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THE SYNTHESIS OF AN AMINOHEXYL-CONTAINING ANALOG OF THE CHROMANOL LEUKOTRIENE B_4 RECEPTOR ANTAGONIST CP-195543: A SCAFFOLD FOR THE PREPARATION OF DERIVATIZED ANALOGS

Brian P. Jones,† Klaas Schildknegt, Kathyrn F. Wright, Henry J. Showell, James P. Dittami,† Keith E. McCarthy, and Lawrence A. Reiter*

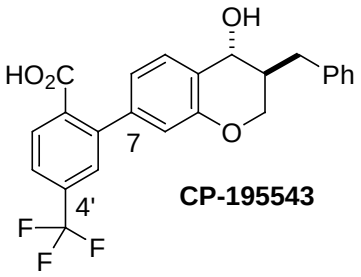
Pfizer Inc, Central Research Division, Eastern Point Rd., Groton, CT 06340 and †Worcester Polytechnic Institute, Department of Chemistry and Biochemistry, 100 Institute Rd., Worcester, MA 01609, U.S.A.
e-mail: lawrence_a_reiter@groton.pfizer.com

Abstract — In order to allow the preparation of labeled derivatives of the leukotriene B_4 (LTB_4) antagonist CP-195543 for the study and/or "visualization" of LTB_4 receptors in *in vitro* and *in vivo* settings, we have synthesized an aminohexyl-containing analog (**2**) as a scaffold from which the requisite compounds can be prepared. The key reactions in the preparation of **2** include the DAST-mediated introduction of a difluoromethylene group in the presence of an azide and a Suzuki coupling between this highly functionalized benzoate and a chromanol-derived boronic acid. 2-(3*S*,4*R*)-(3-Benzyl-4-hydroxychroman-7-yl)-4-(1,1-difluoro-7-methanesulfonamidoheptyl)benzoic acid (**12**), prepared from **2** by methanesulfonylation and saponification, is a potent LTB_4 receptor antagonist but displays a high degree of non-specific binding.

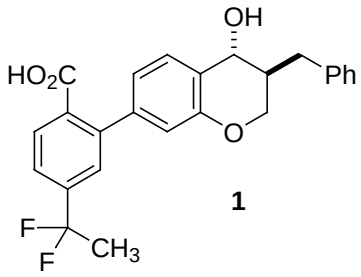
The chromanol LTB_4 receptor antagonist CP-195543 is being studied in humans for its ability to attenuate LTB_4 mediated inflammation in a variety of disease states.[1] This compound has more potent activity against the high affinity receptor than against the low affinity receptor (Kd's ~0.5 nM vs. ~5.0 nM), binding to the former non-competitively and to the latter competitively.[1] In order to study these differences, as well as to investigate the localization of LTB_4 receptors in neutrophils and eosinophils and the interaction of chromanol-based antagonists with LTB_4 receptors on other cell types, we sought analogs of CP-195543 which would facilitate such studies. Since each avenue of exploration would likely

require a different tool, the strategy we elected was to identify a single key intermediate which when derivatized, for example, through radiolabeling or conjugation with biotin, would provide compounds with the requisite properties.

Since none of the available CP-195543 analogs contained functionality which could be derivatized without expecting a severe reduction in potency, we needed to develop a new analog specifically for the present purpose. Earlier work established that the most potent compounds in the CP-195543 series contain an electron withdrawing group at C-4´.[2] We have also observed that a long chain substituent at C-4´ is not incompatible with LTB_4 antagonist activity.[3] We therefore sought to synthesize **1** and **2**, the former as a probe to examine the effect on potency of changing the 4´-trifluoromethyl group to a 1,1-difluoroalkyl group and the latter as the key intermediate which could be functionalized to provide, after saponification, the desired tools.



CP-195543



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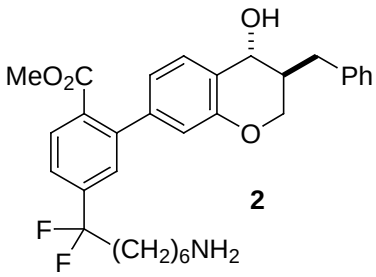


