Synthesis of Phenolic Components of Grains of Paradise

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ABSTRACT: Two vanilloids, (5*E*)-8-(4-hydroxy-3-methoxyphenyl)oct-5-en-4-one (**1**) and 4-[3-hydroxydecyl]-2-methoxyphenol (**2**), isolated from the dried seeds of Grains of Paradise (*Aframomum melegueta*), were synthesized; the latter compound was made as the *S*-enantiomer and the material derived from the seeds was found to be a 1:1.7 mixture of the *R* and *S* isomers. The synthetic route used should allow the preparation of analogs having extended alkyl chains and consequently different lipophilicity, and **3**, a homolog of **2**, was also prepared.

Keywords:
Grains of Paradise
anti-obesity
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Wittig reaction
Horner-Wadsworth Emmons olefination
Hydrogenolyis

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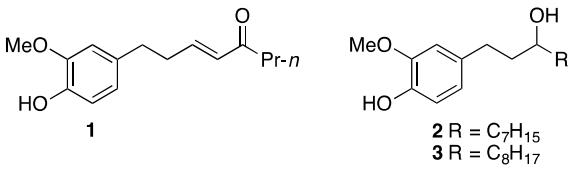
1. Introduction

Grains of Paradise is one of the names given[1] to the dried seeds of the tropical plant *Aframomum melegueta*, which is widely distributed throughout West Africa. The seeds have long been used in folkloric herbal remedies[2] and are known to have, among other properties, antioxidant,[3] antibacterial[4] and antinociceptive[1] activity. In preliminary studies (HH and TM)[5] it was found that intake of a methanol extract of Grains of Paradise has an anti-obesity effect in mice and lowers hepatic and serum fats. A reduction in visceral fat has also been observed in humans, using an ethanol extract.[6] Some of the phenolic compounds present in the seeds[7] were also

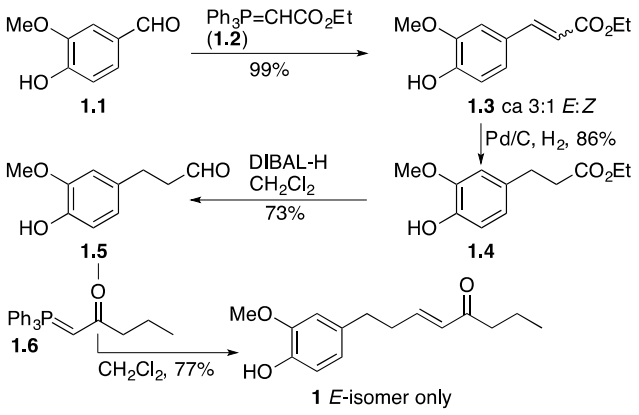
isolated (HH and TM)[8] and found to share structural features with vanilloids that were already known[9] to have anti-obesity properties. Consequently, it was of interest to establish if the vanilloids from *Aframomum melegueta* were responsible for the anti-obesity effect. Most of the compounds could be isolated in adequate quantities and several were found to possess anti-obesity properties,[10] but the isolated amounts of the vanilloids **1**[8] and **2**[8,11] were insufficient for biological evaluation in mice. For this reason we have synthesized both **1** and **2**, as well as the homolog **3**, and the synthetic work is described below. Independently of the initial report of **1**[8] the same compound was isolated from a different plant.[12] Compound **2** has been isolated as a *racemate* by hexane extraction from *Aframomum melegueta*;[13] and by supercritical CO_2 extraction from the rhizomes of ginger (*Zingiber officinale* Roscoe),[14] and has been prepared[15] in *racemic* form by $NaBH_4$ reduction of [6]-shogaol. Racemic **2** has been found to promote cholesterol efflux from THP-1-derived macrophages.[16] Our sample of natural **2**,[8,11] as isolated, contained a small impurity[8] and had $[\alpha]_D$ –0.46 (*c* = 0.29 g/100 mL). After we had prepared the *S*-enantiomer we established that the natural material was not racemic but was a 1:1.7 mixture of the *R* and *S* enantiomers.[17]



2. Results and discussion

2.1 Synthesis of compound 1

Compound **1** was synthesized by the method summarized in Scheme 1. Vanillin (**1.1**) underwent efficient Wittig reaction with ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate (**1.2**) to form a 3:1 mixture of *E* and *Z* esters **1.3**.[18] Hydrogenation afforded the saturated ester **1.4** and DIBAL-H reduction then gave aldehyde **1.5**.[18] This underwent Wittig reaction with the readily available



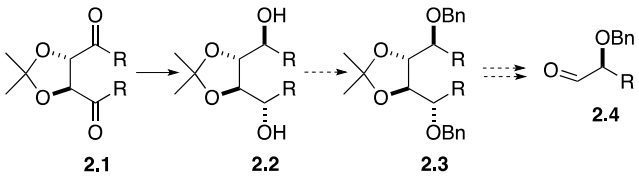
Scheme 1. Synthesis of compound 1

keto ylide **1.6**,[19] and the resulting enone **1** could be isolated in good yield as the desired *E* isomer which was spectroscopically identical with the compound extracted[8] from Grains of Paradise. Unlike the natural material which was an oil, the synthetic enone was obtained as a crystalline solid, mp 35–38 °C.

2.2 Synthesis of compound 3

We first developed a route to the unnatural homolog **3** before making the natural material **2**.

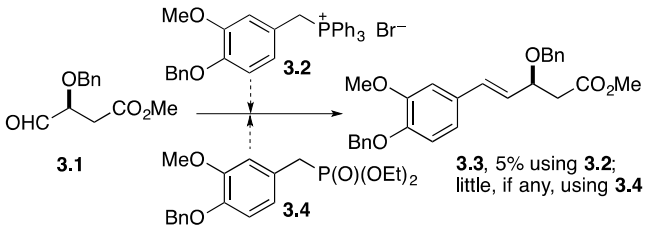
As the absolute configuration and optical purity of compound **2** was unknown at the time, we made the arbitrary decision to use tartaric acid for our work, along the lines shown in Scheme 2. This plan was based on a report[20] that the diketone **2.1** (R = *n*-C_5H_{11}) derived from D-(–)-tartaric acid could be reduced stereoselectively with K-Selectride to the diol **2.2** (R = *n*-C_5H_{11}). However, when we attempted to follow an analogous sequence to make **2.4** (R = *n*-C_8H_{17}), using *n*-octylmagnesium bromide instead of the reported pentyl reagent, we obtained low yields (ca



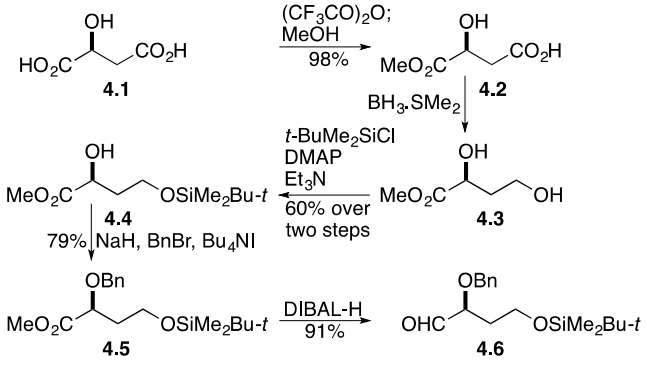
Scheme 2. Initial approach based on tartaric acid

43%) of the desired diketone **2.1** (R = C_8H_{17}). This outcome prompted us to change to a route based on L-(–)-malic acid. The enantiomer is, of course, available, although it is more expensive, and there would also be an opportunity to invert the stereochemistry of the hydroxyl-bearing carbon at a suitable stage.

Initially, we converted malic acid into its *O*-benzyl dimethyl ester and reduced that selectively (Scheme 3) to methyl (2*S*)-4-oxo-3-(phenylmethoxy)butanoate (**3.1**),[21] but in our hands (working at –78 °C instead of the reported[21a] temperature of –90 °C) the yield in the reduction step (DIBAL-H) was low (47%). In addition, attempts to form the olefin **3.3** either by Wittig reaction with the phosphonium salt **3.2**[22] or by the Horner-Wadsworth-Emmons process, using phosphonate **3.4**,[23] were unsatisfactory (Scheme 3). Accordingly, we modified the route to one that involves conversion of malic acid into aldehyde **4.6** (Scheme 4), followed by olefination with a benzylic phosphonate.



