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## COMMUNICATION

# Studies Towards Asymmetric Synthesis of 4(S)-11-Dihydroxydocosahexaenoic acid (diHDHA) Featuring Cross-Coupling of Chiral Stannane under Mild Conditions

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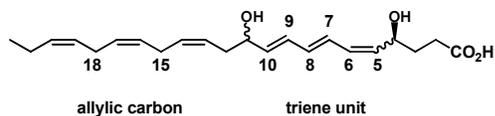
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An efficient and asymmetric synthetic approach towards one of the biologically interesting 4(S)-11-diHDHA derivatives was developed. This process mainly relied on two reactions, one is the copper-catalyzed mild cross-coupling that allows for the efficient construction of chiral  $\alpha$ -alkynyl  $\alpha$ -hydroxy motif and another is the synthesis of chiral  $\alpha$ -hydroxy  $\alpha$ -stannanes that has previously been developed by our groups featuring the asymmetric stannylation using the well-established tributyltin hydride/diethyl zinc system from aldehyde.

Docosahexaenoic acid (DHA) is a carboxylic acid with a 22-carbon chain, six *cis* double bonds. It is the most abundant omega-3 fatty acid in the brain and retina.<sup>1</sup> DHA hydroxy derivatives are usually found in the metabolism process, and show powerful bioactivities such as antiinflammatory and pro-resolving activities in isolated human leukocytes.<sup>2</sup> For example, 7(S)-14(S)-diHDHA was confirmed with anti-inflammatory and pro-resolving biological activities.<sup>3</sup> This novel molecule was obtained through enzyme incubation of 4(S)-HDHA. Based on a long-term structure-activity relationships research, a specific compound, 4(S)-11-diHDHA (Fig. 1), was assumed to have considerable bioactivity.<sup>4</sup>

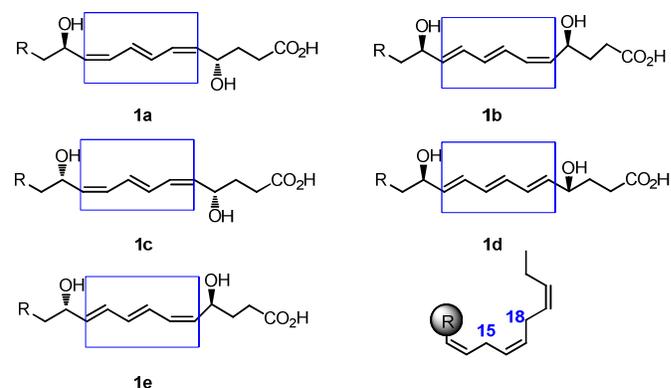
Figure 1. Structure of 4(S)-11-dihydroxydocosahexaenoic acid (diHDHA).



4(S)-11-dihydroxydocosahexaenoic acid (diHDHA) include a sensitive triene unit (Fig. 2, in the box unit), two sensitive methylene (carbon 15 and 18, both are in allylic position), and two chiral hydroxy groups (with one stereochemistry unclear). The potent biological activities, the complex architecture and the unclear stereochemistry of the hydroxy groups make it a considerably popular and challenging topic in drug discovery community. The

long-term goal of our lab is to gain several of the most possible analogs of 4(S)-11-dihydroxydocosahexaenoic acid (diHDHA) which was depicted in Figure 2. The subsequent conduct of relevant studies will evaluate its structure-activity relationships.

Figure 2. 4(S)-11-dihydroxydocosahexaenoic acid (diHDHA) analogues (1).