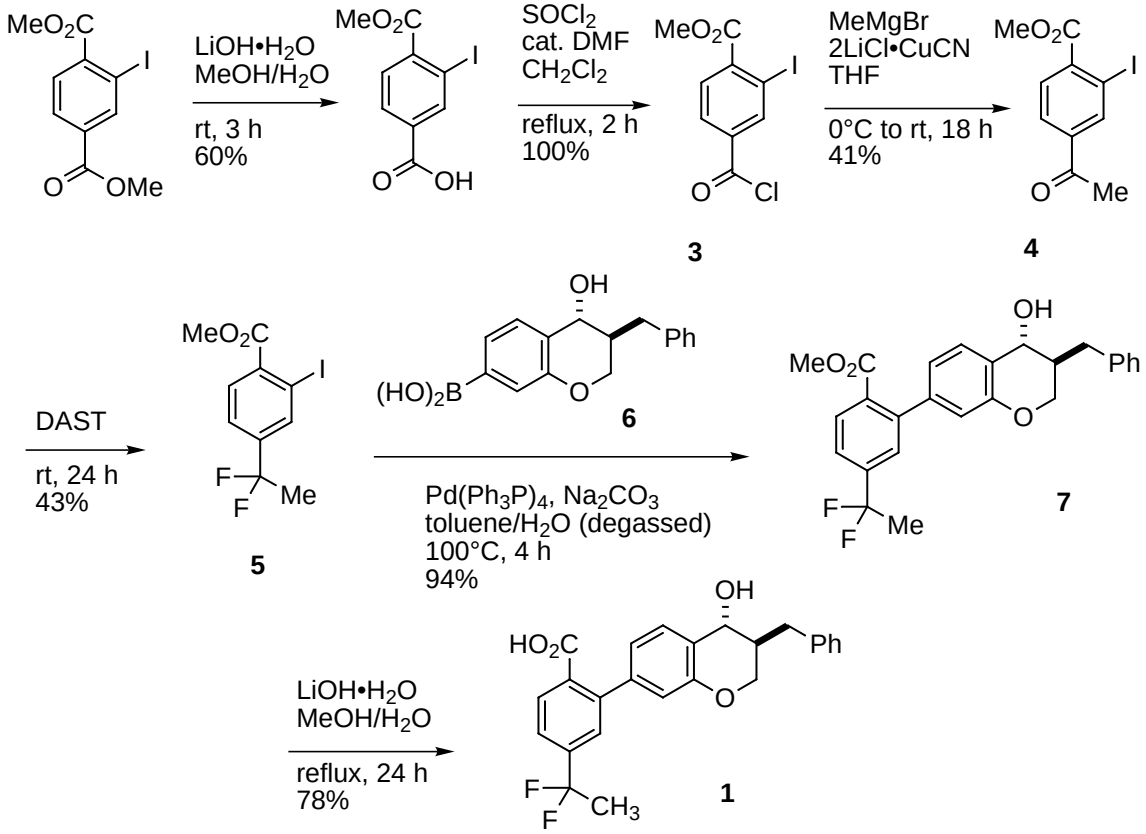
2

Selective functionalization of the primary amino group of **2** in the presence of the unprotected secondary alcohol was not expected to be a problem. Therefore, the challenges inherent to our goal were to incorporate a difluoromethylene moiety without affecting the chromanol and to install an amino group, or a precursor thereto, at a suitable point. Since the chromanol was unlikely to survive a DAST-mediated conversion of a carbonyl group into a difluoromethylene unit, we chose to incorporate the latter on the C-7 aryl ring prior to coupling to the chromanol nucleus.

The synthesis of **1** is outlined in Scheme 1. The ester function at C-4 of dimethyl 2-iodoterephthalate was selectively saponified[4] and the mono-acid converted to the acid chloride (**3**) under standard conditions. This was reacted with methylmagnesium bromide in the presence of a copper catalyst to give the desired ketone (**4**). The 1,1-difluoroethyl group was introduced by treating **4** with neat DAST. The boronic acid (**6**) was prepared from the corresponding bromochromanol by sequential treatment with methyllithium, *n*-butyllithium, and then borane. An aqueous quench of the resulting borohydride gave the boronic acid.[5] Coupling of the iodide (**5**) to **6** under standard Suzuki conditions gave a good yield of the biaryl derivative (**7**). Saponification of **7** yielded **1**. Evaluation of **1** in a ^{3}H- LTB_4 binding assay with human neutrophils[1] revealed the compound to have an IC_{50} of 5.5 nM, essentially equipotent to CP-195543 (see

Table 1). Furthermore, the functional activities of **1** and CP-195543 in human neutrophil chemotaxis and CD11b up-regulation assays[1] were essentially equivalent which encouraged us to proceed with the synthesis of **2**.

