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Stereoselective Syntheses of the 2-Isopropenyl-2,3-dihydrobenzofuran Nucleus: Potential Chiral Building Blocks for the Syntheses of Tremetone, Hydroxytremetone, and Rotenone

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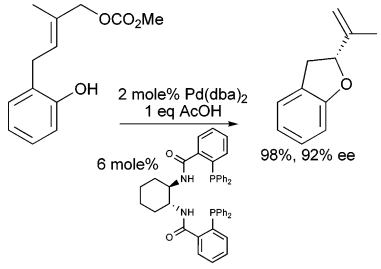

The first enantioselective synthesis of the 2-isopropenyl-2,3-dihydrobenzofuran skeleton of tremetone and hydroxytremetone from (*E*)-4-(2-hydroxyphenyl)-2-methyl-2-butenyl methyl carbonate and (*E*)-4-(2,6-dihydroxyphenyl)-2-methyl-2-butenyl methyl carbonate, respectively, is described. The key step is a catalytic palladium-mediated reaction in the presence of the chiral Trost ligand.

Introduction

A number of biologically active compounds possess a 2-isopropenyl-2,3-dihydrobenzofuran skeleton that contains an asymmetric carbon at the 2-position. Simple examples would include the toxins tremetone (also spelt trematone) **1a**,[1−3] hydroxytremetone (or 4-hydroxytrematone) **1c**, and fomannoxin **1d**.[4,5] More complex compounds such as rotenone **2**,[6−8] an insecticidal principle, or 3′,4′-deoxypsorospermin **3**[9] also contain the same embedded unit.

Stereoselective syntheses of the 2-isopropenyl-2,3-dihydrobenzofuran skeleton have until now only been achieved by resolution methods. The first chiral synthesis of **1a** was described in 1963 and involved a number of simple transformations from the corresponding chiral dihydrobenzofuran-2-carboxylic acid **4** (Figure 2, eq 1), both enantiomers of **4** were obtained by a chiral resolution procedure.[1] Unfortunately, the chiral resolution step was poor yielding but nevertheless allowed for synthesis of tremetone **1a** and its enantiomer **1b**. More recently, Yamaguchi et al. utilized the Sharpless asymmetric dihydroxylation procedure to kinetically resolve the enantiomers of racemic 4,6-dimethoxy-2-isopropenyl-2,3-dihydrobenzofuran. This kinetic resolution proved not to be as efficient as expected, and the yields of the desired enantiomers had to be severely compromised in order to obtain acceptable enantiomeric excesses (ee's).[10]

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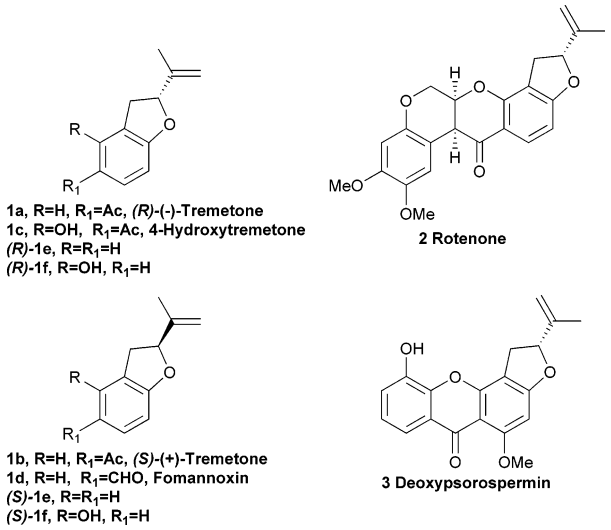


FIGURE 1. Natural products containing the 2-isopropenyl-2,3-dihydrobenzofuran skeleton.

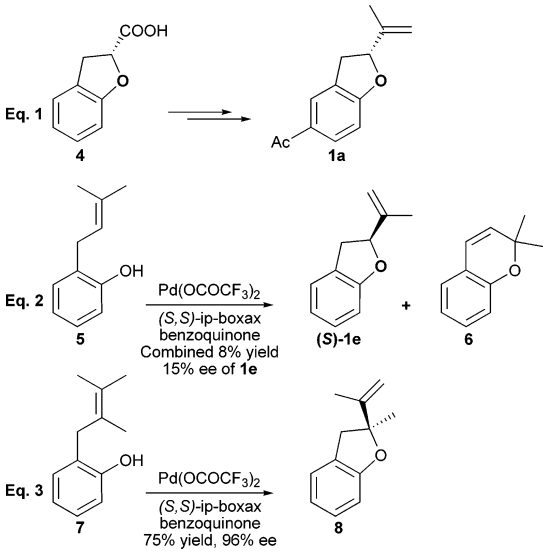
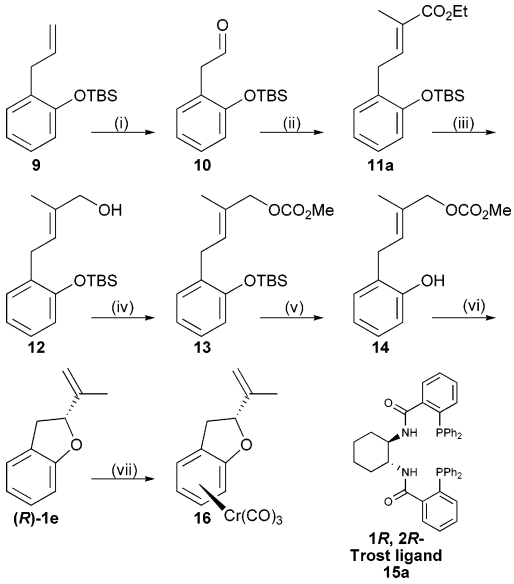


FIGURE 2. Previous asymmetric syntheses of 2-isopropenyl-2,3-dihydrobenzofuran systems.

As an alternative, several attempted asymmetric cyclizations have been reported in the literature, but these have all proven unsuccessful in providing high enantiomeric excesses of 2-isopropenyl-2,3-dihydrobenzofuran **1e**. For example, treatment of 2-(3-methylbut-2-enyl)phenol **5** with a chiral ligand and catalytic palladium, as shown in Figure 2 (eq 2), afforded both the desired product **1e** and the unwanted compound **6** in a combined yield of 8%. Moreover, this reaction only afforded **1e** in 15% ee.[10] Interestingly, when this same procedure was applied to 2-(2,3-dimethylbut-2-enyl)phenol **7**, which contains an extra methyl substituent, excellent ee's were obtained for the corresponding dihydrobenzofuran **8** (eq 3).[11]

In this paper we wish to report the asymmetric syntheses of two different 2-isopropenyl-2,3-dihydrobenzofuran skeletons. The first outlines the stereoselective synthesis of (*R*)-**1e**, a precursor to *R*-(−)-tremetone **1a**, as well as synthesis of (*S*)-**1e**. The second describes the stereoselective syntheses of the (*S*)- and (*R*)-enantiomers of **1f**. Elaboration of (*R*)-**1f** to synthesize 4-hydroxytremetone **1c** might be feasible via a Fries rearrangement of the corresponding acetate (*R*)-**26**. Moreover, (*R*)-**1f** could potentially be a building block for the synthesis of rotenone **2**. In all syntheses, Trost palladium-catalyzed asymmetric allylic alkylation (AAA) chemistry constitutes the key step for introduction of the stereogenic center at the 2-position of the dihydrobenzofuran nucleus.[12]

SCHEME 1[a]



[a] Reagents and conditions: (i) (a) O_3, CH_2Cl_2, (b) Zn, AcOH, 89%; (ii) $(EtO)_2P(O)CH(Me)CO_2Et$, DBU, LiCl, MeCN, 75%; (iii) $LiAlH_4$, THF, 65%; (iv) MeOCOCl, pyridine, CH_2Cl_2, 77%; (v) TBAF, THF, 0 °C, 98%; (vi) 2 mol % $Pd(dba)_2$, CH_2Cl_2, 6 mol % ligand **15a**, 1 equiv of AcOH, 98%, 92% ee; (vii) $Cr(CO)_6$, *n*-heptane, Bu_2O, THF, reflux, 74% (two diastereoisomers, one diastereoisomer separated by SiO_2 chromatography and recrystallized from CH_2Cl_2/hexane).