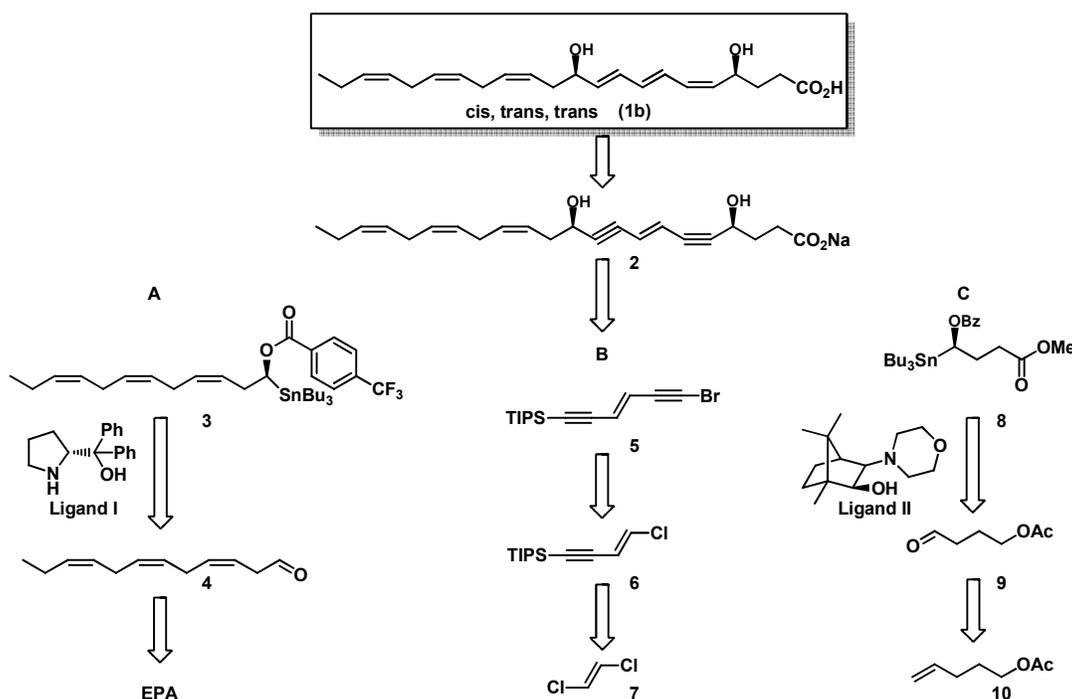
Our research group has synthesized active HDHA analogues since 1980s.<sup>5</sup> These compounds show considerable biological activities against several disease and act as a precursor for prostaglandin-3 (it inhibits platelet aggregation), thromboxane-3, and leukotriene-5 groups (all eicosanoids). Notably, our group has recently established a powerful protocol.<sup>6</sup> In this process, copper thiophene carbonate mediated and palladium catalyzed cross-coupling between chiral stannane with different coupling partners was developed. Herein, we disclosed an efficient route to construct the core segment of 4(S)-11-diHDHA and trials towards to this novel compound.

The retrosynthetic analysis of 4(S)-11-diHDHA (**1b**) was shown in Scheme 1. Target molecule could be obtained by regioselective reduction of triple bonds of compound **2**; compound **2** could be assembled by three segments, chiral stannane (**3**), conjugated bromide (**5**), and another chiral stannane (**8**). In this paper, we will

focus on the asymmetric syntheses of chiral stannane **3** and **8**, and the subsequent assembly of three units into key intermediate **2**. Chiral stannane (**3**), the most challenging segment with a continuous allylic motif and one chiral  $\alpha$ -hydroxy  $\alpha$ -stannane group, can be achieved using the ligand-controlled asymmetric synthesis of aldehyde **4**, which previously has been developed by our group.<sup>6</sup> The aldehyde **4** was synthesized through multistep linear synthesis from commercial available eicosapentaenoic acid (EPA). Conjugated bromide (**5**), a continuous triple-double-triple unit, was prepared through multistep synthesis, which was mainly relied on the renowned palladium catalyzed Sonogashira cross-coupling<sup>7</sup> under optimized reaction condition. In our synthesis, the chiral  $\alpha$ -hydroxy  $\alpha$ -stannane (**8**) can also be produced by applying the well-established stannylation reaction with C4-aldehyde (**9**) and tributyltin hydride/diethyl zinc. C4-aldehyde (**9**) was readily synthesized from

of the solvents indicated that toluene was the best choice. With the epoxide (**13**) in hand, the next step was aimed at transformation of the hydroxy group to its corresponding aldehyde **4**. The epoxide (**13**) was hydrolyzed to triol by treatment with aqueous perchloric acid; periodate scission of the vicinal diol was employed again. The resultant aldehyde (**4**) was intermediately used for next asymmetric stannylation step due to its reactive property. Based on our well-established protocol, the stannylation reaction of the aldehyde (**4**) with tributyltin hydride/diethyl zinc followed by one-pot protection was utilized, the chiral  $\alpha$ -hydroxy  $\alpha$ -stannane (**3**)<sup>10</sup> was obtained in 27% yield from the epoxide **13**. Notably, ligands screening indicated that the chiral ligand (**I**) ((*R*)-(+)- $\alpha$ -diphenyl-2-pyrrolidinemethanol) was identified as the best one.<sup>6</sup> Thus, there are 5 linear steps with total 10% yield to afford segment A ( $\alpha$ -hydroxy  $\alpha$ -stannane **3**) from EPA.

