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Convergent total synthesis of (±) myricanol, a cyclic natural diarylheptanoid†

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Myricanol **1**, a constituent of *Myrica* species, has been reported to lower the levels of the microtubule-associated protein tau (MAPT), whose accumulation plays an important role in some neurodegenerative diseases, such as Alzheimer's disease (AD). Herein we described a new synthetic route to prepare myricanol in 9 steps and 4.9% overall yield starting from commercially available 2,3-dimethoxyphenol and methyl 3-(4-benzyloxyphenyl)propanoate. The key steps are a cross-metathesis to obtain a linear diarylheptanoid intermediate and a Suzuki–Miyaura domino reaction to generate the challenging macrocycle.

Introduction

The cyclic diaryl heptanoid myricanol **1** was first isolated from the stem-bark of Indian *Myrica nagi* in 1970 by M. J. Begley and D. A. Whiting[1] and later from different *Myrica species*: *Myrica esculenta*,[2a] *Myrica rubra*[2b,c,d] and *Myrica cerifera*.[2e,f]

Myricanol (**1**) is a *meta*, *meta* bridged diarylheptanoid[3] bearing a C-11 stereogenic carbinol. Its stereomeric distribution varies from one natural source to another and (+)-a*R*,11*S*-myricanol was extracted with 86% enantiomeric excess from *Myrica cerifera* (bayberry/southern wax myrtle).[2f] Myricanol displays various biological properties from anti-oxidant, anti-inflammatory, anti-androgenic to anti-cancer[4] and anti-tau.[2f,5]

These two last important properties were the subject of many recent studies which prove growing interest in this natural molecule. Dickey *et al.*[2f] observed a robust tau-lowering activity of natural myricanol by investigation of protein tau levels in HeLa-C3 cells and recently they attributed this property mainly to the (−)-a*S*,11*R*-myricanol enantiomer, which was obtained by chiral HPLC resolution of the synthesized racemic myricanol.[6] Considering the antitumoral activities, Dai *et al.* published two important papers showing undoubtedly the powerful activity of myricanol to reduce and treat human lung adenocarcinoma A549 cells.[4,7]

Besides these biological properties, the synthesis of such strained cyclophanes is of high interest.[8] The first synthesis of racemic myricanol **1** was reported by Whiting *et al.*[9] and relied upon an intermolecular coupling between a Grignard species and an aldehyde to afford the linear diarylheptanoid in 42% yield and a Ni(0)-mediated coupling of a bis-iodide intermediate giving myricanol (**1**) in ~10% yield. Thus, starting from commercially available 1,2,3-trimethoxybenzene and *p*-benzyloxypropionaldehyde, Whiting's synthesis included 14 steps with 0.21% overall yield.[9b–d] Dickey *et al.*[6] reported in 2015 the second total synthesis of racemic myricanol using an aldol condensation to generate the linear diarylheptanoid and an intramolecular cross coupling between an aryl boronic acid pinacol ester and an aryl iodide to obtain the macrocycle in 22% yield. Dickey claimed to achieve the total synthesis of racemic myricanol over 7 steps in 2.03% yield, although the advanced starting substrates were not commercially available.

In relation to a program devoted to the synthesis of biaryl compounds[10] and considering the biological importance of such a natural product, only available in small quantities, we report herein the third total synthesis of racemic myricanol. Knowing that the macrocyclisation and the formation of the *meta*, *meta* heptylene linkage were the key synthetic challenges, we explored a domino Miyaura arylborylation-intramolecular Suzuki cross-coupling of the bis-halide intermediate **A**, which could result from a cross-metathesis between **2** and **B** (Scheme 1).

The arylallyl moiety **2** could be synthesized starting from 2,3-dimethoxyphenol through a Claisen rearrangement while the homoallylic alcohol could arise from commercially available methyl 3-(4-benzyloxyphenyl)propanoate through allylboration of the corresponding aldehyde.

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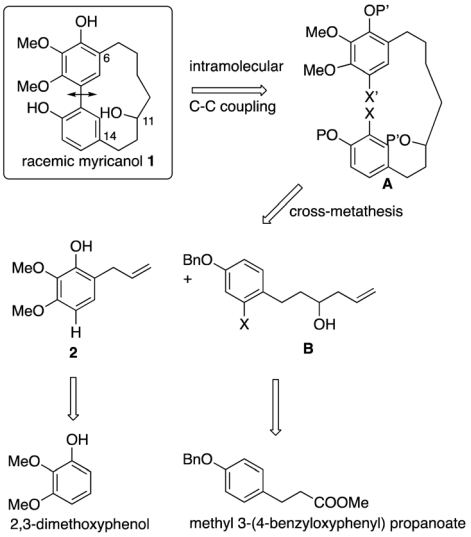
† Electronic supplementary information (ESI) available: Copy of ^{1}H and ^{13}C NMR spectra of compounds **7–22**. See DOI: 10.1039/c8ob02052c

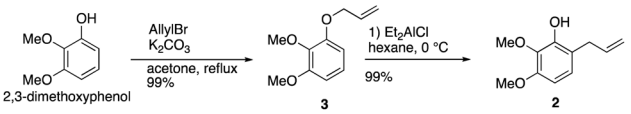


Scheme 1 Retrosynthesis of myricanol **1**.

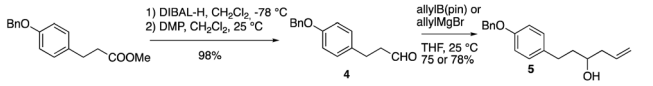
Results and discussion

The synthesis of fragment **2** commenced with the formation of the allyl ether **3** in quantitative yield under classical conditions, and subsequent *ortho*-Claisen rearrangement[11] to install the allylic fragment at C-6 of 2,3-dimethoxyphenol. An extensive optimization of the reaction conditions was necessary to avoid the competitive *para*-Claisen rearrangement.[11] Finally the use of a Lewis acid (Et_2AlCl or Me_2AlCl) at 0 °C led to the desired regioisomer **2** in quantitative yield (Scheme 2). An important point was the careful acidic workup at low temperature (below 10 °C) in order to avoid the formation of a side-product due to hydrolysis of the methyl ether at C-2.

On the other hand the preparation of the **B** type fragment **5** started with the reduction of methyl 3-(4-benzyloxyphenyl)propanoate with DIBAL-H in CH_2Cl_2 at −78 °C followed by subsequent oxidation with DMP in CH_2Cl_2 at 25 °C to afford the crude aldehyde **4** in an excellent yield of 98% which was not purified for the next step. The addition of either allylmagnesium bromide in diethyl ether or allylpinacol borane in THF to the aldehyde **4** led to the homoallylic alcohol **5** in 78 and 75% yield, respectively (Scheme 3). Enantioselective allylboration of **4** was also tested using either Brown's B-allyldiisocamphenylborane[12] or Roush's (*R*,*R*)-diisopropyltartrate allylboronate[13] giving the enantioenriched homoallylic alcohol (*R*)-**5** with 74% yield and 86% ee or 64% yield and 78% ee respectively. Finally a better ee of 90% was reached by allyltitanation using Cossy's (*S*,*S*)-Duthaler–Hafner reagent[14] in 70% yield. Importantly this promising result could be exploited towards an enantioselective synthesis of myricanol (Scheme 4).



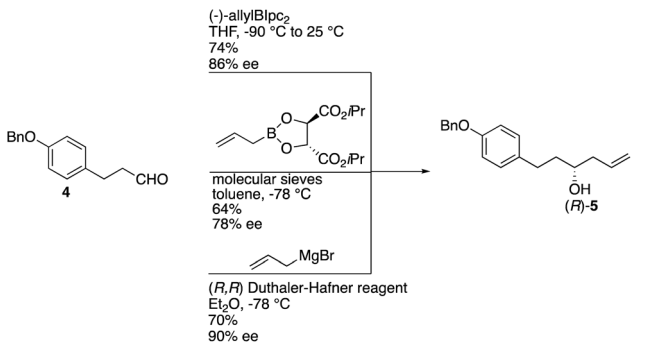
Scheme 2 Preparation of fragment **2**.



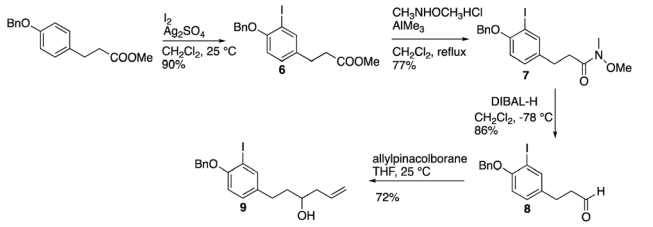
Scheme 3 Preparation of **B**-type fragment **5**.

In view of the final macrocyclization, iodination in the *meta* position of the starting methyl 3-(4-benzyloxyphenyl)propanoate was studied. A direct iodination of the allylic alcohol **5** was not envisaged due to the presence of the allylic alcohol. Therefore on treatment of methyl 3-(4-benzyloxyphenyl)propanoate with I_2, Ag_2SO_4 followed by transformation of the iodinated ester **6** into the Weinreb amide **7**, reduction with DIBAL-H in CH_2Cl_2 and addition of the allylborane on the resulting aldehyde **8** afforded the corresponding iodide **9** in 40% overall yield (Scheme 5).