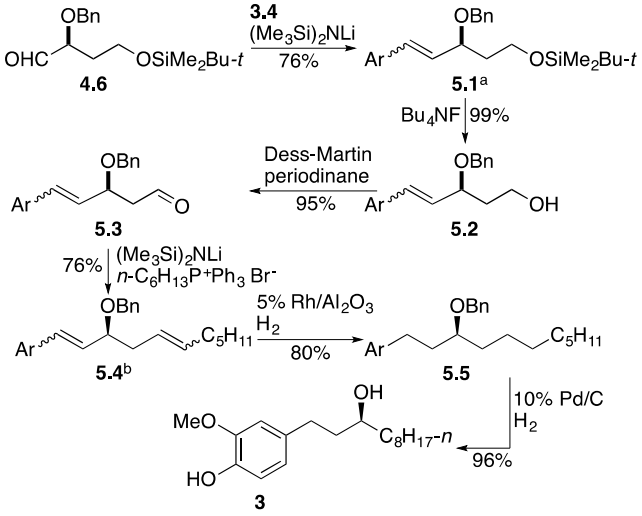
Scheme 3. Initial approach based on malic acid



Scheme 4. Synthesis of aldehyde 4.6

The aldehyde **4.6** was made by regioselective esterification of L-malic acid (**4.1**→**4.2**), following a literature procedure.[24] The remaining carboxyl group was then easily reduced[24] with

$BH_3.SMe_2$ and the resulting primary hydroxyl was protected by silylation (**4.2**→**4.3**→**4.4**). The next step, *O*-benzylation of the secondary hydroxyl in **4.4** was tried by two methods. Use of freshly-prepared Ag_2O[25] and BnBr in CH_2Cl_2[26] gave the desired product in 30% yield, but the efficiency of the benzylation was improved (79% yield) by using NaH and BnBr in DMF in the presence[27] of Bu_4NI. Finally, DIBAL-H reduction afforded the aldehyde **4.6** needed as one of the components for the intended olefination.



[a]Ar = (4-benzyloxy-3-methoxy)phenyl. [b]A single isomer was obtained when starting from *E*-**5.3**.

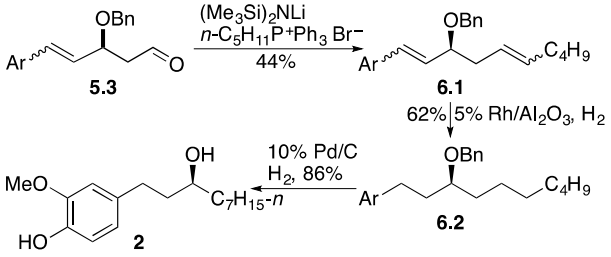
Scheme 5. Olefination of aldehyde 4.6 [Ar = (4-benzyloxy-3-methoxy)phenyl]

Deprotonation of phosphonate **3.4** with $(Me_3Si)_2NLi$ in a 4:1 (v/v) mixture of THF and HMPA,[28] followed by addition of aldehyde **4.6** gave the olefins **5.1**. In the first experiment the *E* and *Z* isomers were isolated in yields of 70% and 6%, respectively, but in subsequent work the isomer mixture was used. Use of HMPA in the olefination was essential; without it very low yields were obtained. Desilylation proceeded without incident, but oxidation of the resulting alcohols (**5.2**) with PCC gave a very low yield. Fortunately, the Dess-Martin periodinane was extremely effective in generating the desired aldehyde **5.3** (95% yield), and a Wittig reaction then took the route as far as **5.4**, which was obtained as a mixture of isomers. We had originally intended to subject **5.4** to hydrogenation of the double bonds over Pd/C and then in situ hydrogenolysis of the benzyloxy groups but, in the event, significant hydrogenolysis of the allylic C—O bond occurred. Therefore **5.4** was first reduced over 5% Rh-Al_2O_3 to saturate the double bonds (monitored by ^1H NMR and tlc), and then the benzyl groups were removed by hydrogenolysis (Pd/C) so as to obtain the target alcohol (**5.4**→**5.5**→**3**).

In order to establish the optical purity of **3** we needed a racemic sample. Several attempts to selectively oxidize the aliphatic hydroxyl of **3** were unsuccessful,[29] but the phenolic hydroxyl was easily benzylated (BnBr, K_2CO_3, 96%) and the remaining secondary hydroxyl could be oxidized with the Dess-Martin reagent. Then reduction ($NaBH_4$) and hydrogenolysis provided a reference sample of racemic **3**. Chiral HPLC analysis served to establish that the ee of (*S*)-**3** was 90%.

2.3 Synthesis of compound 2

With a practical route to (*S*)-**3** we next diverted the advanced intermediate **5.3** to the natural product **2**. To this end, **5.3** was subjected to Wittig reaction with the ylide generated from pentyltriphenylphosphonium bromide (Scheme 6). The resulting dienes were first hydrogenated over Rh-Al_2O_3 and then subjected to hydrogenolysis over Pd/C to afford (*S*)-**2** as a crystalline solid (**6.1**→**6.2**→**2**). To make a racemic sample, the phenolic hydroxyl of (*S*)-**2** was benzylated, following our earlier procedure, and the secondary alcohol was oxidized to a ketone, which was then reduced ($NaBH_4$) and subjected to hydrogenolysis to liberate the phenol. With racemic and optically active samples in hand, chiral HPLC showed that synthetic (*S*)-**2** had an ee of 68% and, surprisingly, that the natural sample was a 1:1.7 mixture of *R* and *S* isomers. We did not establish why the optical purity of (*S*)-**2** is lower than that of the homolog (*S*)-**3**. The negative value of the specific rotation of natural phenolic alcohol **2** must be due to a minor impurity, as the predominance of the *S*-isomer should result in a positive value.



Scheme 6. Conversion of 5.3 to 6.3

3. Conclusions

The two naturally occurring vanilloids **1** and **2**, isolated from the seeds of *Aframomum melegueta*, were synthesized by routes that provide adequate quantities for biological testing and that should allow variation in alkyl chain length with consequent alteration in the lipophilicity of the final vanilloid. Unlike other reports on the isolation of **2**, the natural material was not

racemic but was a 1:1.7 mixture of *R* and *S* isomers, and the present synthetic route should allow biological evaluation of the individual enantiomers since both enantiomers of malic acid are available.

4. Experimental section

4.1 *General procedures*.

Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230−400 mesh). Dry solvents were prepared under an inert atmosphere (N_2) and transferred by syringe or cannula. Unless otherwise indicated, all reactions were done under an inert atmosphere (N_2). The symbols s, d, t, and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Optical rotations were measured at 20 °C. Solutions were evaporated under water pump vacuum, and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometric analyses were done with an orthogonal time-of-flight analyzer, and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer. Gradient flash chromatography was done by stepwise small increases in the proportion of the more polar solvent, as described for the individual experiments.

*Synthesis of (**1**)*

*4.1.1 Ethyl (2E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate and Ethyl (2Z)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate (**1.3**)*[18,30]

Dry PhH (150 mL) was added to a flask containing vanillin (8.0 g, 52.6 mmol) and the Wittig reagent **1.2**[31] (19.0 g, 54.6 mmol). The solution was stirred and heated at 80 °C for 4.5 h (oil bath) by which time the reaction was complete (tlc, silica, 1:1 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (23 × 5 cm), using 1:1 EtOAc-hexane, gave **1.3** (11.638 g, 99%) as an oil which was a mixture of *Z* and *E* isomers (ca 3:1 *E*:*Z*).

In an earlier run we separated the *Z* and *E* isomers. The *Z* isomer had: FTIR ($CDCl_3$, cast) 3419, 2925, 1515, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.31 (t, *J* = 7.0 Hz, 3 H), 3.95 (s, 3 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 5.83 (d, *J* = 13.0 Hz, 1 H), 5.83 (d, *J* = 13.0 Hz, 1 H), 6.81 (d, *J* = 13.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.13 (dd, *J* = 1.5, 8.5 Hz, 1 H), 7.79 (d, *J* = 2.0 Hz, 1 H); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{13}O_4$ $(M–H)^–$ 221.0819, found 221.0816.

The *E* isomer had: FTIR ($CDCl_3$, cast) 3392, 2927, 1514, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 (t, *J* = 7.0 Hz, 3 H), 3.94 (s, 3 H), 4.27 (q, *J* = 7.0 Hz, 2 H), 5.92 (s, OH), 6.31

(d, J = 15.9 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 7.05 (br s, 1 H), 7.09 (br d, J = 8.0 Hz, 1 H), 7.63 (d, J = 15.9 Hz, 1 H); exact mass (electrospray) m/z calcd for $C_{12}H_{13}O_4$ $(M–H)^-$ 221.0819, found 221.0817.

*4.1.2 Ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (**1.4**)*[18,30]

10% Pd/C (1.2 g) was added to a solution of **1.3**[18,30] (*Z*,*E* isomer mixture, 11.8 g, 56.0 mmol) in EtOH (120 mL). The flask was flushed with hydrogen (balloon) several times, then kept under a slight pressure of H_2 (balloon), and the mixture was stirred overnight by which time the reaction was over (tlc, silica, 1:4 EtOAc-hexane). The mixture was diluted with EtOH and passed through a short pad of Celite. Evaporation of the filtrate gave **1.4** (10.2 g, 86%) as an oil which was pure enough for the next step. The material had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, J = 7.2 Hz, 3 H), 2.59 (t, J = 7.2 Hz, 2 H), 2.88 (t, J = 7.6 Hz, 2 H), 3.87 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.48 (s, OH), 6.69 (dd, J = 2.0, 8.0 Hz, 1 H), 6.71 (d, J = 2.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H).