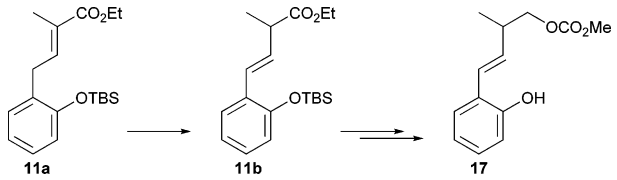


FIGURE 3. Synthesis of undesired **17**.

Results and Discussion

Synthesis of (*R*)-**1e** commenced by protecting commercially available 2-allylphenol to form TBS ether **9** (Scheme 1). Ozonolysis of **9**, affording **10**, required some care to avoid overoxidation of the benzene ring. A Horner−Wadsworth−Emmons reaction using $(EtO)_2P(O)CH(Me)CO_2Et$ and DBU afforded the required (*E*)-alkene **11a**. Initially, this reaction proved to be problematic as the alkene in **11a** readily isomerized to be in conjugation with the benzene ring, forming **11b** in significant quantities (Figure 3). Moreover, these two compounds (**11a** and **11b**) proved completely inseparable by column chromatography at this stage and through the subsequent steps.

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Only at the end of the synthesis could they be separated as the isomerized product **17** (Figure 3) was not susceptible to the Trost π-allyl Pd cyclization reaction (vide infra). Fortunately, this base-induced isomerization could be completely circumvented by altering the order of addition of the reagents and using slightly less than 1 equiv of DBU (see Experimental Section for details). Although these modified conditions completely prevented isomerization of **11a** to **11b**, a small amount of the unwanted (*Z*)-isomer of **11a** was produced. Fortunately, this did not prove to be problematic as the (*E*)- and (*Z*)-isomers could be separated in the next step.

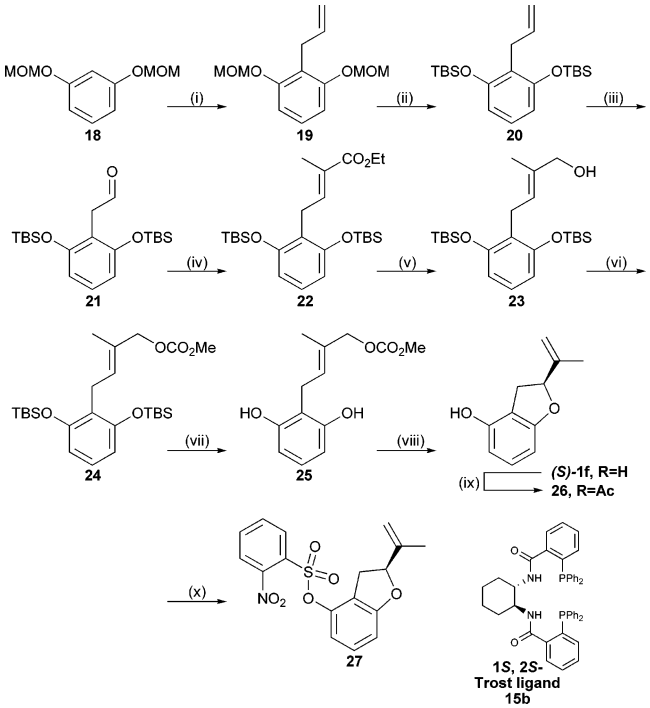
Having overcome the problems pertaining to the synthesis of **11a**, reduction of the ester afforded alcohol **12**, which was readily converted to carbonate **13**. Treatment with TBAF cleaved the silyl ether in excellent yield, forming **14**. Exposure of **14** to the conditions developed by Trost for the synthesis of chiral 2-substituted-2-vinyl chromans using chiral ligand **15a**[12] and catalytic $Pd(dba)_2$ furnished the required volatile 2-isopropenyl-2,3-dihydrobenzofuran, (*R*)-**1e**, in excellent yield and with high enantiomeric excess (92% ee), which was determined by chiral HPLC (Chiralcel OJ). Comparison of our obtained optical rotation ($[\alpha]_D^{19}$ +10.3°, ethanol) to that previously reported (*R*-**1e** $[\alpha]_D^{25}$ +10.9°; *S*-**1e** $[\alpha]_D^{25}$ −10.4°, ethanol)[13] indicated that the (*R*)-enantiomer had been formed. The stereochemistry was confirmed to be (*R*) at the C-2 position after converting **1e** to the arene−$Cr(CO)_3$ complex **16**, which could then be crystallized and analyzed by X-ray crystallography.

Having successfully synthesized (*R*)-**1e** using the chiral ligand **15a**, the opposite enantiomer, (*S*)-**1e**, was also synthesized in good yield and high ee (94% ee) when **14** was similarly treated with $Pd(dba)_2$ in the presence of acetic acid and using the opposite Trost chiral ligand, **15b**.

Encouraged by the above results, synthesis of the 2-isopropenyl-2,3-dihydrobenzofuran subunit of rotenone, which requires an extra phenolic substituent at C-4, was undertaken. Initial experiments to introduce an allyl substituent between silicon-protected resorcinol derivatives led to complications as a result of rearrangements of the silyl ether protecting group. Therefore, resorcinol was initially protected as the bis-MOM derivative **18**, which could then be allylated affording **19**. At this point, it was necessary to switch protecting groups so that the phenols could be liberated near the end of the synthesis. Since this would have to be accomplished in the presence of the required carbonate, use of acid- or base-mediated cleavage would not be possible. This necessitated removal of the MOM groups directly after allylation, replacing them with silyl ether groups, which could later be cleaved under neutral conditions. To this end, **18** was treated with catalytic acid in refluxing methanol, and the resulting phenols were subsequently reprotected using TBSCl, thereby affording **20** in good yield over the two steps (Scheme 2). Thereafter, using the same reaction conditions as previously described in Scheme 1, it was possible to transform **20** through an analogous sequence of steps into **25**. Moreover, it should mentioned that the isomerization problem previously encountered where **11a** readily converted to **11b** was not observed during this Horner−Wadsworth−Emmons reaction to synthesize **22**, even when the original conditions were employed.

Treatment of **25** with $Pd(dba)_2$, chiral ligand **15b**, and acetic acid afforded mainly a single enantiomer of the desired product (*S*)-**1f** in 94% yield and 92% ee, as determined by chiral HPLC

SCHEME 2[a]



[a] Reagents and conditions: (i) CH_2=$CHCH_2Br$, THF, *n*-BuLi, 0 °C, 78%; (ii) (a) cat. HCl, MeOH/THF, 99%, (b) TBSCl, imidazole, MeCN, 79%; (iii) (a) O_3, CH_2Cl_2, (b) Zn, AcOH, 89%; (iv) $(EtO)_2P(O)CH(Me)CO_2Et$, DBU, LiCl, MeCN, 86%; (v) $LiAlH_4$, THF, 77%; (vi) MeOCOCl, pyridine, CH_2Cl_2, 82%, (vii) TBAF, THF, 0 °C (viii) 3 mol % $Pd(dba)_2$, CH_2Cl_2, 10 mol % ligand **15b**, 1.1 equiv of AcOH, 94%, 92% ee; (ix) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 97%, 92% ee; (x) 2-NO_2ArSO_2Cl, Et_3N, CH_2Cl_2, 80%.

analysis of the acetate (*S*)-**26** (see Experimental Section). Since **1f** has not previously been synthesized chirally, the stereochemistry at C-2 was initially uncertain yet believed to be (*S*) based upon our previous work (Scheme 1). Therefore, conversion of (*S*)-**1f** into the crystalline derivative **27** was accomplished using 2-nitrobenzenesulfonyl chloride and triethylamine (Scheme 2). Finally, X-ray crystallography revealed that C-2 of **27** did indeed have the absolute stereochemistry (*S*), consistent with our previous work.

