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Synthesis and Characterization of BODIPY-α-Tocopherol: A Fluorescent Form of Vitamin E

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Abstract

Fluorescent nitrobenzoxadiazole analogues of α-tocopherol (NBD-α-Tocs; λ_{ex} = 468 nm, λ_{em} = 527 nm) have been made previously to aid study of the intracellular location and transfer of vitamin E. However, these analogues are susceptible to photobleaching while under illumination for confocal microscopy as well as in in vitro FRET transfer assays. Here we report the synthesis of three fluorescent analogues of α-tocopherol incorporating the more robust dipyrromethene boron difluoride (BODIPY) fluorophore. A BODIPY-linked chromanol should have no intervening polar functional groups that might interfere with binding to the hydrophobic binding site of the tocopherol transfer protein (α-TTP). A key step in bringing the two ring systems together was a metathesis reaction of vinyl chromanol and an alkenyl BODIPY. An *o*-tolyl containing second generation Grubbs catalyst was identified as the best catalyst for effecting the metathesis without detectable alkene isomerization which, when it occurred produced a mixture of chain lengths in the alkyl linker. C8-BODIPY-α-Toc **10c** (λ_{ex} = 507 nm, λ_{em} = 511 nm, ε_{507} = 83,000 $M^{-1}cm^{-1}$) having an eight-carbon chain between the chromanol and fluorophore, had the highest affinity for α-TTP (K_d = 94 ± 3 nM) and bound specifically as it could not be displaced with cholesterol.

Keywords

Tocopherol; Vitamin E; BODIPY; Tocopherol transfer protein; α-TTP

1. Introduction

Vitamin E is a family of eight hydrophobic chromanols including four tocopherols and four tocotrienols. One of these compounds, (*RRR*)-α-tocopherol (hereafter referred to as α-tocopherol), is selectively retained by mammals in plasma and tissues following ingestion due to the actions of a specific binding and transfer protein called the tocopherol transfer protein (TTP).[1-3] TTP facilitates the secretion of α-tocopherol from hepatocytes to the plasma where it is carried to other tissues by very-low-density lipoproteins (VLDL).[1,3]

Following the discovery of biological activities[4] that would later be ascribed to α-tocopherol[5], research on this vitamin was dominated by its activity as a chain-terminating antioxidant of free radical lipid peroxidation.[6] The kinetics and physical chemistry of this action has been well-described for in vitro conditions[7-13] and there is evidence for similar in vivo actions[12,14,15] and in cells.[16,17] Recently described biological actions of α-tocopherol and other forms of vitamin E may be unrelated to radical scavenging activity.[18-20]

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Supporting Information Available: Proton and carbon NMR spectra for compounds 2-4, 6, 8-10. This material is available free of charge via the Internet at http://pubs.acs.org.

Most investigations of the nature of vitamin E absorption and distribution have used deuterium labelled samples to enable detection of tocopherols by GC-MS following organic solvent extraction of plasma and tissue samples.[21-26] More recently, we prepared a series of fluorescent analogues of vitamin E[27] that has expanded our ability to follow the localization and trafficking of α-tocopherol at the cellular level.[28-31] The most useful of these fluorescent analogues contains a 7-nitrobenz-2-oxa-1,3-diazole (NBD) fluorophore separated from a 6-hydroxychromanol similar to α-tocopherol by a C9-*n*-alkyl linker. This so-called C9-NBD-α-Toc bound specifically and reversibly to TTP with a dissociation constant, K_d, of approximately 60 nM.[27]

The NBD fluorophore has been used extensively in lipid probes[32] but its significant polarity is known to accelerate spontaneous intermembrane transfer of phospholipid analogues[33] and to perturb the behaviour of NBD-modified acyl chains,[34] which is a drawback for molecules designed to probe protein-catalyzed transfer of hydrophobic ligands to and from membranes. The tendency of the NBD chromophore to photobleach during prolonged observation in fluorescence confocal microscopy also detracts from its use as an intracellular probe of lipid trafficking.

Dipyrromethene boron difluoride (BODIPY) is a fluorophore that has been widely incorporated into lipid probes because of its high photostability, large extinction coefficient, high quantum yield, and low polarity.[35,36] The lipophilicity of BODIPY readily allows entry into cell membranes and other hydrophobic environments such as plasma lipoproteins.[37,38] Unlike NBD and other common fluorophores such as dansyl and anthroyloxy that are linked to molecules by heteroatom-containing functional groups such as esters, BODIPY analogues can be prepared with an alkyl linker that maximizes lipophilicity. The fluorescence quantum yield of BODIPY is two to three times greater than NBD and its fluorescence intensity is approximately four to five times greater.[39] Seeking to incorporate the advantages of a BODIPY fluorphore in our work with vitamin E, we describe here the synthesis of three BODIPY-containing α-tocopherol analogues (C6-, C7-, and C8-BODIPY-α-Toc, **10a-c**) as new probes to assist monitoring the location of tocopherol within cells. The binding affinities of these analogues to α-TTP are also reported.

2. Results and discussion

Reagents are available commercially[1] that include an intact fluorophore with a short alkanoic side chain (Figure 2). This allows functionalization of amines and alcohols with a BODIPY fluorophore. However, for a desired BODIPY-tocopherol analogue this would install a polar functional group between the fluorophore and the chromanol nucleus. The x-ray crystal structure of TTP with bound α-tocopherol[40,41] shows that the tocopherol is held in a deep hydrophobic site of the protein, suggesting that polar functional groups might reduce binding affinity. Consequently, we wished to prepare a dipyrromethene structure that would contain a hydrophobic linkage between fluorophore and chromanol.

The BODIPY nucleus can be prepared with 3,5-dihalogen substituents[42] and these groups used as substrates for Suzuki and Heck cross-couping reactions.[43] We attempted to couple BODIPY halides with an appropriate alkene, but with no success (Scheme 1). TLC showed several products that weakly fluoresced, but after chromatography none could be confirmed as the expected product. The BODIPY halides were never recovered from these reactions, suggesting that lack of a substituent at the *meso*-position introduces alternate reactivities. There has been one other reported failure of a cross-coupling in the presence of a BODIPY halide fluorophore,

[1]BODIPY®-FL, 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionic acid, is available from Molecular Probes

in this case using the Sonogashira reaction.[44] Interestingly, this fluorophore also lacked a substituent at the *meso*-position and multiple uncharacterizable products were formed.

We then considered whether a BODIPY system functionalized with a suitable alkene could be used in a metathesis reaction. The successful olefin metathesis of a BODIPY dye functionalized with a terminal olefin was reported in the synthesis of sphingosine analogues.[45] The BODIPY used lacked a *meso*-substituent and yet remained intact after this reaction. The alkenyl BODIPYs that are required for this metathesis can be prepared from ω-alkenoic acids. If the ω-alkenoic acids are not commercially available, they can be prepared by Grignard reaction, as was required for obtaining 7-octenoic acid **1** (Scheme 2).

2-Ketopyrroles can be produced by the acylation of pyrrylmagnesium chloride with acyl halides or esters.[46] Acylations with esters are more favourable because they react less vigorously than other acylating agents and are less likely to form tars.[47] 2-Ketopyrroles are stable species that can be purified by chromatography.

Alkenylpyrroles **4a-c** were synthesized in yields near 50% after treating the 2-ketopyrroles with sodium borohydride[48] (Scheme 3). Compounds **4a-c** tended to decompose on silica during attempted chromatography, therefore the products were best obtained by simply passing them through a short alumina plug prior to using them in the the next step.

Despite hydrobromic acid being used to condense the alkenylpyrroles with substituted pyrrole carboxaldehydes in the methods described by Peters *et al.*,[45] multiple attempts by us did not yield the expected precipitate. The use of phosphorus oxychloride[44], however, successfully generated dipyrromethenes **5a-c** *in situ* as the $PO_2Cl_2^-$ salts.[49] Treating solutions of **5a-c** with boron trifluoride diethyl etherate and base yielded alkenyl BODIPYs **6a-c**.

The olefin metathesis between one equivalent of vinyl Trolox **7**, prepared from Trolox aldehyde[50] and two equivalents of alkenyl BODIPY **6a-c** produced **8a-c** with yields that varied from 48-65% (Scheme 4). Two equivalents of alkenyl BODIPY are required to obtain the best yields of the cross coupled product. A dimerization by-product arising from coupling of the alkenyl BODIPY (a bis-BODIPY) and can be easily removed by silica gel chromatography. We never observed any dimerized Trolox by-product from this metathesis.

We did not explore the geometry of the alkenes as they were to be reduced to prepare the target molecules. However, it has been noted[45,51] that the cross-metathesis products are formed almost exclusively in the *E* geometry. The double bonds in **8a-c** need to be reduced to obtain the saturated alkyl linker of the target molecules. There are also multiple reports of functional groups on molecules that possess a BODIPY fluorophore being reduced using standard hydrogen conditions (10% Pd/C, H_2) without decomposition.[52-56] However, when **8a-c** was treated with hydrogen gas and Pd/C, TLC showed rapid decomposition of the starting material within minutes, and formed an uncharacterizable transparent oil that gave a fluorescent blue spot on the TLC baseline. Again, the dyes that were successfully transformed using Pd/C [52-56] possessed *meso*-aryl groups, which must increase the stability of the backbone during noble metal reductions. A report of the synthesis of the bile pigment nonylprodigiosin (also a pyrrole) reported similar difficulties in reducing a double bond using hydrogen gas and Pd/C[48] but good yields were obtained when Wilkinson's catalyst was used instead.[48] This was also noted in the reduction of the BODIPY-ceramide analogues reported by Boath *et al.*[57] When Wilkinson's catalyst was applied to the reduction of **8a-c** selective reduction of the alkene only began at pressures of 40 psi or greater and was sensitive to the concentration of alkene. Decomposition of the fluorophore was still observed, but there was enough chemoselectivity to obtain **9a-c** in decent yields. The best conditions (70% yield) for the catalytic hydrogenation

of **8a-c** with Wilkinson's catalyst were in ethanol, 80 psi H_2, for 28 h with an alkene concentration of ~20 mM.

Deprotection of the TBS-group from **9a-c** using tetrabutylammonium fluoride also resulted in decomposition and loss of the characteristic BODIPY fluorescence. The desilylation of an intermediate for the synthesis of an anthracene-BODIPY analogue, also lacking a substituent at the *meso*-position, was reported to occur with great difficulty.[58] This step was specifically stated as being the most troublesome in the entire synthesis and could only be successfully transformed if run with extreme care. In the end, we removed the protecting group in HCl/methanol/THF[45,59]to provide BODIPY-α-Tocs **10a-c** in yields of 66-77%.

The NMR spectra of **10a-c** appeared straightforward, but the HPLC chromatograms showed multiple peaks (Figure 3) when detection was at the BODIPY absorbance maximum of 511 nm. LC-MS analysis of the expected C7-BODIPY-α-Toc product **10b** revealed that the main peak at 13.38 min was the desired material, but that peaks with shorter and longer retention times gave molecular ions differing by mass 14, suggesting a group of analogues with differing numbers of methylenes in the alkyl linker. H-NMR cannot easily detect the relatively minor abundance of shorter and longer chain-length materials. Inspection of synthetic intermediates prior to **8a-c** by HPLC showed them to be free of such homologues suggesting that they arose during the metathesis reactions.