*4.1.3 3-(4-Hydroxy-3-methoxyphenyl)propanal (**1.5**)*[18]

DIBAL-H (1.1 M in cyclohexane, 30 mL, 33 mmol) was added dropwise by syringe to a stirred and cooled (–78 °C) solution of **1.4** (4.23 g, 18.9 mmol) in dry CH_2Cl_2 (200 mL). After the addition, stirring at –78 °C was continued for 3.5 h, and then the mixture was quenched by addition of MeOH (15 mL). Saturated aqueous Rochelle salt (400 mL) was added, the cold bath was left in place but not recharged, and stirring was continued overnight. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 × 23 cm), using first 20% EtOAc-hexane, and then 50% EtOAc-hexane, gave **1.5** (2.5 g, 73%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (t, J = 7.2 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 2 H), 3.88 (s, 3 H), 5.48 (s, OH), 6.67–6.70 (m, 2 H), 6.84 (d, J = 8.0 Hz, 1 H), 9.82 (s, 1 H); exact mass (EI) m/z calcd for $C_{10}H_{14}O_3$ $(M)^+$ 182.0943; found: 182.0943.

*4.1.4 (5E)-8-(4-Hydroxy-3-methoxyphenyl)oct-5-en-4-one (**1**)*

A solution of ylide **1.6**[19,32] (1.3 g, 3.68 mmol) in dry CH_2Cl_2 (24 mL) was added dropwise by syringe to a cooled (ice bath) flask containing **1.5** (552.3 mg, 3.07 mmol) and a magnetic stirring bar. The mixture was stirred and the ice bath was left in place but not recharged. Stirring was continued for 18 h by which time the reaction was over (tlc control, silica, 1:4 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (20 × 2 cm), using 1:3 EtOAc-hexane, gave **1** (1.3 g, 77%) as a pale yellow solid which was a single *E* isomer, corresponding spectroscopically (^{1}H and ^{13}C NMR) to the natural

product: mp 35–38 °C; FTIR ($CDCl_3$, cast) 3418, 2962, 1516, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.92 (t, *J* = 7.7 Hz, 3 H), 1.62 (sextet, *J* = 7.7 Hz, 2 H), 2.48–2.52 (m, 4 H), 2.71 (t, *J* = 7.0 Hz, 2 H), 3.87 (s, 3 H), 5.54 (s, OH), 6.10 (dt, *J* = 1.4, 15.4 Hz, 1 H), 6.66–6.68 (m, 2 H), 6.81–6.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 13.8 (q), 17.7 (t), 34.2 (t), 34.4 (t), 42.1 (t), 55.9 (q), 110.9 (d), 114.3 (d), 120.9 (d), 130.8 (d), 132.7 (s), 144.0 (s), 145.9 (d), 146.4 (s), 200.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{19}O_3$ $(M–H)^–$ 247.134, found 247.1339.

Synthesis of ***(3)***

*4.1.5 (3S)-3-Hydroxy-4-methoxy-4-oxobutanoic acid (**4.2**)*[24,33]

The L-malic acid used in this experiment (99%) had $[\alpha]_D$ –3.22 (*c* = 30.036, MeOH); Lit.[34] $[\alpha]_D$ –2.92 (*c* = 30, MeOH).

$(CF_3CO)_2O$ (29.3 mL, 207.6 mmol) was added to a stirred sample of L-(–)-malic acid (**4.1**) (11.1 g, 83.0 mmol) and stirring was continued for 90 min (N_2 atmosphere). Residual $(CF_3CO)_2O$ was evaporated under water pump vacuum (protection from moisture). Dry MeOH (35 mL) was added and stirring was continued for 2 h. The MeOH was evaporated and the residue was crystalized from Et_2O to afford **4.2** (12.1 g, 98%): $[\alpha]_D$ –5.57 (*c* = 9.5 g/100 mL); FTIR (MeOH, cast) 3440, 3116, 1732, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.84 (dd, *J* = 6.5, 16.9 Hz, 1 H), 2.92 (dd, *J* = 4.5, 16.9 Hz, 1 H), 3.81 (s, 3 H), 4.52 (dd, *J* = 4.0, 6.5 Hz, 1 H); ^{13}C NMR (CD_3OD, 175 MHz) δ 39.8 (t), 52.7 (q), 68.6 (d), 173.9 (s), 175.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_5H_8O_5$ $(M–H)^–$ 147.0299, found 147.0300.

*4.1.6 Methyl (2S)-2,4-dihydroxybutanoate (**4.3**)*[24]

$BH_3.SMe_2$ (9.0 mL, 94.9 mmol) was added dropwise by syringe over ca 15 min to a stirred and cooled (0 °C) solution of **4.2** (3.5 g, 23.7 mmol) in THF (20 mL). The ice bath was left in place but not recharged, and stirring was continued overnight. The mixture was quenched by slow addition of MeOH and the solvents were evaporated at *room temperature* under water pump vacuum. The residual oil was diluted with MeOH and the solution was evaporated at room temperature. This procedure was repeated four more times to remove $B(OMe)_3$. The resulting crude diol (**4.3**) was used directly for the next step without purification. The material had: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.88–1.95 (m, 1 H), 2.05–2.11 (m, 2 H), 3.80 (s, 3 H), 4.40 (dd, *J* = 3.5, 7.5 Hz, 1 H).

*4.1.7 Methyl (2S)-4-[(tert-butyldimethylsilyl)oxy]-2-hydroxybutanoate (**4.4**)*[35]

Crude **4.3** (5.5 g, 41.2 mmol), was dissolved in dry CH_2Cl_2 (25 mL), and Et_3N (6.9 mL, 49.4 mmol) and DMAP (503.2 mg, 4.12 mmol) were then added (N_2 atmosphere). The stirred solution was cooled in an ice bath and solid *t*-$BuMe_2SiCl$ (6.8 g, 45.3 mmol) was added in

several small portions by momentarily removing the septum used to close the reaction flask. The ice bath was left in place but not recharged, and stirring was continued for 30 h. Water (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (25 × 4.5 cm), using 15:85 EtOAc-hexane, gave **4.4** (5.6 g, 60% over two steps) as an oil: which contained a small impurity (^{1}H NMR signals at δ 0.13 and 0.16 ppm); $[\alpha]_D$ –5.29 (*c* = 1.369, $CHCl_3$); Lit[35] –37.5 (*c* = 0.5, $CHCl_3$); FTIR ($CHCl_3$, cast) 3494, 2955, 1739, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.83–1.90 (m, 1 H), 2.00–2.06 (m, 1 H), 3.77 (s, 3 H), 3.78–3.82 (m, 2 H), 4.35 (dd, *J* = 3.5, 7.0 Hz, 1 H); ^{13}C NMR (CD_3OD, 175 MHz) δ –5.59 (q), 18.2 (s), 25.8 (q), 36.2 (t), 52.3 (q), 59.8 (t), 68.9 (d), 175.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{24}NaO_4Si$ $(M+Na)^+$ 271.1336, found 271.1333.

*4.1.8 Methyl (2S)-2-(benzyloxy)-4-[(tert-butyldimethylsilyl)oxy]butanoate (**4.5**)*[36]

(a) Use of Ag_2O[26]

Freshly-prepared Ag_2O[25] (7.4 g, 32.0 mmol) was tipped into a stirred solution of **4.4** (5.3 g, 21.3 mmol) and BnBr (3.8 mL, 32.0 mmol) in CH_2Cl_2 (60 mL). Stirring was then continued at 35 °C for 15 h with protection from light. The mixture was filtered through a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (20 × 6 cm), using 7:93 EtOAc-hexane, gave **4.5** (2.2 g, 30%) as an oil.

(b)Use of NaH[27]

Bu_4NI (939.5 mg, 2.54 mmol) was tipped into a stirred mixture of NaH (57–63% dispersion in oil, 1.29 g, 30.5 mmol) in dry DMF (30 mL). Dry DMF (15 mL) was injected into another flask containing **4.4** (6.3 g, 25.4 mmol), followed by BnBr (3.65 mL, 30.5 mmol). The resulting solution was taken up into a syringe and added at a fast dropwise rate to the stirred mixture in the first flask. Stirring was continued for 6 h. The mixture was quenched with ice-cold water and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (26 × 5.5 cm), using 5:95 EtOAc-hexane, gave **4.5** (6.9 g, 79%) as an oil: $[\alpha]_D$ –48.28 (*c* = 1.110, $CHCl_3$); FTIR ($CHCl_3$, cast) 2954, 1753, 1255, 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6 H), 0.90 (s, 9 H), 1.90–2.04 (m, 2 H), 3.69–3.81 (m, 2 H), 3.75 (s, 3 H), 4.17 (dd, *J* = 4.4, 8.4 Hz, 1 H), 4.43 (d, *J* = 11.2 Hz, 1 H) , 4.71 (d, *J* = 11.2 Hz, 1 H) , 7.27–7.37 (m, 5 H); ^{13}C NMR (CD_3OD, 125 MHz) δ –5.4 (q), 18.3 (s), 25.9 (q), 36.1 (t), 51.8 (q), 58.6 (t), 72.6 (t), 75.0 (d), 127.8 (d), 128.0 (d), 128.4 (d), 137.6 (s), 173.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{30}NaO_4Si$ $(M+Na)^+$ 361.1806, found 361.1802.