Scheme 1. Synthesis of **1**

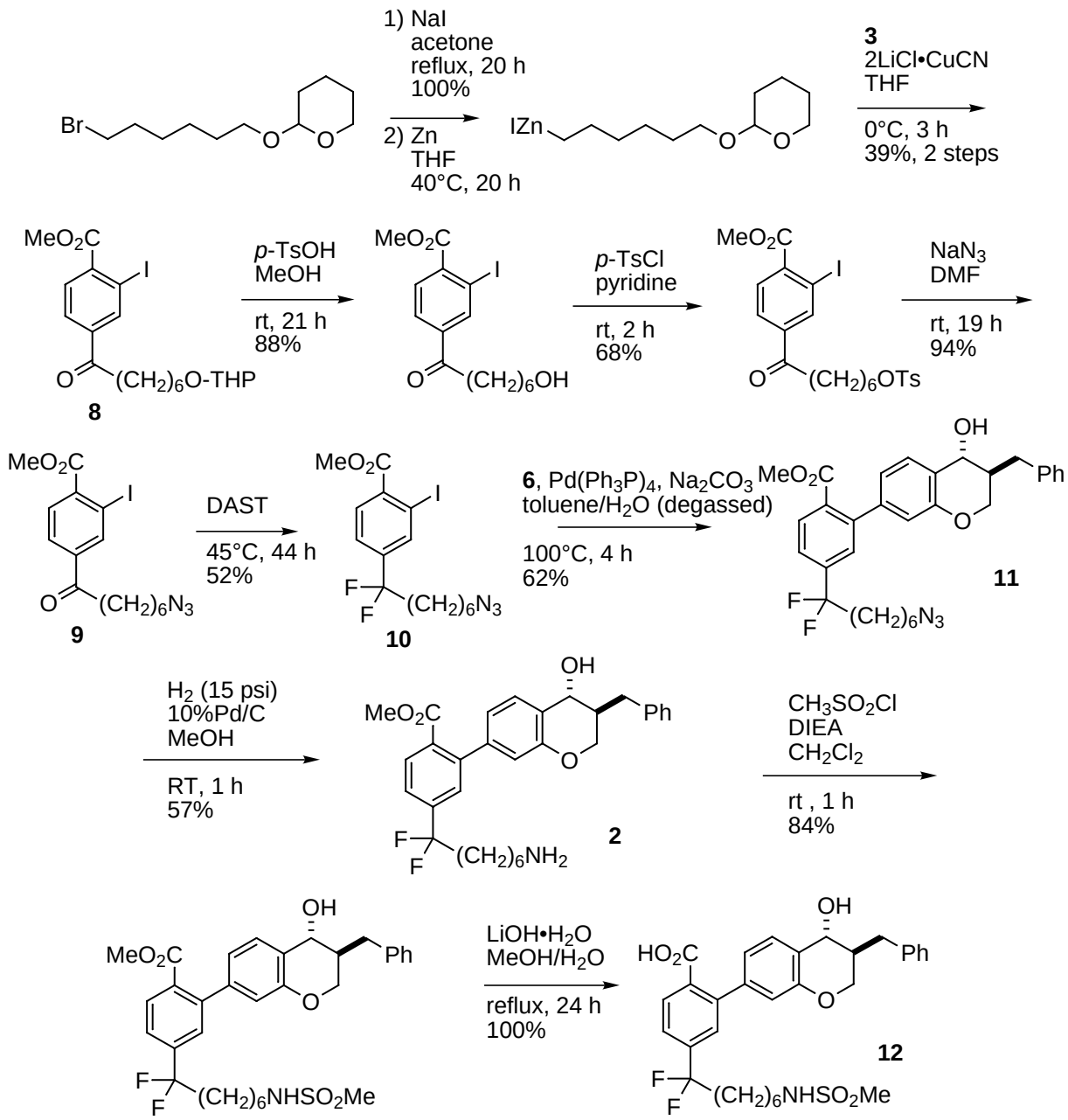


Of the various approaches taken to the synthesis of **2**, the order of key reactions that proved successful included introduction of an azido group on the alkyl side chain after formation of the aryl ketone, but before the DAST reaction,[6] and subsequent reduction of the azide after formation of the biaryl system (Scheme 2). Thus, the commercially available THP ether of 6-bromohexan-1-ol was converted to the iodide and the corresponding organozinc iodide prepared using Knochel' s procedure.[7] Conversion of this to the cuprate and coupling to the acid chloride (**3**) gave the ketone (**8**).[7] Removal of the THP ether, tosylation, and displacement of the tosylate with sodium azide gave ω-azido ketone (**9**). Treatment of this with DAST yielded the desired difluoro derivative (**10**). The biaryl system was again formed by a Suzuki coupling; thus, **10** and **6** yielded **11**. Hydrogenation gave **2**, the key intermediate.

In order to demonstrate that the aminohexyl side chain was compatible with LTB_4 antagonist activity we converted **2** into **12** by methanesulfonylation and saponification. This derivative was chosen since the corresponding ^{35}S-radiolabeled compound promised to be a useful tool owing to the high specific activity

of ^{35}S[8] combined with its emission profile, nearly identical to that of ^{14}C, which allows for efficient detection and safe handling. ^{35}S-$MeSO_2Cl$ is a known derivatizing agent.[9]