By utilizing the alternative Trost ligand (**15a**), **25** was similarly transformed efficiently into the alternative enantiomer, forming (*R*)-**1f** in 80% yield and 92% ee, as determined by chiral HPLC on the acetate derivative, (*R*)-**26**.

Direct comparison of the mechanistic model proposed by Trost for the formation of the related chiral 2-substituted-2-vinyl chromans to our benzofuran system proved to be useful.[12] We were able to rationalize the stereochemistry of all of our benzofurans using this model. Figure 4 illustrates this model using our allyl carbonate **14** and Trost's representation of the (*R*,*R*′)-ligand, **15a**. Initially, upon ionization, the chiral π-palladium intermediate **28** is formed to facilitate departure of carbonate from under the right-front flap of the ligand. However, once this has occurred, the complex is no longer in the most favorable steric arrangement with respect to the shape of the ligand. The mismatched cyclization that would result from this arrangement is not favorable, and therefore, a $\pi-\sigma-\pi$ rearrangement occurs, forming the thermodynamically preferred **29**. Following this, attack of the phenolic hydroxyl occurs from the bottom face, leading to the (*R*)-benzofuran, (*R*)-**1e**, in a matched cyclization process. The alternative argument would

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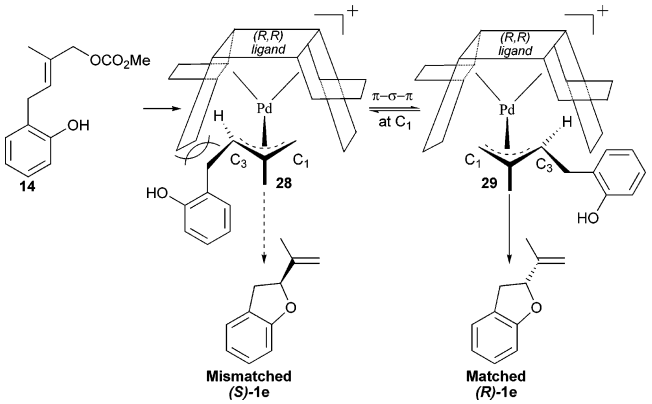

FIGURE 4. Schematic diagram of Trost's (*R*,*R*′)-ligand to rationalize stereochemical outcome.

similarly apply for the (*S*,*S*′)-Trost ligand, **15b**, leading to the (*S*)-benzofuran, (*S*)-**1e**.

In summary, this paper outlines the first high-yielding enantioselective synthesis of either enantiomer of the 2-isopropenyl-2,3-dihydrobenzofuran skeletons of tremetone and rotenone using a catalytic palladium-mediated reaction in the presence of the chiral Trost ligand. Moreover, the synthesis of (*R*)-**1e** and (*S*)-**1e** constitutes a formal synthesis of both fomannoxin and tremetone as both compounds have previously been converted into these natural products.[14]

Experimental Section

(2-Allylphenoxy)(*tert*-butyl)dimethylsilane 9. Into a 250 mL round-bottom flask containing Ar was placed MeCN (200 mL) followed by 2-allylphenol (5.01 g, 37.3 mmol). Imidazole (3.05 g, 44.8 mmol) was then added in one portion at rt followed by TBSCl (6.75 g, 44.8 mmol), also added in one portion. The solution was stirred at rt under Ar for 18 h. The solvent was removed in vacuo, and then EtOAc (200 mL) was added in one portion. Water was then added (200 mL), and after vigorous shaking the salt dissolved into the aqueous layer. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (200 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, affording an orange oil which was purified by column chromatography (2% EtOAc/hexane), affording the desired product **9** as a clear oil (8.36 g, 90%). δ_H/ppm (300 MHz): 7.22−7.06 (2H, overlapping signals), 6.92 (1H, t, J = 7.4), 6.83 (1H, d, J = 8.0), 6.01 (1H, tdd, J = 19.3, 9.4, 6.6), 5.10−5.04 (2H, overlapping signals), 3.41 (2H, d, J = 6.6), 1.05 (9H, s), 0.27 (6H, s). δ_C/ppm (100 MHz): 153.4, 137.1, 130.7, 130.1, 127.0, 121.1, 118.4, 115.4, 34.4, 25.8, 18.3, −4.1. ν_{max}/cm^{-1} (film): 3077, 2958, 1600, 1491, 1266, 936. HRMS: calcd for $C_{15}H_{24}OSi$ 248.1596; found 248.1597. MS: *m*/*z* 248.1597 (7), 191.0902 (100), 163.0522 (25), 151.0456 (13), 135.0247 (5), 115.0546 (5).

2-(2-(*tert*-Butyldimethylsilyloxy)phenyl)acetaldehyde 10. Into a three-neck round-bottom flask fitted with two glass bubbling tubes was placed CH_2Cl_2 (150 mL) followed by (2-allylphenoxy)(*tert*-butyl)dimethylsilane **9** (3.50 g, 14.1 mmol). The reaction mixture was cooled to −85 °C while bubbling a steady stream of N_2 into the solution. The N_2 bubbler was removed, and ozone was introduced into the reaction mixture at −85 °C for periods of 10 min followed by TLC analysis until all the starting material had been consumed. After each 10 min period, the residual ozone was rapidly removed from the solution by reintroducing the N_2 bubbler. Acetic acid was then added (15.8 g, 262 mmol, 15.0 mL) followed immediately by Zn powder (2.00 g, 30.6 mmol). Once the slurry warmed to about −30 °C the ozonide rapidly reduced to the aldehyde **10**. The reaction mixture was quickly filtered while the solution was still below 0 °C, and the acetic acid was neutralized by careful addition of an aqueous sodium bicarbonate solution. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent in vacuo afforded the crude product as an off-white oil, and this was purified by column chromatography (2−5% EtOAc/hexane), affording the desired aldehyde **10** as an oil at rt or a waxy solid at 0 °C (3.13 g, 89%). δ_H/ppm (300 MHz): 9.70 (1H, t, J = 2.1), 7.24−7.10 (2H, m), 6.95 (1H, t, J = 7.4), 6.88 (1H, d, J = 8.1), 3.64 (2H, d, J = 1.9), 1.00 (9H, s), 0.26 (6H, s). δ_C/ppm (100 MHz): 200.0, 154.1, 131.5, 128.7, 123.4, 121.4, 118.4, 45.6, 25.7, 18.2, −4.2. ν_{max}/cm^{-1} (film): 2956, 1732, 1584, 1495, 1296, 922. HRMS: calcd for $C_{14}H_{22}O_2Si$ 250.1389; found 250.1394. MS: *m*/*z* 250.1394 (1), 209.0593 (28), 193.0632 (100), 179.0537 (49), 149.0382 (15).