Second generation olefin metathesis catalysts are known to facilitate olefin isomerization by 1,3-hydride shifts during the intended metathesis.[60] As a result, chain-length homologues can be generated. Unfortunately, these side-reactions are not always reported in the many papers that perform metatheses. It is not clear if the isomerization is caused by the ruthenium catalyst itself, by some decomposition product of the catalyst, or by some impurity made during the synthesis of the catalyst.[60] The suggested mechanism for this isomerization has been reported.[61,62] To obtain homologues that are one or two methylenes less, the isomerization of the terminal alkene must occur more than once. To obtain a homologue with an extra methylene the alkene can isomerize after the first successful metathesis, then undergo a second metathesis, as depicted in Figure 4.[60] An isolated bis-BODIPY **11** (from reaction of **6a**) which we expected to have an alkyl spacer length of ten carbons, in fact showed a range of chain lengths from nine to eleven carbons, suggesting that the sterically encumbered vinyl chroman **7** reacts only slowly, allowing time for isomerization (and coupling) of the more accessible alkenyl BODIPY (Scheme 5). Bis-BODIPY mixture **11** was also subjected to cross coupling conditions with **7** and produced BODIPY chromans of an even more complex mixture of chain lengths, showing that bis-BODIPY was an intermediate in the original reactions, capable of continued rounds of metathesis, and is the likely source for homologues of chain lengths higher than the sum of carbons in the starting alkenes **7** and **6a-c**.

We did manage to isolate milligram amounts of pure **10a-c** using preparative HPLC, but also wished to find a more efficient means of synthesis that avoided olefin isomerization. A summary of metathesis reactions performed using different catalysts is provided in Table 1. Grubbs Generation I Catalyst was used in attempts to metathesize vinyl Trolox **7** with heptenyl-BODIPY **6b**, but was presumably not active enough to complex to the bulky chromanol; only the bis-BODIPY was produced from metathesis of the alkenyl BODIPY. In other attempts to eliminate olefin isomerization,[63] acids (e.g. trifluoroacetic acid, phenylphosphoric acid) or benzoquinones have been added to titrate the species responsible for the isomerization. Removal of impurities from the catalyst by silica gel chromatography has been reported to eliminate isomerization activity as well.[64] Both of these methods were applied to this metathesis using Grubbs Generation II catalyst. The composition of products dramatically improved (93-95% C7 and 5-7% C6), but these product mixtures would still need purification by preparative HPLC. When Hoveyda-Grubbs Generation II catalyst was used, the composition

and yield improved as well, but purification would again be required. The *o*-tolyl derivative of Hoveyda-Grubbs Generation II catalyst has been developed to facilitate easy interaction with bulkier substrates.[65] When this catalyst was used the crude product showed only one peak by analytical HPLC that corresponded to the desired homologue. While the yield was significantly lower, it saved considerable effort in obtaining pure material.

In order for BODIPY-α-Tocs **10a-c** to be of any utility, they must show some affinity towards α-TTP. Binding should be both specific and reversible in order for these fluorescent probes to be suitable analogues of vitamin E. The dissociation constants were assessed from fluorescence titrations of α-TTP with BDP-α-Tocs **10a-c** (Figure 5) and calculated using a one-site binding model with Prism software. The average results of the multiple titrations on a range of ligand concentrations (3-640 nM) are listed in Table 2. C8-BODIPY-α-Toc **10c** appears to have the best affinity to α-TTP (K_d = 94 nM). The dissociation constant for α-tocopherol, the natural ligand for α-TTP, is 25 nM.[66]

To illustrate the specificity of binding, α-TTP was first equilibrated with **10c** and then titrated with α-tocopherol or cholesterol, the latter of which is known not to bind.[66] C8-BODIPY-α-Toc exhibited a dose-dependent decrease in fluorescence upon the addition of α-tocopherol suggesting that the environmentally sensitive fluorophore is displaced from the hydrophobic-binding pocket of α-TTP by the native ligand (Figure 6). After the addition of 5 μM α-tocopherol to the assay, there is near total displacement of C8-BODIPY-α-Toc by the native ligand. After 5 uM cholesterol had been added fluorescence had been reduced by ~15% which is in large part due to the presence of ethanol as the carrier solvent which is known to interfere with the binding of hydrophobic ligands to lipid transfer proteins.[67] Together, Figures 5 & 6 show that there is specific competitive binding of C8-BDP-α-Toc to α-TTP.

3. Conclusions

Three BODIPY analogues of α-tocopherol **10a-c** were successfully prepared. They all bind specifically and reversibly to α-TTP with high affinity and thus can serve as fluorescent probes in the study of the location and the intracellular transfer of vitamin E. We will use these probes in cultured hepatocytes to explore the mechanism of α-TTP-mediated transfer and secretion of tocopherol.

Experimental Section

Fluorescent Binding Assays of BODIPY-α-Tocopherols 10a-c

Human α-TTP was expressed and purified following published methods as were fluorescence titrations.[27] Briefly, 0.2 μM of α-TTP was incubated with each of the BODIPY analogues at concentrations ranging from 0 to 5 μM in SET buffer (250 mM sucrose, 100 mM KCl, 1 mM EDTA, 50 mM Tris-HCl pH 7.4). The ligands were added from ethanolic stock solutions such that the total volume of ethanol was only 0.1 % of the total sample. After brief vortexing, samples were agitated on a rocker for 25–40 minutes at room temperature. Subsequently, the fluorescence of each sample was measured at 514 nm on a QuantaMaster2000 fluorometer (Photon Technologies International, London, Ontario) using an excitation wavelength of 506 nm and 5 nm slit widths. Fluorescence values were plotted in Prism Graphpad 4.0 and fit to a non-linear regression one-site binding model.[68]

Competition assays were performed under similar conditions. To a 0.2 μM solution of α-TTP in 3 mL SET buffer was added 2 μl of a stock solution of fluorescent analogue in absolute ethanol (1.5 mM) such that the final concentration of fluorophore was 1 μM. The solution was then mixed until the fluorescence signal reached a constant value. To this solution were added 2 μl aliquots of α-tocopherol (or cholesterol) in absolute ethanol (1.5 mM to 15 mM stock

solutions) to yield final concentrations of tocopherol ranging from 1 to 5 μM. After each addition of tocopherol, the samples were equilibrated for 15 min, and the final fluorescence recorded. Control experiments included an identical competition substituting cholesterol as the competitor.

Synthesis

(*S*)-*tert*-butyldimethyl(2,5,7,8-tetramethyl-2-vinylchroman-6-yloxy)silane (7)[50]— Methyltriphenylphosphonium bromide (169 mg, 0.473 mmol) was dissolved in tetrahydrofuran (10 mL) under nitrogen and to this was added dropwise a 1.0 M solution of LHMDS in tetrahydrofuran (753 μl, 0.753 mmol). After stirring for 1 h, a solution of (*S*)-Trolox aldehyde (150 mg, 0.430 mmol) in tetrahydrofuran (5 mL) was added and stirred for 3 h. The reaction was then quenched with saturated ammonium chloride solution and extracted with dichloromethane. The crude material was subjected to chromatography (hexanes/dichloromethane 3:1) to afford product **7** (132 mg, 0.380 mmol, 88%). White solid, R_f = (0.30, hexanes/dichloromethane 3:1), mp 54 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94-5.85 (dd, *J* = 17.1 Hz, *J* = 10.8 Hz, 1H), 5.20-5.13 (dd, *J* = 17.1 Hz, *J* = 1.1 Hz, 1H), 5.07-5.03 (dd, *J* = 10.8 Hz, *J* = 1.1 Hz, 1H), 2.66-2.48 (m, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 2.01-1.81 (m, 2H), 1.44 (s, 3H), 1.10 (s, 9H), 0.17 (s, 6H). ^{13}C NMR (75 MHz, CDCl3) δ 146.0, 144.2, 141.9, 125.8, 123.4, 122.2, 117.5, 113.1, 75.2, 31.9, 27.0, 26.1, 21.1, 18.6, 14.3, 13.4, 12.0, -3.3. MS (+EI) *m/z* 346 (M^+, 100%), 331 (8.6%), 289 (12.4%), 278 (27.3%), 234 (10.9%), 221 (49.5%), 163 (9.0%), 129 (6.7%), 73 (53.8%), 59 (13.6%). HRMS (EI) calculated for $C_{21}H_{34}O_2Si$: 346.23281, found 346.23288.

Oct-7-enoic acid (1)[48]—To a stirring solution of 7-bromo-1-heptene (2.00g, 11.3 mmol) in dry diethyl ether (10 mL) was added magnesium turnings (302 mg, 12.4 mmol) and a catalytic amount of iodine. The mixture was heated to 34 °C for 3.5 h and then cooled to −20 °C upon which carbon dioxide (dry ice subliming through a Drierite® drying tube) was bubbled into the solution. After 2 h, the reaction was quenched with 19% hydrochloric acid (10 mL) and extracted with diethyl ether to obtain acid **1** (452 mg, 2.94 mmol, 26%). Clear and colorless liquid, R_f = (0.25, hexanes/ethyl acetate 5:1, visualized by H_2SO_4/MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.79 (br s, 1H), 5.82-5.73 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, 1H), 5.02-4.90 (m, 2H), 2.36-2.31 (t, *J* = 1.5 Hz, 2H), 2.08-2.01 (m, 2H), 1.66-1.61 (m, 2H), 1.43-1.28 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 138.4, 114.3, 33.9, 33.4, 28.4, 24.4. MS (+FAB) *m/z* 143 ($[MH]^+$, 20.4%), 137 (15.2%), 125 (28.2%), 107 (9.3%), 97 (34.0%), 81 (16.1%), 67 (13.4%), 55 (100%), 41 (39.2%). HRMS (FAB) calculated for $C_8H_{15}O_2^+$: 143.10720, found 143.10647.

***S*-pyridin-2-yl hex-5-enethioate (2a, n = 1)[48]—**To a solution of 5-hexenoic acid (1.12 g, 9.81 mmol) in dry toluene (10 mL) was added 2,2′-dipyridyl disulfide (2.81 g, 12.8 mmol) and triphenylphosphine (3.34 g, 12.8 mmol). This mixture was stirred overnight. After washing the toluene with water and then washing the combined water fractions with diethyl ether, the organic phases were combined, condensed *in vacuo*, and the crude material was loaded onto a silica gel column eluting with hexanes/ethyl acetate 6:1 to afford pure thioate **2a** (1.95 g, 9.42 mmol, 96%). Light yellow syrup, R_f = (0.35, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40-8.38 (dd, *J* = 4.8 Hz, *J* = 0.9 Hz, 1H), 7.52-7.47 (m, 1H), 7.42-7.39 (d, *J* = 8.1 Hz, 1H), 7.06-7.02 (m, 1H), 5.61-5.52 (ddt, *J* = 16.8 Hz, *J* = 10.4 Hz, *J* = 6.6 Hz, 1H), 4.88-4.79 (m, 2H), 2.53-2.48 (t, *J* = 7.5 Hz, 2H), 1.96-1.89 (m, 2H), 1.67-1.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 150.9, 149.7, 136.6, 136.4, 129.4, 122.8, 115.1, 42.7, 32.1, 23.7. MS (+EI) *m/z* 207 (M^+, 0.4%), 179 (1.2%), 166 (3.1%), 125 (4.3%), 111 (100%), 78 (12.2%), 69 (19.4%), 55 (32.5%), 41 (38.2%). HRMS (EI) calculated for $C_{11}H_{13}NOS$: 207.07179, found 207.07210.