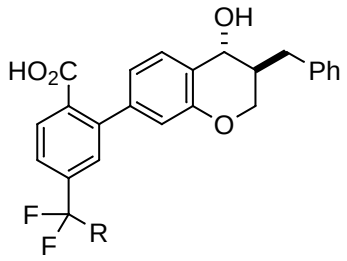
Scheme 2. Synthesis of **2** and **12**



Evaluation of **12** in the ^3H- LTB_4 binding assay with human neutrophils revealed the compound to have an IC_{50} of 26.7 nM, only ~4-fold less potent than CP-195543 indicating that the presence of the functionalized aminohexyl side chain was compatible with potent LTB_4 receptor antagonist activity. As a result, we prepared ^{35}S-**12** from **2** using ^{35}S-methanesulfonyl chloride derived from sodium ^{35}S-methanesulfonate (oxalyl chloride/DMF). While the above experiments with cold **12** had shown that it

could displace ^{3}H- LTB_4 from its receptor, experiments in which cold LTB_4 was used to displace ^{35}S-**12** revealed the latter to have a high degree of non-specific binding. This non-specific binding presumably derives from the physical properties of the compound, i.e. it is highly lipophilic (clogP = 5.0) and may also be responsible for the diminished functional activity of **12** (see Table 1).

Table 1: LTB_4 Binding and Functional Activities



Compound	-R	PMN[a] IC_{50} (nM)	CTX[b] IC_{50} (nM)	CD11b[c] IC_{50} (nM)
CP-195543	-F	6.8	2.4	280
1	-Me	5.5	7.0	200
12	$-(CH_2)_6NHSO_2Me$	26.7 ± 5.7	~1000	10900

[a]inhibition of LTB_4 binding to receptors on isolated human neutrophils (ref. 1).
[b]inhibition of LTB_4-induced chemotaxis of isolated human neutrophils (ref. 1).
[c]inhibition of LTB_4-induced CD11b up-regulation on isolated human neutrophils (ref. 1).

Owing to its non-specific binding ^{35}S-**12** itself was not a useful tool; nevertheless, the binding activity of cold **12** demonstrates that a functionalized aminohexyl side chain at C-4´ of the CP-195543 nucleus is compatible with potent LTB_4 antagonist activity. Thus, the availability of **2** will allow the preparation of other derivatized analogs of CP-195543 with varying physical properties that can be used for studying LTB_4 receptors and/or for imaging purposes.[10]

ACKNOWLEDGMENT

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EXPERIMENTAL

General Methods: ^{19}F NMR spectra are reported in ppm relative to trichlorofluoromethane. Gas chromatograph mass spectra were recorded on a Hewlett Packard GC-MS on a HP-1 column, 12 meters by 200 micrometers, with a helium flow of 1mL / min and with 12 psi of head pressure. Initial column temperature was 133°C and final column temperature was 325°C with an 18°C / min increase. HPLCs

were performed on a Waters NovaPak C18 column (3.9 mm x 15 cm) using acetonitrile (0.1%TFA) : water (0.1%TFA) (1 mL/min) and a 30% to 90% gradient (2%/min) with detection at 220 nm. HPLC purities were determined by integration of the 220 nm UV trace and are not corrected for extinction coefficients. Flash chromatography was performed on J.T. Baker 40_ silica gel under positive pressure of nitrogen. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl. Toluene and methylene chloride were distilled under nitrogen from calcium hydride.

4-Carbomethoxy-3-iodobenzoic acid: In a flask under nitrogen, dimethyl 2-iodoterephthalate (24.13 g, 75.4 mmol) and lithium hydroxide monohydrate (3.80 g, 90.48 mmol) were taken up in water (12 mL) and methanol (108 mL). The solution was stirred at rt for 3 h 20 min after which time it was diluted with ethyl acetate (250 mL). The organic layer was washed twice with 1N HCl, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to provide a white solid. Product was purified by silica gel chromatography (5% ethyl acetate/ 5% acetic acid/ hexane) to afford the mono acid as a white solid (13.83 g, 59.9%): ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.79 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 8.65 (s, 1H); MS 305 (M^+ - 1).

4-Carbomethoxy-3-iodobenzoyl chloride (3): In a flask under nitrogen, 4-carbomethoxy-3-iodobenzoic acid (2.53 g, 8.27 mmol) and thionyl chloride (3.02 mL, 41.35 mmol) were taken up in methylene chloride (80 mL) and dimethylformamide (3 drops). The mixture was stirred at reflux for 2 h after which time it was concentrated *in vacuo*. The residue was taken up in methylene chloride and re-concentrated *in vacuo* (three times) to remove excess thionyl chloride, affording the acid chloride as a yellow oil (2.67 g, 100%): ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.80 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 8.65 (s, 1H); MS 305 (M^+ - 1 (for acid)).

Methyl 4-acetyl-2-iodobenzoate (4): In a flame dried flask under nitrogen at 0°C methylmagnesium bromide (2.94 mL, 4.11 mmol, 1.4M), lithium chloride (0.37 g, 4.11 mmol, dried at 150°C overnight), and copper cyanide (0.35 g, 8.22 mmol) were taken up in dry THF (30 mL). The mixture was stirred at 0°C for 10 min at which time **3** (1.33 g, 4.11 mmol) was added dropwise in dry THF (5 mL). The mixture was stirred an additional hour at 0°C and then at rt overnight after which it was quenched with saturated ammonium chloride solution (10 mL). The solution was concentrated *in vacuo* and the resulting residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to provide a green solid. The crude product was purified by silica gel chromatography (20% ethyl acetate / hexane) to afford **4** as a white solid (511 mg, 40.8%): ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 3.92 (s, 3H), 7.79 (d, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.47 (s, 1H); MS 305 (M^+ + 1); GC MS 3.53min: 304 (M^+), 289 (M^+ - CH_3) (>99% pure).