(*E*)-Ethyl 4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate 11a. Into a two-neck round-bottom flask containing Ar was placed 2-(2-(*tert*-butyldimethylsilyloxy)phenyl)acetaldehyde **10** (2.60 g, 10.4 mmol) followed by MeCN (150 mL). To the solution was added ethyl 2-(diethoxyphosphoryl)propanoate (2.28 g, 9.56 mmol, 2.05 mL) and LiCl (1.05 g, 24.8 mmol). While stirring under Ar, the solution was cooled to 0 °C, and then DBU (1.44 g, 9.43 mmol, 1.41 mL) in MeCN (20 mL) was added dropwise over a 20 min period. The reaction was left to proceed for another 1 h, and then water was added (150 mL) followed by EtOAc (300 mL). After thoroughly mixing the phases, the organic phase was separated and then the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent in vacuo afforded a yellow oil, which was purified by column chromatography (5% EtOAc/hexane), affording the desired (*E*)-alkene **11a** (2.35 g, 68% if based upon the aldehyde **10** or 75% if based upon the limiting DBU) with slight contamination from the (*Z*)-alkene. δ_H/ppm (300 MHz): 7.17−7.08 (2H, overlapping signals), 7.02−6.87 (2H, overlapping signals), 6.84 (1H, d, J = 8.1), 4.20 (2H, q, J = 7.1), 3.52 (2H, d, J = 7.3), 1.96 (3H, s), 1.30 (3H, t, J = 7.1), 1.04 (9H, s), 0.28 (6H, s). δ_C/ppm (100 MHz): 168.1, 153.5, 140.4, 123.0, 129.7, 128.2, 127.4, 121.2, 118.4, 60.4, 29.7, 25.8, 18.3, 14.3, 12.5, −4.1. ν_{max}/cm^{-1} (film): 2931, 2859, 1713, 1495, 1255. HRMS: calcd for $C_{19}H_{30}O_3Si$ 334.1964; found 334.1947. MS: *m*/*z* 334.1947 (3), 289.1639 (12), 277.1237 (100), 264.9920 (6), 231.0825 (45), 193.0693 (17), 161.0462 (9).

(*E*)-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol 12. Into a two-neck round-bottomed flask containing Ar was placed the ester **11a** (1.90 g, 5.68 mmol) followed by dry THF (30 mL). The reaction mixture was cooled to 0 °C, and then $LiAlH_4$ (280 mg, 7.38 mmol) was added in one portion. The reaction was stirred under Ar at 0 °C and monitored every 20 min by TLC to observe the progress of the reaction. After 1.5 h, ice cold water (50 mL) was carefully added. The reaction mixture was diluted with EtOAc (50 mL), and after thoroughly mixing the phases the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 30 mL), and then the combined organic fractions were washed with brine (100 mL) and finally dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, affording the crude product as an off-white colored oil. Purification by column chromatography (10% EtOAc/hexane) afforded the desired alcohol **12** as a clear oil (1.08 g, 65%). δ_H/ppm (300 MHz): 7.15−7.03 (2H, overlapping signals), 6.91−6.86 (1H, m), 6.79 (1H, d, J = 7.9), 5.62 (1H, dt, J = 7.2, 1.2), 4.05 (2H, s), 3.37 (2H, d, J = 7.1), 1.77 (3H, s), 1.33 (1H, brs), 1.02 (9H, s), 0.25 (6H, s). δ_C/ppm (100 MHz): 153.4, 135.6, 131.4, 129.7, 126.9,

(14) Kawase, Y.; Yamaguchi, S.; Kondo, Y.; Shimokawa, K. *Chem. Lett.* **1978**, 253−254.

124.6, 121.1, 118.4, 69.0, 28.3, 25.8, 18.3, 13.8, −4.1. ν_{max}/cm^{-1} (film): 3307, 2956, 2858, 1599, 1489, 1253. HRMS: calcd for $C_{17}H_{28}O_2Si$, 292.1859; found 292.1845. MS: *m*/*z* 292.1845 (10), 235.1124 (82), 217.1073 (89), 195.0884 (29), 177.0759 (77), 143.0834 (28).

(*E*)-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl Methyl Carbonate 13. Into a two-neck round-bottomed flask containing CH_2Cl_2 (50 mL) was placed the alcohol **12** (2.20 g, 7.52 mmol). Pyridine (2.35 g, 29.7 mmol, 2.40 mL) was added followed by chloromethylformate (1.47 g, 15.5 mmol, 1.20 mL). The reaction was left to proceed under Ar at rt for 18 h. Water (20 mL) was added, and the reaction mixture was then further diluted by addition of CH_2Cl_2 (50 mL) and more water (50 mL). The phases were thoroughly mixed, and after separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with dilute HCl (2 × 100 mL), then water (1 × 100 mL), and finally with brine (1 × 100 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting crude oil was purified by column chromatography (5% EtOAc/hexane), affording (*E*)-4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate **13** as a clear viscous oil (2.04 g, 77%). δ_H/ppm (300 MHz): 7.11−7.06 (2H, overlapping signals), 6.88 (1H, t, J = 7.4), 6.79 (1H, d, J = 8.0), 5.71 (1H, t, J = 7.1), 4.57 (2H, s), 3.79 (3H, s), 3.38 (2H, d, J = 7.2), 1.77 (3H, s), 1.01 (9H, s), 0.24 (6H, s). δ_C/ppm (100 MHz): 155.8, 153.4, 130.8, 130.4, 129.6, 128.7, 127.0, 121.1, 118.4, 73.7, 54.7, 28.4, 25.8, 18.3, 13.9, −4.1. ν_{max}/cm^{-1} (film): 2956, 2859, 1750, 1491, 1452, 1278. HRMS: calcd for $C_{19}H_{30}O_4Si$ 350.19134; found 350.1921. MS: *m*/*z* 350.1921 (2), 293.1217 (57), 275.1833 (34), 249.1278 (37), 217.1051 (96), 177.0738 (38), 161.0418 (31), 133.0328 (91).

(*E*)-4-(2-Hydroxyphenyl)-2-methylbut-2-enyl Methyl Carbonate 14. Into a 250 mL round-bottom flask containing Ar was placed dry THF (120 mL) followed by **13** (1.80 g, 5.14 mmol). The solution was cooled to 0 °C, and then TBAF (5.20 mmol, 5.20 mL, 1 M solution in THF) was added in one portion. The reaction was left to proceed for 5 min at 0 °C. The reaction mixture was transferred into a separating funnel and diluted with water (150 mL) and EtOAc (200 mL). After vigorously mixing the phases, the organic phase was separated and the aqueous phase extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent in vacuo the resulting crude oil was purified by column chromatography (10% EtOAc/hexane), affording the desired phenol **13** as a viscous clear oil (1.19 g, 98%). δ_H/ppm (300 MHz): 7.11−7.07 (2H, m), 6.89−6.75 (2H, overlapping m), 5.71 (1H, dt, J = 7.2, 1.1), 5.02 (1H, s), 4.57 (2H, s), 3.79 (3H, s), 3.41 (2H, d, J = 7.3), 1.81 (3H, s). δ_C/ppm (100 MHz): 155.8, 153.7, 131.2, 129.9, 127.7, 127.5, 126.2, 120.9, 115.4, 73.4, 54.8, 28.6, 13.9. ν_{max}/cm^{-1} (film): 3454, 2958, 1722, 1594, 1456, 1274, 938. HRMS: calcd for $C_{13}H_{16}O_4$ 236.1049; found, 236.1033. MS: *m*/*z* 236.1033 (2), 196.0753 (4), 160.0849 (67), 145.0621 (100), 127.0507 (7), 120.0571 (59), 107.0510 (20).