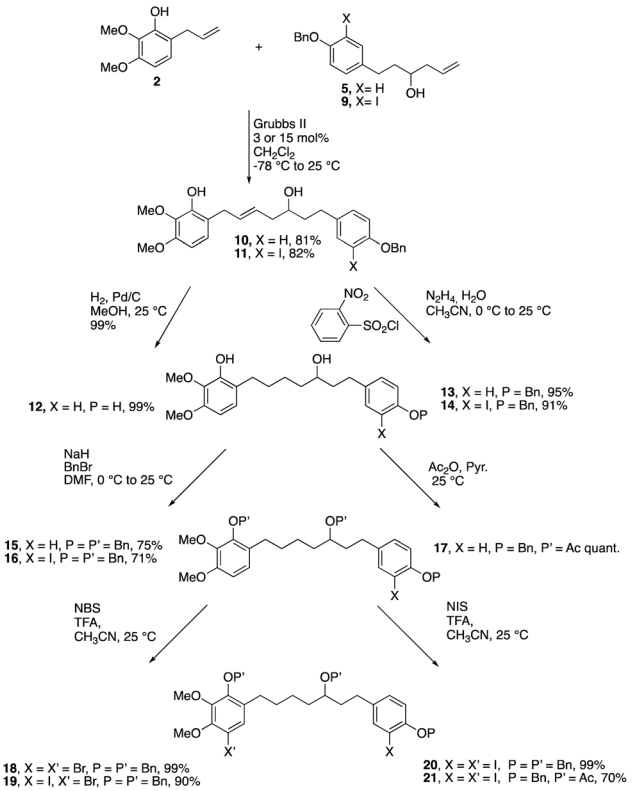
With the key fragments **2**, **5** and **9** in hand, we attempted cross-metathesis (CM) reaction as depicted in Scheme 6.[15] Hence after an extensive optimization study, on modifying the temperature of addition of the catalyst and the molar ratio between reagents, the treatment of **2** (4 eq.) with **5** in the presence of a G-II catalyst (3 mol%) in dichloromethane from −78 °C to room temperature provided diarylheptanoid **10** in a gratifying 81% yield.[16] Addition of the G-II catalyst at −78 °C was mandatory to obtain good yields. Excess of partner **2** was almost recovered after flash chromatography and could be recycled. In a similar way, cross-metathesis between **2** and the iodinated **9**, in the presence of 15 mol% of G-II catalyst, gave



Scheme 4 Enantioselective allylation of **4**.



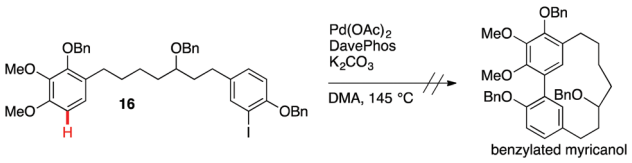
Scheme 5 Synthesis of the iodinated **B** type fragment **9**.



Scheme 6 Synthesis of the linear diarylheptanoids **15–21**.

rise to alkene **11** in an excellent 82% yield. Subsequent alkene reduction and debenzylation of **10** H_2, Pd/C in MeOH gave **12** which was protected as benzyl ether **15** and dibrominated with NBS to give **18**. On the other hand chemoselective hydrogenation of the C–C double-bond of **10** and **11** was performed by reduction with 2-nitrobenzenesulfonylhydrazide,[17] obtained *in situ* by mixing hydrated hydrazine and 2-nitrobenzenesulfonylchloride, to afford **13** and **14** in excellent yield which were subsequently benzylated to ethers **15** and **16**, respectively. This protocol could lead to different protections of the three hydroxyl functions on the linear diarylheptanoid; indeed acetylation of **13** afforded **17** in quantitative yield. Subsequent functionalization of **15** and **16** by NBS in CH_3CN afforded the dibromo-**18** and the iodo-bromo-diarylheptanoid **19** respectively, while treatment of **16** and **17** with NIS resulted in the formation of the bis-iodo **20** and **21** respectively (Scheme 6).

Having in hand the linear diarylheptanoids **15–21**, the challenging macrocyclization step was explored. In a first attempt drawing inspiration from an intramolecular biaryl macrocyclization involving C–H arylation with arylhalide reported by Fagnou[18] in the total synthesis of allocolchicine, we applied the same reaction conditions, *i.e.* $Pd(OAc)_2$, DavePhos with K_2CO_3 in DMA, to the oxidative macrocyclization of the iodinated diarylheptanoid **16**. Unfortunately we obtained the deiodinated product together with some other unidentified products (Scheme 7).

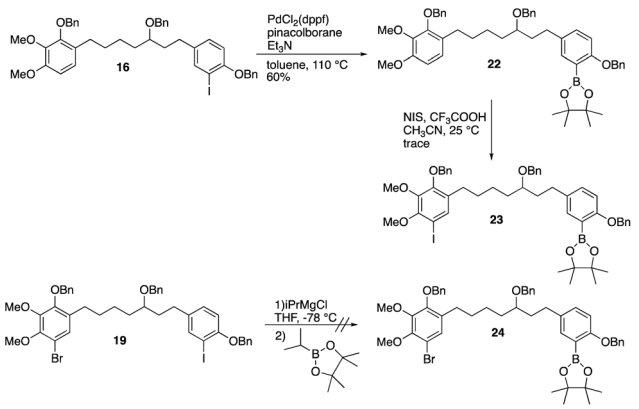


Scheme 7 Oxidative macrocyclization of **16**.

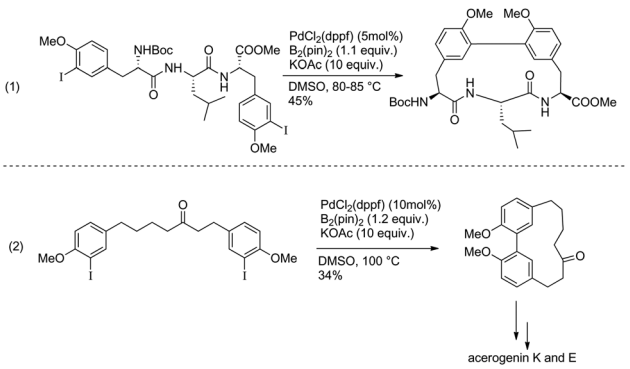
Therefore we decided to explore the intramolecular Suzuki cross coupling reaction. Accordingly we tried to synthesize the corresponding precursors bearing a boronic ester and a halide.

Starting from **16**, palladium-catalysed borylation afforded smoothly the pinacol boronic ester **22** which was then subjected to the iodination with NIS, CF_3COOH in CH_3CN. Unfortunately only a trace amount of the iodinated compound **23** was obtained. We suspected the *ipso*-substitution of the boronic acid with iodine.[19] Moreover a chemoselective magnesium–iodine exchange on substrate **19** followed by addition of the borane species did not allow one to obtain the corresponding boronic ester **24** (Scheme 8).

Consequently we turned our attention to the domino Miyaura arylborylation-intramolecular Suzuki cross-coupling reaction[20] inspired by the macrocyclization reported by Zhu[21] involving such a domino process in the frame of the total synthesis of biphenomycin A, a 15-membered *meta*, *meta* cyclophane. As depicted in Scheme 9 (1), the desired product was obtained in 45% yield after numerous attempts which clearly demonstrated the delicate outcome of this reaction and that little variations of the reaction conditions could drastically lower the yield of the cyclization to 10% or trace amounts of products. Three years later Usuki[22] *en route* to the total synthesis of acerogenin E and K applied Zhu's conditions for the macrocyclization of a di-iodo linear diarylheptanoid and they obtained the 13-membered *meta*, *meta* cyclophane in 35% yield showing again in all attempts performed, a strong influence of the reaction conditions and the molarity of this crucial macrocyclization (Scheme 9 (2)). Such a Suzuki–Miyaura domino process was also employed by Hutton[23] in the total synthesis of mycocyclosin.



Scheme 8 Synthesis of Suzuki–Miyaura cross-coupling precursors.

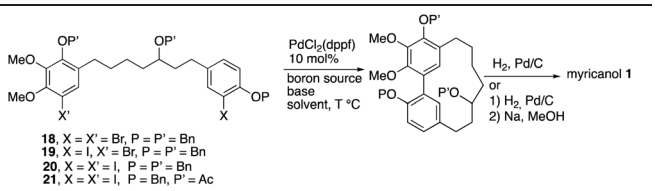


Scheme 9 Domino-Suzuki–Miyaura macrocyclization by Zhu and Usuki.