Methyl 4-(1,1-difluoroethyl)-2-iodobenzoate (5): In a flame dried flask under nitrogen **4** (250 mg, 0.822 mmol) and DAST (0.22 mL, 1.64 mmol) were combined and stirred at rt for 24 h. The resulting mixture was poured over ice water (20 mL) and diluted with ethyl acetate (30mL). The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to provide a brown oil. The product was purified by silica gel chromatography (10% ethyl acetate / hexane) to afford **5** as a yellow oil (114 mg, 42.5%): ^{1}H NMR ($CDCl_3$) δ 1.87 (t, J = 18 Hz, 3H), 3.93 (s, 3H), 7.51 (d, J = 8 Hz, 1H), 7.8 (d, J = 8 Hz, 1H), 8.07 (s, 1H); ^{19}F NMR ($CDCl_3$) δ -89.46 (q, J = 18 Hz); GC MS 2.41min: 326 (M^+), 295 (M^+ - OCH_3) (>99% pure).

(3*S*,4*R*)-(3-Benzyl-4-hydroxychroman-7-yl)boronic acid (6): To a flame dried flask under nitrogen were added (3*S*,4*R*)-7-bromo-3-benzyl-4-chromanol (500 mg, 1.57 mmol) and dry THF (8.0 mL). The resulting solution was cooled to -78 °C and a solution of methyllithium (2.10 mL, 3.14 mmol, 1.5 M in ether) was added dropwise over 10 min. The mixture stirred for 1.5 h at -78 °C after which a solution of n-butyllithium (0.70 mL, 1.72 mmol, 2.5 M in hexanes) was added and stirring was continued at -78 °C for 1 h. Borane/THF solution (7.85 mL, 7.85 mmol, 1.0 M) was added over 20 min and the resulting solution was allowed to stir at -78 °C for 40 min. TLC showed no remaining starting material at this time. The solution was allowed to warm to 0 °C and the reaction was quenched by addition of 4 mL of water. The pH was adjusted to ~2 by addition of 1N HCl and the resulting solution was stirred at rt overnight. The solution was extracted twice with ether and the combined organic layers were washed with NaOH solution (0.5 N, 50 mL). The aqueous layer was acidified using 1N HCl and extracted twice with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford **6** as a yellow solid (381 mg, 86%). TLC (20% ethyl acetate/hexane) showed no remaining starting material and a baseline product spot. The crude product was used directly in next step.

Methyl 2-(3*S*,4*R*)-(3-benzyl-4-hydroxychroman-7-yl)-4-(1,1-difluoroethyl)benzoate (7): In a flask under nitrogen, **6** (168 mg, 0.591 mmol) was taken up in toluene (1.5 mL) and water (1.0 mL). To the resulting mixture was added sodium carbonate (125 mg, 1.18 mmol) followed by **5** (107 mg, 0.328 mmol). The solution was gently degassed and vented with nitrogen three times. Tetrakis-(triphenylphosphine) Pd(0) (20 mg) catalyst was added and the reaction mixture was heated in a 120 °C oil bath. The solution was refluxed for 4 h after which TLC analysis (30% ethyl acetate / hexane) showed complete disappearance of **5**. The solution was cooled to rt to provide a two phase mixture. The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to provide an oil. The crude product was purified by silica gel chromatography (30% ethyl acetate / hexanes) to afford **7** as a yellow oil (135 mg, 93.8%): ^{1}H NMR ($CDCl_3$) δ 1.90 (t, J = 18 Hz, 3H), 2.23 (m, 1H), 2.54 (m, 1H),

2.72 (m, 1H), 3.68 (s, 3H), 3.98 (dd, J = 5 and 11 Hz, 1H), 4.22 (dd, J = 3 and 11 Hz, 1H), 4.52 (m, 1H), 6.80-7.95 (m, 11H); MS 421 (M^+ - H_2O); HPLC retention time 21.2 min (95% pure).