*4.1.9 (2S)-2-(Benzyloxy)-4-[(tert-butyldimethylsilyl)oxy]butanal (**4.6**)*

DIBAL-H (1 M in hexane, 8.12 mL, 8.12 mmol) was added by syringe at a slow dropwise rate to a stirred and cooled (–78 °C) solution of **4.5** (2.3 g, 6.76 mmol) in dry hexane (10 mL). Stirring at –78 °C was continued for 6 h and the mixture was quenched by dropwise addition of MeOH (5 mL), followed by saturated aqueous Rochelle salt (40 mL). The cold bath was left in place but not recharged, and stirring was continued overnight. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (22.5 × 4 cm), using 7:93 EtOAc-hexane, gave **4.6** (1.90 g, 91%) as an oil: $[\alpha]_D$ –20.64 (*c* = 1.149, $CHCl_3$); FTIR ($CDCl_3$, cast) 2929, 1732, 1255, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.88–1.98 (m, 2 H), 3.71–3.81 (m, 2 H), 3.97–3.99 (m, 1 H), 4.57 (d, *J* = 12.0 Hz, 1 H) , 4.69 (d, *J* = 11.5 Hz, 1 H) , 7.30–7.36 (m, 5 H), 9.69 (br s, 1 H); ^{13}C NMR (CD_3OD, 125 MHz) δ –5.47 (q), 18.2 (s), 25.9 (q), 33.9 (t), 58.1 (t), 72.6 (t), 80.8 (d), 127.9 (d), 128.0 (d), 128.5 (d), 137.5 (s), 203.4 (d); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{28}NaO_3Si$ $(M+Na)^+$ 331.17, found 331.1709.

*4.1.10 Diethyl {[4-(benzyloxy)-3-methoxyphenyl]methyl}phosphonate (**3.4**)*[23a]

4-(Benzyloxy)-3-methoxybenzaldehyde[37] was reduced ($NaBH_4$)[38] and the resulting alcohol was converted into the corresponding bromide (PBr_3)[38] to afford 1-(benzyloxy)-4-(bromomethyl)-2-methoxybenzene.

$(EtO)_3P$ (24.4 mL, 142.5 mmol) was added dropwise by syringe to a stirred solution of the bromide (8.8 g, 28.5 mmol) in PhH (50 mL) and the mixture was refluxed (oil bath at 100 °C) for 20 h. The mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (11.5 × 5.5 cm), using 1:4 EtOAc-hexane, gave **3.4** (9.9 g, 95%) as an oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, *J* = 7.0 Hz, 3 H), 3.08 (d, *J* = 21.4 Hz, 2 H), 3.88 (s, 3 H), 3.96–4.04 (m, 4 H), 5.13 (s, 2 H), 6.73–6.76 (m, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.88 (t, *J* = 2.0 Hz, 1 H), 7.27–7.43 (m, 5 H).

*4.1.11 {[(3S,4E)-3-Benzyloxy)-5-[4-benzyloxy)-3-methoxyphenyl]pent-4-en-1-yl]oxy}(tert-butyl)dimethylsilane (E-**5.1**) and {[(3S,4Z)-3-Benzyloxy)-5-[4-benzyloxy)-3-methoxyphenyl]-pent-4-en-1-yl]oxy}(tert-butyl)dimethylsilane (Z-**5.1**)*

$(Me_3Si)_2NLi$ (1 M in THF, 5.37 mL, 5.37 mmol) was added dropwise by syringe to a stirred and cooled (–78 °C) solution of the phosphonate **3.4** (1.95 g, 5.37 mmol) in THF (12 mL) and HMPA (3 mL). Stirring at –78 °C was continued for 1 h and a solution of aldehyde **4.6** (1.4 g, 4.41 mmol) in THF (5 mL) was added dropwise. The cold bath was left in pace but not recharged, and stirring was continued for 23 h. The mixture was quenched with saturated

aqueous $NaHCO_3$ and extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (21.5 × 4.5 cm), using 1:19 EtOAc-hexane, gave *E*-**5.1** (1.6 g, 70%) and *Z*-**5.1** (140.5 mg, 6%) as colorless oils: *Z*-**5.1** had: $[\alpha]_D$ –30.42 (*c* = 1.208, $CHCl_3$); FTIR ($CDCl_3$, cast) 2928, 1513, 1255, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (d, *J* = 1.6 Hz, 6 H), 0.90 (s, 9 H), 1.83–2.00 (m, 2 H), 3.72–3.77 (m, 1 H), 3.83–3.89 (m, 1 H), 3.88 (s, 3 H), 4.26 (d, *J* = 11.6 Hz, 1 H), 4.55 (d, *J* = 11.6 Hz, 1 H), 4.71 (dt, *J* = 4.0, 12.8 Hz, 1 H), 5.19 (s, 2 H), 5.61 (dd, *J* = 9.6, 12.0 Hz, 1 H), 6.61 (d, *J* = 11.6 Hz, 1 H), 6.82–6.84 (m, 3 H), 7.22–7.49 (m, 10 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.4 (q), 18.3 (s), 25.9 (q), 38.6 (t), 56.0 (q), 59.4 (t), 70.2 (t), 71.1 (t), 112.9 (d), 113.8 (d), 121.5 (d), 127.2 (d), 127.3 (d), 127.81 (d), 127.83 (d), 128.2 (d), 128.6 (d), 130.2 (s), 131.6 (d), 132.6 (d), 137.2 (s), 138.7 (s) 147.4 (s), 149.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{42}NaO_4Si$ $(M+Na)^+$ 541.2745, found 541.2745.

E-**5.1** had: $[\alpha]_D$ –33.95 (*c* = 1.121, $CHCl_3$); FTIR ($CDCl_3$, cast) 2928, 1512, 1258, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.79 (sextet, *J* = 6.0 Hz, 1 H), 1.97 (sextet, *J* = 6.0 Hz, 1 H), 3.68–3.78 (m, 2 H), 3.92 (s, 3 H), 4.11 (dd, *J* = 8.0, 13.6 Hz, 1 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 5.17 (s, 2 H), 5.99 (dd, *J* = 8.0, 16.0 Hz, 1 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.87 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.98 (d, *J* = 1.6 Hz, 1 H), 7.28–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ –5.3 (q), 18.3 (s), 26.0 (q), 39.2 (t), 56.0 (q), 59.4 (t), 70.2 (t), 71.1 (t), 109.4 (d), 114.0 (d), 119.6 (d), 127.2 (d), 127.4 (d), 127.7 (d), 127.8 (d), 128.3 (d), 128.5 (d), 128.6 (s), 130.3 (d), 132.0 (d), 137.1 (s), 138.8 (s) 148.1 (s), 149.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{42}NaO_4Si$ $(M+Na)^+$ 541.2745, found 541.274.

*4.1.12 Preparation of Z,E-**5.1** without separation*

$(Me_3Si)_2NLi$ (1 M in THF, 7.26 mL, 7.26 mmol) was added dropwise by syringe to a stirred and cooled (–78 °C) solution of the phosphonate **3.4** (2.65 g, 7.26 mmol) in THF (15 mL) and HMPA (5 mL). Stirring at –78 °C was continued for 1 h and a solution of aldehyde **4.6** (1.9 g, 6.1 mmol) in THF (5 mL) was added dropwise. The cold bath was left in pace but not recharged, and stirring was continued for 18 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (20 × 4.5 cm), using 7:93 EtOAc-hexane, gave *E*,*Z*-**5.1** (2.3 g, 72%) as a colorless oil.