Taking into account these encouraging results, we decided to apply the domino Miyaura arylborylation-intramolecular Suzuki cross-coupling reaction on our linear diarylheptanoids to obtain the 13-membered *meta*, *meta* cyclophane of myricanol. Table 1 summarizes the trials starting from the different di-halogenated substrates with different protections of the hydroxyl groups. With the di-brominated substrate **18** bearing three benzyloxy groups following exactly the conditions reported by Zhu *i.e.* $PdCl_2(dppf)$, $B_2(pin)_2$, KOAc in DMSO (0.002 M) at 80 °C, we did not observe the formation of the macrocycle (Table 1, entry 1). However replacing KOAc by NaOAc led to the desired 13-membered ring of benzylated myricanol which after quantitative debenzylation afforded myricanol **1** in 10% yield over 2 steps (Table 1, entry 2). The ^{1}H-NMR spectra were identical to the one reported for the myricanol natural product.[2f] Encouraged by this result, an extensive optimization study by changing the solvent (dioxane), the boron source (PinB-H) and the temperature (80 to 100 °C) did not improve the reactivity. Moreover no macrocyclization occurred starting from the bromo-iodo or the bis-iodo substrates **19** and **20** (Table 1, entries 3 and 4). Surprisingly, starting from the bis-iodo **21** bearing two acetoxy groups, myricanol was obtained after successive deacetylation (Na in MeOH) and debenzylation in a comparable yield of 12% over 3 steps.

Finally our macrocyclization's yields are in agreement with the one obtained by Whiting[9] in the Ni(0) catalyzed process (7.3%). Importantly the crucial difference between Zhu's and Usuki's studies and ours which could explain the decrease of the macrocyclization's yield is that their linear diarylheptanoids are symmetrical exhibiting the same electronic properties of the two aryl moieties involved in the biaryl coupling.

Table 1 Intramolecular Suzuki–Miyaura process



18, X = X' = Br, P = P' = Bn
19, X = I, X' = Br, P = P' = Bn
20, X = X' = I, P = P' = Bn
21, X = X' = I, P = Bn, P' = Ac

Entry	Substrate	Boron source	Base 10 equiv.	Solvent (0.002 M)	*T*, °C	Yield of **1**
1	**18**	$(BPin)_2$	KOAc	DMSO	80	—
2	**18**	$(BPin)_2$	NaOAc	DMSO	80	10%
3	**19**	$(BPin)_2$	NaOAc	DMSO	100	—
4	**20**	$(BPin)_2$	NaOAc	DMSO	100	Trace
5	**21**	$(BPin)_2$	KOAc	DMSO	80	12%

Reagent and conditions: Substrate (1 equiv.), boron source (1.2 equiv.), base (10 equiv.), solvent (0.002 M), 24 h.

Conclusion

In conclusion we have reported herein the total synthesis of racemic myricanol in 4.9% yield over 9 steps from methyl 3-(4-benzyloxyphenyl)propanoate. This strategy involved a convergent access to the linear diarylheptanoids through a cross-metathesis in excellent yields and a Suzuki–Miyaura intramolecular cross-coupling reaction to perform the final macrocyclization. This third total synthesis of racemic myricanol can undoubtedly compete with the two previous one described by Whiting[9b] and Dickey.[6]

Experimental section

Materials, chemicals, and equipment

Commercially obtained reagents and solvents were used as received from Sigma Aldrich, TCI and Alfa Aesar. Et_2O, 1,4-dioxane and THF were dried by distillation over sodium/benzophenone. DCM was dried over CaH_2 under argon. Diisopropylamine and triethylamine were dried over KOH under argon. Melting ranges (M.p.) given were found to be reproducible after recrystallization.

NMR spectra were recorded on a Bruker Avance (400 MHz and 300 MHz) and on a Varian (400 MHz and 500 MHz). Samples were prepared using $CDCl_3$. Chemical shifts were referred to 7.27 ppm (^{1}H) and 77.00 ppm (^{13}C) for $CDCl_3$. Chemical shifts are expressed in parts per million (ppm) and coupling constants *J* in hertz. Multiplicities were abbreviated as s (singlet), bs (broad singlet) d (doublet), t (triplet), q (quartet) and m (multiplet) for ^{1}H-NMR. For ^{13}C-NMR q is referred to a quaternary carbon.

Purifications were performed by column chromatography on silica gel by using MERCK silica (70–230 mesh, Merck). Reactions were monitored by analysis over thin layer chromatography (TLC) with Alugram® Xtra SIL G/UV (Macherey-Nagel) plates and 0.25 mm Merck silica-gel (60-F254) plates. TLC was visualized by UV fluorescence at 250 nm and revealed with a solution of anisaldehyde (5.1 mL of *p*-anisaldehyde, 2.1 mL of acetic acid, 6.9 mL of concentrated sulfuric acid, 186 mL of EtOH 95%).

Mass spectra were recorded by using a Hewlett Packard GC/MS 6890-5973 with an EI source. The angles of rotation were measured on a PerkinElmer Polarimeter 341 and denoted as specific rotations: $[\alpha]_D^{20}$.

1-(Allyloxy)-2,3-dimethoxybenzene (3).[11] To a solution of 2,3-dimethoxyphenol (46.3 mmol, 9.0 g) in acetone (185 mL), K_2CO_3 (92.6 mmol, 12.8 g) was added and after 10 min allyl bromide (55.5 mmol, 4.72 mL) was added. The reaction mixture was stirred at reflux for 5 h until complete transformation of the starting phenol and then quenched with H_2O and extracted with EtOAc (3 × 50 mL mmol^{-1}). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude reaction was purified through a silica pad to afford the desired **3** (9.0 g, 46.3 mmol, 99% yield) as a brown oil. R_f = 0.5 (petroleum ether/Et_2O 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.59 (d, J = 5.2 Hz, 2H, Ar–OCH_2), 5.26 (dd, 1H, J_{cis} = 10.4 Hz, 0.8 Hz, CH-allyl), 5.39 (dd, J_{trans} = 17.2 Hz, 0.8 Hz, 1H, CH-allyl), 6.04 (m, 1H, CH-allyl), 6.57 (d, J = 8.4 Hz, 2H, 2Ar–H), 6.94 (t, J = 8.0 Hz, 1H, Ar–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 56.1, 60.8, 69.9, 105.5, 107.2, 117.4, 123.4, 133.5, 138.7 (q), 152.5 (q), 153.7 (q); **GC-MS(EI)** m/z 194 $[M]^+$ (100), 179 (10), 153 (80), 138 (10), 125 (100), 110 (70), 95 (50); anal. C 68.05, H 7.24%, calcd for $C_{11}H_{14}O_3$, C 68.02, H 7.27%.

6-Allyl-2,3-dimethoxyphenol (2).[11] To a solution of **3** (5.50 mmol, 1.1 g) in dry hexane (10 mL) was added dropwise a 1 M solution of Et_2AlCl in hexane (7.7 mmol, 7.7 mL) at 0 °C and under an inert atmosphere. The mixture was strongly stirred at 0 °C for 1 h 15 min. Formation of an orange solid (gum) was observed. The reaction was quenched by diluting the mixture with hexane (200 mL) and pouring it into a cold aqueous solution of HCl solution (4 M, 350 mL). Dissolution of the orange gum was observed. The mixture was extracted with EtOAc (3 × 200 mL), dried over Na_2SO_4 and evaporated under reduced pressure to dryness to obtain the product **2** (1.1 g, 99%) as a brown oil. R_f = 0.5 (petroleum ether/Et_2O 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.34 (d, J = 6.0 Hz, 2H, CH_2-allyl), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.02 (d, J_{cis} = 10.4 Hz, 1H, CH-allyl), 5.04 (d, J_{trans} = 17.0 Hz, 1H, CH-allyl), 5.88 (bs, 1H, OH), 5.96 (m, 1H, CH-allyl), 6.42 (d, J = 8.4 Hz, 1H, Ar–H), 6.78 (d, J = 8.4 Hz, 1H, Ar–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.7, 56.1, 61.1, 103.6, 115.5, 119.4 (q), 124.3, 135.6, 137.1 (q), 147.4 (q), 150.9 (q); **GC-MS(EI)** m/z 194 $[M]^+$(100), 179 (20), 163 (14), 147 (40); anal. C 68.05, H 7.24%, calcd for $C_{11}H_{14}O_3$, C 68.02, H 7.27%.

3-(4-(Benzyloxy)phenyl)propanal (4). To a solution of methyl 3-(4-benzyloxyphenyl)propanoate (3.70 mmol, 1.0 g) in DCM (30 mL) DIBAL-H (7.4 mL, 1 M in toluene) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (40 mL) at −78 °C. The temperature was allowed to warm to r.t. and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain aldehyde **4** in a mixture with the corresponding alcohol (1 : 1 evaluated by ^{1}H-NMR). The crude product (0.98 g) was dissolved in DCM (15 mL) and Dess–Martin periodinane (3.70 mmol, 1.57 g) was added at room temperature. The mixture was stirred for 2 h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4, filtered and concentrated under reduced pressure to give quantitatively aldehyde **4** (observed on GC-MS). The aldehyde was recovered as a dense viscous white liquid. The crude was rapidly characterized with ^{1}H-NMR and immediately put in a reaction chamber or stocked in the freezer at −20 °C. R_f = 0.4 (cyclohexane/EtOAc 8 : 2), **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.74 (t, J = 7.6 Hz, 2H, CH_2), 2.88 (t, J = 7.6 Hz, 2H, CH_2), 5.04 (s, 2H, CH_2–Bn), 6.89 (d, J = 8.4 Hz, 2H, Ar–H), 7.09 (d, J = 8.5 Hz, 2H, Ar–H), 7.42 (m, 5H, Bn–H), 9.81 (s, 1H, CHO). Identity was confirmed by the literature data.[24]

1-(4-(Benzyloxy)phenyl)hex-5-en-3-ol (5). Procedure A: To a solution of crude aldehyde **4** (4.08 mmol, 0.98 g) in THF (13.6 mL) was added at −78 °C, dropwise and under argon, a solution of allylmagnesium bromide (4.04 mmol, 1 M in diethyl ether). The solution was stirred for 2 h and allowed to warm to r.t. The mixture was then quenched with water (40 mL) and stirred for 10 minutes. The mixture was extracted with DCM (3 × 40 mL) and the organic layers were dried on Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 4 : 1) to obtain product **5** (0.86 g, 75% yield) as a white solid.