(*R*)-2-Isopropenyl-2,3-dihydrobenzofuran (*R*)-1e. Into a two-neck round-bottom flask was placed CH_2Cl_2 (10 mL) followed by $Pd(dba)_2$ (5.0 mg, 0.0087 mmol), thus forming a wine red solution. The solution was thoroughly degassed by bubbling Ar into the solution for 5 min. The (*R*,*R*′)-Trost ligand **15a** (18.0 mg, 0.0261 mmol) was added in one portion, and the solution gradually changed color from wine-red to yellow as the ligand exchange occurred. The solution was stirred for 30 min after adding the phosphine to ensure complete exchange of the ligand. To this yellow solution at rt was added thoroughly degassed acetic acid (26 mg, 0.44 mmol, 25 μL), and after 5 min of stirring, the allyl carbonate **14** (100 mg, 0.423 mmol) was added in one portion. The reaction was left to proceed for 18 h at rt, during which time it was observed that the yellow color had faded somewhat. Analysis of the reaction mixture by TLC indicated that a new product had formed at a higher R_f and that a small amount of starting material still persisted in the solution. Evaporation of the solvent and purification by column chromatography (10% EtOAc/hexane) afforded the desired benzofuran (*R*)-**1e** (66.6 mg, 98%) and 92% ee as determined by chiral HPLC. (Chiralcel OJ 10μ 250 × 4.6 mm, 2% isopropyl alcohol/hexane). $[\alpha]_D^{19}$ +10.3° (ethanol) (lit: *R*-**1e** $[\alpha]_D^{25}$ +10.9°; *S*-**1e** $[\alpha]_D^{25}$ −10.4°, ethanol).[13] δ_H/ppm (300 MHz): 7.17−7.09 (2H, overlapping signals), 6.86−6.79 (2H, overlapping signals), 5.17 (1H, t, J = 8.9), 5.10 (1H, s), 4.92 (1H, s), 3.34 (1H, dd, J = 15.6, 9.5), 3.05 (1H, dd, J = 15.6, 8.2), 1.78 (1H, s). δ_C/ppm (100 MHz): 159.7, 144.0, 128.0, 126.6, 124.8, 120.3, 112.0, 109.2, 85.6, 34.7, 17.2. HRMS: calcd for $C_{11}H_{12}O$ 160.0888; found 160.0888. MS: *m*/*z* 160.0888 (80), 145.0637 (100), 127.0459 (15), 115.0533 (10), 91.0514 (17).

If **11b** was formed a few steps earlier this would be carried through to this step forming (*E*)-4-(2-hydroxyphenyl)-2-methylbut-3-enyl methyl carbonate **17**, which could be separated and characterized. δ_H/ppm (300 MHz): 7.30 (1H, dd, J = 7.6, 0.9), 7.10 (1H, dt, J = 8.0, 1.4), 6.88 (1H, t, J = 7.2), 6.79 (1H, d, J = 8.0), 6.65 (1H, d, J = 16.1), 6.08 (1H, dd, J = 16.1, 7.7), 5.28 (1H, s), 4.13 (2H, ddd, J = 25.5, 10.5, 6.7), 3.77 (3H, s), 2.75 (1H, td, J = 13.7, 6.8), 1.16 (3H, d, J = 6.8). δ_C/ppm (100 MHz): 156.0, 152.7, 133.4, 128.4, 127.5, 125.2, 124.4, 120.8, 115.9, 71.9, 54.8, 37.2, 16.7. ν_{max}/cm^{-1} (film): 3428 (OH str), 2961, 1725, 1454, 1270. HRMS: calcd for $C_{13}H_{16}O_4$ 236.1049; found 236.1047. MS: *m*/*z* 236.1047 (1), 219.9711 (8), 160.0873 (44), 145.0672 (100), 115.0560 (8), 107.0490 (17).

(*S*)-2-Isopropenyl-2,3-dihydrobenzofuran (*S*)-1e. Into a two-neck round-bottomed flask containing Ar was placed $Pd(dba)_2$ (2.5 mg, 0.0044 mmol) followed by dry CH_2Cl_2 (5 mL), thus forming a wine-red solution. The solution was degassed by bubbling Ar into the solution for 5 min, and then the (*S*,*S*′)-Trost ligand **15b** (9.0 mg, 0.013 mmol) was added in one portion. The solution was stirred at room temperature for 30 min, during which time the color changed from wine-red to yellow. Degassed acetic acid (14 mg, 23 mmol, 13 μL) was added in one portion, and after 2 min of stirring, the allyl carbonate **14** (50.0 mg, 0.212 mmol) was added in one portion. The reaction was left to proceed under Ar at room temperature for 18 h. Analysis of the reaction mixture after this time indicated that all the starting material had reacted, and so the solvent was removed in vacuo and the crude material purified by column chromatography (10% EtOAc/hexane), affording the desired chiral benzofuran (*S*)-**1e** (25.0 mg, 74%) and 94% ee as determined by chiral HPLC (Chiralcel OJ 10μ 250 × 4.6 mm, 2% isopropyl alcohol/hexane). $[\alpha]_D^{19}$ −10.8° (ethanol) (lit: *R*-**1e** $[\alpha]_D^{25}$ +10.9°; *S*-**1e** $[\alpha]_D^{25}$ −10.4°, ethanol).[13] The spectroscopic data were found to be analogous to (*R*)-2-isopropenyl-2,3-dihydrobenzofuran (*R*)-**1e**.

(*R*)-2-Isopropenyl-2,3-dihydrobenzofuran-λ^6-chromium Tricarbonyl 16. Into a solution consisting of Bu_2O (10 mL) and heptane (10 mL) was added (*R*)-2-isopropenyl-2,3-dihydrobenzofuran (*R*)-**1e** (60.0 mg, 0.374 mmol) followed by $Cr(CO)_6$ (149 mg, 0.677 mmol). The solution was then thoroughly degassed by repeated evacuation and Ar purging (ca. 5 times). Dry THF (1 mL) was added, and the solution was once again degassed before heating the mixture to reflux for 72 h. During this time the solution gradually changed color from clear to yellow. The solution was allowed to cool to rt before being filtered through a plug of silica gel that was then washed with excess EtOAc. The resulting yellow solution was concentrated in vacuo and purified by column chromatography (20% EtOAc/hexane), affording two products (assumed to be diastereomers). Complete separation of these two compounds was not possible. However, yellow solids (33.8 mg, top spot; 29.3 mg, bottom spot on TLC) as well as a mixed fraction containing (18.9 mg), also as a yellow solid, were isolated. In total 82 mg of product was obtained (74%). The higher R_f product was selected for X-ray analysis, and crystals suitable for this purpose were obtained by recrystallization from CH_2Cl_2/hexane. Analysis by X-ray crystallography revealed that the identity as the *anti*-facial diastereomer **16**. Mp 77−79 °C; $[\alpha]_D^{19}$ −94.4° ($CHCl_3$). HRMS:

calcd for $C_{14}H_{12}CrO_4$ 296.0141; found 296.0135. MS: *m*/*z* 296.0135 (36), 240.0285 (11), 212.0268 (100), 172.0086 (15), 157.9803 (15). X-ray data for **16** $C_{14}H_{12}CrO_4$; M = 296.24; tetragonal; a = 8.33980(10) Å, b = 8.33980(10) Å, c = 37.0388(9) Å; U = 2576.13(8) Å^3, T = 173(2) K, space group, $P4(3)2(1)2$, Z = 8; μ(Mo Kα) = 0.073 mm^{-1}; 18 307 reflections measured, 3100 unique [R(int) = 0.0366] which were used in all calculations. Final R indices [$I > 2\sigma(I)$], R_1 = 0.0261, w$R(F^2)$ = 0.0657. CCDC number 616087.