*4.1.13 (3S,4E)-3-(Benzyloxy)-5-[[4-(benzyloxy)-3-methoxyphenyl)pent-4-en-1-ol (**5.2**)*

Bu_4NF (1 M in THF, 10.6 mL, 10.6 mmol) was added by syringe at a fast dropwise rate to a stirred solution of *E*-**5.1** (1.567 g, 3.02 mmol, containing ca 3% of the *Z* isomer as judged by

^{1}H NMR) in THF (10 mL). Stirring was continued for 44 h, and the mixture was diluted with water and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (23 × 4 cm), using 1:1 EtOAc-hexane, gave *E*-**5.2** (1.142 g, 93%) and *Z*-**5.2** (78 mg, 6%) as oils. *Z*-**5.2** had: $[\alpha]_D$ –65.10 (*c* = 2.139, $CHCl_3$); FTIR ($CDCl_3$, cast) 3457, 2926, 1513, 1256, 1139 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85–1.91 (m, 1 H), 1.97–2.04 (m, 1 H), 3.74–3.78 (m, 1 H), 3.82–3.86 (m, 1 H), 3.83 (s, 3 H), 4.23 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.69 (dt, *J* = 4.0, 13.4 Hz, 1 H), 5.18 (s, 2 H), 5.63 (dd, *J* = 9.5, 12.0 Hz, 1 H), 6.65 (d, *J* = 12.0 Hz, 1 H), 6.72 (dd, *J* = 2.0, 8.5 Hz, 1 H), 6.79 (d, *J* = 2.0 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 7.15–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.5 (t), 56.0 (q), 60.6 (t), 70.2 (t), 71.0 (t), 73.3 (d), 112.6 (d), 113.7 (d), 121.4 (d), 127.2 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.3 (d), 128.6 (d), 130.0 (s), 131.5 (d), 132.2 (d), 137.1 (s), 138.1 (s) 147.5 (s), 149.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{28}NaO_4$ $(M+Na)^+$ 427.188, found 427.188.

E-**5.2** had: $[\alpha]_D$ –54.53.10 (*c* = 1.136, $CHCl_3$); FTIR ($CDCl_3$, cast) 3443, 2935, 1512, 1265, 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85–1.91 (m, 1 H), 1.97–2.04 (m, 1 H), 3.76–3.86 (m, 2 H), 3.94 (s, 3 H), 4.19 (dt, *J* = 4.5, 16.4 Hz, 1 H), 4.43 (d, *J* = 11.5 Hz, 1 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 5.18 (s, 2 H), 6.04 (dd, *J* = 8.5, 15.9 Hz, 1 H), 6.52 (d, *J* = 15.9 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 6.90 (dd, *J* = 1.5, 8.5 Hz, 1 H), 7.00 (d, *J* = 1.5 Hz, 1 H), 7.29–7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.3 (t), 56.1 (q), 60.6 (t), 70.3 (t), 71.1 (t), 79.7 (d), 109.5 (d), 114.0 (d), 119.8 (d), 127.3 (d), 127.6 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.5 (d), 128.6 (d), 129.9 (s), 132.5 (d), 137.0 (s), 138.3 (s), 148.3 (s), 149.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{28}NaO_4$ $(M+Na)^+$ 427.188, found 427.1878.

*4.1.14 (3S,4E)-3-(Benzyloxy)-5-[[4-(benzyloxy)-3-methoxyphenyl)pent-4-enal (E-**5.3**)*

Dess-Martin reagent (1.30 g, 3.07 mmol) was added in portions to a stirred and cooled (0 °C) mixture of *E*-**5.2** (992.7 mg, 2.45 mmol), $NaHCO_3$ (1.44 g, 17.2 mmol)[39] and CH_2Cl_2 (10 mL). The ice bath was left in place and stirring was continued for 3 h, during which time all the ice melted. The mixture was cooled to 0 °C, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (23.5 × 4 cm), using 1:2 EtOAc-hexane, gave *E*-**5.3** (943 mg, 95%) as a yellowish oil: $[\alpha]_D$ –51.26 (*c* = 2.233, $CHCl_3$); FTIR ($CDCl_3$, cast) 3031, 2863, 1724, 1512, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.64 (qd, *J* = 1.6, 4.8, 16.0 Hz, 1 H), 2.85 (qd, *J* = 2.4, 8.0, 16.4 Hz, 1 H), 3.94 (s, 3 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.48–4.52 (m, 1 H), 4.67 (d, *J* = 12.0 Hz, 1 H), 5.18 (s, 2 H), 6.03 (dd, *J* = 8.0, 15.6 Hz, 1 H), 6.58 (d, *J* = 16.0 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.90 (dd, *J* = 1.6, 8.4 Hz, 1 H), 6.99 (d, *J* = 1.6 Hz, 1 H), 7.29–7.47 (m, 10 H), 9.81 (t, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.6

(t), 56.0 (q), 70.3 (t), 71.0 (t), 75.2 (d), 109.5 (d), 114.0 (d), 119.9 (d), 126.2 (d), 127.2 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.4 (d), 128.6 (d), 129.5 (s), 133.2 (d), 137.0 (s), 138.0 (s), 148.4 (s), 149.8 (s), 200.7 (d); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{26}NaO_4$ $(M+Na)^+$ 425.1723, found 425.1725.

*4.1.15 (3S,4E)-3-(Benzyloxy)-5-[[4-(benzyloxy)-3-methoxyphenyl)pent-4-enal and (3S,4Z)-3-(Benzyloxy)-5-[[4-(benzyloxy)-3-methoxyphenyl)pent-4-enal (E,Z-**5.3**)*

Dess-Martin reagent (1.95 g, 4.59 mmol) was added in portions to a stirred and cooled (0 °C) mixture of *E*,*Z*-**5.2** (1.55 g, 3.82 mmol), $NaHCO_3$ (2.25 g, 26.8 mmol)[39] and CH_2Cl_2 (10 mL). The ice bath was left in place and stirring was continued for 4 h, during which time all the ice melted. The mixture was cooled to 0 °C, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (22 × 5 cm), using 1:2 EtOAc-hexane, gave *E*,*Z*-**5.3** (1.46 g, 94%) as a yellowish oil.

*4.1.16 1-(Benzyloxy)-4-[(1E,3S)-3-(benzyloxy)undeca-1,5-dien-1-yl]-2-methoxybenzene (1E-**5.4**) from E-**5.3***

$(Me_3Si)_2NLi$ (1 M in THF, 4.69 mL, 4.69 mmol) was added dropwise by syringe to a stirred and cooled (–78 °C) solution of hexyltriphenylphosphonium bromide[40] (2.00 g, 4.69 mmol) in a mixture of THF (40 mL) and HMPA (5 mL). Stirring at –78 °C was continued for 1 h and then a solution of *E*-**5.3** (926.0 mg, 2.30 mmol) in THF (5 mL) was added dropwise by syringe over ca 5 min. The cold bath was left in place but not recharged, and stirring was continued for 22 h. The mixture was quenched by addition of aqueous phosphate buffer [pH 7.2, prepared[41] by mixing aqueous 1 M Na_2HPO_4 (3.42 volumes) and 1 M NaH_2PO_4 (1.58 volumes)] and extracted with Et_2O (3 × 60 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (21.5 × 4.5 cm), using 7:93 EtOAc-hexane, gave **5.4** (827.1 mg, 76%) as a yellowish oil, which appeared to be a single isomer (^{1}H NMR, ^{13}C NMR) of unestablished C5–C6 geometry: $[\alpha]_D$ –57.70 (*c* = 1.003, $CHCl_3$); FTIR ($CDCl_3$, cast) 2926, 1265, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.26–1.38 (m, 6 H), 2.05 (dd, *J* = 6.5, 13.9 Hz, 2 H), 2.38–2.44 (m, 1 H), 2.51–2.56 (m, 1 H), 3.92–3.96 (m, 1 H), 3.93 (s, 3 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 5.18 (s, 2 H), 5.43–5.52 (m, 2 H), 6.02 (dd, *J* = 8.0, 15.9 Hz, 1 H), 6.48 (d, *J* = 15.4 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 6.89 (dd, *J* = 2.0, 8.5 Hz, 1 H), 6.99 (d, *J* = 2.0 Hz, 1 H), 7.27–7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.1 (q), 22.6 (t), 27.5 (t), 29.3 (t), 31.6 (t), 33.9 (t), 56.0 (q), 70.1 (t), 71.1 (t), 80.2 (d), 109.6 (d), 114.1 (d), 119.6 (d), 124.8 (d), 127.2 (d), 127.4 (d), 127.7 (d), 127.9 (d), 128.3 (d), 128.4 (d), 128.6 (d), 130.3 (s), 132.2 (d), 137.1 (s), 138.8 (s),

148.1 (s), 149.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{38}NaO_3$ $(M+Na)^+$ 493.2713, found 493.2716.

*4.1.17 1-(Benzyloxy)-4-[(3S)-3-(benzyloxy)undeca-1,5-dien-1-yl]-2-methoxybenzene (1E,1Z-**5.4**) from E,Z-**5.3***

$(Me_3Si)_2NLi$ (1 M in THF, 7.25 mL, 7.25 mmol) was added dropwise by syringe to a stirred and cooled (–78 °C) solution of hexyltriphenylphosphonium bromide[40] (3.1 g, 7.25 mmol) in a mixture of THF (55 mL) and HMPA (7.5 mL). Stirring at –78 °C was continued for 1.5 h and then a solution of *E*,*Z*-**5.3** (1.43 g, 3.55 mmol) in THF (5 mL) was added dropwise by syringe over ca 10 min. The cold bath was left in place but not recharged, and stirring was continued for 15 h. The mixture was quenched by addition of aqueous phosphate buffer [pH 7.2, prepared[41] by mixing aqueous 1 M Na_2HPO_4 (3.42 volumes) and 1 M NaH_2PO_4 (1.58 volumes)] and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (22 × 4.5 cm), using 5:95 EtOAc-hexane, gave 1*E*-**5.4** as a single isomer and 1*E*,1*Z*-**5.4** (1.5 g in total, 88%) as yellowish oils.