Procedure B: To a solution of allyl boronic acid pinacol ester (4.08 mmol) in THF (4 mL) a solution of crude aldehyde **4** (4.08 mmol, 0.98 g) in THF (13.6 mL) was added under argon. The solution was stirred at room temperature for 5 h. The reaction mixture was then quenched with water (40 mL) and stirred for 10 minutes. The mixture was extracted with DCM (3 × 40 mL) and the organic layers were dried on Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 4 : 1) to obtain product **5** (0.90 g, 78% yield) as a white solid. M.p. 62–63 °C; R_f = 0.5 (cyclohexane/EtOAc 6 : 4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.76 (m, 2H, ArCH$_2$CH_2CHOH), 2.18 (m, 1H, OHCHCH_2CH=CH$_2$), 2.34 (m, 1H, OHCHCH_2CH=CH$_2$), 2.63 (m, 1H, ArCH_2), 2.75 (m, 1H, ArCH_2), 3.67 (m, 1H, CHOH), 5.05 (s, 2H, CH_2–Bn), 5.15 (dd, J = 12 Hz, J = 2 Hz, 2H, CH=CH_2), 5.82 (m, 1H, CH=CH$_2$), 6.91 (d, J = 8.5 Hz, 2H, Ar–H), 7.12 (d, J = 8.5 Hz, 2H, Ar–H), 7.37 (m, 5H, Bn–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.1, 38.6, 42.0, 69.9, 70.1, 118.2, 114.8, 127.4, 127.8, 128.5, 129.3, 134.4 (q), 134.6, 137.3 (q), 157.1 (q); **GC-MS (EI)** m/z 282 $[M]^+$(30), 191(40), 91(100), anal. C 80.85, H 7.87%, calcd for $C_{19}H_{22}O_2$, C 80.82, H 7.85%. Identity was confirmed by the literature data.[25]

(*R*)-1-(4-(Benzyloxy)phenyl)hex-5-en-3-ol (5). Method A of Brown's allylation:[12] To a solution of (−)-B-chlorodiisopinocamphenylborane (0.55 mmol, 0.173 g) in dry THF (2.5 mL) allylmagnesium bromide (0.55 mmol, 0.55 mL, 1 M in Et_2O) was added dropwise at −78 °C. The mixture was stirred at this temperature for 1 h and then warmed to room temperature within 1 h 20 min. The reaction mixture was cooled down to −90 °C and a solution of aldehyde **4** (0.42 mmol, 0.10 g) in THF (0.20 mL, 2 M) was added dropwise. The mixture was

maintained at this temperature during the addition. The reaction mixture was stirred for 1 h at −90 °C and then allowed to warm to r.t. within 1 h. The mixture was quenched with 30% H_2O_2 (2 mL) and an aqueous solution of NaOH (2 M, 2 mL) at 0 °C and stirred for 1.5 h at r.t. and then extracted with EtOAc (3 × 10 mL), washed with water (20 mL) and brine (20 mL). Organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to dryness. The crude product was purified by silica gel chromatography (cyclohexane to cyclohexane/EtOAc 4 : 1) to obtain the product as a white solid (0.065 g, 74% yield, 86% ee). The optical purity was determined by HPLC chiral chromatography using a CHIRACEL OD-H column (250 mm, 4.6 mm, 3.5 μm), eluent: 80 : 20 hexane/isopropanol, flow: 0.5 mL min^{-1}, sample concentration: 1 mg mL^{-1}, injection volume: 20 μL, retention time: (*S*: 12.3 min, *R*: 14.5 min).

Method B of Roush's allylation:[13] A solution of triisopropyl borate (4.33 mmol, 1 mL) in dry Et_2O (1.1 mL) and allylmagnesium bromide in Et_2O (4.4 mL, 1 M) was added dropwise simultaneously, but separately, to 1.1 mL of dry Et_2O at −78 °C. This mixture was stirred for 0.5 h at −78 °C, allowed to warm to room temperature and stirred for 3 h. The slurry was recooled to 0 °C, and then an aqueous solution of HCl (4 mL, 1N solution saturated with NaCl) was added dropwise. The mixture was stirred for 15 min at 0 °C and warmed to room temperature, and stirring was continued for 15 min. The organic layer was separated and directly treated with (+)-(*R*,*R*)-diisopropyl L-tartrate (DIPT) (4.74 mmol, 1 mL). The aqueous phase was extracted with dry DCM/Et_2O solution (1 : 5, 3 × 6 mL) and transferred to the Schlenk tube containing first organic layer and (*R*,*R*)-DIPT. The combined organic layers were stirred for 1 h and anhydrous Na_2SO_4 was added. The mixture was stirred for 1 night at r.t. It was then evaporated under reduced pressure to give a clear, slightly yellow, semi viscous liquid (1.23 g) of 4,5-bis(propan-2-yl)(4*R*,5*R*)-2-(prop-2-en-1-yl)-1,2,3-dioxaborolane-4,5-dicarboxylate. A solution of the just prepared crude product in dry toluene (0.8 mL, 0.22 g mL^{-1}) was treated with 4 Å molecular sieves (powder, 90 mg) and was stirred for 15 min. Then, it was cooled to −78 °C, and a solution of starting aldehyde **4** (0.62 mmol, 0.150 g) in dry toluene (1 mL, 0.62 M) was added dropwise. The mixture was stirred for 5 h at the same temperature. The reaction mixture was quenched with NaOH (5 mL, 1 M) and 5 mL of Et_2O. The two phase mixtures were stirred for 30 min at room temperature to hydrolyse DIPT and then were separated extracting with Et_2O (3 × 7 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to dryness to give a crude product. The crude was purified twice by chromatography (cyclohexane to cyclohexane/EtOAc, 4 : 1) affording the desired product **5** (0.11 g, 78% ee) in 64%yield.

Method C for allyltitanation:[14] Allylmagnesium bromide in Et_2O (0.28 mmol, 0.28 mL, 1 M solution) was added dropwise at 0 °C under argon to a solution of (*R*,*R*) Duthaler–Hafner reagent (0.33 mmol, 0.20 g), in dry Et_2O (4 mL, 0.083 M). After stirring for 1.5 h at 0 °C, the slightly orange suspension was cooled to −78 °C and starting aldehyde **4** (0.24 mmol, 0.057 g) dissolved in dry ether (0.75 mL, 0.32 M) was added. The mixture was stirred at −78 °C for 5.5 h after which it was treated with 4 mL of a saturated aqueous solution of NH_4Cl and warmed to room temperature for 15 h. It was filtered over Celite and extracted with ether (3 × 7 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a solid. This crude solid was stirred with pentane (5 mL) and filtered. The filtrate was evaporated under reduced pressure to give a white solid which was purified by silica gel column chromatography (cyclohexane to cyclohexane/EtOAc, 4 : 1) affording the desired product **5** (0.047 g, 90% ee, 70% yield).

Methyl 3-(4-(benzyloxy)-3-iodophenyl)propanoate (6)

Methyl 3-(4-(benzyloxy)phenyl)propanoate (8.17 mmol, 2.2 g), I_2 (8.17 mmol, 1.0 g) and Ag_2SO_4 (8.17 mmol, 2.5 g) were dissolved in DCM (32 mL, 0.25 M) and stirred at room temperature until halogenation, monitored by TLC was completed. The solution was filtered, washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 × 16 mL), H_2O (2 × 16 mL) and brine (2 × 16 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the pure final product **6** (2.91 g, 90% yield) as a white solid. M.p. = 67–70 °C, R_f = 0.5 (cyclohexane/EtOAc 6 : 5) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.59 (t, J = 7.8 Hz, 2H, CH_2), 2.86 (t, J = 7.8 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 5.13 (s, 2H, CH_2–Bn), 6.78 (d, J = 8.5 Hz, 2H, Ar–*H*), 7.11 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.2 Hz, 2H, Ar–*H*), 7.38 (m, 5H, C*H*–Bn), 7.65 (dd, J_{ortho} = 2.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.5, 35.6, 51.6, 76.6, 86.8 (q), 112.7, 127.0, 127.8, 128.5, 129.2, 135.1 (q), 136.6 (q), 139.2 (q), 155.8 (q), 173.1 (q); **GC-MS(EI)** *m*/*z* 396 $[M]^+$(40), 305 (60), 270 (30), 91 (100); anal. C 51.57, H 4.39%, calcd for $C_{17}H_{17}IO_3$, C 51.53, H 4.32%. Identity was confirmed by the literature data.[26]

