 (1H, s, *meso*-C*H*), 6.79 (1H, d, *J* 8.0 Hz, C*H*), 5.94–5.87 (1H, m, $CH_2CH{=}CH_2$), 5.24–5.17 (2H, m, $CH_2CH{=}CH_2$), 4.53 (2H, d, *J* 5.6 Hz, $CH_2CH{=}CH_2$), 4.17 (2H, q, *J* 7.2 Hz, OCH_2Me), 2.95 (3H, s, C*Me*), 1.08 (3H, t, *J* 7.2 Hz, OCH_2Me); δ_C (125 MHz, DMSO-d_6) 163.0, 161.4, 158.5, 152.5, 148.2, 145.1, 142.1, 135.7, 135.4, 134.0, 131.4, 130.8, 130.6, 130.3, 129.8, 129.7, 128.4, 128.3, 121.5, 117.8, 96.3, 60.7, 49.8, 15.2, 14.1; LC–MS: *m*/*z* MH^+, found 538. $C_{31}H_{26}BF_2N_3O_3$ requires 537.38.

*4.2.10. 2-Carbethoxy-3-styryl-7-(1-butyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta-[b]fluoren-8-on (**8**).* The mixture of pyridone **4c** (200 mg, 0.361 mmol), benzaldehyde (53 mg, 0.5 mmol), piperidine (215 mg, 2.53 mmol), and acetic acid (300 mg, 5.0 mmol) in benzene (10 mL) was refluxed for 2 h. After cooling to room temperature, the mixture was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from *i*-PrOH. Yield (168 mg, 72%), green solid, mp 168–169 °C; [found: C, 73.34; H, 5.27; N, 6.31. $C_{39}H_{34}BF_2N_3O_3$ requires C, 73.02; H, 5.34; N, 6.55%]; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr) 2980, 1720, 1680, 1600, 1450, 1295, 1225, 1190, 1135, 1040, 1010, 995, 915, 850, 745, 685, 585 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.84–7.83 (2H, m, C*H*=C*H*), 7.67 (2H, d, *J* 6.8 Hz, Ph), 7.56 (2H, d, *J* 6.8 Hz, Ph), 7.40–7.34 (11H, m, Ph), 7.28 (1H, d, *J* 6.8 Hz, C*H*), 7.14 (1H, s, *meso*-C*H*), 6.81 (1H, d, *J* 6.8 Hz, C*H*), 4.20 (2H, q, *J* 7.2 Hz, OCH_2Me), 3.89 (2H, t, *J* 7.2 Hz, $CH_2(CH_2)_2Me$), 1.70–1.67 (2H, m, $CH_2CH_2CH_2Me$), 1.38–1.33 (2H, m, $(CH_2)_2CH_2Me$), 1.05 (3H, t, *J* 7.2 Hz, OCH_2Me), 0.91 (3H, t, *J* 7.2 Hz, $(CH_2)_3Me$); δ_C (125 MHz, DMSO-d_6) 164.5, 158.7, 146.7, 144.9, 142.7, 141.6, 137.1, 136.1, 136.0, 131.5, 131.1, 130.9, 130.8, 130.1, 129.9, 129.8, 129.0, 128.8, 128.3, 128.0, 126.5, 117.1, 114.6, 95.8, 61.7, 48.0, 44.2, 31.5, 22.7, 19.8, 14.1; LC–MS: *m*/*z* MH^+, found 642. $C_{39}H_{34}BF_2N_3O_3$ requires 641.53.