*4.1.18 1-(Benzyloxy)-4-[(3S)-3-(benzyloxy)undecyl]-2-methoxybenzene (**5.5**)*

5% Rh/Al_2O_3 (28.4 mg) was added to a solution of 1*E*-**5.4** (single compound of unestablished C5–C6 geometry, 567.8 mg, 1.21 mmol) in EtOH (4 mL) and the diene was hydrogenated at room temperature (H_2-filled balloon) for 3 h. The mixture was filtered through a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (22.5 × 2 cm), using 1:19 EtOAc-hexane, gave **5.5** (551.3 mg, 96%) as an oil: $[\alpha]_D$ 9.14 (*c* = 1.996, $CHCl_3$); FTIR ($CDCl_3$, cast) 2927, 1513, 1263, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.28–1.42 (m, 12 H), 1.51–1.66 (m, 2 H), 1.77–1.90 (m, 2 H), 2.56–2.62 (m, 1 H), 2.68–2.74 (m, 1 H), 3.42 (quint, *J* = 6.0 Hz, 1 H), 3.87 (s, 3 H), 4.49 (d, *J* = 11.5 Hz, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 5.13 (s, 2 H), 6.65 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.73 (d, *J* = 2.0 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 7.27–7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.1 (q), 22.7 (t), 25.3 (t), 29.3 (t), 29.6 (t), 29.8 (t), 31.4 (t), 31.9 (t), 33.8 (t), 35.9 (t), 56.0 (q), 70.8 (t), 71.3 (t), 78.4 (d), 112.4 (d), 114.3 (d), 120.2 (d), 127.3 (d), 127.4 (d), 127.7 (d), 127.8 (d), 128.3 (d), 128.5 (d), 135.9 (s), 137.5 (s), 139.1 (s), 146.3 (s), 149.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{42}NaO_3$ $(M+Na)^+$ 497.3026, found 497.3026.

*4.1.19 4-[(3S)-3-Hydroxyundecyl]-2-methoxyphenol [(S)-**3**]*

10% Pd/C (7.2 mg) was added to a solution of **5.5** (144.1 mg, 0.30 mmol) in EtOH (3 mL) and the compound was hydrogenated at room temperature (H_2-filled balloon) for 2.5 h. The

mixture was filtered through a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (17 × 2 cm), using EtOAc, gave (*S*)-**3** (86.2 mg, 96%) as a white solid: mp 53–55 °C; $[\alpha]_D$ 8.35 (*c* = 1.233, $CHCl_3$); FTIR ($CDCl_3$, cast) 3338, 3245, 1516, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 6.8 Hz, 3 H), 1.28–1.51 (m, 14 H), 1.66–1.81 (m, 2 H), 2.57–2.64 (m, 1 H), 2.69–2.76 (m, 1 H), 3.60–3.66 (m, 1 H), 3.86 (s, 3 H), 6.68–6.71 (m, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.1 (q), 22.6 (t), 25.6 (t), 29.2 (t), 29.6 (t), 29.7 (t), 31.8 (t), 31.9 (t), 37.6 (t), 39.4 (t), 55.9 (q), 71.4 (d), 111.0 (d), 114.2 (d), 120.9 (d), 134.1 (s), 143.7 (s), 146.4 (s); exact mass (EI) *m*/*z* calcd for $C_{18}H_{30}O_3$ $(M)^+$ 294.2195, found 294.2191.

Chiral HPLC (CHIRALCEL OD column, 250 × 4.6 mm, 15:85 *i*-PrOH:hexane, 0.5 mL/min, wavelength 230 and 280 nm, 20 °C) showed the compound to have an ee of 90%.

*Preparation of (±)-3 for establishing enantiomeric purity of [(S)-**3**]*

*4.1.20 (±)-1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-3-ol [(±)-**3**]*

(a) (3S)-1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-3-ol

K_2CO_3 (218.8 mg, 1.59 mmol) was added to a stirred solution of (*S*)-**3** (155.4 mg, 0.53 mmol) in dry acetone (6 mL) and then BnBr (0.13 mL, 1.06 mmol) was added. The stirred mixture was heated at 60 °C for 10 h. The solvent was evaporated and water (20 mL) was added to the residue. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (21.5 × 2 cm), using 1:4 EtOAc-hexane, gave (3*S*)-1-[4-(benzyloxy)-3-methoxyphenyl]undecan-3-ol (194.4 mg, 95%) as a white solid: mp 53–54 °C; $[\alpha]_D$ 6.78 (*c* = 1.15, $CHCl_3$); FTIR ($CDCl_3$, cast) 3328, 2924, 1514, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.25–1.49 (m, 14 H), 1.67–1.81 (m, 2 H), 2.58–2.64 (m, 1 H), 2.70–2.76 (m, 1 H), 3.60–3.65 (m, 1 H), 3.88 (s, 3 H), 5.12 (s, 2 H), 6.67 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.76 (d, *J* = 2.0 Hz, 1 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 7.28–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.1 (q), 22.6 (t), 25.6 (t), 29.2 (t), 29.6 (t), 29.7 (t), 31.7 (t), 31.9 (t), 37.6 (t), 39.2 (t), 56.0 (q), 71.2 (t), 71.4 (d), 112.4 (d), 114.4 (d), 120.2 (d), 127.3 (d), 127.7 (d), 128.5 (d), 135.6 (s), 137.4 (s), 146.4 (s), 149.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{36}NaO_3$ $(M+Na)^+$ 407.2557, found 407.2552.

(b) 1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-3-one

$NaHCO_3$ (105.9 mg, 1.26 mmol) and Dess-Martin periodinane (213.9 mg, 0.50 mmol) were added sequentially to a stirred and cooled (0 °C) solution of (3*S*)-1-[4-(benzyloxy)-3-methoxyphenyl]undecan-3-ol (161.5 mg, 0.42 mmol) in dry CH_2Cl_2 (3 mL). Stirring at 0 °C was continued for 3.5 h. The reaction mixture was quenched by addition of saturated aqueous

$Na_2S_2O_3$ (4 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (24 × 2 cm), using 1:4 EtOAc-hexane, gave 1-[4-(benzyloxy)-3-methoxyphenyl]undecan-3-one (125.6 mg 78%) as a white solid: mp 70–72 °C; FTIR ($CDCl_3$, cast) 2920, 1701, 1512, 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.24–1.30 (m, 10 H), 1.55 (quint, *J* = 7.0 Hz, 2 H), 2.37 (t, *J* = 7.0 Hz, 2 H), 2.69 (t, *J* = 7.0 Hz, 2 H), 2.83 (t, *J* = 7.0 Hz, 2 H), 3.87 (s, 3 H), 5.12 (s, 2 H), 6.64 (dd, *J* = 2.1, 7.7 Hz, 1 H), 6.73 (d, *J* = 2.1 Hz, 1 H), 6.79 (d, *J* = 7.7 Hz, 1 H), 7.28–7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.1 (q), 22.6 (t), 23.8 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 31.8 (t), 43.1 (t), 44.4 (t), 56.0 (q), 71.2 (t), 112.3 (d), 114.3 (d), 120.1 (d), 127.2 (d), 127.7 (d), 128.5 (d), 134.5 (s), 137.4 (s), 146.5 (s), 149.6 (s), 210.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{34}NaO_3$ $(M+Na)^+$ 405.24, found 405.2401.

(c) (±)-1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-3-ol

$NaBH_4$ (10.4 mg, 0.27 mmol) was added in portions to a stirred solution of 1-[4-(benzyloxy)-3-methoxyphenyl]undecan-3-one (105 mg, 0.27 mmol) in dry MeOH (4 mL). Stirring was continued for 2 h, ice water (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (20 × 2 cm), using 7:93 EtOAc-hexane, gave (±)-1-[4-(benzyloxy)-3-methoxyphenyl]undecan-3-ol (101.3 mg 96%) as a white solid: mp 59–62 °C; FTIR ($CDCl_3$, cast) 3226, 2918, 1515, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.25–1.58 (m, 14 H), 1.67–1.81 (m, 2 H), 2.58–2.64 (m, 1 H), 2.71–2.77 (m, 1 H), 3.60–3.65 (m, 1 H), 3.88 (s, 3 H), 5.13 (s, 2 H), 6.68 (dd, *J* = 1.5, 8.0 Hz, 1 H), 6.77 (d, *J* = 1.5 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 7.28–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.3 (t), 29.6 (t), 29.7 (t), 31.7 (t), 31.9 (t), 37.6 (t), 39.2 (t), 56.0 (q), 71.3 (t), 71.4 (d), 112.4 (d), 114.4 (d), 120.2 (d), 127.3 (d), 127.7 (d), 128.5 (d), 135.6 (s), 137.5 (s), 146.4 (s), 149.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{36}NaO_3$ $(M+Na)^+$ 407.2557, found 407.2555.