3-(4-(Benzyloxy)-3-iodophenyl)-*N*-methoxy-*N*-methylpropanamide (7). *N*,*O*-Dimethylhydroxylamine hydrochloride (37.86 mmol, 3.69 g) was dissolved in dry DCM (144 mL) under an inert atmosphere. Then, a solution of $AlMe_3$ (37.86 mmol, 18.93 mL, 2 M in toluene) was added dropwise at room temperature. The mixture was stirred for 30 min and a solution of ester **6** (12.62 mmol, 5.0 g) in dry DCM (54 mL) was added to the mixture. The mixture was heated to reflux overnight becoming yellow. The reaction was slowly hydrolysed (after 20 h) with an aqueous solution of HCl (0.5 M, 40 mL). The aqueous layer was extracted with DCM (3 × 40 mL). The organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried on Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 3 : 2) to obtain the pure product **7** (4.13 g, 77% yield) as a transparent oil. R_f = 0.57 (cyclohexane/EtOAc 4 : 6); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.69 (t, J = 7.5 Hz, 2H, CH_2), 2.86 (t, J = 7.5 Hz, 2H, CH_2), 3.17 (s, 3H, N–CH_3), 3.61 (s, 3H, N–OCH_3), 5.12 (s, 2H, CH_2–Bn), 6.77 (d, J = 8.5 Hz, 2H, Ar–*H*), 7.13 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.0 Hz, 2H, Ar–*H*), 7.38 (m, 5H, Bn–*H*); 7.66 (d, J_{meta} = 1.9 Hz, 1H, Ar–*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.3, 32.2, 33.7, 61.3, 71.0, 86.8 (q), 112.7, 127.0, 127.9, 128.5, 129.5, 136.0 (q), 136.7

(q), 139.3, 155.7 (q), 173.6 (q); anal. C 50.79, H 4.74, N 3.27%, calcd for $C_{18}H_{20}INO_3$, C 50.84, H 4.74, N 3.29%.

3-(4-(Benzyloxy)-3-iodophenyl)propanal (8). To a solution of the previously synthesized Weinreb amide **7** (2.35 mmol, 1.0 g) in DCM (20 mL) was added DIBAL-H (4.70 mL, 1 M in toluene) dropwise at −78 °C. The mixture was stirred at −78 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (30 mL) at −78 °C. The temperature was allowed to warm to r.t. and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde **8** (86% yield evaluated by ^{1}H-NMR).

The aldehyde was recovered as a dense viscous white liquid easily degradable at room temperature and not purifiable by column chromatography. The crude product was rapidly characterized with ^{1}H-NMR and immediately put in a reaction chamber or stocked in the freezer at −20 °C. A not clean ^{13}C-NMR was also obtained, and the characteristic peaks of the aldehyde were individuated. R_f = 0.35 (cyclohexane/EtOAc = 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.75 (t, J = 7.6 Hz, 2H, CH_2), 2.87 (t, J = 7.6 Hz, 2H, CH_2), 5.13 (s, 2H, CH_2–Bn), 6.78 (d, J = 8.4 Hz, 2H, Ar–H), 7.10 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.2 Hz, 2H, Ar–H), 7.39 (m, 3H, Bn–H), 7.49 (d, J = 7.0 Hz, 2H, Bn–H), 7.65 (d, J_{meta} = 2.2 Hz, 1H, Ar–H), 9.81 (s, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.7, 45.3, 71.0, 87.0 (q), 112.8, 127.0, 127.9, 128.5, 129.3, 134.9 (q), 136.5 (q), 139.2, 155.8 (q,), 201.1 (q). **GC-MS (EI)** m/z 366 $[M]^+$(10), 276(25), 91 (100).

1-(4-(Benzyloxy)-3-iodophenyl)hex-5-en-3-ol (9). To a solution of allyl boronic acid pinacol ester (2.73 mmol, 0.53 mL) in THF (2.73 mL, 1 M) a solution of crude aldehyde **8** (2.73 mmol, 1.0 g) in THF (9.10 mL, 0.3 M) was added under argon. The solution was stirred at room temperature for 5 h. The mixture was then quenched with water (27 mL) and stirred for 10 minutes. The reaction mixture was extracted with DCM (3 × 27 mL) and the organic layers were dried on Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 4 : 1) to obtain product **9** (0.80 g, 72% yield) as a white solid. M.p. = 66–68 °C R_f = 0.5 (cyclohexane/EtOAc 6 : 4) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74 (m, 2H, ArCH$_2$CH_2CHOH), 2.16 (m, 1H, OHCHCH_2CH=CH$_2$), 2.29 (m, 1H, OHCHCH_2CH=CH$_2$), 2.61 (m, 1H, ArCH_2), 2.70 (m, 1H, ArCH_2), 3.65 (m, 1H, CHOH), 5.12 (s, 2H, CH_2–Bn), 5.12 (dd, J = 12 Hz, J = 2 Hz, 2H, CH=CH_2), 5.80 (m, 1H, CH=CH$_2$), 6.77 (d, J = 8.5 Hz, 2H, Ar–H), 7.10 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.1 Hz, 2H, Ar–H), 7.40 (m, 5H, Bn–H), 7.65 (d, J_{meta} = 2.1 Hz, 1H, Ar–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.0, 38.4, 42.1, 69.7, 71.0, 86.9 (q), 112.7, 118.5, 127.0, 127.8, 128.5, 129.3, 134.5 (q), 136.7, 136.7 (q), 139.3, 155.5 (q); anal. C 55.92, H 5.13%, calcd for $C_{19}H_{22}IO_2$, C 55.89, H 5.18%.

General procedure of cross-metathesis reaction

To a solution of homoallylic alcohol (**5** or **9**, 1 eq.) and the allylphenol **3** (4 eq.) in dry DCM (0.08 M), a solution of second generation Grubbs catalyst (3 or 15 mol%) in dry DCM (0.02 M) was added dropwise, under an Ar atmosphere at −78 °C. The reaction mixture was stirred at −78 °C and allowed to warm to r.t. for 1 day under stirring. The mixture was evaporated and the crude was purified by column chromatography on silica gel (from pure cyclohexane to cyclohexane/EtOAc, to 3 : 2).

6-(7-(4-(Benzyloxy)phenyl)-5-hydroxyhept-2-en-1-yl)-2,3-dimethoxyphenol (10). The desired product **10** (1.12 g, 81% yield) was obtained according to the general procedure after 24 h from allylphenol **2** (13.0 mmol, 2.5 g), homoallylic alcohol **5** (3.22 mmol, 0.90 g) and 3 mol% of Grubbs catalyst (0.097 mmol, 0.082 g). The addition of catalyst was done rigorously at −78 °C. R_f = 0.35 (cyclohexane/EtOAc 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73 (m, 2H, ArCH$_2$CH_2), 2.21 (m, 1H, OHCHCH_2CH=CH), 2.27 (m, 1H, OHCHCH_2CH=CH), 2.63 (m, 1H, ArCH_2CH$_2$), 2.75 (m, 1H, ArCH_2CH$_2$), 3.32 (d, J = 6.4 Hz, 2H, ArCH_2CH=CH), 3.62 (m, 1H, OHCH), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.05 (s, 2H, OCH_2Bn), 5.46 (m, 1H, CH=CH), 5.72 (m, 1H, CH=CH), 5.88 (s, 1H, OH), 6.42 (d, J = 8.4 Hz, 1H, Ar–H), 6.77 (d, J = 8.4 Hz, 1H, Ar–H), 6.90 (d, J = 8.4 Hz, 2H, Ar–H), 7.11 (d, J = 8.4 Hz, 2H, Ar–H), 7.38 (m, 5H, Bn–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.1, 32.9, 38.6 (OHCHCH$_2$CH$_2$Ar), 40.7 (OHCHCH$_2$CH=CH), 55.8 (OCH$_3$), 60.9, 70.1, 73.1, 103.6, 114.8, 119.5 (q), 124.1, 126.7, 127.6, 128.0, 128.6, 129.3, 132.8, 134.6 (q), 137.4 (q), 137.4 (q), 147.2 (q), 150.8 (q), 157.2 (q); anal. C 80.00, H 7.21%, calcd for $C_{28}H_{32}O_5$, C 74.97, H 7.19%.