2-(3*S*,4*R*)-(3-Benzyl-4-hydroxychroman-7-yl)-4-(1,1-difluoroethyl)benzoic acid (1): In a flask under nitrogen, **7** (115 mg, 0.262 mmol) and lithium hydroxide monohydrate (55 mg, 1.31 mmol) were taken up in water (0.5 mL) and methanol (4.5 mL). The mixture was stirred at reflux for 24 h after which time it was cooled to rt and diluted with ethyl acetate (20 mL). The organic layer was separated and washed twice with 1N HCl, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to provide a brown foam. The crude product was purified by silica gel chromatography (30% ethyl acetate / 5% acetic acid / hexane) to afford **1** as a white solid (86 mg, 77.5%): ^{1}H NMR ($CDCl_3$) δ 1.91 (t, J = 18 Hz, 3H), 2.22 (m, 1H), 2.48 (m, 1H), 2.73 (m, 1H), 3.95 (m, 1H), 4.19 (m, 1H), 4.59 (m, 1H), 6.80-8.00 (m, 11H); ^{19}F NMR ($CDCl_3$) δ -89.15 (q, J = 18 Hz); MS 423 (M^+ - 1); HPLC retention time 22.0 min (>98% pure); Anal. Calcd for $C_{25}H_{22}O_4F_2$: C, 70.75; H, 5.22. Found: C, 70.63; H, 5.62.

2-(6-Iodohexyloxy)tetrahydropyran: In a flask under nitrogen, 2-(6-bromohexyloxy)tetrahydropyran (5.0 g, 18.85 mmol) and sodium iodide (14.13 g, 94.25 mmol) were taken up in acetone (100 mL). The resulting solution was stirred at reflux for 20 h at which time the acetone was removed *in vacuo*. The residue was taken up in ethyl acetate (200 mL), washed with 1N HCl, saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The mixture was concentrated *in vacuo* to afford 2-(6-iodohexyloxy)tetrahydropyran as a yellow oil which was used in the next step without further purification (5.88 g, 100%): ^{1}H NMR ($CDCl_3$) δ 1.20-2.00 (m, 14H), 3.15 (m, 2H), 3.40 (m, 1H), 3.50 (m, 1H), 3.75 (m, 1H), 3.90 (m, 1H), 4.64 (m, 1H).

6-(2-Tetrahydropyranyloxy)hexylzinc iodide: In a flame dried flask under nitrogen zinc powder (2.07 g, 31.72 mmol) and 1,2-dibromoethane (0.18 mL, 2.00 mmole) were taken up in dry THF (6 mL) and heated at 65°C for 5 min (effervescence noted). Reaction cooled to rt and chlorotrimethylsilane (0.20 mL, 1.60 mmol) was added and the resulting mixture was stirred at rt for 15 min. Evolution of gas was noted at this time. A solution of 2-(6-iodohexyloxy)tetrahydropyran (4.39 g, 14.06 mmol) in dry THF (10 mL) was added and the resulting mixture was stirred at 40°C for 20 h after which time it was cooled to rt and transferred to a new flame dried flask for use in the next step.

Methyl 2-iodo-4-(1-oxo-7-(2-tetrahydropyranyloxy)heptylbenzoate (8): In a flame dried flask under nitrogen the solution of 6-(2-tetrahydropyranyloxy)hexylzinc iodide prepared above (14.06 mmol) was cooled to -10°C and a solution of lithium chloride (1.19 g, 28.12 mmol) and copper cyanide (1.26 g, 14.06 mmol) in dry THF (15 mL) was added. The mixture was stirred at 0°C for 10 min at which time a solution of **3** (4.62 g, 14.25 mmol) in dry THF (15 mL) was slowly added at -25°C. The mixture was stirred at 0°C for 3 h 20 min after which time it was quenched with saturated ammonium chloride

solution (10 mL). The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate, washed with water and then brine, dried over anhydrous magnesium sulfate and concentrated to afford a yellow oil. The crude product was purified by silica gel chromatography (10% ethyl acetate / hexane) to provide **8** as a colorless oil (2.57 g, 38.5%): ^{1}H NMR ($CDCl_3$) δ 1.00 - 1.90 (m, 14H) 2.91 (t, J = 7 Hz, 2H), 3.35 (m, 1H), 3.46 (m, 1H), 3.68 (m, 1H), 3.81 (m, 1H), 3.91 (s, 3H), 4.52 (s, 1H), 7.77 (d, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 8.44 (s, 1H); MS 492 ($M^+ + H_2O$).

Methyl 2-iodo-4-(7-hydroxy-1-oxoheptyl)benzoate: In a flask under nitrogen **8** (3.68 g, 7.76 mmol) and *p*-toluenesulfonic acid monohydrate (2.21 g, 11.64 mmol) were taken up in methanol (80 mL). The resulting mixture was stirred at rt for 21 h at which time the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate, washed with saturated sodium bicarbonate solution, 1N HCl, and dried over anhydrous magnesium sulfate. The organic phase was concentrated *in vacuo* to afford methyl 2-iodo-4-(7-hydroxy-1-oxoheptyl)benzoate as an oil which was used in the next step without further purification (2.67 g, 88.1%): ^{1}H NMR ($CDCl_3$) δ 1.20 - 1.80 (m, 8H), 2.91 (t, J = 7 Hz, 2H), 3.61 (t, J = 7 Hz, 2H), 3.91 (s, 3H), 7.80 (d, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 8.46 (s, 1H); MS 391.1 ($M^+ + 1$), 373 ($M^+ + 1 - H_2O$).