*(d) (±)-4-[(3-Hydroxyundecyl]-2-methoxyphenol [(±)-**3**]*

10% Pd/C (3.5 mg) was added to a solution of (±)-1-[4-(benzyloxy)-3-methoxyphenyl]undecan-3-ol (70.1 mg, 0.18 mmol) in EtOH (3 mL) and the mixture was stirred under H_2 (balloon) for 1.5 h. The mixture was filtered through a short pad of Celite which was rinsed with EtOAc. Evaporation of the filtrate gave (±)-**3** (52.8 mg, 98%) as a white solid that was pure (^1H NMR): 62–63 °C; FTIR ($CDCl_3$, cast) 3390, 2920, 1516, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.25–1.54 (m, 14 H), 1.66–1.80 (m, 2 H), 2.57–

2.63 (m, 1 H), 2.70–2.75 (m, 1 H), 3.60–3.65 (m, 1 H), 3.86 (s, 3 H), 6.69 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.71 (d, *J* = 1.5 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.3 (t), 29.6 (t), 29.7 (t), 31.8 (t), 31.9 (t), 37.6 (t), 39.3 (t), 55.8 (q), 71.4 (d), 111.0 (d), 114.3 (d), 120.9 (d), 134.1 (s), 143.7 (s), 146.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{29}O_3$ $(M–H)^-$ 293.2122, found 293.2122.

*Synthesis of (**2**)*

*4.1.21 1-(Benzyloxy)-4-[(1E,3S)-3-(benzyloxy)deca-1,5-dien-1-yl]-2-methoxybenzene (1E-**6.1**) and 1-(Benzyloxy)-4-[(1E,1Z,3S)-3-(benzyloxy)deca-1,5-dien-1-yl]-2-methoxybenzene (1E,1Z-**6.1**)*

$(Me_3Si)_2NLi$ (1 M in THF, 14.9 mL, 14.9 mmol) was added dropwise by syringe to a stirred and cooled (–78 °C) solution of pentyltriphenylphosphonium bromide[42] (6.16 g, 14.9 mmol) in a mixture of THF (70 mL) and HMPA (10 mL). Stirring at –78 °C was continued for 1.5 h and then a solution of *Z*,*E*-**5.3** (3.0 g, 7.5 mmol) in THF (5 mL) was added dropwise by syringe over ca 10 min. The cold bath was left in place but not recharged, and stirring was continued for 22 h. The mixture was quenched by addition of aqueous phosphate buffer [pH 7.2, prepared[41] by mixing aqueous 1 M Na_2HPO_4 (3.42 volumes) and 1 M NaH_2PO_4 (1.58 volumes)] and extracted with Et_2O (3 × 80 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (27 × 5.5 cm), using 5:95 EtOAc-hexane, gave 1*Z*,1*E*-**6.1** (1.5 g, 44%) and 1*E*-**6.1** (178.2 mg, 5%), both as yellowish oils. The 1*Z*,1*E* mixture (mainly *E*) had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.31–1.37 (m, 4 H), 2.08 (dd, *J* = 6.5, 13.4 Hz, 2 H), 2.41–2.46 (m, 1 H), 2.53–2.60 (m, 1 H), 3.94–3.98 (m, 1 H), 3.94 (s, 3 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 4.68 (d, *J* = 12.5 Hz, 1 H), 5.19 (s, 2 H), 5.45–5.54 (m, 2 H), 6.04 (dd, *J* = 8.0, 15.4 Hz, 1 H), 6.50 (d, *J* = 15.9 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 6.90 (dd, *J* = 1.5, 8.5 Hz, 1 H), 7.01 (d, *J* = 1.5 Hz, 1 H), 7.28–7.49 (m, 10 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.0 (q), 22.4 (t), 27.2 (t), 31.8 (t), 33.9 (t), 56.0 (q), 70.1 (t), 71.1 (t), 80.2 (d), 109.5 (d), 114.0 (d), 119.7 (d), 124.9 (d), 127.2 (d), 127.4 (d), 127.7 (d), 127.9 (d), 128.3 (d), 128.4 (d), 128.6 (d), 130.3 (s), 132.1 (d), 132.2 (d), 137.1 (s), 138.8 (s), 148.1 (s), 149.8 (s).

The 1*E* isomer had: $[\alpha]_D$ –39.19 (*c* = 1.043, $CHCl_3$); FTIR ($CDCl_3$, cast) 2928, 1512, 1266, 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, *J* = 7.0 Hz, 3 H), 1.26–1.35 (m, 4 H), 2.05 (dd, *J* = 6.5, 13.4 Hz, 2 H), 2.37–2.43 (m, 1 H), 2.50–2.55 (m, 1 H), 3.91–3.95 (m, 1 H), 3.92 (s, 3 H), 4.44 (d, *J* = 12.0 Hz, 1 H), 4.65 (d, *J* = 12.5 Hz, 1 H), 5.18 (s, 2 H), 5.42–5.51 (m, 2 H), 6.01 (dd, *J* = 8.0, 15.9 Hz, 1 H), 6.47 (d, *J* = 15.9 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.88 (dd, *J* = 2.0, 8.5 Hz, 1 H), 6.98 (d, *J* = 2.0 Hz, 1 H), 7.28–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.0 (q), 22.4 (t), 27.2 (t), 31.7 (t), 33.9 (t), 56.0 (q), 70.1 (t), 71.0 (t), 80.1 (d), 109.5 (d),

114.0 (d), 119.6 (d), 124.8 (d), 127.2 (d), 127.4 (d), 127.6 (d), 127.8 (d), 128.30 (d), 128.34 (d), 128.5 (d), 130.2 (s), 132.1 (d), 132.2 (d), 137.1 (s), 138.8 (s), 148.0 (s), 149.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{36}NaO_3$ $(M+Na)^+$ 479.2557, found 479.2558.

For both fractions the C5–C6 double bond geometry was not determined.

*4.1.22 1-(Benzyloxy)-4-[(3S)-3-(benzyloxy)decyl]-2-methoxybenzene (**6.2**)*

5% Rh/Al_2O_3 (32.5 mg) was added to a solution of 1*E*,1*Z*-**6.1** (unestablished C5–C6 geometry, 650.7 mg, 1.43 mmol) in EtOH (10 mL) and the diene was hydrogenated at room temperature (H_2-filled balloon) for 4 h. The mixture was filtered through a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (26.0 × 4 cm), using 1:19 EtOAc-hexane, gave **6.2** (407.2 mg, 62%) as an oil: $[\alpha]_D$ 6.53 (*c* = 1.041, $CHCl_3$); FTIR ($CDCl_3$, cast) 2928, 1513, 1262, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, *J* = 7.0 Hz, 3 H), 1.26–1.53 (m, 10 H), 1.54–1.68 (m, 2 H), 1.79–1.92 (m, 2 H), 2.59–2.65 (m, 1 H), 2.71–2.77 (m, 1 H), 3.44 (quint, *J* = 5.5 Hz, 1 H), 3.88 (s, 3 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.57 (d, *J* = 11.5 Hz, 1 H), 5.15 (s, 2 H), 6.67 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.76 (d, *J* = 2.0 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 7.28–7.48 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 22.7 (t), 25.3 (t), 29.3 (t), 29.9 (t), 31.4 (t), 31.9 (t), 33.8 (t), 36.0 (t), 56.0 (q), 70.9 (t), 71.3 (t), 78.5 (d), 112.5 (d), 114.4 (d), 120.2 (d), 127.3 (d), 127.5 (d), 127.75 (d), 127.79 (d), 128.4 (d), 128.5 (d), 136.0 (s), 137.5 (s), 139.1 (s), 146.3 (s), 149.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{40}NaO_3$ $(M+Na)^+$ 483.287, found 483.2873.

Larger scale experiment

5% Rh/Al_2O_3 (65.0 mg) was added to a solution of 1*E*,1*Z*-**6.1** (unestablished C5–C6 geometry, 1.07 g, 2.35 mmol) in EtOH (10 mL) and the diene was hydrogenated at room temperature (H_2-filled balloon) for 4 h. The mixture was filtered through a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (25.5 × 4 cm), using 1:19 EtOAc-hexane, gave **6.2** (684 mg, 63%) as an oil.