***S*-pyridin-2-yl hept-6-enethioate (2b, n = 2)—**(1.42 g, 6.43 mmol, 95%). Light yellow syrup, R_f = (0.35, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29-8.26 (m, 1H), 7.37-7.30 (m, 2H), 6.93-6.89 (m, 1H), 5.48-5.42 (m, 1H), 4.74-4.64 (m, 2H), 2.42-2.37 (t, *J* = 7.5 Hz, 2H), 1.79-1.71 (m, 2H), 1.47-1.37 (m, 2H), 1.20-1.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 150.8, 149.3, 137.1, 136.0, 128.9, 122.4, 113.9, 42.9, 32.3, 27.0, 23.8. MS (+EI) *m/z* 221 (M^+, 0.2%), 188 (1.1%), 160 (3.1%), 125 (2.7%), 111 (100%), 78 (10.0%), 67 (13.9%), 55 (31.1%), 41 (23.8%). HRMS (EI) calculated for $C_{12}H_{15}NOS$: 221.08744, found 221.08726.

***S*-pyridin-2-yl oct-7-enethioate (2c, n = 3)—**(733 mg, 3.12 mmol, 98%). Light yellow syrup, R_f = (0.35, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36-8.34 (dd, *J* = 4.8 Hz, *J* = 1.2 Hz, 1H), 7.47-7.36 (m, 2H), 7.01-6.96 (m, 1H), 5.59-5.50 (ddt, *J* = 16.8 Hz, *J* = 10.2 Hz, *J* = 6.6 Hz, 1H), 4.80-4.69 (m, 2H), 2.47-2.43 (t, *J* = 7.5 Hz, 2H), 1.84-1.77 (m, 2H), 1.53-1.43 (m, 2H), 1.22-1.09 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 151.0, 149.5, 137.8, 136.3, 129.2, 122.7, 113.8, 43.3, 32.7, 27.7, 27.5, 24.4. MS (+EI) *m/z* 235 (M^+, 0.8%), 174 (2.2%), 125 (2.7%), 111 (100%), 78 (10.3%), 67 (13.0%), 55 (43.7%), 41 (15.1%). HRMS (EI) calculated for $C_{13}H_{17}NOS$: 235.10309, found 235.10277.

1-(1*H*-pyrrol-2-yl)hex-5-en-1-one (3a, n = 1)[48]—Pyrrole (669 μl, 9.65 mmol) was dissolved in tetrahydrofuran (4 mL) and cooled to 0 °C under nitrogen. To this was slowly added a 3.0 M solution of methylmagnesium chloride in tetrahydrofuran (2.41 mL, 7.24 mmol) and the resulting solution was stirred for 15 min. Next, the solution was cooled further to −78 °C and a solution of thioate **2a** (500 mg, 2.41 mmol) in tetrahydrofuran (18 mL) was added. The reaction was warmed to 0 °C and stirred for 1 h. Afterward, the reaction mixture was condensed *in vacuo* and then extracted with dichloromethane. This crude material was purified via column chromatography (hexanes/diethyl ether 3:2) to yield pure ketopyrrole **3a** (356 mg, 2.17 mmol, 90%). Clear and colorless oil, R_f = (0.40, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (br s, 1H), 7.06 (m, 1H), 6.93 (m, 1H), 6.27-6.26 (m, 1H), 5.89-5.76 (ddt, *J* = 17.0 Hz, *J* = 10.1 Hz, *J* = 6.9 Hz, 1H), 5.07-4.98 (m, 2H), 2.82-2.77 (t, *J* = 7.2 Hz, 2H), 2.18-2.11 (m, 2H), 1.89-1.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 138.0, 131.9, 124.9, 116.4, 115.1, 110.4, 37.1, 33.2, 24.3. MS (+EI) *m/z* 163 (M^+, 25.3%), 146 (1.1%), 122 (1.6%), 109 (100%), 94 (63.0%), 80 (6.7%), 66 (14.9%), 55 (5.1%), 44 (15.4%). HRMS (EI) calculated for $C_{10}H_{13}NO$: 163.09971, found 163.09972.

1-(1*H*-pyrrol-2-yl)hept-6-en-1-one (3b, n = 2)—(1.11 g, 6.23 mmol, 97%). Clear and colorless oil, R_f = (0.45, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.21 (br s, 1H), 7.12-7.10 (m, 1H), 6.99-6.98 (m, 1H), 6.31-6.28 (m, 1H), 5.91-5.80 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, 1H), 5.12-5.01 (m, 2H), 2.87-2.82 (t, *J* = 7.2 Hz, 2H), 2.18-2.11 (m, 2H), 1.88-1.77 (m, 2H), 1.58-1.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 138.1, 131.6, 125.2, 116.6, 114.2, 109.9, 37.3, 33.2, 28.2, 24.5. MS (+EI) *m/z* 177 (M^+, 21.8%), 149 (2.1%), 134 (2.2%), 122 (25.9%), 109 (91.7%), 94 (100%), 80 (6.8%), 67 (36.2%), 55 (11.9%), 41 (15.4%). HRMS (EI) calculated for $C_{11}H_{15}NO$: 177.11536, found 177.11487.

1-(1*H*-pyrrol-2-yl)oct-7-en-1-one (3c, n = 3)—(551 mg, 2.88 mmol, 93%). Clear and colorless oil, R_f = (0.45, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.81 (br s, 1H), 7.09-7.06 (m, 1H), 6.97-6.94 (m, 1H), 6.28-6.26 (m, 1H), 5.87-5.78 (ddt, *J* = 17.0 Hz, *J′* = 10.3 Hz, *J″* = 6.7 Hz, 1H), 5.05-4.95 (m, 2H), 2.83-2.78 (t, *J* = 7.2 Hz, 2H), 2.11-2.04 (m, 2H), 1.80-1.75 (m, 2H), 1.48-1.39 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3, 138.6, 131.8, 125.2, 116.5, 114.2, 110.1, 37.7, 33.4, 28.7, 28.5, 25.1. MS (+EI) *m/z* 191 (M^+, 20.8%), 148 (2.2%), 136 (1.7%), 122 (18.5%), 109 (100%), 94 (77.5%), 80 (8.1%), 67 (19.6%), 55 (8.9%), 41 (10.1%). HRMS (EI) calculated for $C_{12}H_{17}NO$: 191.13101, found 191.13106.

2-(hex-5-enyl)-1*H*-pyrrole (4a, n = 1)[48]—Ketopyrrole **3a** (194 mg, 1.19 mmol) was dissolved in *iso*-propanol (6 mL) and heated to reflux. To this boiling solution was added a suspension of sodium borohydride (126 mg, 3.33 mmol) in *iso*-propanol (4 mL). The reaction refluxed overnight. Afterward, the crude material was condensed *in vacuo* and passed through a neutral alumina column (hexanes/ethyl acetate 10:1) to afford crude **4a** that was reacted immediately in the next step. *Note: extreme care must be used when handling these alkenyl pyrroles for they readily decompose, especially in the presence of an acid, and must be used immediately*. Clear and colorless liquid, fruity odour, R_f = (0.50, hexanes/ethyl acetate 6:1, alumina).

2-(hept-6-enyl)-1*H*-pyrrole (4b, n = 2)—Clear and colorless liquid, fruity odour, R_f = (0.60, hexanes/ethyl acetate 6:1, alumina).

2-(oct-7-enyl)-1H-pyrrole (4c, n = 3)—Clear and colorless liquid, fruity odour, R_f = (0.60, hexanes/ethyl acetate 6:1, alumina).

7-(hex-5-enyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2] diazaborinin-4-ium-5-uide (6a, n = 1)[44]—Crude **4a** and 3,5-dimethylpyrrole-2-carboxaldehyde (70.0 mg, 0.568 mmol) were dissolved in dry dichloromethane (8.5 mL) and cooled to 0 °C under nitrogen. A solution of phosphorus oxychloride (52.0 μl, 0.568 mmol) in dichloromethane (0.5 mL) was added via syringe and the resulting solution was kept on ice for 1 h. Afterward, the reaction was brought to room temperature and stirred overnight. This solution was then cooled back to 0 °C and boron trifluoride diethyl etherate (288 μl, 2.27 mmol) and DIPEA (396 μl, 2.27 mmol) were added. After warming back to room temperature and stirring for 6 h, the crude product was extracted in dichloromethane and condensed *in vacuo*. The residue was loaded onto a silica column (hexanes/diethyl ether 3:1) to afford pure **6a** (143 mg, 0.476 mmol, 40% over two steps). Dark red oil, R_f = (0.30, hexanes/diethyl ether 3:2). λ_{max} excitation in ethanol = 507 nm (ε_{507} = 87 000 M^{-1} cm^{-1}), λ_{max} emission in ethanol = 511 nm. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.89-6.87 (d, *J* = 3.9 Hz, 1H), 6.28-6.26 (d, *J* = 3.9 Hz, 1H), 6.07 (s, 1H), 5.89-5.76 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, 1H), 5.05-4.94 (m, 2H), 3.01-2.96 (t, *J* = 7.8 Hz, 2H), 2.55 (s, 3H), 2.21 (s, 3H), 2.16-2.09 (m, 2H), 1.81-1.70 (m, 2H), 1.58-1.48 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 160.5, 142.9, 138.7, 134.6, 133.3, 128.4, 123.4, 119.8, 118.9, 116.7, 114.5, 33.5, 28.7, 28.4, 28.0, 14.8, 11.2. ^{11}B NMR (193 MHz, $CDCl_3$) 1.11-0.77 (t, *J* = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, CDCl3) -145.2 – -145.5 (overlapping q and sextet, *J* = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 302 (M^+, 50.3%), 282 ([M-HF]$^+$, 3.5%), 248 (11.6%), 233 (100%), 213 (24.1%), 195 (7.5%), 149 (19.3%), 111 (12.9%), 97 (8.6%), 83 (9.6%), 71 (12.9%), 57 (22.7%), 43 (17.7%). HRMS (EI) calculated for $C_{17}H_{21}BF_2N_2$: 302.17659, found 302.17684.