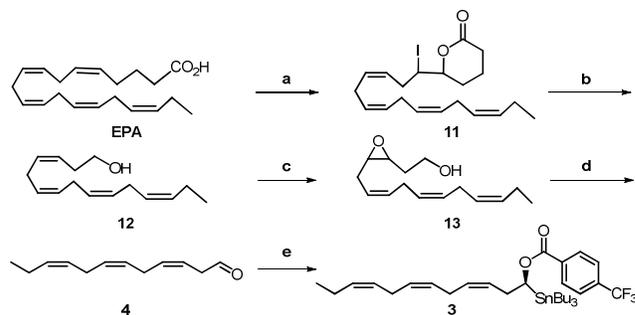
Scheme 1. Retrosynthetic analysis one of the 4(S)-11-diHDHA derivatives **1b**.



commercial available 4-pentenyl acetate (**10**). Therefore, asymmetric synthesis of chiral  $\alpha$ -hydroxy  $\alpha$ -stannane compounds (**3** and **8**) from the relevant aldehydes (**4** and **9**) was successfully realized using the chiral ligands **I** and **II**, respectively, and  $\text{Bu}_3\text{SnH}/\text{ZnEt}_2$  system. It allows for facile preparation of both chiral stannane **3** and **8**, thus providing a convenient access to the synthesis of 4(S)-11-diHDHA.

The chiral  $\alpha$ -hydroxy  $\alpha$ -stannane (**3**) was synthesized by the route shown in Scheme 2. Firstly, the iodine-promoted iodolactonization was utilized; the eicosapentaenoic acid was successfully transformed into iodolactone (**11**) in 62% yield. This compound was immediately used for next step as it may decompose when exposure to light. Secondly, a continuous 3-step synthesis was employed.<sup>8</sup> Under basic condition (5% KOH), the iodolactone (**11**) was transformed to the vicinal diol; subsequent sodium periodate scission of the vicinal diol allows for the rapid and efficient construction of its corresponding aldehyde; immediate reduction of the aldehyde which was generated in situ led to the alcohol (**12**). Thirdly, the epoxide **13** was obtained by regioselective oxidation of the allylic double bond with  $\text{VO}(\text{acac})_2/\text{TBHP}$  system assisted by hydroxy group of the alcohol (**12**) in 75% yield.<sup>9</sup> Notably, screening

Scheme 2. Segment A ( $\alpha$ -hydroxy  $\alpha$ -stannane **3**) synthesis.

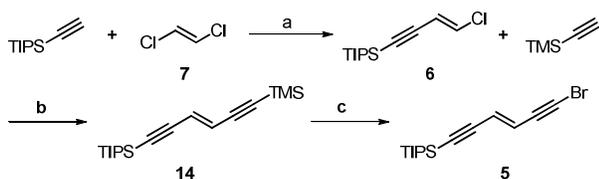


**Reagents and Conditions:** a.  $\text{I}_2$ ,  $\text{KHCO}_3$ , KI,  $\text{THF}/\text{H}_2\text{O}$ , rt, 62%. b. (i) 5% KOH,  $\text{MeOH}/\text{H}_2\text{O}$ , 60 °C; (ii)  $\text{NaIO}_4$ ,  $\text{THF}/\text{H}_2\text{O}$ , 0 °C; (iii)  $\text{NaBH}_4$ ,  $\text{MeOH}$ , 0 °C. 76% for 3 steps. c.  $\text{VO}(\text{acac})_2$  (5 mol %), TBHP, toluene, rt, 75%. d. (i)  $\text{HClO}_4$ ,  $\text{DME}/\text{H}_2\text{O}$ , rt; (ii)  $\text{NaIO}_4$ ,  $\text{THF}/\text{H}_2\text{O}$ , 0 °C. e. (i)  $\text{Bu}_3\text{SnZnEt}$ , ligand **I**,  $\text{DME}$ , -25 °C; (ii) 4- $\text{CF}_3$ -BzCl, pyridine, 27% for 4 steps.