2-Allyl-1,3-bis(methoxymethoxy)benzene 19. Into a dry two-neck 250 mL round-bottomed flask, fitted with a dropping funnel and under Ar, was placed dry THF (170 mL) followed by 1,3-bis-(methoxymethoxy)benzene **18** (4.00 g, 20.2 mmol). The solution was cooled to 0 °C, and the dropping funnel was charged with *n*-BuLi (17.0 mL, 24.0 mmol, 1.4 M). The *n*-BuLi was added dropwise over a period of 10 min, thus forming a yellow solution, which was stirred at 0 °C for another 90 min. During this time the yellow color intensified and eventually turned pale orange. The dropping funnel was then charged with allyl bromide (3.50 mL, 40.0 mmol) in THF (10 mL), and this solution was added dropwise to the reaction mixture over a period of 10 min. The reaction was left to proceed at 0 °C for another 60 min and then allowed to warm to rt and left for 18 h. The reaction mixture was transferred to a separating funnel and diluted with EtOAc (100 mL) and water (100 mL). After mixing, the organic phase was separated and the aqueous phase extracted once with EtOAc (100 mL). The combined organic fractions were washed with brine (200 mL) and then dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent in vacuo the crude oil was purified by column chromatography (2% EtOAc/hexane), affording the desired compound **19** as a clear oil (3.74 g, 78%). δ_H/ppm (300 MHz): 7.09 (1H, t, J = 8.3), 6.77 (2H, d, J = 8.3), 5.96 (1H, tdd, J = 6.1, 10.0 and 16.2), 5.17 (4H, s), 5.01−4.91 (2H, overlapping signals), 3.48−3.46 (10H, overlapping signals). δ_C/ppm (100 MHz): 155.8, 136.7, 127.1, 118.3, 114.1, 107.9, 94.4, 55.9, 27.6. ν_{max}/cm^{-1} (film): 2901, 1596, 1471, 1154, 1041. HRMS: calcd for $C_{13}H_{18}O_4$ 238.1205; found 238.1216. MS: *m*/*z* 238.1216 (25), 174.0687 (6), 161.0575 (34), 147.0454 (10).

2-Allylbenzene-1,3-diol. Into a 250 mL flask fitted with a condenser was placed 2-allyl-1,3-bis(methoxymethoxy)benzene **19** (4.20 g, 17.6 mmol) followed by THF (100 mL) and MeOH (50 mL). The solution was acidified slightly by addition of three drops of an aqueous 32% HCl solution and then heated to reflux for 18 h, after which time analysis of the reaction mixture indicated that a significant amount of starting material still persisted. Another addition of acid was made (5 drops), and the solution was refluxed for another 18 h. The solvent was then evaporated in vacuo, affording a clear oil. Removal of trace amounts of water was achieved by dissolving the crude material in EtOAc and adding $MgSO_4$. After filtration, the solvent was removed in vacuo, affording the crude product, which was purified by column chromatography (10% EtOAc/hexane), affording 2-allylbenzene-1,3-diol as a clear oil in quantitative yield (2.97 g). δ_H/ppm (300 MHz): 6.97 (1H, t, J = 8.1), 6.43 (2H, d, J = 8.1), 6.02 (1H, tdd, J = 6.0, 10.1 and 16.1), 5.41 (2H, s), 5.20−5.11 (2H, overlapping signals), 3.50−3.48 (2H, m). δ_C/ppm (100 MHz): 155.0, 135.9, 127.6, 115.9, 112.1, 108.2, 27.5. ν_{max}/cm^{-1} (film): 3413, 1614, 1465, 1294. HRMS: calcd for $C_9H_{10}O_2$ 150.0681; found 150.0694. MS: *m*/*z* 150.0694 (100), 135.0457 (30), 123.0475 (20), 107.0453 (18), 103.0523 (8).

2-Allyl-1,3-bis(*tert*-butyldimethylsilyloxy)benzene 20. Into a dry two-neck flask was placed 2-allylbenzene-1,3-diol (2.40 g, 16.0 mmol) followed by dry MeCN (180 mL). Imidazole was added in one portion (3.26 g, 47.9 mmol) followed by TBSCl (6.02 g, 39.9 mmol), and the reaction was left to proceed under Ar at rt for 18 h. The MeCN was evaporated in vacuo, affording an oil containing the imidazole hydrochloride as a white precipitate. The crude mixture was taken up into EtOAc (150 mL), and water was added (150 mL). After thoroughly mixing the phases and then allowing them to separate, the organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 100 mL). The organic phases were combined and washed with brine (200 mL), separated, and dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent in vacuo, the crude product was obtained as a clear oil. Purification by column chromatography (2% EtOAc/hexane) afforded **20** as a clear oil (4.79 g, 79%). δ_H/ppm (300 MHz): 6.93 (1H, t, J = 8.2), 6.45 (2H, d, J = 8.1), 5.93 (1H, tdd, J = 5.9, 9.4, and 17.8), 4.94−4.88 (2H, overlapping signals), 3.39 (2H, d, J = 5.8), 1.01 (18H, s), 0.23 (12H, s). δ_C/ppm (100 MHz): 154.8, 136.8, 126.3, 121.6, 114.0, 111.5, 28.4, 25.8, 18.3, −4.1. ν_{max}/cm^{-1} (film): 2931 (CH str), 1588, 1465, 1259. HRMS: calcd for $C_{21}H_{38}O_2Si_2$ 378.2410; found, 378.2413. MS: *m*/*z* 378.2414 (8), 321.1720 (64), 293.1399 (10), 279.1541 (15), 256.2368 (62), 149.0200 (48).

2-(2,6-Bis(*tert*-butyldimethylsilyloxy)phenyl)acetaldehyde 21. Into a three-neck round-bottom flask was placed alkene **20** (4.40 g, 11.6 mmol) followed by dry CH_2Cl_2 (180 mL). While bubbling N_2 gas into the solution, the flask was immersed into an acetone bath cooled to about −80 °C. After allowing the reaction mixture to cool for several minutes and maintaining a temperature between −80 and −70 °C, the nitrogen bubbler was removed and ozone gas was bubbled into the solution for 5 min. The ozone bubbler was then removed, and residual ozone was rapidly dispersed from the solution by reintroduction of the nitrogen bubbler. Analysis of the reaction mixture by TLC indicated that significant amounts of the alkene still persisted, and so this process was repeated until only trace amounts of starting material were observable by TLC analysis. The reaction mixture was then warmed to 0 °C and maintained at this temperature while a large excess of acetic acid was added (ca. 10 mL) followed by an excess of Zn powder (added in small portions every 10 min until all the ozonalide was reduced to the aldehyde **21**). The reaction mixture was then filtered, washed twice with saturated sodium bicarbonate solution, and then finally washed once with brine before being dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent in vacuo the crude product was purified by column chromatography (2% EtOAc/hexane), affording the desired aldehyde **21** as an oil at rt (3.92 g, 89%). δ_H/ppm (300 MHz): 9.61 (1H, s), 7.03 (1H, t, J = 8.2), 6.51 (2H, d, J = 8.2), 3.65 (2H, d, J = 1.5), 0.98 (18H, s), 0.23 (12H, s). δ_C/ppm (100 MHz): 200.8, 155.3, 127.8, 115.0, 111.4, 39.4, 25.7, 18.2, −4.2. ν_{max}/cm^{-1} (film): 2859 (CH str), 1729 (C═O str), 1589, 1465, 1259. HRMS: calcd for $C_{20}H_{36}O_3Si_2$ 380.2203; found 380.2213. MS: *m*/*z* 380.2213 (2), 365.1962 (5), 323.1448 (100), 265.0726 (9), 237.0270 (6), 115.0918 (11).