7-(hept-6-enyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2] diazaborinin-4-ium-5-uide (6b, n = 2)—(313 mg, 0.988 mmol, 34% over two steps). Dark red oil, R_f = (0.45, hexanes/diethyl ether 3:2). λ_{max} excitation in ethanol = 507 nm (ε_{507} = 86 000 M^{-1} cm^{-1}), λ_{max} emission in ethanol = 511 nm. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.84-6.83 (d, *J* = 3.9 Hz, 1H), 6.25-6.23 (d, *J* = 3.9 Hz, 1H), 6.02 (s, 1H), 5.88-5.75 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, 1H), 5.05-4.92 (m, 2H), 3.00-2.95 (t, *J* = 7.8 Hz, 2H), 2.53 (s, 3H), 2.15 (s, 3H), 2.08-2.04 (m, 2H), 1.79-1.69 (m, 2H), 1.48-1.43 (m, 4H). ^{13}C NMR (75 MHz, CDCl3) δ 160.3, 158.6, 142.7, 138.7, 134.4, 133.2, 128.4, 123.3, 119.6, 116.5, 114.1, 33.5, 28.9, 28.5, 28.4, 28.3, 14.6, 10.9. ^{11}B NMR (96 MHz, $CDCl_3$) 1.29-0.60 (t, *J* = 32.7 Hz, $\underline{B}$F2). ^{19}F NMR (282 MHz, $CDCl_3$) -144.7 – -145.1 (overlapping q and sextet, *J* = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 316 (M^+, 49.0%), 277 (2.1%), 248 (61.2%), 233 (100%), 213 (23.0%), 194 (4.3%), 149 (3.9%), 116 (9.9%), 81 (4.2%), 69 (7.6%), 55 (7.5%), 43 (13.2%). HRMS (EI) calculated for $C_{18}H_{23}BF_2N_2$: 316.19224, found 316.19279.

7-(oct-7-enyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2] diazaborinin-4-ium-5-uide (6c, n = 3)—(370 mg, 1.12 mmol, 39% over two steps). Dark red oil, R_f = (0.50, hexanes/diethyl ether 3:2). λ_{max} excitation in ethanol = 507 nm (ε_{507} = 85 000 M^{-1} cm^{-1}), λ_{max} emission in ethanol = 511 nm. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.87-6.85 (d, *J* = 3.9 Hz, 1H), 6.26-6.25 (d, *J* = 3.9 Hz, 1H), 6.04 (s, 1H), 5.89-5.75 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, 1H), 5.02-4.92 (m, 2H), 3.00-2.95 (t, *J* = 7.8 Hz, 2H), 2.54 (s, 3H), 2.18 (s, 3H), 2.07-2.02 (m, 2H), 1.78-1.69 (m, 2H), 1.52-1.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 158.7, 142.7, 139.0, 134.5, 133.2, 128.4, 123.4, 119.7, 116.6, 114.1, 33.7, 29.3, 28.8, 28.7, 28.6, 28.5, 14.7, 11.0. ^{11}B NMR (96 MHz, $CDCl_3$) 1.29-0.60 (t, *J* = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -144.9 – -145.3 (overlapping q and sextet, *J* = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 330 (M^+, 10.2%), 248 (100%), 233 (40.5%), 218 (15.4%), 149 (10.6%), 116 (15.3%), 94 (10.9%), 83 (7.9%), 69 (14.3%), 57 (16.0%), 44 (40.8%). HRMS (EI) calculated for $C_{19}H_{25}BF_2N_2$: 330.20789, found 330.20818.

(*S*,*E*)-7-(6-(6-(*tert*-butyldimethylsilyloxy)-2,5,7,8-tetramethylchroman-2-yl) hex-5-enyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2] diazaborinin-4-ium-5-uide (8a, n = 1)[45]—Vinyl Trolox **7** (61.9 mg, 0.179 mmol) and hexenylBODIPY **6a** (108 mg, 0.357 mmol) were dissolved in dry dichloromethane (1.5 mL). Grubbs Catalyst 2nd Generation (15.2 mg, 0.018 mmol) was then added and the reaction refluxed for 6 h. The mixture was condensed *in vacuo* and the crude residue was loaded onto a silica column (hexanes/diethyl ether 6:1) to obtain **8a** (72.3 mg, 0.117 mmol, 65%). Dark red oil, R_f = (0.50, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.89-6.88 (d, *J* = 3.9 Hz, 1H), 6.21-6.19 (d, *J* = 3.9 Hz, 1H), 6.08 (s, 1H), 5.54-5.50 (m, 2H), 2.96-2.91 (t, *J* = 7.8 Hz, 2H), 2.56-2.50 (m, 5H), 2.24 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H), 2.07-2.00 (m, 1H), 1.94-1.71 (m, 3H), 1.68-1.60 (m, 2H), 1.46-1.40 (m, 2H), 1.38 (s, 3H), 1.07 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 158.9, 146.1, 144.1, 142.8, 134.6, 134.2, 133.3, 128.6, 128.5, 128.3, 125.7, 123.4, 122.2, 119.8, 117.7, 116.8, 74.8, 32.3, 31.9, 29.0, 28.4, 27.8, 27.3, 26.1, 21.2, 18.6, 14.8, 14.3, 13.4, 12.0, 11.2, -3.4. ^{11}B NMR (96 MHz, $CDCl_3$) 1.27-0.58 (t, *J* = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.0 – -145.5 (overlapping q and sextet, *J* = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 620 (M^+, 0.6%), 378 (1.3%), 346 (13.2%), 316 (26.8%), 278 (6.1%), 233 (100%), 213 (25.4%), 149 (25.3%), 129 (6.5%), 97 (11.0%), 83 (20.2%), 71 (32.7%), 57 (54.0%), 43 (78.6%). HRMS (EI) calculated for $C_{36}H_{51}BF_2N_2O_2Si$: 620.37810, found 620.37428.

(*S*,*E*)-7-(7-(6-(*tert*-butyldimethylsilyloxy)-2,5,7,8-tetramethylchroman-2-yl) hept-6-enyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2] diazaborinin-4-ium-5-uide (8b, n = 2)—(61.8 mg, 0.097 mmol, 53%). Dark red oil, R_f = (0.55, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.92-6.90 (d, *J* = 3.9 Hz, 1H), 6.29-6.28 (d, *J* = 3.9 Hz, 1H), 6.10 (s, 1H), 5.54-5.51 (m, 2H), 2.99-2.94 (t, *J* = 7.8 Hz, 2H), 2.58 (s, 3H), 2.56-2.49 (m, 2H), 2.26 (s, 3H), 2.16 (s, 3H), 2.14 (s, 3H), 2.00 (s, 3H), 1.96-1.54 (m, 6H), 1.51-1.39 (m, 4H), 1.39 (s, 3H), 1.07 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 158.9, 146.1, 144.1, 142.8, 134.6, 134.2, 133.3, 128.8, 128.6, 128.5, 125.7, 123.4, 122.2, 119.8, 117.7, 116.8, 74.7, 32.4, 32.0, 29.0, 28.8, 28.6, 28.4, 27.2, 26.1, 21.2, 18.6, 14.8, 14.3, 13.4, 12.0, 11.2, -3.4. ^{11}B NMR (96 MHz, $CDCl_3$) 1.30-0.61 (t, *J* = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -144.9 – -145.5 (overlapping q and sextet, *J* = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 634 (M^+, 0.1%), 422 (1.2%), 346 (20.7%), 278 (11.6%), 233 (100%), 213 (24.6%), 195 (3.8%), 149 (11.4%), 116 (2.6%), 73 (11.5%), 41 (7.9%). HRMS (EI) calculated for $C_{37}H_{53}BF_2N_2O_2Si$: 634.39375, found 634.39555.

(*S*,*E*)-7-(8-(6-(*tert*-butyldimethylsilyloxy)-2,5,7,8-tetramethylchroman-2-yl)oct-7-enyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2]diazaborinin-4-ium-5-uide (8c, n = 3)—(174 mg, 0.268 mmol, 48%). Dark red oil, R_f = (0.55, hexanes/

diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.90-6.89 (d, *J* = 3.9 Hz, 1H), 6.29-6.28 (d, *J* = 3.9 Hz, 1H), 6.08 (s, 1H), 5.53-5.50 (m, 2H), 3.00-2.95 (t, *J* = 7.8 Hz, 2H), 2.57-2.49 (m, 5H), 2.23 (s, 3H), 2.16 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H), 2.02-1.67 (m, 6H), 1.46-1.32 (m, 6H), 1.39 (s, 3H), 1.07 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 158.8, 146.1, 144.0, 142.7, 134.5, 133.9, 133.3, 128.8, 128.5, 128.4, 125.6, 123.4, 122.1, 119.7, 117.6, 116.7, 74.7, 32.3, 32.1, 29.1, 28.9, 28.7, 28.6, 28.5, 27.2, 26.1, 21.1, 18.5, 14.7, 14.3, 13.4, 12.0, 11.1, -3.4. ^{11}B NMR (96 MHz, $CDCl_3$) 1.31-0.62 (t, *J* = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.0 – -145.4 (overlapping q and sextet, *J* = 33.0 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 648 (M^+, 0.8%), 406 (11.8%), 344 (23.8%), 233 (100%), 213 (26.2%), 194 (3.8%), 117 (2.5%), 55 (4.0%), 41 (5.4%). HRMS (EI) calculated for $C_{38}H_{55}BF_2N_2O_2Si$: 648.40940, found 648.41062.

(*R*)-7-(6-(6-(*tert*-butyldimethylsilyloxy)-2,5,7,8-tetramethylchroman-2-yl) hexyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2]diazaborinin-4-ium-5-uide (9a, n = 1)[48]—A mixture of **8a** (93.6 mg, 0.151 mmol) and Wilkinson's catalyst (69.8 mg, 0.075 mmol) in absolute ethanol (25 mL) was shaken under an atmosphere of hydrogen gas (80 psi) for 52 h. Afterward, the crude product was condensed *in vacuo* and purified via column chromatography (hexanes/diethyl ether 6:1) to afford pure **9a** (32.6 mg, 0.052 mmol, 35%). Dark red oil, R_f = (0.50, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.91-6.89 (d, *J* = 3.9 Hz, 1H), 6.28-6.27 (d, *J* = 3.9 Hz, 1H), 6.08 (s, 1H), 3.00-2.94 (t, *J* = 7.8 Hz, 2H), 2.56-2.53 (m, 5H), 2.24 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.87-1.27 (m, 12H), 1.22 (s, 3H), 1.05 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 158.9, 145.9, 144.0, 142.8, 134.6, 133.3, 128.5, 125.8, 123.5, 123.1, 122.7, 119.8, 117.5, 116.7, 74.4, 39.6, 31.5, 29.9, 29.7, 28.7, 28.6, 26.1, 23.8, 23.5, 20.9, 18.6, 14.8, 14.3, 13.4, 11.9, 11.2, -3.4. ^{11}B NMR (96 MHz, $CDCl_3$) 1.29-0.60 (t, *J* = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.1 – -145.5 (overlapping q and sextet, *J* = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 622 (M^+, 2.6%), 433 (100%), 302 (2.8%), 233 (16.5%), 208 (7.7%), 168 (53.1%), 149 (26.8%), 69 (12.2%), 55 (18.4%), 43 (30.8%). HRMS (EI) calculated for $C_{36}H_{53}BF_2N_2O_2Si$: 622.39375, found 622.39439.