(*E*)-6-(7-(4-(Benzyloxy)-3-iodophenyl)-5-hydroxyhept-2-en-1-yl)-2,3-dimethoxyphenol (11). The desired product **11** (0.60 g, 82% yield) was obtained according to the general procedure, after 24 h from allylphenol **2** (5.15 mmol, 1.0 g), homoallylic alcohol **9** (1.28 mmol, 0.52 g) and 15 mol% of Grubbs catalyst (0.19 mmol, 0.163 g). The addition of catalyst was done rigorously at −78 °C. R_f = 0.3 (cyclohexane/EtOAc 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.82–1.65 (m, 2H, ArCH$_2$CH_2), 2.09 (m, 1H, OHCHCH_2CH=CH), 2.37–2.20 (m, 1H, OHCHCH_2CH=CH), 2.81–2.53 (m, 2H, ArCH_2CH$_2$), 3.34 (d, J = 6.4 Hz, 2H, ArCH_2CH=CH), 3.61 (m, 1H, OHCH), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.13 (s, 2H, OCH_2Bn), 5.57–5.40 (m, 1H, CH=CH), 5.83–5.66 (m, 1H, CH=CH), 5.97 (s, 1H, OH), 6.43 (d, J = 8.4 Hz, 1H, Ar–H), 6.78 (d, J = 8.4 Hz, 2H, Ar–H), 7.09 (dd, J_{ortho} = 8.4 Hz, J_{meta} = 2.1 Hz, 1H, Ar–H), 7.45–7.29 (m, 3H, Bn–H), 7.51 (d, J = 7.4 Hz, 2H, Bn–H), 7.66 (d, J_{meta} = 2.1 Hz, 1H, Ar–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.6, 32.9, 38.3, 40.7, 55.8, 60.9, 69.8, 71.0, 86.8 (q), 103.5, 112.7, 119.5 (q), 124.0 (q), 126.5, 127.0, 127.8, 128.5, 129.3, 132.9, 135.5 (q), 136.7 (q), 136.9 (q), 139.2, 147.2 (q), 150.8 (q), 155.4 (q); anal. C 58.55, H 5.45%, calcd for $C_{28}H_{31}IO_5$, C 58.54, H 5.44%.

6-(5-Hydroxy-7-(4-hydroxyphenyl)heptyl)-2,3-dimethoxyphenol (12). Substrate **10** (0.37 mmol, 0.2 g) was treated with Pd/C (5%) (0.037 mmol, 0.079 g, 10 mol%) in MeOH (0.74 mL, 0.5 M) in H_2. The reaction was monitored by TLC and after 18 h the mixture was passed through a pad of Celite and washed with MeOH. The solvent was removed under vacuum to afford the pure desired product **12** (0.134 g, 99% yield); R_f = 0.35

(cyclohexane/EtOAc 6 : 4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.67–1.35 (m, 8H, CH_2), 2.66–2.52 (m, 3H, ArCH_2CH$_2$), 2.78–2.64 (m, 1H, ArCH_2CH$_2$), 3.67–3.57 (m, 1H, OHCH), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.39 (d, J = 8.4 Hz, 1H, Ar–H), 6.74 (d, J = 8.4 Hz, 2H, Ar–H), 6.75 (d, J = 8.5 Hz, 1H, Ar–H), 7.05 (d, J = 8.4 Hz, 2H, Ar–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.3, 29.4, 29.9, 31.1, 37.3, 39.2, 55.8, 60.9, 71.4, 103.3, 115.2, 121.7 (q), 124.1, 129.5, 134.2 (q), 135.4 (q), 147.3 (q), 150.4 (q), 153.7 (q); anal. C 70.01, H 7.85%, calcd for $C_{21}H_{28}O_5$, C 69.98, H 7.83%.

6-(7-(4-(Benzyloxy)phenyl)-5-hydroxyheptyl)-2,3-dimethoxyphenol (13). To a cooled (0 °C) and vigorously stirred solution of 2-nitrobenzenesulfonylchloride (0.76 mmol, 0.170 g) and alkene **10** (0.38 mmol, 0.17 g) in dry MeCN (2 mL) was slowly added (dropwise) hydrazine hydrate (1.53 mmol, 0.05 mL). The resulting suspension was allowed to slowly warm to room temperature, stirring vigorously for all night long. After 18 h of reaction, the crude was filtered and washed with EtOAc. The residue was dried over Na_2SO_4, filtered and dried under vacuum. The crude was subsequently purified by using a short silica gel pad to obtain the desired compound **13** (0.162 g, 95% yield). R_f = 0.4 (cyclohexane/EtOAc 6 : 4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65–1.33 (m, 8H, CH_2), 2.60–2.44 (m, 3H, ArCH_2CH$_2$), 2.80–2.62 (m, 1H, ArCH_2CH$_2$), 3.67–3.57 (m, 1H, OHCH), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.05 (s, 2H, CH_2–Bn), 6.41 (d, J = 8.4 Hz, 1H, Ar–H), 6.78 (d, J = 8.4 Hz, 2H, Ar–H), 6.91 (d, J = 8.4 Hz, 2H, Ar–H), 7.12 (d, J = 8.4 Hz, 2H, Ar–H), 7.45–7.33 (m, 5H, Bn–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.3, 29.3, 29.9, 31.1, 37.4, 39.2, 54.8, 60.8, 70.0, 71.3, 103.3, 114.8, 121.6 (q), 124.0, 127.5, 127.9, 128.6, 129.3, 134.6 (q), 135.4 (q), 137.2 (q), 147.3 (q), 150.4 (q), 156.0 (q). Anal. C 74.66, H 7.64%, calcd for $C_{28}H_{34}O_5$, C 74.64, H 7.61%.

6-(7-(4-(Benzyloxy)-3-iodophenyl)-5-hydroxyheptyl)-2,3-dimethoxyphenol (14). To a cooled (0 °C) and vigorously stirred solution of 2-nitrobenzenesulfonylchloride (1.04 mmol, 0.231 g) and alkene **11** (0.52 mmol, 0.30 g) in dry MeCN (2.6 mL) was slowly added (dropwise) hydrazine hydrate (2.08 mmol, 0.07 mL). The resulting suspension was allowed to slowly warm to room temperature and to stir vigorously for all night long. After 18 h of reaction, the crude was filtered and washed with EtOAc. The residue was dried on Na_2SO_4, filtered and concentrated *in vacuo*. The crude was subsequently purified by using a short silica gel pad to obtain the desired compound **14** (0.27 g, 91% yield). R_f = 0.45 (cyclohexane/EtOAc 6 : 4) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.82–1.30 (m, 8H, CH_2), 2.65–2.51 (m, 3H, ArCH_2CH$_2$), 2.78–2.65 (m, 1H, ArCH_2CH$_2$), 3.68–3.54 (m, 1H, OHCH), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.13 (s, 2H, CH_2–Bn), 5.87 (bs, 1H, OH phenolic), 6.41 (d, J = 8.5 Hz, 1H, Ar–H), 6.77 (d, J_{ortho} = 8.5 Hz, 2H, Ar–H), 7.10 (dd, J_{ortho} = 8.3 Hz, J_{meta} = 2.0 Hz, 1H, Ar–H), 7.32 (t, J = 7.3 Hz, 1H, Bn–H), 7.40 (t, J = 7.4 Hz, 2H, Bn–H), 7.50 (d, J = 7.4 Hz, 2H, Bn–H), 7.65 (d, J = 2.0 Hz, 1H, Ar–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.3, 29.4, 29.9, 30.6, 37.4, 39.0, 55.8, 60.9, 71.0, 71.1, 86.8 (q), 103.3, 112.7, 121.6 (q), 124.0, 127.0, 127.8, 128.5, 129.3, 135.4 (q), 136.7 (q), 136.9 (q), 139.3, 147.3 (q), 150.4 (q), 155.4 (q). Anal. C 58.36, H 5.78%, calcd for $C_{28}H_{33}IO_5$, C 58.34, H 5.77%.

General procedure of benzylation of compounds 12 and 14

To a solution of compound **12** or **14** (1 eq.) in anhydrous DMF (0.25 M) NaH 60% dispersion in mineral oil (2.5 eq.) was added at 0 °C. The mixture was stirred for almost 10 min after which benzyl bromide (1.2 eq.) and NaI (0.07 eq.) were added. The reaction mixture was stirred at room temperature until complete benzylation of the starting material. The reaction was quenched at 0 °C adding slowly a saturated aqueous solution of NH_4Cl (25 mL mmol^{-1}). The aqueous phase was extracted with EtOAc (3 × 30 mL mmol^{-1}). The combined organic layers were washed with brine. The resulting organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel to remove excess of DMF and benzylbromide.

2-(Benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)phenyl)heptyl)-3,4-dimethoxybenzene (15). The desired product was obtained after 15 h of benzylation of **12** (2.22 mmol, 1.0 g) following the general procedure reported above. Purification by column chromatography (cyclohexane/EtOAc 8 : 2) furnished compound **15** (1.05 g, 75%) as a transparent oil. R_f = 0.5 (cyclohexane/EtOAc 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.68–1.35 (m, 8H, CH_2), 2.55–2.49 (m, 3H, ArCH_2CH$_2$), 2.70–2.62 (m, 1H, ArCH_2CH$_2$), 3.50–3.30 (m, 1H, OHCH), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.47 (AB$_{system}$, J = 6.0 Hz, $\Delta\nu$ = 12 Hz, 2H, CH_2-Bn, aliphatic chain), 5.05 (s, 4H, CH_2-Bn), 6.63 (d, J = 8.4 Hz, 1H, Ar–H), 6.82 (d, J = 8.4 Hz, 1H, Ar–H), 6.89 (d, J = 8.4 Hz, 2H, Ar–H), 7.07 (d, J = 8.4 Hz, 2H, Ar–H), 7.45–7.33 (m, 15H, Bn–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.2, 29.7, 30.7, 31.0, 33.5, 35.9, 56.0, 60.9, 70.1, 70.7, 75.1, 78.3, 107.4, 114.7, 123.8, 127.4, 127.5, 127.8, 127.9, 127.9, 128.1, 128.3, 128.4, 128.5, 129.0 (q), 129.3, 134.9 (q), 137.2 (q), 138.0 (q), 139.0 (q), 142.4 (q), 150.7 (q), 151.9 (q), 156.9 (q); anal. C 79.99, H 7.36%, calcd for $C_{42}H_{46}O_5$, C 79.97, H 7.35%.