*4.2.11. 2-Carbethoxy-3-(2-(4-methoxyphenyl)vinyl)-7-(1-butyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (**9**).* The product was prepared using anisaldehyde analogously to **8**. Yield (240 mg, 70%), brown solid, mp 206–207 °C; [found: C, 71.88; H, 5.32; N, 6.11. $C_{40}H_{36}BF_2N_3O_4$ requires C, 71.54; H, 5.40; N, 6.26%]; R_f (25% EtOAc/hexane) 0.30; ν_{max} (KBr) 2975, 2270, 1720, 1680, 1600, 1530, 1480, 1450, 1390, 1320, 1270, 1220, 1190, 1140, 1040, 920, 850, 800, 745, 685, 590 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.84 (1H, d, *J* 16.0 Hz, CH=C*H*), 7.75 (1H, d, *J* 16.0 Hz, C*H*=CH), 7.63 (2H, d, *J* 8.8 Hz, Ar*H*), 7.56 (2H, d, *J* 6.8 Hz, Ph), 7.40–7.34 (8H, m, Ph), 7.27 (1H, d, *J* 7.6 Hz, C*H*), 7.10 (1H, s, *meso*-C*H*), 6.94 (2H, d, *J* 8.8 Hz, Ar*H*), 6.81 (1H, d, *J* 7.6 Hz, C*H*), 4.19 (2H, q, *J* 7.2 Hz, OCH_2Me), 3.90–3.85 (5H, m, $CH_2(CH_2)_2Me$+O*Me*), 1.68–1.67 (2H, m, $CH_2CH_2CH_2Me$), 1.38–1.32 (2H, m, $(CH_2)_2CH_2Me$), 1.04 (3H, t, *J* 7.2 Hz, OCH_2Me), 0.91 (3H, t, *J* 7.2 Hz, $(CH_2)_3Me$); δ_C (125 MHz, DMSO-d_6) 164.6, 161.8, 158.7, 153.9, 152.1, 146.9, 143.6, 142.0, 136.8, 135.6, 131.5, 131.1, 130.0, 129.9, 129.6, 129.0, 128.8, 128.2, 127.4, 123.2, 117.7, 115.4, 114.7, 96.1, 95.7, 61.7, 55.9, 47.9, 31.5, 25.9, 19.8, 14.0; LC–MS: *m*/*z* MH^+, found 672. $C_{40}H_{36}BF_2N_3O_4$ requires 671.56.

*4.2.12. 2-Carbethoxy-3-(4-phenylbuta-1,3-dienyl)-7-(1-butyl)-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (**10**).* The mixture of pyridone **4c** (200 mg, 0.361 mmol), 3-phenyl-2-propenal (85 mg, 0.65 mmol), piperidine (215 mg, 2.53 mmol), and acetic acid (300 mg, 5.0 mmol) in benzene (10 mL) was refluxed for 2.5 h. After cooling to room temperature, the solution was washed with water, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by silica gel column chromatography (25% EtOAc/hexane) to give (70 mg, 30%) of **10**. Dark green solid, mp 195–196 °C; [found: C, 73.98; H, 5.34; N, 6.13. $C_{41}H_{36}BF_2N_3O_3$ requires C, 73.77; H, 5.44; N, 6.29%]; R_f (30% EtOAc/hexane) 0.45; ν_{max} (KBr) 2985, 1725, 1680, 1595, 1535, 1485, 1440, 1390, 1275, 1220, 1180, 1130, 1010, 920, 850, 750, 690, 650, 590 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.83–7.65 (1H, m, CH=C*H*), 7.55–7.49 (3H, m, Ph+C*H*=CH), 7.40–7.27 (14H, m, Ph+C*H*), 7.16–7.14 (1H, m, CH=C*H*), 7.09 (1H, s, *meso*-C*H*), 6.95 (1H, d, *J*

16.0 Hz, C*H*=CH), 6.80 (1H, d, *J* 8.0 Hz, C*H*), 4.19 (2H, q, *J* 7.2 Hz, OCH_2Me), 3.89 (2H, t, *J* 7.2 Hz, CH_2(CH_2)$_2$Me), 1.70–1.67 (2H, m, CH$_2$CH_2CH$_2$Me), 1.38–1.33 (2H, m, (CH$_2$)$_2$CH_2Me), 1.03 (3H, t, *J* 7.2 Hz, OCH$_2$*Me*), 0.91 (3H, t, *J* 7.2 Hz, (CH$_2$)$_3$*Me*); LC–MS: *m*/*z* MH$^+$, found 668. $C_{41}H_{36}BF_2N_3O_3$ requires 667.57.

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Supplementary data

These data include copies of ^{1}H and ^{13}C NMR spectra. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.050.

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