(*R*)-7-(7-(6-(*tert*-butyldimethylsilyloxy)-2,5,7,8-tetramethylchroman-2-yl) heptyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2] diazaborinin-4-ium-5-uide (9b, n = 2)—(27.3 mg, 0.043 mmol, 58%). Dark red oil, R_f = (0.55, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.90-6.89 (d, *J* = 3.9 Hz, 1H), 6.29-6.27 (d, *J* = 3.9 Hz, 1H), 6.08 (s, 1H), 2.99-2.94 (t, *J* = 7.8 Hz, 2H), 2.56-2.53 (m, 5H), 2.24 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.83-1.68 (m, 4H), 1.46-1.42 (m, 4H), 1.41-1.27 (m, 6H), 1.22 (s, 3H), 1.05 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.0, 158.9, 145.9, 144.0, 142.8, 134.6, 133.3, 128.5, 125.6, 123.5, 123.4, 122.7, 119.9, 117.5, 116.9, 74.5, 39.6, 31.5, 30.0, 29.7, 29.5, 28.7, 28.6, 26.1, 23.8, 23.5, 20.9, 18.6, 14.7, 14.2, 13.4, 12.0, 11.3, -3.3. ^{11}B NMR (96 MHz, $CDCl_3$) 1.29-0.60 (t, *J* = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.1 – -145.6 (overlapping q and sextet, *J* = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 636 (M^+, 1.1%), 394 (46.0%), 380 (31.0%), 318 (5.4%), 248 (13.0%), 233 (100%), 213 (38.3%), 149 (6.1%), 115 (2.4%), 91 (14.8%), 57 (4.5%), 43 (14.5%). HRMS (EI) calculated for $C_{37}H_{55}BF_2N_2O_2Si$: 636.40940, found 636.40915.

(*R*)-7-(8-(6-(*tert*-butyldimethylsilyloxy)-2,5,7,8-tetramethylchroman-2-yl) octyl)-5,5-difluoro-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2]diazaborinin-4-ium-5-uide (9c, n = 3)—(122.8 mg, 0.189 mmol, 70%). Dark red oil, R_f = (0.55, hexanes/diethyl ether 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.91-6.89 (d, *J* = 3.9 Hz, 1H), 6.30-6.29 (d, *J* = 3.9 Hz, 1H), 6.08 (s, 1H), 3.02-2.97 (t, *J* = 7.8 Hz, 2H), 2.58-2.55 (m, 5H), 2.24 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 1.89-1.30 (m, 16H), 1.22 (s, 3H), 1.05 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 158.8, 145.9, 144.0, 142.7, 134.5,

133.3, 128.5, 125.7, 123.5, 123.4, 122.6, 119.8, 117.4, 116.8, 74.4, 39.6, 31.5, 29.6, 29.5, 29.4, 29.3, 28.7, 28.6, 26.1, 23.7, 23.6, 20.9, 18.6, 14.8, 14.3, 13.4, 11.9, 11.2, -3.4. ^{11}B NMR (96 MHz, $CDCl_3$) 1.32-0.63 (t, J = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.0 – -145.4 (overlapping q and sextet, J = 33.0 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 650 (M^+, 4.1%), 360 (14.2%), 346 (42.9%), 332 (26.2%), 233 (100%), 213 (21.7%), 195 (6.3%), 149 (3.5%), 55 (2.1%), 43 (4.2%). HRMS (EI) calculated for $C_{38}H_{57}BF_2N_2O_2Si$: 650.42505, found 650.42546.

(*R*)-5,5-difluoro-7-(6-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)hexyl)-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2]diazaborinin-4-ium-5-uide (10a, n = 1) [59]**—9a** (30.0 mg, 0.048 mmol) was dissolved in tetrahydrofuran (1.2 mL) and a 10% solution of hydrochloric acid in methanol (1.2 mL) was added dropwise. The reaction stirred for 4.5 h and then was extracted in dichloromethane. After condensation, the crude residue was loaded onto a column (hexanes/diethyl ether 3:1) to afford final compound **10a** (18.8 mg, 0.039 mmol, 77%). Dark red oil, R_f = (0.25, hexanes/diethyl ether 3:2), R_t = (25.8 min, acetonitrile, 1.00 mL/min, pHPLC). λ_{max} excitation in ethanol = 507 nm (ε_{507} = 81 000 M^{-1} cm^{-1}), λ_{max} emission in ethanol = 511 nm. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.93-6.92 (d, J = 3.9 Hz, 1H), 6.30-6.29 (d, J = 3.9 Hz, 1H), 6.11 (s, 1H), 2.99-2.96 (t, J = 7.8 Hz, 2H), 2.63-2.61 (t, J = 7.2 Hz, 2H), 2.58 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H), 2.13 (s, 6H), 1.84-1.71 (m, 4H), 1.63-1.50 (m, 2H), 1.47-1.41 (m, 4H), 1.39-1.35 (m, 2H), 1.22 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.9, 159.0, 145.5, 144.5, 142.8, 134.6, 133.3, 128.5, 123.5, 122.6, 121.0, 119.9, 118.5, 117.4, 116.8, 74.5, 39.4, 31.5, 29.9, 29.6, 28.7, 28.6, 23.8, 23.5, 20.8, 14.9, 12.2, 11.8, 11.3. ^{11}B NMR (96 MHz, $CDCl_3$) 1.28-0.60 (t, J = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.1 – -145.5 (overlapping q and sextet, J = 33.3 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 508 (M^+, 2.4%), 488 ([M-HF]$^+$, 44.4%), 368 (2.8%), 325 (16.8%), 277 (3.9%), 227 (6.9%), 213 (14.2%), 149 (10.4%), 129 (19.1%), 112 (10.7%), 83 (15.2%), 71 (16.2%), 57 (30.4%), 43 (100%). HRMS (EI) calculated for $C_{30}H_{38}BFN_2O_2$: 488.30104, found 488.30050.

(*R*)-5,5-difluoro-7-(7-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)heptyl)-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2]diazaborinin-4-ium-5-uide (10b, n = 2)—(14.8 mg, 0.029 mmol, 66%). Dark red oil, R_f = (0.10, hexanes/diethyl ether 3:1), R_t = (29.1 min, acetonitrile, 1.00 mL/min, pHPLC). λ_{max} excitation in ethanol = 507 nm (ε_{507} = 85 000 M^{-1} cm^{-1}), λ_{max} emission in ethanol = 511 nm. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.93-6.92 (d, J = 3.9 Hz, 1H), 6.30-6.29 (d, J = 3.9 Hz, 1H), 6.11 (s, 1H), 2.99-2.98 (t, J = 7.8 Hz, 2H), 2.63-2.61 (t, J = 7.2 Hz, 2H), 2.58 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H), 2.13 (s, 6H), 1.82-1.72 (m, 4H), 1.62-1.53 (m, 2H), 1.45-1.28 (m, 8H), 1.22 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.0, 159.0, 145.5, 144.5, 142.8, 134.6, 133.3, 128.5, 123.5, 122.6, 121.0, 119.9, 118.5, 117.4, 116.8, 74.5, 39.5, 31.5, 30.0, 29.5, 29.4, 28.7, 28.6, 23.8, 23.6, 20.8, 14.9, 12.2, 11.8, 11.3. ^{11}B NMR (96 MHz, $CDCl_3$) 1.29-0.60 (t, J = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.1 – -145.5 (overlapping q and sextet, J = 33.0 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 522 (M^+, 12.1%), 502 ([M-HF]$^+$, 100%), 368 (4.8%), 302 (26.1%), 227 (14.1%), 213 (25.1%), 205 (12.5%), 165 (12.8%), 149 (22.8%), 129 (32.7%), 112 (19.5%), 86 (31.3%), 73 (49.7%), 57 (53.5%), 45 (26.1%). HRMS (EI) calculated for $C_{31}H_{40}BFN_2O_2$: 502.31669, found 502.31872.

(*R*)-5,5-difluoro-7-(8-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)octyl)-1,3-dimethyl-5*H*-dipyrrolo[1,2-c:1′,2′-f][1,3,2]diazaborinin-4-ium-5-uide (10c, n = 3)—(17.0 mg, 0.033 mmol, 74%). Dark red oil, R_f = 0.25 (hexanes/diethyl ether 3:2), R_t = (33.4 min, acetonitrile, 1.00 mL/min, pHPLC). λ_{max} excitation in ethanol = 507 nm (ε_{507} = 83 000 M^{-1} cm^{-1}), λ_{max} emission in ethanol = 511 nm. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.93-6.92 (d, J = 3.9 Hz, 1H), 6.31-6.30 (d, J = 3.9 Hz, 1H), 6.11 (s, 1H), 2.99-2.97 (t, J = 7.8 Hz, 2H), 2.63-2.61 (t, J = 7.2 Hz, 2H), 2.58 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H), 2.13 (s, 6H), 1.84-1.71 (m, 4H), 1.62-1.54 (m, 2H), 1.44-1.41 (m, 4H), 1.35-1.28 (m, 6H), 1.23 (s,

3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.0, 159.0, 145.5, 144.5, 142.8, 134.6, 133.3, 128.5, 123.5, 122.6, 121.0, 119.9, 118.5, 117.4, 116.9, 74.5, 39.5, 31.5, 30.1, 29.6, 29.5, 29.4, 28.7, 28.6, 23.8, 23.6, 20.8, 14.9, 12.2, 11.8, 11.3. ^{11}B NMR (96 MHz, $CDCl_3$) 1.29-0.60 (t, J = 32.7 Hz, $\underline{B}F_2$). ^{19}F NMR (282 MHz, $CDCl_3$) -145.2 – -145.5 (overlapping q and sextet, J = 33.0 Hz, $B\underline{F}_2$). MS (+EI) *m/z* 536 (M^+, 1.4%), 516 ($[M\text{-}HF]^+$, 36.8%), 408 (3.1%), 353 (10.1%), 298 (33.3%), 278 (3.6%), 233 (17.6%), 213 (18.4%), 191 (3.8%), 171 (100%), 129 (14.1%), 97 (17.0%), 69 (22.3%), 55 (33.3%), 43 (47.1%). HRMS (EI) calculated for $C_{32}H_{42}BFN_2O_2$: 516.33234, found 516.33308.

Bis-BODIPY mixture (11)—(21.0 mg, 0.037 mmol, 17% based on starting material 6a). Copper red oil, R_f = 0.20 (hexanes/diethyl ether 3:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (s, 2H), 6.91 (d, J=4.0 Hz, 2H), 6.30 (d, J=3.6 Hz, 2H), 5.43-5.52 (m, 2H), 2.99 (t, J=7.6 Hz, 4H), 2.57 (s, 6H), 2.26 (s, 6H), 2.19 (m, 4H), 2.06-2.14 (m, 4H), 1.72-1.82 (m, 4H), 1.51-1.60 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.9, 158.9, 142.7, 134.6, 133.3, 130.7, 130.3, 129.9, 129.8, 128.5, 123.4, 119.8, 116.9, 32.5, 32.4, 31.0, 29.6, 29.43, 29.39, 28.6, 28.5, 28.3, 28.09, 28.06, 27.1, 14.9, 11.3. MS (+EI) *m/z* 548 (4.0%), 562 (5.6%), and 576 (5.2%) corresponding to chain lengths of 9-11 carbons in the linking alkyl chain. HRMS (EI) calculated for $C_{30}H_{34}B_2F_4N_4$: 548.2906, found 548.2911; calculated for $C_{31}H_{36}B_2F_4N_4$: 562.3062, found 562.3063; calculated for $C_{32}H_{38}B_2F_4N_4$: 576.3219, found 576.3212.