Methyl 2-iodo-4-(1-oxo-7-tosyloxyheptyl)benzoate: In a flask under nitrogen compound methyl 2-iodo-4-(7-hydroxy-1-oxoheptyl)benzoate (2.67 g, 6.84 mmol) and tosyl chloride (1.96 g, 10.26 mmol) were taken up in pyridine (10 mL). The resulting solution was stirred at rt for 2 h 15 min after which time it was poured over ice, acidified with concentrated HCl, and extracted with ethyl acetate. The organic layer was separated and washed with 1N HCl, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to provide an oil. The crude product was purified via silica gel chromatography (15% ethyl acetate / hexane) to afford methyl 2-iodo-4-(1-oxo-7-tosyloxyheptyl)benzoate as an oil (2.54 g, 68.1%): ^{1}H NMR ($CDCl_3$) δ 1.31 (m, 4H), 1.63 (m, 4H), 2.41 (s, 3H), 2.88 (t, J = 7 Hz, 2H), 3.92 (s, 3H), 4.00 (t, J = 6 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.75 (d, J = 8 Hz, 2H), 7.80 (d, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.45 (s, 1H); MS 545 ($M^+ + 1$), 531 ($M^+ - CH_3$); HPLC retention time 24.1 min (81% pure).

Methyl 2-iodo-4-(7-azido-1-oxoheptyl)benzoate (9): In a flask under nitrogen compound methyl 2-iodo-4-(1-oxo-7-tosyloxyheptyl)benzoate (2.54 g, 4.67 mmol) and sodium azide (364 mg, 5.60 mmol) were taken up in dimethylformamide (50 mL). The solution stirred at rt for 19 h after which the DMF was removed *in vacuo*. The residue was taken up in ethyl acetate, washed twice with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford **9** as an oil which was used without further purification in the next step (1.83 g, 94.3%): ^{1}H NMR ($CDCl_3$) δ 1.20 - 1.80 (m, 8H), 2.91 (m, 2H), 3.23 (m, 2H), 3.91 (s, 3H), 7.79 (m, 1H), 7.90 (m, 1H), 8.45 (s, 1H); MS 414 ($M^+ - 1$); HPLC retention time 22.5 min (77% pure).

Methyl 2-iodo-4-(7-azido-1,1-difluoroheptyl)benzoate (10): In a flame dried flask under nitrogen **9** (1.73 g, 4.17 mmol) was taken up in DAST (1.38 mL, 10.425 mmol). The resulting solution was stirred at 45°C for 44 h at which time it was poured into ice water, extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to a brown oil. The crude product was purified by silica gel chromatography (10% ethyl acetate / hexanes) to afford **10** as an oil (920 mg, 52.2%): ^{1}H NMR ($CDCl_3$) δ 1.20 - 1.60 (m, 8H), 2.03 (m, 2H), 3.22 (t, J = 7 Hz, 2H), 3.90 (s, 3H), 7.45 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 1H), 8.02 (s, 1H); ^{19}F NMR ($CDCl_3$) δ -97.13 (t, J = 17 Hz); HPLC retention time 25.5 min (66% pure).

Methyl 2-(3*S*,4*R*)-(3-benzyl-4-hydroxychroman-7-yl)-4-(7-azido-1,1-difluoroheptyl)benzoate (11): In a flask under nitrogen, **6** (780 mg, 2.74 mmol) was partitioned between toluene (7 mL) and water (7 mL). To the resulting mixture were added sodium carbonate (582 mg, 5.49 mmol) and a solution of **10** (730 mg, 1.67 mmol) in toluene (11 mL). The mixture was gently degassed and purged with nitrogen three times. Tetrakis(triphenylphospine) Pd (0) catalyst (80 mg) was added and the reaction flask was lowered into a preheated oil bath (120°C). The resulting solution was brought to reflux temperature for 4 h 15 min after which time it was cooled to rt. The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to provide a brown oil. The crude product was purified by silica gel chromatography (30% ethyl acetate / hexane) to afford **11** as a yellow oil (572 mg, 62.3%): ^{1}H NMR ($CDCl_3$) δ 1.25-1.70 (m, 8H), 2.11 (m, J = 16 Hz, 2H), 2.26 (m, 1H), 2.56 (m, 1H), 2.75 (m, 1H), 3.24 (t, J = 7 Hz, 2H), 3.71 (s, 3H), 4.00 (dd, J = 5 and 11 Hz, 1H), 4.25 (dd, J = 2 and 11 Hz, 1H), 4.55 (br s, 1H), 6.80-7.90 (m, 11H); ^{19}F NMR ($CDCl_3$) δ -96.75 (t, J = 16 Hz); MS 532 (M^+ - H_2O); HPLC retention time 27.8 min (87% pure).