The synthesis of another key segment, the conjugated bromide (**5**) was carried out as shown in Scheme 3. Firstly, through screening

different copper salts and solvents, we were delighted to find Cu(I) in ether gave the best result. Pd(II)-mediated Sonogashira reaction of ethynyltriisopropylsilane and *trans*-acetylene dichloride (**7**) afforded coupling adduct **6** in 97% isolated yield. Secondly, by applying the same method, Sonogashira coupling of compound **6** and trimethylsilyl acetylene proceeded smoothly to produce compound **14** in 98% yield. Notably, toluene was selected as the best solvent. Importantly, the coupling adducts **6** and **14** should be used immediately for next steps. Thirdly, silver-catalyzed chemical-selective bromination of the silyl-protected and terminal alkyne of compound **14** was successfully utilized to provide conjugated bromide (**5**) in 98% yield. Overall, rapid synthesis of conjugated bromide (**5**) from *trans*-acetylene dichloride (**7**) was developed in three linear steps (93% overall yield).

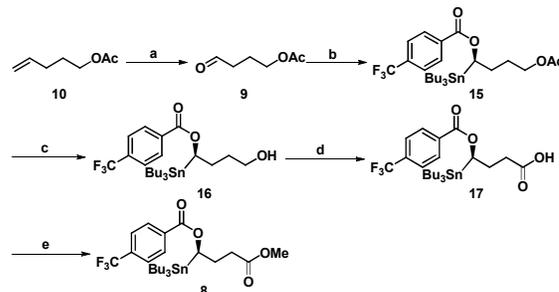
**Scheme 3.** Segment B (the conjugated bromide **5**) synthesis.



**Reagents and Conditions:** a. Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (3 mol %), CuI (3 mol %), piperidine (2 equiv.), ether, 97%. b. Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol %), CuI (10 mol %), piperidine (2 equiv.), toluene, 98%. c. AgNO<sub>3</sub> (20 mol %), NBS (1 equiv.), acetone, 98%.

The synthesis of the chiral  $\alpha$ -hydroxy  $\alpha$ -stannane **8** is illustrated in Scheme 4. The 4-oxobutyl acetate (**9**) is generated via oxidative cleavage of 4-pentenyl acetate (**10**) with ozone in 76% yield.<sup>11-13</sup> Subsequently, the synthesis of chiral  $\alpha$ -hydroxy  $\alpha$ -stannane (**8**) using asymmetric stannylation of the aldehyde (**9**) by utilizing the well-established protocol with tributyltin hydride/diethyl zinc followed by one-pot protection was realized in 60% isolated yield.<sup>6</sup> Notably, the chiral ligand (**II**) is the most suitable one for this particular catalytic stannylation through ligands optimization. Importantly, the enantiomeric excess of compound **15** was investigated and confirmed (93 % *ee*) in comparison to its modified analogue **8** (see our supporting information for more detail). The next stage of the synthesis was concerned with the transformation of the protected alcohol to ester. Firstly, selective deprotection of acetic group of compound **15** using *p*-toluenesulfonic acid (*p*-TsOH) in anhydrous methanol afforded alcohol **16**; Secondly, the combination of PDC and acetic acid in DMF<sup>14</sup> was employed as the best system in the direct transformation of the primary alcohol into acid. Importantly, the majority of the stannyl group in the compound **17** was not decomposed. Finally, diazomethane was utilized to carefully methylate the acid group of compound **17**, affording the chiral  $\alpha$ -hydroxy  $\alpha$ -stannane (**8**) in 60% isolated yields starting from **15**. As stated previously, we investigated the enantiomeric excess of compound **8**, and delightfully found that the good enantioselectivity of the chiral  $\alpha$ -hydroxy  $\alpha$ -stannane (93 % *ee*). In summary, chiral  $\alpha$ -hydroxy  $\alpha$ -stannane **8** was synthesized in five linear steps from commercial available 4-pentenyl acetate **10** (27 % overall yield and 93 % *ee*).