2-(Benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-iodophenyl)heptyl)-3,4-dimethoxybenzene (16). The desired product was obtained after 15 h of benzylation of **14** (1.21 mmol, 0.70 g) following the general procedure reported above. After purification by column chromatography on silica gel (cyclohexane/EtOAc 8 : 2) compound **16** was obtained (0.65 g, 71%) as a transparent oil. R_f = 0.55 (cyclohexane/EtOAc 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.55–1.39 (m, 6H, CH_2), 1.81–1.74 (m, 2H, CH_2), 2.55–2.48 (m, 3H, ArCH_2CH$_2$), 2.65–2.60 (m, 1H, ArCH_2CH$_2$), 3.40–3.34 (m, 1H, OHCH), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.46 (AB$_{system}$, J = 12 Hz, $\Delta\nu$ = 21 Hz, 2H, CH_2–Bn, aliphatic chain), 5.05 (s, 2H, CH_2–Bn), 5.13 (s, 2H, CH_2–Bn), 6.64 (d, J = 8.4 Hz, 1H, Ar–H), 6.76 (d, J = 8.4 Hz, 1H, Ar–H), 6.83 (d, J = 8.4 Hz, 2H, Ar–H), 7.02 (dd, J_{ortho} = 8.4 Hz, J_{meta} = 2.0 Hz, 1H, Ar–H), 7.53–7.33 (m, 15H, Bn–H), 7.60 (d, J_{meta} = 2.0 Hz, 1H, Ar–H);**^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.1, 29.7, 30.3, 31.0, 33.5, 35.7, 56.1, 60.9, 70.8, 71.0, 75.1, 78.1, 86.8 (q), 107.4, 112.7, 123.8, 127.0, 127.5, 127.8, 127.8, 127.9, 128.1, 128.4, 128.4, 128.5, 129.0 (q), 129.2, 136.7 (q), 137.2 (q), 138.1 (q), 138.9 (q), 139.2 (q), 142.5 (q), 150.8 (q), 151.9 (q), 155.4 (q). Anal. C 66.65, H 5.99%, calcd for $C_{42}H_{45}IO_5$, C 66.66, H 5.99%.

2-(Acetoxy)-1-(5-(acetoxy)-7-(4-(benzyloxy)phenyl)heptyl)-3,4-dimethoxybenzene (17). To a solution of compound **13** (0.200 mmol, 0.090 g) in pyridine (0.5 mL) was added acetic anhydride (0.5 mL). The solution was stirred at room temperature until complete transformation of the starting material. After 2 h the reaction was quenched with water and the aqueous layer was extracted with EtOAc (3 × 10 mL $mmol^{-1}$). The resulting organic extracts were washed with a saturated aqueous solution of NaCl. The organic layers were collected, dried on Na_2SO_4 and concentrated under reduced pressure to afford the pure product **17** (0.104 g, quant). R_f = 0.7 (petroleum ether/EtOAc 7 : 3); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.32 (m, 2H, CH_2), 1.52 (m, 4H, CH_2), 1.81 (m, 2H, CH_2), 2.03 (s, 3H, CH_3CO), 2.33 (s, 3H, CH_3CO), 2.43 (m, 2H), 2.53 (m, 2H), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.91 (m, 1H, CHOAc), 5.03 (s, 2H, CH_2Ph), 6.73 (d, J = 8.0 Hz, 1H, Ar–H), 6.85 (d, J = 8.0 Hz, 1H, Ar–H), 6.88 (d, J = 8.5 Hz, 2H, Ar–H), 7.06 (d, J = 8.5 Hz, 2H, Ar–H), 7.29–7.43 (m, 5H, Bn–H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.5, 21.2, 25.0, 29.6, 29.9, 30.9, 34.0, 36.0, 56.1, 60.6, 70.1, 73.8, 110.1, 114.8, 123.6, 127.4, 127.5, 127.9, 128.5, 128.6, 129.2, 134.0, 137.2, 142.7, 151.6, 157.1, 169.1, 170.9; anal. C 71.94, H 7.20%, calcd for $C_{32}H_{38}O_7$, C, 71.89; H, 7.16%.

General procedure for bromination of compounds 15 and 16

To a solution of starting aryl substrate **15** or **16** (1 eq.) in ACN (0.25 M) and TFA (0.3 equiv.) was added NBS (1.1 eq.). The mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material, the mixture was quenched with water. Extraction of aqueous layers was done with EtOAc (3 × 30 mL $mmol^{-1}$) and the combined organic layers were dried over Na_2SO_4 and filtered. Concentration of the organic phase under reduced pressure gave the crude product that was purified by silica gel chromatography.

2-(Benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-bromophenyl) heptyl)-5-bromo-3,4-dimethoxybenzene (18). The desired product was obtained from bis-bromination of compound **15** (0.8 mmol, 0.5 g) with 2.2 eq. of NBS, following the general protocol of bromination reported above. After 18 h of reaction, aqueous quenching, organic extraction and silica gel column chromatography (cyclohexane/EtOAc 8 : 2) compound **18** was obtained (0.5 g, 99% yield) as a yellow-brown oil. R_f = 0.5 (cyclohexane/EtOAc 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.88–1.28 (m, 8H, CH_2), 2.51 (t, J = 7.0 Hz, 2H, ArCH_2), 2.69–2.56 (m, 1H, ArCH_2CH$_2$), 2.75–2.69 (m, 1H, ArCH_2CH$_2$), 3.37–3.34 (m, 1H, OCH), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.45 (AB_{system}, J = 12 Hz, $\Delta\nu$ = 21 Hz, 2H, CH_2–Bn, aliphatic chain), 5.01 (s, 2H, CH_2–Bn), 5.13 (s, 2H, CH_2–Bn), 6.83 (d, J = 8.5 Hz, 2H, Ar–H), 6.96 (dd, J = 8.5 Hz, J = 2.1 Hz, 2H, Ar–H), 7.07 (s, 1H, Ar–H), 7.48–7.34 (m, 16H, 15Bn–H, 1Ar–H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.1, 29.6, 30.4, 30.6, 33.4, 35.6, 61.0, 61.1, 70.8, 70.9, 75.2, 77.9, 111.3 (q), 112.3 (q), 113.9, 127.0, 127.3, 127.5, 127.8, 128.0, 128.1, 128.1, 128.4, 128.5, 128.5, 133.1 (q), 133.4 (q), 136.5 (q), 136.7 (q), 137.5, 138.8, 147.6 (q), 149.2 (q), 150.1 (q), 153.1 (q); anal. C 64.02, H 5.66%, calcd for $C_{42}H_{44}Br_2O_5$, C 63.97, H 5.62%.

2-(Benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-iodophenyl) heptyl)-5-bromo-3,4-dimethoxybenzene (19). Di-halogenated product **19** was prepared by treating diarylheptanoid **16** (1.41 mmol, 1.0 g) with NBS (1.69 mmol, 0.30 g) as reported in the general procedure of bromination. After 18 h of reaction the mixture was quenched with water, extracted with EtOAc, dried and evaporated under vacuum and purified by using a silica gel pad to remove the succinimide and to give pure **19** (1.06 g, 90% yield). R_f = 0.55 (cyclohexane/EtOAc 8 : 2) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.58–1.28 (m, 8H, CH_2), 2.52 (t, J = 8.0 Hz, 2H, ArCH_2), 2.56–2.50 (m, 1H, ArCH_2CH$_2$), 2.65–2.55 (m, 1H, ArCH_2CH$_2$), 3.45–3.35 (m, 1H, OCH–Bn), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.46 (AB_{system}, 2H, J = 12 Hz, $\Delta\nu$ = 21 Hz, CH_2–Bn, aliphatic chain), 5.04 (s, 2H, CH_2–Bn), 5.14 (s, 2H, CH_2–Bn), 6.77 (d, J = 8.5 Hz, 1H, Ar–H), 7.05 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, Ar–H), 7.09 (s, 1H, Ar–H), 7.52–7.31 (m, 15H, Bn–H), 7.62 (d, J = 2.1 Hz, 1H, Ar–H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.1, 29.6, 30.2, 30.6, 33.4, 35.7, 61.0, 61.1, 70.8, 71.0, 75.2, 77.9, 86.8 (q), 111.3 (q), 112.7, 125.9, 127.0, 127.3, 127.5, 127.8, 128.0, 128.1, 128.3, 128.5, 128.5, 129.2, 133.4 (q), 136.7 (q), 137.1 (q), 137.5 (q), 139.2, 147.6 (q), 149.3 (q), 150.2 (q), 155.4 (q,). Anal. C 60.40, H 5.33%, calcd for $C_{42}H_{44}BrIO_5$, C 60.37, H 5.31%.