Methyl 2-(3*S*,4*R*)-(3-benzyl-4-hydroxychroman-7-yl)-4-(7-amino-1,1-difluoroheptyl)benzoate (2): **11** (572 mg, 1.04 mmol) and palladium (10%) on carbon (50 mg) were taken up in methanol (30 mL) in a Parr bottle and shaken under 15 psi hydrogen for 1 h. The catalyst was filtered under a blanket of nitrogen and the filtrate was concentrated *in vacuo* to afford a white foam. The crude product was purified by silica gel chromatography (20% methanol / 1% ammonia / methylene chloride) to provide **2** as a white solid (313 mg, 57.4 %): ^{1}H NMR ($CDCl_3$) δ1.20-1.60 (m, 8H), 2.09 (m, 2H), 2.20-2.80 (m, 5H), 3.68 (s, 3H), 3.97 (dd, J = 5 and 11 Hz, 1H), 4.22 (dd, J = 2 and 11 Hz, 1H), 4.51 (d, J = 4 Hz, 1H), 6.80-7.90 (m, 11H); ^{19}F NMR ($CDCl_3$) δ -96.46 (t, J = 16 Hz); MS 524 (M^+ +1) 506 (M^+ - OH).

Methyl 2-(3*S*,4*R*)-(3-benzyl-4-hydroxychroman-7-yl)-4-(1,1-difluoro-7-methanesulfonamidoheptyl)-benzoate: In a flame dried flask under nitrogen, **2** (100 mg, 0.191 mmol), methanesulfonyl chloride (0.015 mL, 0.191 mmol), and diisopropylethylamine (0.033 mL, 0.191 mmol) were taken up in methylene chloride (2.0 mL). The resulting mixture was stirred at rt for 1 h 10 min after which time the

solution was diluted with ethyl acetate. The reaction mixture was washed with 1N HCl, saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to provide a yellow oil. The crude product was purified by silica gel chromatography (2% methanol / methylene chloride) to afford methyl 2-(3*S*,4*R*)-(3-benzyl-4-hydroxychroman-7-yl)-4-(1,1-difluoro-7-methanesulfonamidoheptyl)benzoate as an oil (96 mg, 83.5%): ^{1}H NMR ($CDCl_3$) δ 1.20-1.70 (m, 8H), 2.15 (m, 2H), 2.26 (m, 1H), 2.56 (m, 1H), 2.76 (m, 1H), 2.92 (s, 3H), 3.08 (m, 2H), 3.71 (s, 3H), 4.00 (dd, J = 5 and 11 Hz, 1H), 4.19 (m, 1H), 4.24 (dd, J = 2 and 11 Hz, 1H), 4.55 (br s, 1H), 6.80-7.90 (m, 11H); ^{19}F NMR ($CDCl_3$) δ -96.62 (t, J = 16 Hz); MS 600 (M^+ -1); HPLC retention time 21.2 min (91% pure).

2-(3*S*,4*R*)-(3-Benzyl-4-hydroxychroman-7-yl)-4-(1,1-difluoro-7-methanesulfonamidoheptyl)benzoic acid (12): In a flame dried flask under nitrogen, compound methyl 2-(3*S*,4*R*)-(3-benzyl-4-hydroxychroman-7-yl)-4-(1,1-difluoro-7-methanesulfonamidoheptyl)benzoate (87 mg, 0.144 mmol) and lithium hydroxide monohydrate (30 mg, 0.72 mmol) were taken up in methanol (4.5 mL) and water (0.5 mL). The resulting solution was stirred at reflux for 19 h at which time it was cooled to rt. The mixture was diluted with ethyl acetate, washed twice with 1N HCl, and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to afford **12** as a white foam (85 mg, 100%): ^{1}H NMR ($CDCl_3$) δ 1.20-1.60 (m, 8H), 2.09 (m, 2H), 2.25 (m, 1H), 2.55 (m, 1H), 2.75 (m, 1H), 2.92 (s, 3H), 3.08 (m, 2H), 3.98 (dd, J = 5 and 11 Hz, 1H), 4.22 (d, J = 11 Hz, 1H), 4.52 (d, J = 4 Hz, 1H), 6.80-8.00 (m, 11H); ^{19}F NMR ($CDCl_3$) δ -96.77 (t, J = 16 Hz); MS 586 (M^+ - 1). HPLC retention time 17.8 min (>98% pure); Anal. Calcd for $C_{31}H_{35}NO_6F_2S$: C, 63.36; H, 6.00; N, 2.38. Found C, 63.63; H, 6.41; N, 2.21.

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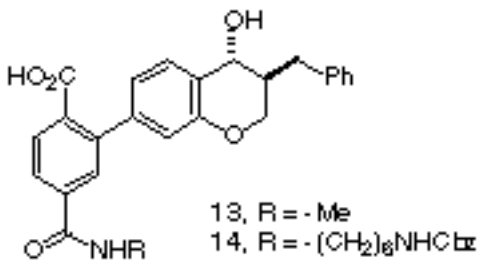

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