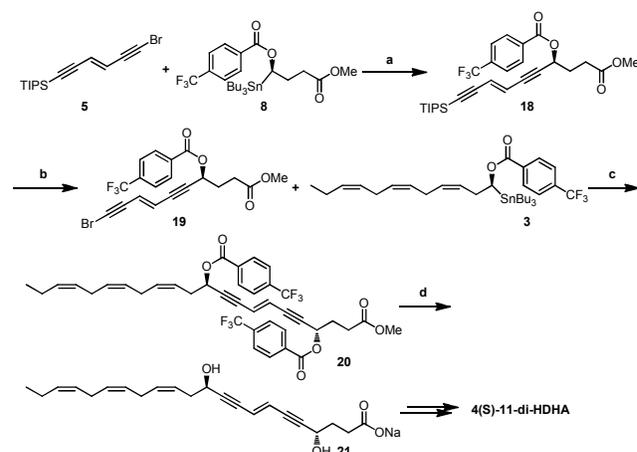
**Scheme 4.** Segment C ( $\alpha$ -hydroxy  $\alpha$ -stannane **8**) synthesis.



**Reagents and Conditions:** a. O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, then PPh<sub>3</sub>, 76%. b. EtZnSnBu<sub>3</sub>, DME; ligand II, -78 °C for 5 min; then aldehyde, -25 °C, 14 h; then 4-CF<sub>3</sub>-BzCl, pyridine, 60%. c. PTSA, MeOH, 50 °C. d. PDC, DMF/ AcOH. e. CH<sub>2</sub>N<sub>2</sub>, THF, 60% for 3 steps.

Stannane units (**3** and **8**) and the conjugated bromide segment (**5**) were now ready for the next stage of assembly to produce 4(S)-11-diHDHA (Scheme 5). Conjugated bromide **5** and chiral stannane **8** was efficiently coupled by treatment of copper(I)-thiophene-2-carboxylate,<sup>15-17</sup> affording coupling adduct **18** in 67% isolated yield. Silver-catalyzed bromination of silyl-protected and terminal alkyne **18** was then employed and the bromide **19** was obtained in 94% yield. This intermediate was used quickly for next step as it may decompose when exposure to light at ambient temperature. Next, by treatment of the copper(I)-thiophene-2-carboxylate,<sup>15-17</sup> the ester **20** was successfully prepared via the mild cross-coupling reaction in 58% yield. Removal of all the protected group of **20** using lithium hydroxide (1.0 M) afforded the sodium salt of acid (**21**).

**Scheme 5.** Formal asymmetric synthesis one of 4(S)-11-diHDHA derivatives **1b**.



**Reagents and Conditions:** a. CuTc (20 mol %), dioxane, 90 °C, 67%. b. AgF (1.1 equiv.), NBS (1.2 equiv.), CH<sub>3</sub>CN, rt., 94%. c. CuTc (20 mol %), dioxane, 90 °C, 58%. d. LiOH, THF/ H<sub>2</sub>O, rt, 67%.

Finally, the regioselective reduction of the conjugated triple bond of **21** to produce the novel molecule 4(S)-11-diHDHA was comprehensively investigated as illustrated in Table 1. It was found that slow addition of the Red-Al<sup>18</sup> under ambient temperature (entry 3) provided the best result. The final compound was elucidated by further crude proton NMR and mass spectrum. However, the compound may not so stable under ambient temperature, we tried to purify and isolate this compound, all these trials ended in failure. More experiments are investigated in our lab and will be disclosed in due course.

**Table 1.** Selective reduction of conjugated triple bonds of **21**.

Entry	Reagents	Solvent	Temp. <sup>b</sup>	Time (h)	Yields <sup>c</sup>
1	Red-Al <sup>a</sup>	THF	-78 °C	2	trace
2	Red-Al <sup>a</sup>	THF	4 °C	2	20%
3	Red-Al <sup>a</sup>	THF	rt	2	61%
4	LiAlH <sub>4</sub>	THF	rt	2	messy
5	Lindlar catalyst, H <sub>2</sub> (1 atm)	MeOH	rt	4	0%
6	Zn, Cu(OAc) <sub>2</sub> , AgNO <sub>3</sub>	MeOH/H <sub>2</sub> O	rt	2	0%

a. Red Al is applied for In situ generation of active hydride species, 2 equiv. B. The exact temperature for rt. is 26 °C. c. Estimated by crude <sup>1</sup>H NMR.