Supplementary Material

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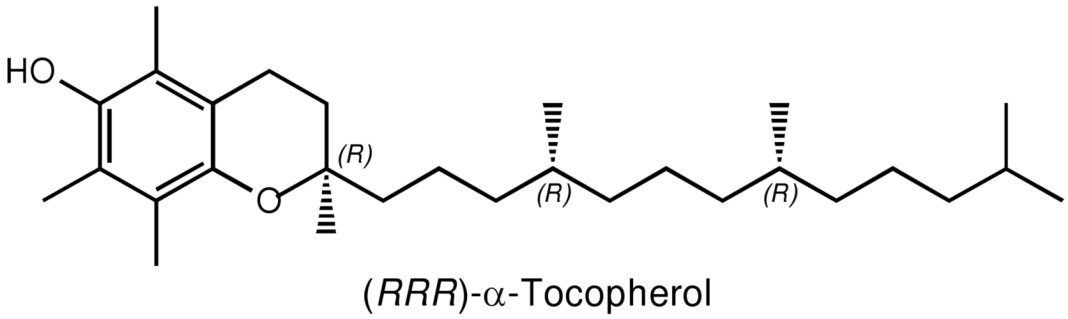


Figure 1.
Structure of naturally occurring α-tocopherol.

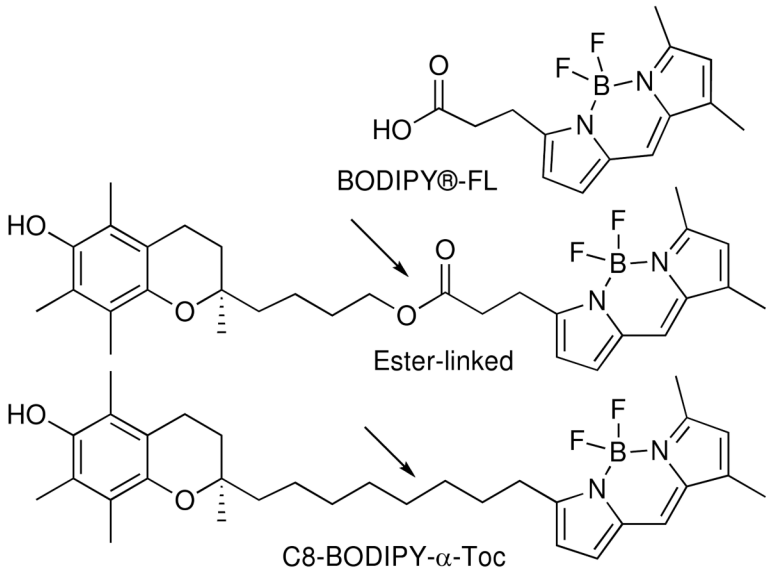


Figure 2.
Structures of the commercially available BODIPY®-FL, a hypothetical ester-linked BODIPY tocopherol, and an *n*-alkyl-linked BODIPY-α-tocopherol prepared in this work.

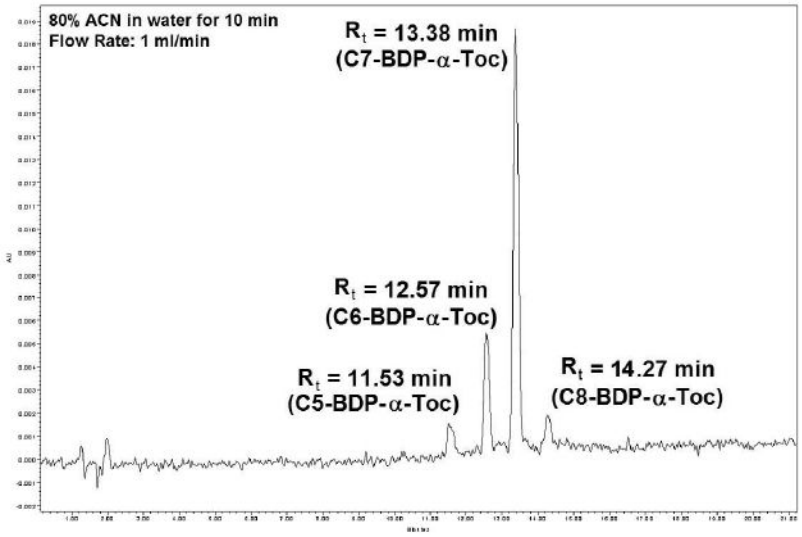


Figure 3.

HPLC chromatogram of the BODIPY-α-tocopherols produced from a metathesis reaction of C7-alkenyl-BODIPY **6b** with vinyl chromanol **7** using Hoveyda-Grubbs second generation catalyst.

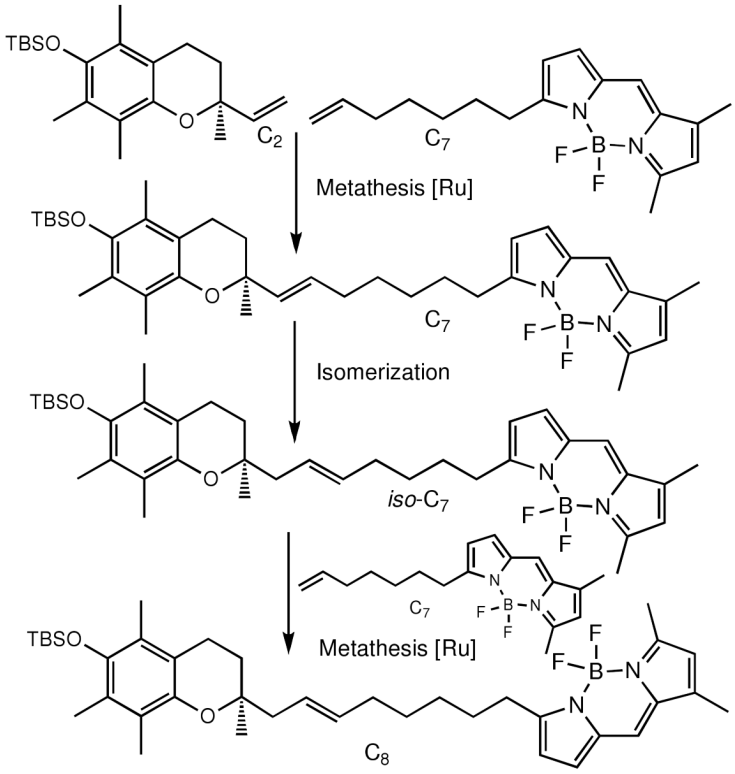


Figure 4.
Proposed pathway for the isomerization and production of a C_8-linker from a C_7-alkenyl BODIPY following metathesis with a vinyl chromanol.

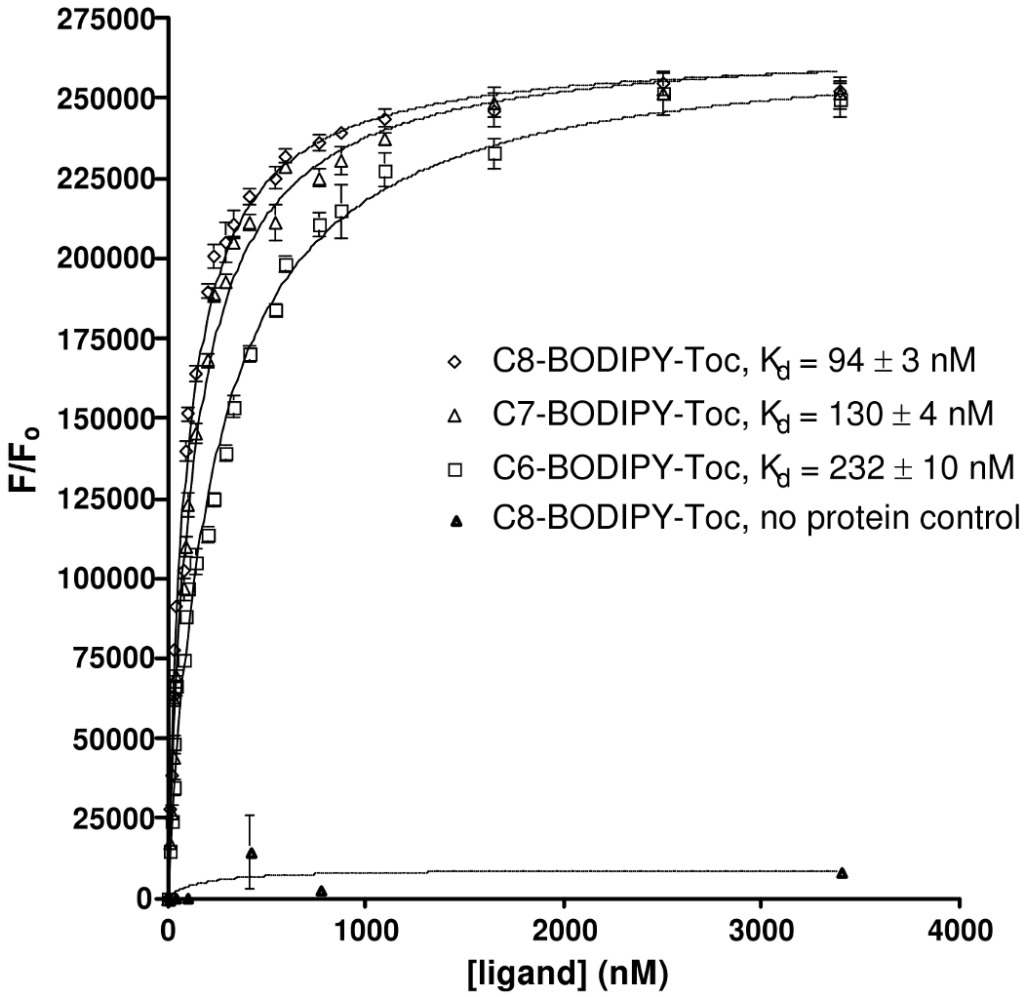


Figure 5.

Titration curves showing the increase in fluorescence intensity at 514 nm (λ_{ex} = 506 nm) following sequential additions of C6-, C7-, and C8-BODIPY-α-Toc, **10a-c**, to a 0.2 μM solution of α-TTP in SET buffer. The resulting saturation curves were fitted to a one-site binding model. Averages of triplicate data sets are graphed with the associated standard errors.