(*E*)-Ethyl-4-(2,6-bis(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate 22. Into a dry two-neck round-bottom flask fitted with a dropping funnel, containing Ar, was placed LiCl (510 mg, 12.0 mmol) followed by dry MeCN (8 mL). Ethyl 2-(diethoxyphosphoryl)propanoate (1.70 mL, 1.89 g, 7.93 mmol) was added in one portion, and then while cooling the reaction mixture in a bath at ca. 5 °C, DBU (1.25 mL, 1.27 g, 8.34 mmol) was added dropwise over a period of 5 min. After 15 min of stirring at 5 °C, 2-(2,6-bis(*tert*-butyldimethylsilyloxy)phenyl)acetaldehyde **21** (2.00 g, 5.25 mmol) in MeCN (2 mL) was added dropwise over a period of 10 min and the reaction was left to proceed for 18 h at rt. The reaction mixture was transferred to a separating funnel and diluted with EtOAc (150 mL) and water (150 mL). After mixing the phases, the organic phase was separated and the aqueous phase extracted with EtOAc (3 × 100 mL). The combined organic fractions were then washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration and evaporation of the volatiles in vacuo, the crude oil was purified by column chromatography to afford (*E*)-ethyl 4-(2,6-bis(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate **22** as a clear oil (2.10 g, 86%). δ_H/ppm (300 MHz): 6.94 (1H, t, J = 8.2), 6.81 (1H, t, J = 6.0), 6.46 (2H, d, J = 8.2), 4.14 (2H, q, J = 7.1), 3.49 (2H, d, J = 6.3), 1.92 (3H, s), 1.23 (3H, t, J = 7.1), 0.98 (18H, s), 0.24 (12H, s). δ_C/ppm (100 MHz): 168.6, 155.3, 142.8, 127.4, 127.0, 121.6, 111.9, 60.5,

26.2, 24.5, 18.7, 14.7, 13.1, −3.7. ν_{max}/cm^{-1} (film): 2931 (CH str), 1712 (C═O), 1648, 1588, 1465, 1248. HRMS: calcd for $C_{25}H_{44}O_4Si_2$ 464.2778; found, 464.2784. MS: *m*/*z* 464.2784 (10), 449.2502 (3), 407.2110 (100), 379.1805 (7), 361.1726 (5), 218.9856 (10).

(*E*)-4-(2,6-Bis(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol 23. Into a two-neck flask containing Ar was placed the ester **22** (643 mg, 1.38 mmol) followed by dry THF (10 mL). The solution was cooled to 0 °C by an ice bath, and $LiAlH_4$ (68.0 mg, 1.79 mmol) was added. The reaction was then closely monitored by TLC approximately every 20 min. After 3 h all the starting material had been consumed, and so ice cold water was added in small portions (50 mL). The reaction mixture was diluted with EtOAc (50 mL), after mixing the two phases an emulsion formed, and this was broken by addition of a small amount of 1 M HCl solution. The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were filtered through Celite and then washed once with brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered, and evaporated, affording the crude product as a pale yellow oil. After purification by column chromatography (2−5% EtOAc/hexane) the desired alcohol **23** was obtained as a viscous clear oil (451 mg, 77%). δ_H/ppm (300 MHz): 6.91 (1H, t, J = 8.2), 6.45 (2H, d, J = 8.1), 5.46 (1H, t, J = 5.6), 3.96 (2H, s), 3.37 (2H, d, J = 5.9), 2.17 (1H, s), 1.78 (3H, s), 0.99 (18H, s), 0.23 (12H, s). δ_C/ppm (100 MHz): 154.7, 134.1, 126.2, 126.1, 122.8, 111.7, 69.2, 25.8, 22.9, 18.3, 14.0, −4.1. ν_{max}/cm^{-1} (film): 3331, 2930, 1587, 1463, 1362, 1244, 1177, 1064, 913, 828, 732, 685. HRMS: calcd for $C_{23}H_{42}O_3Si_2$ 422.2672; found 422.2655. MS: *m*/*z* 422.2655 (15), 365.1943 (100), 347.1858 (12), 309.1293 (15), 273.1638 (5), 218.9856 (11).

(*E*)-4-(2,6-Bis(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl Methyl Carbonate 24. Into a dry two-neck round-bottom flask containing Ar was placed (*E*)-4-(2,6-bis(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-ol **23** (1.00 g, 2.37 mmol) followed by dry CH_2Cl_2 (20 mL). The flask was placed into a cooling bath (approx 5 °C), and pyridine (0.80 mL, 0.78 g, 9.9 mmol) was added in one portion. Chloromethylformate (0.38 mL, 0.46 g, 4.9 mmol) was then added dropwise over a period of about 2 min, and the reaction was left to proceed for 5 min before the cooling bath was removed. After allowing the reaction to proceed at rt for another 30 min, water was carefully added (20 mL) and the mixture decanted into a separating funnel. The mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase extracted once with CH_2Cl_2 (50 mL). The combined organic fractions were then washed with HCl solution (0.2 M, 2 × 50 mL), then water (50 mL), and finally brine (100 mL). After drying over anhydrous $MgSO_4$, the volatiles were removed in vacuo and the crude oil was purified by column chromatography (5% EtOAc/hexane), affording (*E*)-4-(2,6-bis(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate **24** as a clear oil (0.933 g, 82%). δ_H/ppm (300 MHz): 6.92 (1H, t, J = 8.1), 6.45 (2H, d, J = 8.1), 5.56 (1H, t, J = 5.7), 4.49 (2H, s), 3.76 (3H, s), 3.37 (2H, d, J = 5.9), 1.78 (3H, s), 0.99 (18H, s), 0.23 (12H, s). δ_C/ppm (100 MHz): 155.8, 154.8, 130.3, 128.8, 126.2, 122.3, 111.6, 73.9, 54.6, 25.8, 23.1, 18.3, 14.2, −4.1. ν_{max}/cm^{-1} (film): 2959 (CH str), 1751 (C═O str), 1588, 1464, 1261, 1068. HRMS: calcd for $C_{25}H_{44}O_5Si_2$ 480.2727; found 480.2720. MS: *m*/*z* 480.2720 (2), 423.2000 (77), 405.2622 (20), 379.2153 (69), 347.1747 (30), 291.1276 (5), 233.0630 (11), 215.0906 (4).

(*E*)-4-(2,6-Dihydroxyphenyl)-2-methylbut-2-enyl Methyl Carbonate 25. Into a 100 mL round-bottom flask containing Ar was placed (*E*)-4-(2,6-bis(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate (300 mg, 0.624 mmol) followed by dry THF (50 mL). The solution was cooled to 0 °C under Ar, and TBAF (1.24 mmol, 1.24 mL, 1 M) was added in one portion. The reaction was left for 5 min, during which time the color changed to deep purple. Water was added (50 mL), and the mixture was diluted with EtOAc (100 mL). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase extracted with EtOAc (5 × 30 mL). The combined organic fractions were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo and the crude oil purified by column chromatography (20% EtOAc/hexane), affording the desired product **25** as a clear oil containing trace amounts of EtOAc which could not be removed under vacuum (169 mg). δ_H/ppm (300 MHz): 6.90 (1H, t, J = 8.1), 6.37 (2H, d, J = 8.1), 5.63 (1H, t, J = 6.8), 5.80−5.00 (2H, br s), 4.52 (2H, s), 3.77 (3H, s), 3.44 (2H, d, J = 7.1), 1.84 (3H, s). δ_C/ppm (100 MHz): 155.9, 154.9, 130.6, 128.0, 127.2, 113.4, 108.0, 73.7, 54.8, 22.0, 13.8. ν_{max}/cm^{-1} (film): 3364, 2959, 1699, 1615, 1471, 1247, 1167, 1036. HRMS: calcd for $C_{13}H_{16}O_5$ 252.0998; found 252.1015. MS: *m*/*z* 252.1015 (2), 176.0842 (40), 161.0514 (84), 142.1580 (26), 123.0439 (11).