## Conclusions

In summary, we<sup>19</sup> presented herein our studies towards asymmetric synthesis one of the biologically interesting molecule 4(S)-11-dihydroxydocosahexaenoic acid (diHDHA). This protocol mainly relied on two reactions, one was the copper-catalyzed mild cross-coupling that allowed for the efficient construction of chiral  $\alpha$ -alkynyl  $\alpha$ -hydroxy motifs (**18** and **20**) and another is the synthesis of chiral  $\alpha$ -hydroxy  $\alpha$ -stannanes (**3** and **8**) that has previously been developed by our group. The preparation of chiral  $\alpha$ -hydroxy  $\alpha$ -stannanes **3** and **8** both featured the asymmetric stannylation using the well-established tributyltin hydride/diethyl zinc system from aldehydes **4** and **9**, respectively. The total synthesis of 4(S)-11-dihydroxydocosahexaenoic acid (diHDHA) and its analogues for screening of various biological studies are ongoing and will be disclosed in due course.

## Experimental Section

### 1. (*R*)-4-acetoxy-1-(tributylstannyl)-butyl-4-(trifluoromethyl)benzoate (**15**)

To a 250 mL RBF was charged with DME (40 mL) and a stirring bar under Argon, covered with aluminum foil, cooled to -78 °C. Diethyl zinc (1.0 M in hexane, 17.5 mL, 17.5 mmol) and tributyltin hydride (5.1 g, 17.5 mmol) were injected in sequence. The reaction was stirred for 5 min before moved to 4 °C. The mixture was stirred for

24 h at 4 °C. Then the reaction was diluted with DME (50 mL), cooled to -78 °C. Chiral ligand **II** (253.3 mg, 1.0 mmol) dissolved in DME (30 mL) was added. After stirred for 5 min, 4-oxobutyl acetate (**9**) (642.0 mg, 0.6 mL, 5.0 mmol) was added. The reaction was stirred at -25 °C covered with aluminum foil for overnight. The reaction was quenched slowly with sat. NH<sub>4</sub>Cl (100 mL). After warmed up to ambient temperature and stirred for additional 10 min, the organic solvent was evaporated in rotavapor, the aqueous residue was extracted with DCM (80 mL x 4), the DCM layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in rotavapor. Crude residue was quickly filtered through a pad of silica gel (to remove the non-polar and polar tin byproducts), the flask and the silica gel pad was washed with hexane, then gradually increased to 10% EtOAc/ hexane. The crude product fractions (*R<sub>f</sub>* = 0.15, 25% EtOAc in hexane) were combined and concentrated. The residue was stirred with 4-(trifluoro-methyl)-benzoyl chloride (1.6 g, 1.5 mL, 7.5 mmol), pyridine (0.8 g, 0.8 mL, 10.0 mmol) and catalytic amount of DMAP in DCM at room temperature. After 1 h, the reaction was quenched with brine, extracted with DCM (80 mL x 4). DCM layer dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in rotavapor. Crude product was purified by silica gel chromatography with eluent 20% EtOAc in hexane to give (*R*)-4-acetoxy-1-(tributylstannyl)-butyl-4-(trifluoromethyl)-benzoate (**15**) in 60% yield. *R<sub>f</sub>* = 0.5 (25% EtOAc in hexane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.11 (d, *J* = 5.2 Hz, 2H), 7.71 (d, *J* = 4.0 Hz, 2H), 5.08 (s, 1H), 4.10 (s, 2H), 2.16-2.07 (m, 1H), 2.04 (s, 3H), 2.10-1.92 (m, 1H), 1.88-1.68 (m, 2H), 1.54-1.24 (m, 12H), 0.94-0.83 (m, 15H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.3, 165.7, 134.4 (q, *J* = 33.0 Hz), 133.9, 130.1, 129.9, 125.6 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 271.0 Hz), 72.7 (t, *J* = 163.0 Hz), 64.2, 30.8, 29.7 (t, *J* = 10.0 Hz), 27.6 (t, *J* = 29.0 Hz), 27.1, 21.2, 13.9, 9.79 (t, *J* = 153.0 Hz).

### 2. (*S*,3*Z*,6*Z*,9*Z*)-1-(tributylstannyl)dodeca-3,6,9-trien-1-yl-4-(trifluoromethyl)-benzoate (**3**)

The epoxide (**13**) was dissolved in DME (20 mL)/ H<sub>2</sub>O (10 mL) under argon, cooled to 0 °C. Concentrated HClO<sub>4</sub> (60%, 1.5 mL) was injected. The reaction was warmed up to rt and stirred until all epoxide disappeared (followed by TLC, ~5h). Quenched with sat. NaHCO<sub>3</sub> solution (80 mL). After organic solvent was evaporated in rotavapor, the aqueous residue was extracted with EtOAc (50 mL x 5). The combined EtOAc layers were washed with brine (60 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*.