General procedure for iodination of compounds 15, 16, and 17

To a solution of substrate **15**, **16** or **17** (1 eq.) in ACN (0.25 M) and TFA (0.3 eq.) was added NIS (1.1–5.0 eq.). The mixture was stirred at room temperature and followed by TLC, GC-MS or NMR. After disappearance of the starting material, the mixture was quenched with water. Extraction of aqueous layers was done with EtOAc (3 × 30 mL $mmol^{-1}$) and the combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$, dried over Na_2SO_4 and filtered. Concentration of the organic phase under reduced pressure gave the crude product that was purified by silica gel chromatography or if pure used with any further purification.

2-(Benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-iodophenyl) heptyl)-5-iodo-3,4-dimethoxybenzene (20). The di-iodinated product was prepared following the general procedure of iodination described before, by treating diarylheptanoid **15** or **16** with different amounts of NIS. Diarylheptanoid **15** (1 eq., 1.41 mmol, 1.0 g) was treated with 5 eq. of NIS (7.05 mmol, 1.59 g) to give **20** in 70% yield (0.98 mmol, 0.87 g). In this reaction NIS was added portion-wise in 36 h. Diarylheptanoid **16** (1 eq., 1.41 mmol, 1.0 g) treated with 1.2 equiv. of NIS (1.69 mmol, 0.38 g) gave **20** after 18 h. The product **20** (1.24 g, 99% yield) was obtained pure as a yellow oil after a silica gel pad purification to remove the succinimide. R_f = 0.55 (cyclohexane/EtOAc 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.84–1.26 (m, 8H, CH_2), 2.48 (t, J = 8.0 Hz, 2H, ArCH_2), 2.55–2.46 (m, 1H, ArCH_2CH$_2$), 2.67–2.59 (m, 1H, ArCH_2CH$_2$), 3.95–3.33 (m, 1H, OCH–Bn), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.46 (AB_{system}, J = 12 Hz, $\Delta\nu$ = 21 Hz, 2H, CH_2–Bn, aliphatic chain), 5.02 (s, 2H, CH_2–Bn), 5.13 (s, 2H, CH_2–Bn), 6.76 (d, J = 8.5 Hz, 1H, Ar–H), 7.03 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, Ar–H), 7.51–7.29 (m, 16H, 15Bn–H, 1Ar–H), 7.60 (d, J = 2.1 Hz, 1H, Ar–H); **^{13}C**

NMR (100 MHz, $CDCl_3$): δ 25.1, 29.6, 30.3, 30.7, 33.4, 35.7, 60.9, 61.0, 70.8, 71.0, 75.2, 77.9, 85.1 (q), 86.8 (q), 112.7, 127.0, 127.5 (q), 127.6, 127.8, 127.8, 128.0, 128.1, 128.4, 128.4, 128.5, 128.5, 129.2, 133.1 (q), 136.7 (q), 137.1 (q), 137.5 (q), 139.2, 146.7 (q), 151.3 (q), 151.9 (q), 155.4 (q); anal. C 57.17, H 5.03%, calcd for $C_{42}H_{44}I_2O_5$, C 57.15, H 5.02%.

2-(Acetoxy)-1-(5-(acetoxy)-7-(4-(benzyloxy)-3-iodophenyl)heptyl)-5-iodo-3,4-dimethoxybenzene (21). Starting from **17** (0.85 mmol, 0.454 g) and portion-wise addition of NIS (4.4 eq.) after 4 d of reaction and purification by silica gel column chromatography (hexane/EtOAc 8 : 2) compound **21** (0.467 g 70%) was obtained as a pale yellow solid. R_f = 0.6 (hexane/EtOAc 8 : 2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24 (m, 4H, CH_2), 1.56 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 2.04 (s, 3H, CH_3CO), 2.33 (s, 3H, CH_3CO), 2.52 (m, 4H), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.95 (m, 1H, C*H*OAc), 5.12 (s, 2H, CH_2Ph), 6.76 (d, J = 8.4 Hz, 1H, Ar–*H*), 7.07 (dd, J = 8.4 Hz, 2.0 Hz, 1H, Ar–*H*), 7.24 (s, 1H, Ar–*H*), 7.31–7.50 (m, 5H, Bn–*H*), 7.61 (t, J = 2.0 Hz, 1H, Ar–*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.5, 21.2, 25.2, 28.9, 30.4, 33.9, 34.9, 35.8, 56.2, 60.5, 70.9, 73.6, 86.8, 92.2, 112.6, 120.8, 123.6, 126.4, 127.8, 128.5, 129.2, 128.6, 130.7, 136.2, 136.6, 139.1, 141.5, 141.9, 151.9, 155.5, 168.8, 170.8; anal. C 48.91, H 4.63%, calcd for $C_{32}H_{36}I_2O_7$, C 48.87, H 4.61%.

2-(2-(Benzyloxy)-5-(3-(benzyloxy)-7-(2-(benzyloxy)-3,4-dimethoxyphenyl)heptyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22). A flame-dried flask was charged with $PdCl_2$dppf (0.01 mmol, 0.01 g). Vacuum/argon cycle was again repeated in the flask and a solution of starting iodide **16** (0.12 mmol, 0.09 g) in toluene (1 mL) was added. Pinacolborane (0.20 mmol, 0.03 mL) and Et_3N (0.13 mL) were added under argon. The flask was sealed and heated to 110 °C for 20 h. After cooling to rt, the reaction mixture was hydrolysed with aqueous saturated NH_4Cl (3 mL) and extracted with EtOAc (3 × 5 mL). The crude was purified by column chromatography on silica gel (cyclohexane/EtOAc 7 : 3) to eliminate the excess of pinacolborane. A second purification was made (cyclohexane/EtOAc 9 : 1) which afforded the right product as a deliquescent white solid (66 mg, 60% yield). R_f = 0.3 (cyclohexane/EtOAc 9 : 1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.87–1.28 (m, 8H, CH_2), 1.38 (s, 12H, CH_3-pinacol), 2.56 (t, J = 8.0 Hz, 2H, ArCH_2), 2.71–2.52 (m, 2H, ArCH_2CH_2), 3.48–3.36 (m, 1H, OC*H*–Bn), 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.49 (s, 2H, CH_2–Bn, aliphatic chain), 5.06 (s, 2H, CH_2–Bn), 5.11 (s, 2H, CH_2–Bn), 6.64 (d, J = 8.5 Hz, 1H, Ar–*H*), 6.84 (d, J = 8.5 Hz, 1H, Ar–*H*), 6.87 (d, J = 8.5 Hz, 1H, Ar–*H*), 7.60–7.29 (m, 16H, 15Bn–*H*, 1Ar–*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.0, 25.2, 29.7, 30.8, 31.1, 33.6, 36.0, 56.1, 60.9, 70.2, 70.8, 75.2, 78.4, 83.5 (q), 107.4, 112.3, 123.8, 126.8, 127.2, 127.4, 127.8, 127.8, 128.0, 128.1, 128.3, 128.4, 128.9, 132.3, 134.4 (q), 136.5, 137.8 (q), 138.0 (q), 139.0 (q), 142.4 (q), 150.7 (q), 151.8 (q), 161.6 (q); **^{11}B NMR** (128 MHz, $CDCl_3$) δ 31.34; anal. C 76.20, H 7.60%, calcd for $C_{48}H_{57}BO_7$, C 76.18, H 7.59%.

Myricanol (1) To a flask containing KOAc (2.2 mmol, 0.211 g), Pd(dppf)2Cl2 (0.022 mmol, 0.018 g), bis(pinacolato) diboron (0.268 mmol, 0.068 g) and diiodide **21** (0.22 mmol, 0.173 g) was added degassed DMSO (10 mL, 0.02 M). After being heated under argon at 80 °C for 24 h, the reaction mixture was allowed to cool at room temperature and then quenched with a saturated aqueous solution of NH_4Cl (40 mL). The mixture was extracted with EtOAc (3 × 40 mL). The organic layers were separated, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified on silica gel chromatography (pure petroleum ether to petroleum ether/EtOAc 9.5 : 0.5). The recollected fractions (except for the individuated unreacted starting material and its dehalogenated derivatives) were subjected to deacetylation with a catalytic amount of Na in MeOH (2 mL) for 2 h at room temperature. The work-up of reaction was carried out on adding water and extracting with EtOAc. The crude was subjected to catalytic debenzylation by using Pd/C 10%, H_2 and MeOH as the solvent. After purification on silica gel chromatography (petroleum ether/EtOAc 7 : 3) myricanol was obtained (0.009 g, 12% over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52–1.62 (m, 3H), 1.66–1.76 (m, 2H), 1.88–2.00 (m, 3H), 2.28–2.41 (m, 1H), 2.50–2.62 (m, 1H), 2.81 (dt, J = 18 Hz, J = 2.4 Hz, 1H), 2.85–2.94 (m, 2H), 3.88 (s, 3H), 4.01 (s, 3H), 4.06–4.16 (m, 1H), 5.82 (bs, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.91 (s, 1H), 7.10 (dd, J = 8.3 Hz, J = 2.2 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 7.65 (s, 1H).

Conflicts of interest

There are no conflicts to declare.

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