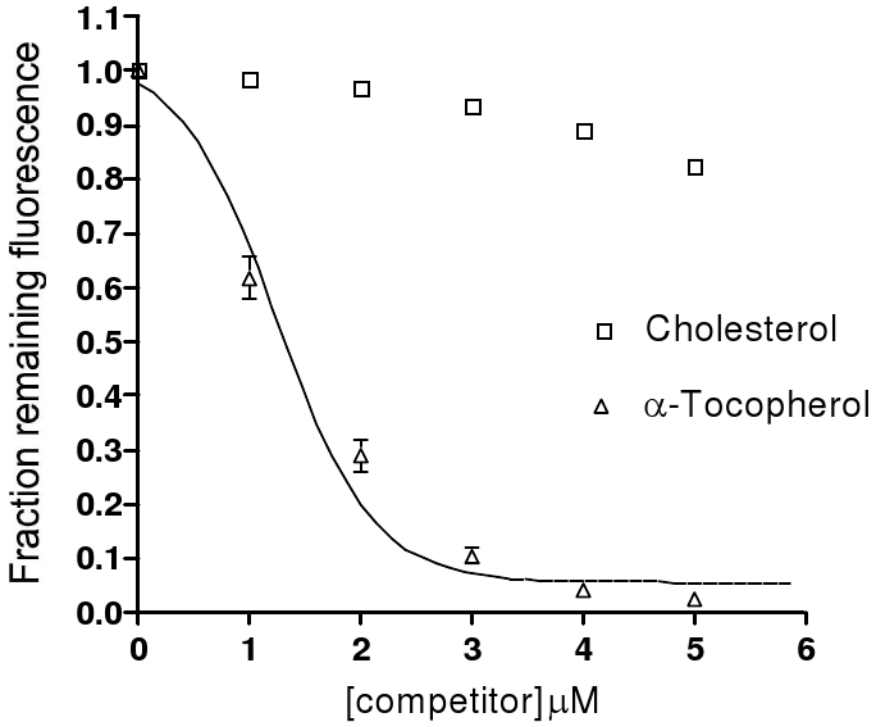
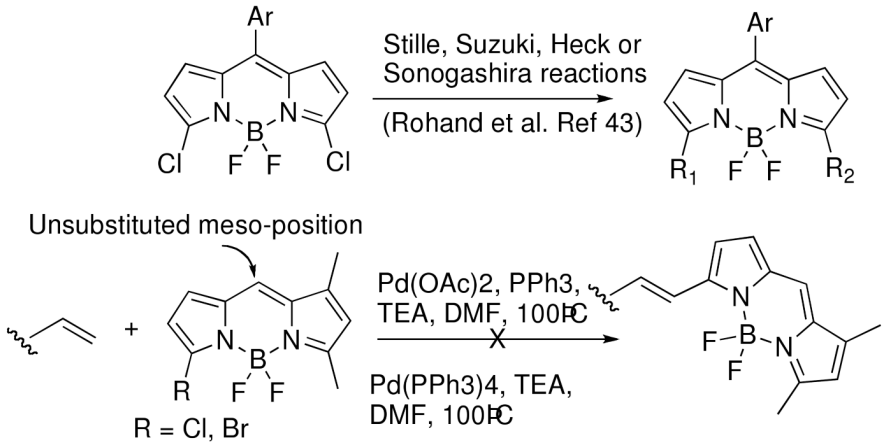
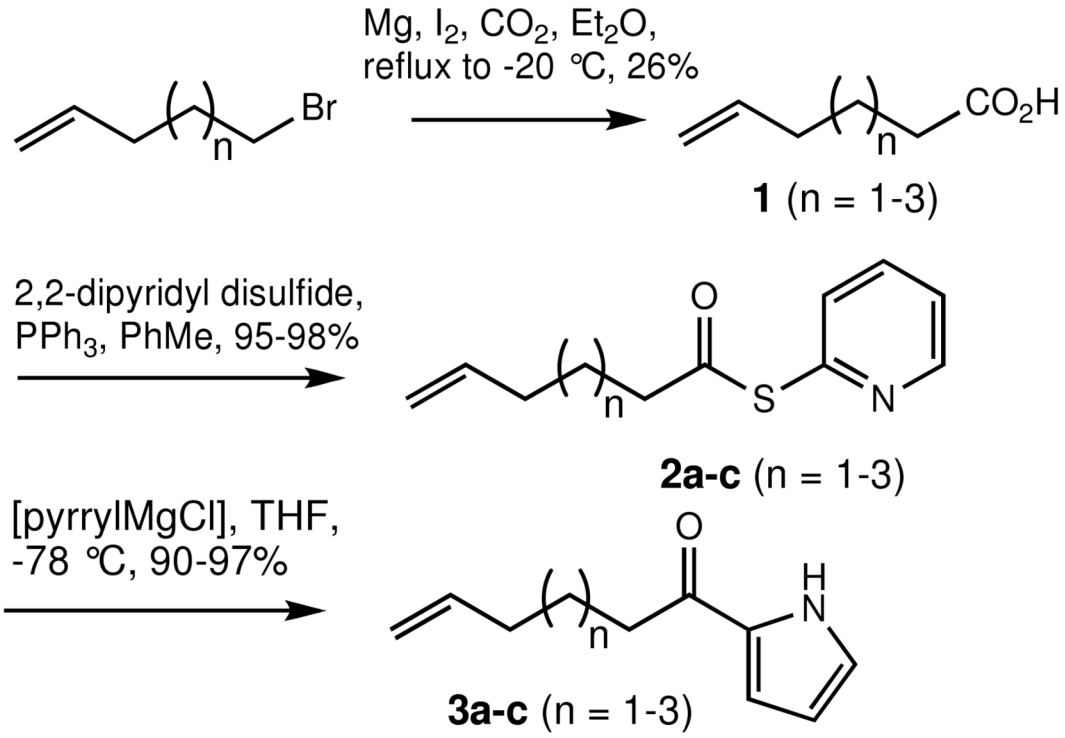


Figure 6.

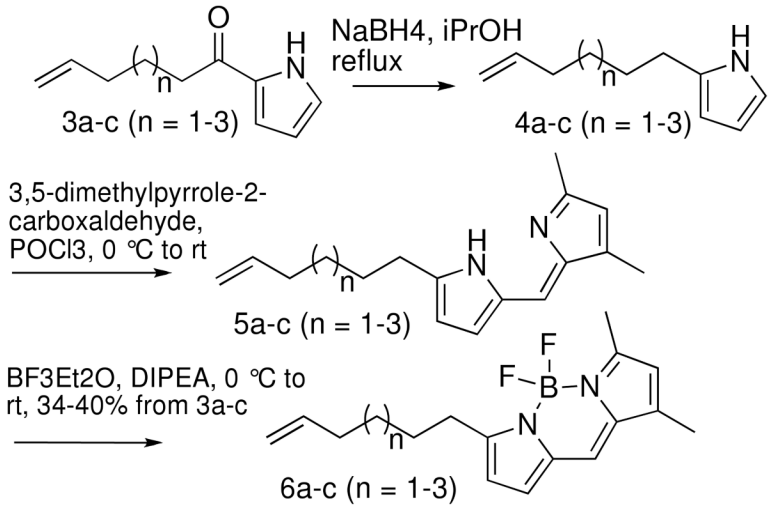
Competitive displacement of 1.0 μM C8-BODIPY-α-Toc, **10c**, bound to 0.2 μM α-TTP in SET buffer by addition of increasing amounts of (*RRR*)-α-tocopherol (△) or cholesterol (• • • • • • • • • • • •). Fluorescence was monitored at 514 nm after excitation at 506 nm. The average of triplicate data sets are reported for tocopherol and standard errors. Data for α-tocopherol was fit to a one-site competition model using GraphPad Prism.



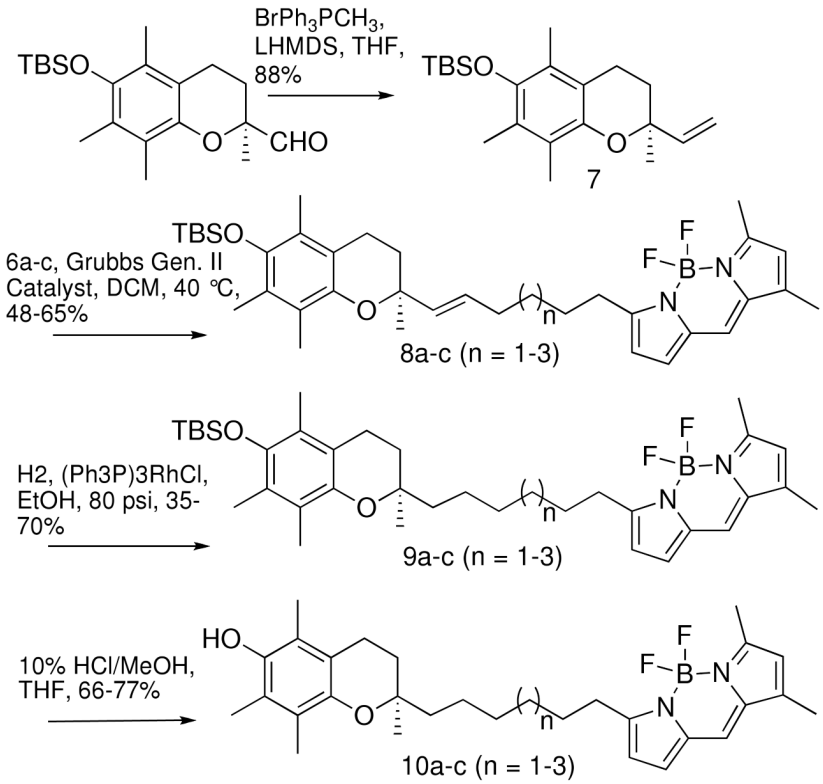
Scheme 1.
Successful[43] and unsuccessful coupling reactions for halogenated BODIPY frameworks.



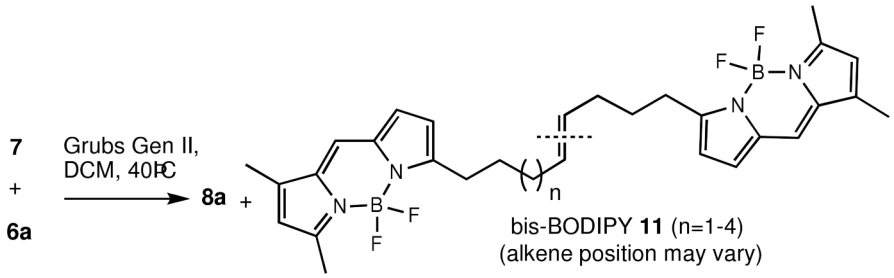
Scheme 2.
Preparation of terminal alkenyl 1-ketopyrroles.



Scheme 3.
Preparation of alkenyl BODIPYs.