*4.1.23 4-[(3S)-3-Hydroxydecyl]-2-methoxyphenol [(S)-**2**]*

10% Pd/C (20.1 mg) was added to a solution of **6.2** (402.5 mg, 0.87 mmol) in EtOH (10 mL) and the compound was hydrogenated at room temperature (H_2-filled balloon) for 2 h. The mixture was filtered through a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (22.5 × 2 cm), using first 1:4 EtOAc-hexane and then 1:1 EtOAc-hexane, gave (*S*)-**2** (211.4 mg, 86%) as a white solid: mp 48–49 °C; $[\alpha]_D$ 6.31 (*c* = 1.049, $CHCl_3$); FTIR ($CDCl_3$, cast) 3423, 2928, 1515, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, *J* = 7.0 Hz, 3 H), 1.28–1.34 (m, 10 H), 1.41–1.51 (m, 2 H), 1.67–

1.80 (m, 2 H), 1.82 (br s, OH), 2.57–2.63 (m, 1 H), 2.70–2.76 (m, 1 H), 3.60–3.65 (m, 1 H), 3.84 (s, 3 H), 5.81 (s, OH), 6.69 (dd, J = 2.0, 8.0 Hz, 1 H), 6.71 (d, J = 2.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 22.7 (t), 25.7 (t), 29.3 (t), 29.7 (t), 31.78 (t), 31.85 (t), 37.6 (t), 39.4 (t), 55.9 (q), 71.5 (d), 111.2 (d), 114.4 (d), 120.9 (d), 134.2 (s), 143.7 (s), 146.6 (s); exact mass (EI) m/z calcd for $C_{17}H_{28}NaO_3$ $(M+Na)^+$ 303.1931, found 301.1931.

Larger scale experiment

10% Pd/C (34.2 mg) was added to a solution of **6.2** (684 mg, 1.49 mmol) in EtOH (10 mL) and the compound was hydrogenated at room temperature (H_2-filled balloon) for 17 h. The mixture was filtered through a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (25 × 3 cm), using first 1:4 EtOAc-hexane and then 1:1 EtOAc-hexane, gave (*S*)-**2** (354 mg, 85%) as a white solid.

Chiral HPLC (CHIRALCEL OD column, 250 × 4.6 mm, 15:85 *i*-PrOH:hexane, 0.5 mL/min, wavelength 230 and 280 nm, 20 °C) showed the compound to have an ee of 68%.

The material isolated from natural sources had: $[\alpha]_D$ –0.46 (c = 0.29, $CHCl_3$). Chiral HPLC (CHIRALCEL OD column, 250 × 4.6 mm, 15:85 *i*-PrOH:hexane, 0.5 mL/min, wavelength 230 and 280 nm, 20 °C) showed the compound to be a 1:1.7 *R*:*S* mixture.

*Preparation of (±)-**2** for establishing enantiomeric purity of [(S)-**2**]*

(a) (3S)-1-[4-(Benzyloxy)-3-methoxyphenyl]decan-3-ol

K_2CO_3 (284.0 mg, 2.06 mmol) was added to a stirred solution of (*S*)-**2** (192.1 mg, 0.69 mmol) in dry acetone (10 mL) and BnBr (0.16 mL, 1.37 mmol) was added. The stirred mixture was then heated at 60 °C for 12 h. The solvent was evaporated, water (20 mL) was added to the residue and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (21 × 2 cm), using 1:4 EtOAc-hexane, gave (3*S*)-1-[4-(benzyloxy)-3-methoxyphenyl]decan-3-ol (247.0 mg, 97%) as a white solid: mp 63–65 °C; $[\alpha]_D$ 5.20 (c = 1.085, $CHCl_3$); FTIR ($CDCl_3$, cast) 3334, 2925, 1514, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.29–1.34 (m, 10 H), 1.43–1.51 (m, 2 H), 1.67–1.81 (m, 2 H), 2.58–2.65 (m, 1 H), 2.71–2.77 (m, 1 H), 3.60–3.65 (m, 1 H), 3.88 (s, 3 H), 5.13 (s, 2 H), 6.68 (dd, J = 1.5, 8.0 Hz, 1 H), 6.77 (d, J = 1.5 Hz, 1 H), 6.81 (d, J = 8.0 Hz, 1 H), 7.28–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 22.7 (t), 25.7 (t), 29.3 (t), 29.7 (t), 31.75 (t), 31.84 (t), 37.7 (t), 39.2 (t), 56.0 (q), 71.3 (t), 71.4 (d), 112.5 (d), 114.4 (d), 120.2 (d), 127.3 (d), 127.7 (d), 128.5 (d), 135.6 (s), 137.5 (s), 146.4 (s), 149.7 (s); exact mass (electrospray) m/z calcd for $C_{24}H_{34}NaO_3$ $(M+Na)^+$ 393.24, found 393.2395.

(b) 1-[4-(Benzyloxy)-3-methoxyphenyl]decan-3-one[43]

$NaHCO_3$ (153.2 mg, 1.82 mmol) and Dess-Martin periodinane (309.5 mg, 0.73 mmol) were added sequentially to a stirred and cooled (0 °C) solution of (3*S*)-1-[4-(benzyloxy)-3-methoxyphenyl]decan-3-ol (225.0 mg, 0.61 mmol) in dry CH_2Cl_2 (4 mL). Stirring at 0 °C was continued for 14 h. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (4 mL) and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (22.5 × 2 cm), using 1:5 EtOAc-hexane, gave 1-[4-(benzyloxy)-3-methoxyphenyl]decan-3-one (203.1 mg, 90%) as a white solid: mp 53–55 °C; FTIR ($CDCl_3$, cast) 2928, 1712, 1514, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, *J* = 7.5 Hz, 3 H), 1.24–1.32 (m, 8 H), 1.53–1.59 (m, 2 H), 2.37 (t, *J* = 7.5 Hz, 2 H), 2.69 (t, *J* = 7.5 Hz, 2 H), 2.83 (t, *J* = 7.5 Hz, 2 H), 3.87 (s, 3 H), 5.12 (s, 2 H), 6.65 (dd, *J* = 1.5, 8.5 Hz, 1 H), 6.74 (d, *J* = 1.5 Hz, 1 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 7.27–7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 22.6 (t), 23.8 (t), 29.1 (t), 29.2 (t), 29.5 (t), 31.7 (t), 43.1 (t), 44.4 (t), 56.0 (q), 71.2 (t), 112.4 (d), 114.4 (d), 120.1 (d), 127.3 (d), 127.8 (d), 128.5 (d), 134.6 (s), 137.4 (s), 146.6 (s), 149.7 (s), 210.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{32}NaO_3$ $(M+Na)^+$ 391.2244, found 391.2240.

(c) (±)-1-[4-(Benzyloxy)-3-methoxyphenyl]decan-3-ol

$NaBH_4$ (20.2 mg, 0.53 mmol) was added in portions to a stirred solution of 1-[4-(benzyloxy)-3-methoxyphenyl]decan-3-one (196.3 mg, 0.53 mmol) in dry MeOH (5 mL). Stirring was continued for 3 h and then ice water (20 mL) was added. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to give (±)-1-[4-(benzyloxy)-3-methoxyphenyl]decan-3-ol (193.7 mg 97%) as a white solid: mp 65–66 °C; FTIR ($CDCl_3$, cast) 3230, 2920, 1515, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.26–1.34 (m, 10 H), 1.42–1.52 (m, 2 H), 1.67–1.81 (m, 2 H), 2.59–2.65 (m, 1 H), 2.71–2.77 (m, 1 H), 3.60–3.65 (m, 1 H), 3.88 (s, 3 H), 5.13 (s, 2 H), 6.68 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.77 (d, *J* = 2.0 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 7.28–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 22.7 (t), 25.7 (t), 29.3 (t), 29.7 (t), 31.76 (t), 31.84 (t), 37.7 (t), 39.2 (t), 56.0 (q), 71.3 (t), 71.4 (d), 112.5 (d), 114.4 (d), 120.2 (d), 127.3 (d), 127.7 (d), 128.5 (d), 135.6 (s), 137.5 (s), 146.4 (s), 149.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{34}NaO_3$ $(M+Na)^+$ 393.2400, found 393.2401.

*(d) (±)-4-[(3-Hydroxydecyl]-2-methoxyphenol [(±)-**2**]*[15]

10% Pd/C (9.4 mg) was added to a solution of (±)-1-[4-(benzyloxy)-3-methoxyphenyl]decan-3-ol (190.0 mg, 0.51 mmol) in EtOH (6 mL) and the mixture was stirred

under H_2 (balloon) for 1.5 h. The mixture was filtered through a short pad of Celite which was rinsed with EtOAc. Evaporation of the solvent gave (±)-**2** (143.5 mg, 99%) as a white solid that was pure (^{1}H NMR): 59–60 °C; FTIR ($CDCl_3$, cast) 3400, 2921, 1517, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.25–1.34 (m, 10 H), 1.41–1.52 (m, 2 H), 1.54 (br s, OH), 1.67–1.80 (m, 2 H), 2.57–2.63 (m, 1 H), 2.70–2.76 (m, 1 H), 3.60–3.65 (m, 1 H), 3.86 (s, 3 H), 6.69–6.71 (m, 2 H), 6.83 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.3 (t), 29.7 (t), 31.79 (t), 31.83 (t), 37.6 (t), 39.4 (t), 55.9 (q), 71.5 (d), 111.1 (d), 114.3 (d), 120.9 (d), 134.2 (s), 143.7 (s), 146.5 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{27}O_3$ $(M–H)^–$ 279.1966, found 279.1966.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/

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