The crude residue was stirred with sodium periodate (600.0 mg) in THF/ H<sub>2</sub>O (2:1, 20 mL) at 0 °C under argon. After 1h, the reaction mixture was diluted with brine (80 mL), extracted with DCM (60 mL x 5). Combined DCM extractions were dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in rotavapor. Crude residue was again dissolved in 10% EtOAc/ hexane, quickly filtered through a pad of silica gel (to remove the polar byproduct). The flask and the silica gel pad were washed with more 10% EtOAc in hexane. The aldehyde fractions was condensed to give crude (3*Z*, 6*Z*, 9*Z*)-dodeca-3,6,9-trienal (**4**) (*R<sub>f</sub>* = 0.49, EtOAc/ hexane 1:4) which was used immediately for the next step. (The triol and aldehyde are not stable, so this reaction should be performed the next day after the setting up of the Et<sub>2</sub>Zn/ Bu<sub>3</sub>SnH reaction!)

Et<sub>2</sub>Zn (1.0 M in hexane, 4.0 mL) was injected to anhydrous DME (10 mL) under argon. After cooled to -78 °C, Bu<sub>3</sub>SnH (1.06 mL, 4.0 mmol) was injected. The reaction was stirred at -4 °C with aluminum foil cover and argon protection. After stirred for 1 day at 4 °C, the reaction was diluted with 20 mL more DME, cooled to -78

°C. Chiral ligand **I** (48 mg, 0.2 mmol, dissolved in 5 mL DME under argon) was added. After stirred for 5 min, crude aldehyde (in 5 mL DME under argon) was added. The reaction mixture was stirred at -25 °C overnight covered with aluminum foil. After the reaction was complete (followed by TLC, ~15h. Alcohol  $R_f$  = 0.54 EtOAc/hexane 1:6, strong PMA active), 4-(trifluoromethyl)benzoyl chloride (1.5 mL) was injected, the power of the Cryogenic Cooler was turned off to let the reaction slowly warmed up to rt, and stirred for another 1h. After carefully quenched with sat.  $\text{NaHCO}_3$  (30 mL), the organic solvent was evaporated in rotavapor, the aqueous residue was extracted with DCM (30 mL x 4). Combined DCM extractions were washed with sat.  $\text{NH}_4\text{Cl}$ ,  $\text{H}_2\text{O}$ , brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in rotavapor. Crude product was purified by silica gel chromatography ( $R_f$  = 0.71 EtOAc/hexane 1:6) to give (*S*, 3*Z*, 6*Z*, 9*Z*)-1-(tributylstannyl)-dodeca-3,6,9-trien-1-yl-4-(trifluoro-methyl)benzoate (**3**) (220.0 mg, 27% from epoxide) as colorless oil (sometimes pale yellow if there is some impurity).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (d,  $J$  = 8.0 Hz, 2H), 7.68 (d,  $J$  = 8.0 Hz, 2H), 5.46-5.31 (m, 6H), 5.11 (dd,  $J$  = 6.0, 3.0 Hz, 1H), 2.85-2.79 (m, 5H), 2.67-2.64 (m, 1H), 2.10-2.04 (m, 2H), 1.57-1.18 (m, 12H), 0.94-0.84 (m, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.8, 134.3 (q,  $J$  = 32.0 Hz), 134.1, 132.3, 130.3, 129.9, 128.9, 127.9, 127.1, 127.0, 125.5 (q,  $J$  = 4.0 Hz), 123.9 (q,  $J$  = 271.0 Hz), 72.2 (t,  $J$  = 155.0 Hz), 32.1, 29.3 (t,  $J$  = 10.0 Hz), 27.6 (t,  $J$  = 29.0 Hz), 26.0, 25.8, 20.8, 14.5, 13.9, 10.0 (t,  $J$  = 161.0 Hz). (The product was covered with aluminum foil, kept in -78 °C freezer under argon when not using.)

## Notes and references

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† Structure and activation relationship of relevant derivatives is investigated in our lab and will be disclosed in due course.

Electronic Supplementary Information (ESI) available: [Synthesis detail and proton and carbon NMR spectrum]. See DOI: 10.1039/c000000x/

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