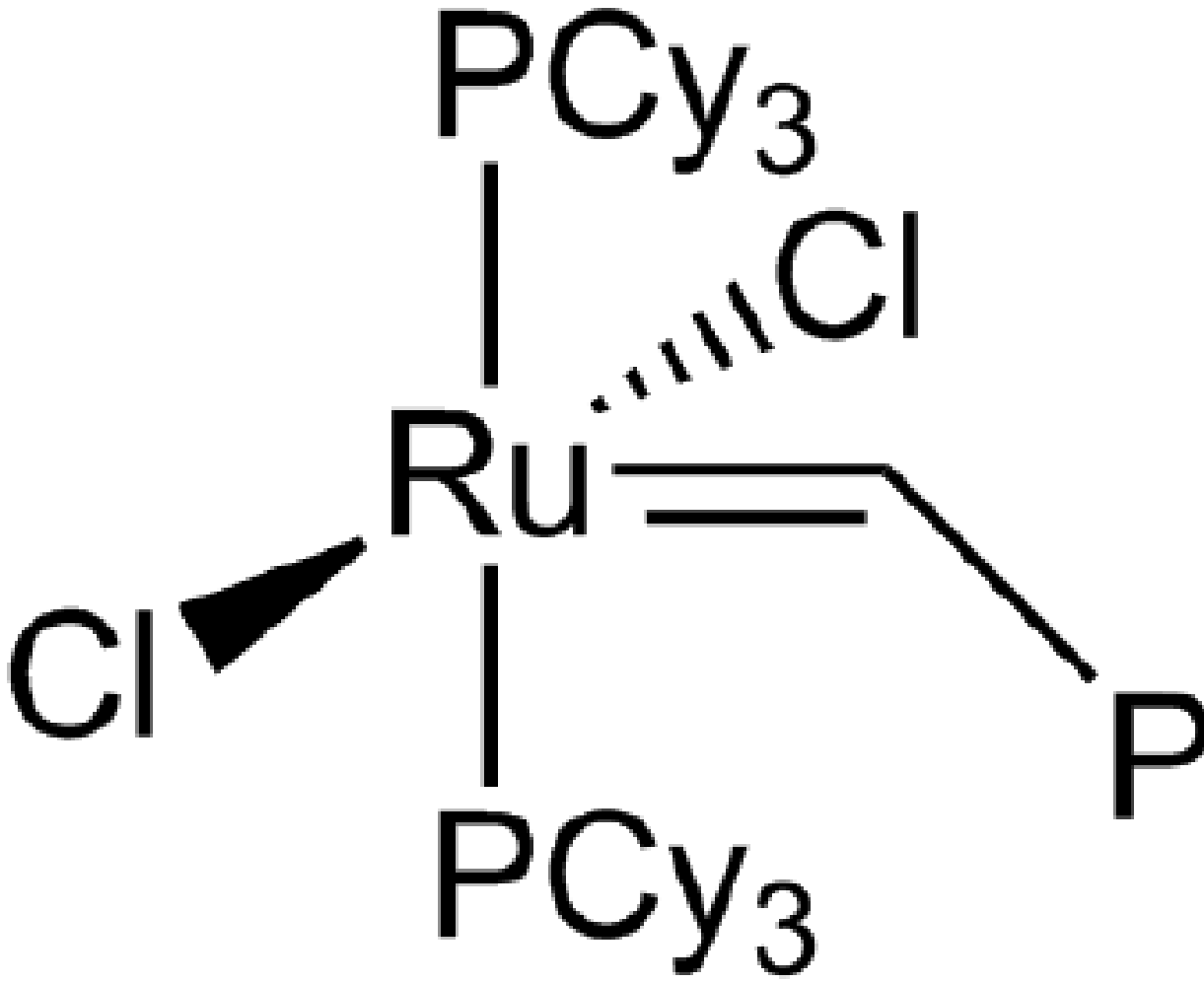
Scheme 4.
Preparation of BODIPY-α-tocopherols of varying linker chain length via cross coupling olefin metathesis

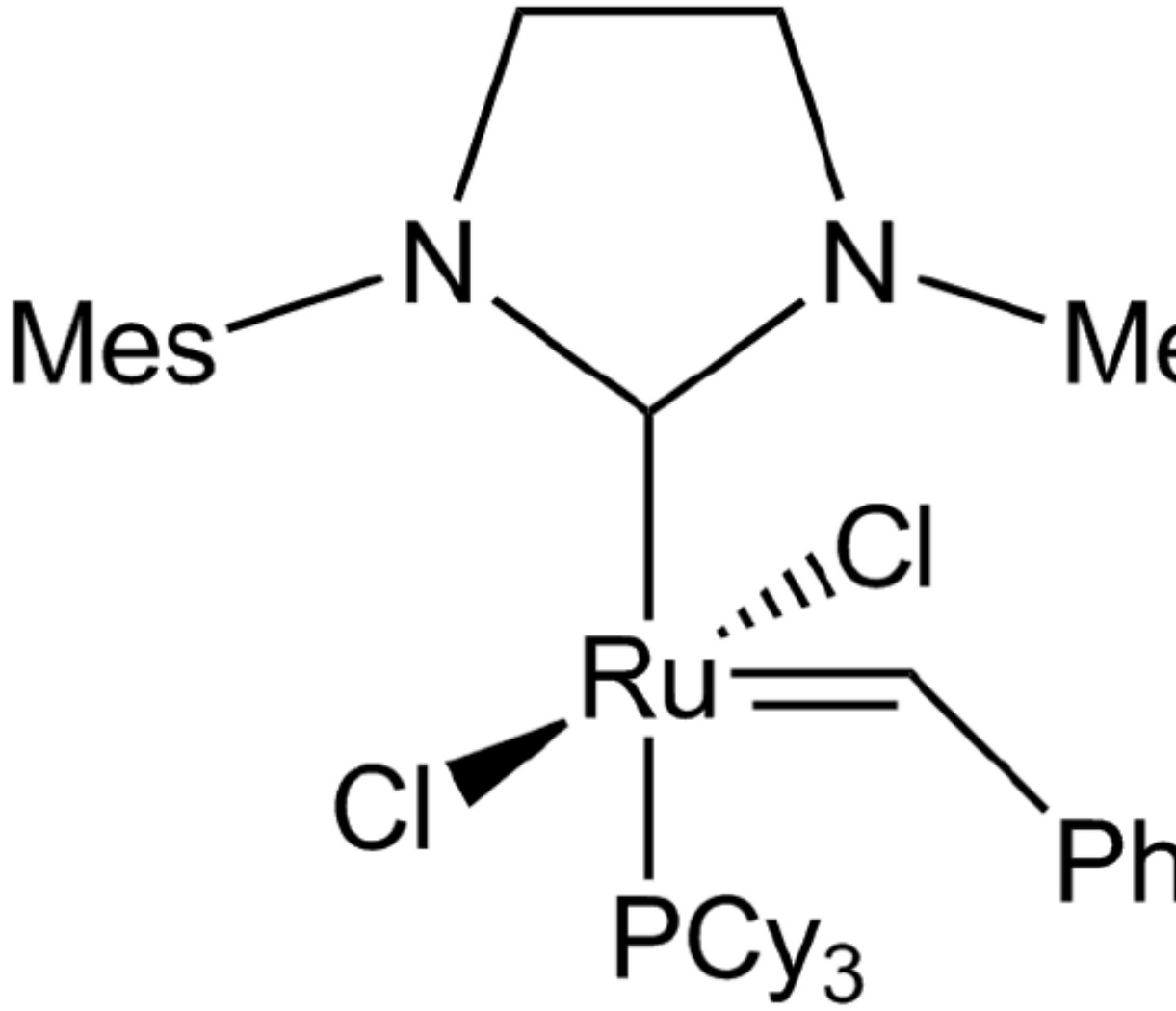
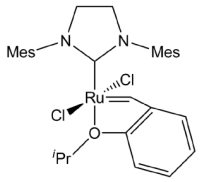


Scheme 5.

Generation of a cross-coupled bis-BODIPY during attempted coupling of vinyl Trolox **7** and alkenyl BODIPY **6a**.

Table 1
Summary of metathesis reactions with various ruthenium catalysts

Catalyst
Grubbs I 

Catalyst	
Grubbs II	
Hoveyda-Grubbs II	

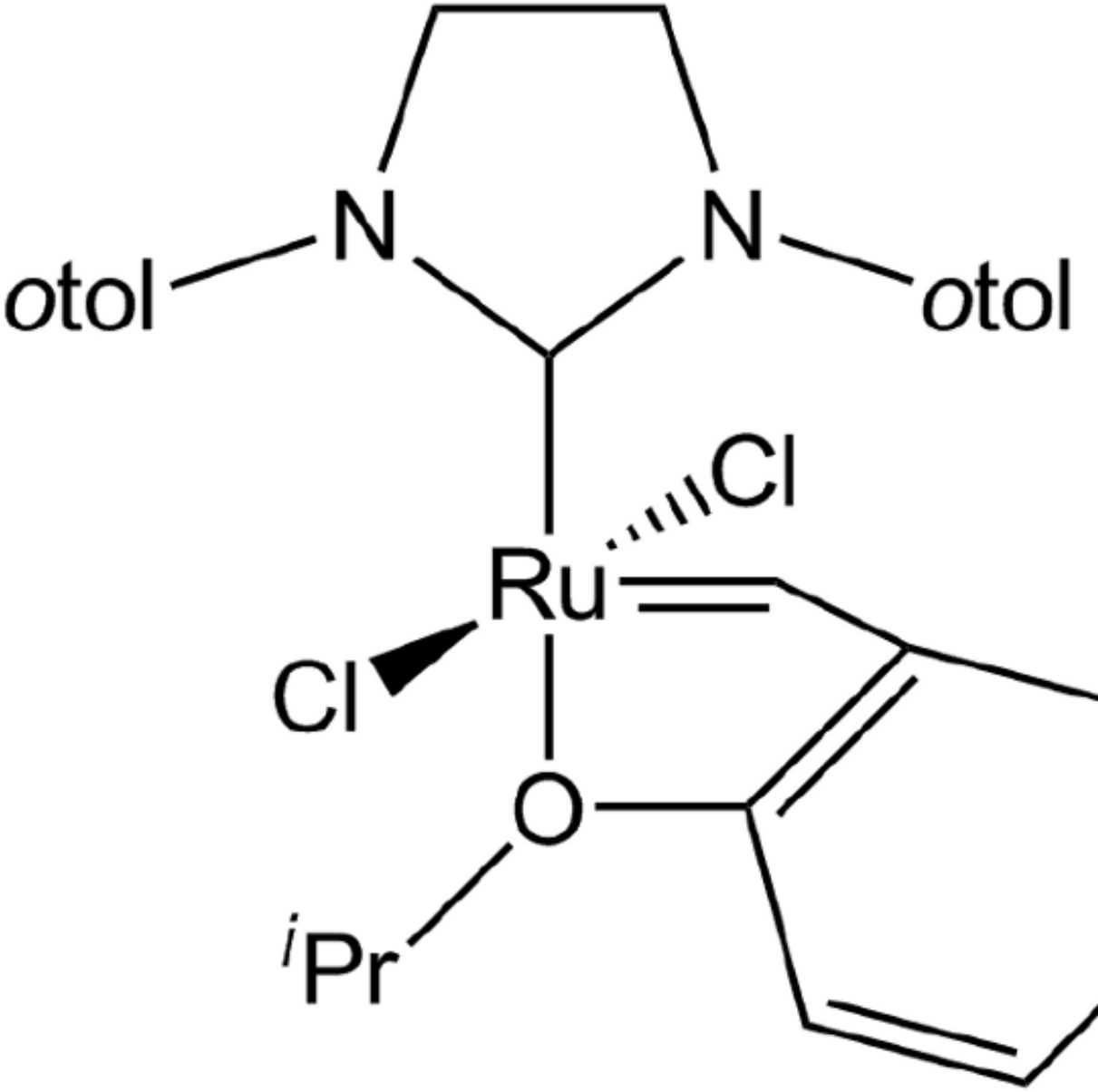
Catalyst
 Hoveyda-Grubbs II (*o*-tolyl derivative)

Table 2
Dissociation constants for NBD-α-Tocs and BODIPY-α-Tocs

NBD-α-Toc	K_d (nM)	BDP-α-Toc	K_d (nM)
C6	299 ± 37	C6	232 ± 10
C7	106 ± 21	C7	130 ± 4
C8	142 ± 35	C8	94 ± 3
C9	56 ± 15		