(*S*)-2-Isopropenyl-2,3-dihydrobenzofuran-4-ol (*S*)-1f. Into a dry two-neck round-bottom flask containing Ar was placed CH_2Cl_2 (2.5 mL) followed by $Pd(dba)_2$ (6.8 mg, 0.012 mmol). The solution was degassed for 3 min by bubbling Ar directly into the solution by means of a Pasteur pipet. The Trost ligand **15b** (28.0 mg, 0.0405 mmol) was then added in one portion against a gentle flow of Ar, and a color change occurred over a 15 min period from deep purple to a light yellow color. The reaction was left to stir at rt for another 10 min, and then degassed AcOH was added in one portion (26 mg, 0.44 mmol, 25 μL). After 5 min of stirring the diol **25** was added in one portion (100 mg, 0.396 mmol). The reaction was left to proceed at rt for 18 h under Ar. The reaction mixture was then concentrated in vacuo, and the crude material was adsorbed onto silica gel and purified by column chromatography (5−10% EtOAc/hexane), affording (*S*)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (*S*)-**1f** (65.3 mg, 94%, 92% ee). The ee was determined by HPLC analysis (Chiralcel OJ 10μ 250 × 4.6 mm, 10% isopropyl alcohol/hexane) after conversion of (*S*)-**1f** to the *O*-acetate (*S*)-**26**. Spectroscopic data for (*S*)-**1f**: $[\alpha]_D^{19}$ +17.3°, $CHCl_3$. δ_H/ppm: 6.99 (1H, t, J = 8.0), 6.44 (1H, d, J = 7.9), 6.32 (1H, d, J = 8.0), 6.00−4.30 (1H, br s), 5.21 (1H, t, J = 8.8), 5.10 (1H, s), 4.92 (1H, s), 3.31 (1H, dd, J = 9.7 and 15.3), 2.98 (1H, dd, J = 8.0 and 15.3), 1.78 (3H, s). δ_C/ppm: 161.4, 152.4, 143.8, 129.1, 112.2, 112.1, 107.7, 102.2, 86.1, 31.7, 17.1. ν_{max}/cm^{-1}: 3387 (OH str), 1607, 1464, 1317, 1278, 1233. HRMS: calcd for $C_{11}H_{12}O_2$ 176.0837; found 176.0820. MS: *m*/*z* 176 (45), 161 (100), 145 (33), 117 (7), 115 (10).

(*R*)-2-Isopropenyl-2,3-dihydrobenzofuran-4-ol (*R*)-1f. Into a dry two-neck round-bottom flask containing Ar was placed dichloromethane (5 mL) followed by $Pd(dba)_2$ (6.0 mg, 0.010 mmol). The solution was degassed for 3 min by bubbling Ar directly into the solution by means of a Pasteur pipet. The (*R*,*R*′)-Trost ligand (20.0 mg, 0.0290 mmol) **15a** was then added in one portion against a gentle flow of Ar, and a color change occurred over a 15 min period from deep purple to a light yellow color. The reaction was left to stir at room temperature for another 10 min, then degassed acetic acid was added in one portion (23 mg, 0.38 mmol, 22 μL), and after 5 min of stirring, the carbonate **25** was added in one portion (90.0 mg, 0.357 mmol). The reaction was left to proceed at rt overnight under Ar at 25 °C. The reaction mixture was then concentrated in vacuo, and the crude material was adsorbed onto silica gel and purified by column chromatography, affording (*R*)-(−)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (*R*)-**1f** (50.5 mg, 80%, 92% ee). The ee was determined by HPLC (Chiralcel OJ 10μ 250 × 4.6 mm, 10% isopropyl alcohol/hexane) after conversion to the acetate (*R*)-**26**. Optical rotation for (*R*)-**1f**: $[\alpha]_D^{19}$ −18.1°, $CHCl_3$. The spectroscopic data were found to be analogous to (*S*)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (*S*)-**1f**.

(*S*)-2-Isopropenyl-2,3-dihydrobenzofuran-4-yl Acetate (*S*)-26. Into a two-neck round-bottom flask containing Ar was placed 2-isopropenyl-2,3-dihydrobenzofuran-4-ol (*S*)-**1f** (25.0 mg, 0.142 mmol) followed by CH_2Cl_2 (1.5 mL). To the solution, at rt, was added Et_3N (28 mg, 0.28 mmol, 39 μL) followed by DMAP (5 mg, 0.01 mmol) and Ac_2O (19 mg, 0.19 mmol, 18 μL), and the

reaction was left to proceed for 18 h at rt under Ar. The solvent was evaporated in vacuo, and the crude material was adsorbed onto silica gel and purified by column chromatography (10% EtOAc/hexane), affording the desired acetate (*S*)-**26** as a clear oil (30.0 mg, 97%). Analysis of the acetate by HPLC (Chiralcel OJ 10μ 250 × 4.6 mm, 10% isopropyl alcohol/hexane) confirmed that (*S*)-**26** had been produced in 92% ee. $[\alpha]_D^{19}$ + 25.0°, $CHCl_3$. δ_H/ppm (300 MHz): 7.12 (1H, t, J = 8.0), 6.69 (1H, d, J = 8.0), 6.57 (1H, d, J = 8.1), 5.20 (1H, t, J = 8.8), 5.08 (1H, s), 4.91 (1H, s), 3.23 (1H, dd, J = 9.6 and 15.7), 2.93 (1H, dd, J = 8.1 and 15.7), 2.28 (3H, s), 1.76 (3H, s). δ_C/ppm (100 MHz): 168.4, 161.3, 147.3, 143.6, 129.0, 119.3, 113.4, 112.4, 107.0, 86.2, 32.7, 20.9, 17.1. ν_{max}/cm^{-1} (film): 2920, 1767 (C═O str), 1462, 1370, 1036. HRMS: calcd for $C_{13}H_{14}O_3$ 218.0943; found 218.0945. MS: *m*/*z* 218.0945 (24), 176.0804 (30), 161.0628 (100).

(*R*)-2-Isopropenyl-2,3-dihydrobenzofuran-4-yl Acetate (*R*)-26. Into a two-neck round-bottom flask containing Ar was placed (*R*)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (*R*)-**1f** (48.2 mg, 0.274 mmol) followed by CH_2Cl_2 (5 mL). To the solution, at rt, was added Et_3N (56 mg, 0.55 mmol, 77 μL) followed by DMAP (5 mg) and Ac_2O (37 mg, 0.36 mmol, 34 μL). The reaction was left to proceed for 18 h at rt under Ar. Analysis of the reaction mixture indicated that all of the starting material had been consumed, and so the solvent was evaporated in vacuo and the crude material adsorbed onto silica gel. Purification by column chromatography (10% EtOAc/hexane) afforded the desired acetate as a clear oil (59.0 mg, 99%). Analysis of the acetate by chiral HPLC (Chiralcel OJ 10μ 250 × 4.6 mm, 10% isopropyl alcohol/hexane) confirmed that the (*R*)-**26** had been produced in 92% ee. $[\alpha]_D^{19}$ −25.8°, $CHCl_3$. The spectroscopic data were found to be analogous to (*S*)-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate (*S*)-**26**

(*S*)-2-Isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate 27. Into a two-neck round-bottom flask was placed the chiral benzofuran (*S*)-**1f** (28.0 mg, 0.159 mmol) followed by dry CH_2Cl_2 (5 mL). To the solution, at rt, was added triethylamine (30 mg, 0.30 mmol, 42 μL) followed by 2-nitrobenzenesulfonyl chloride (43.0 mg, 0.194 mmol). The solution was stirred at rt for 18 h under Ar. The reaction mixture was concentrated in vacuo and purified by column chromatography (20% EtOAc/hexane), affording **27** as a white solid (45.9 mg, 80%). Recrystallization of this compound from diethyl ether afforded white needle-like crystals. Mp 82−83 °C. $[\alpha]_D^{20}$ + 12.0°, $CHCl_3$. δ_H/ppm (300 MHz): 8.00 (1H, d, J = 7.8), 7.89−7.81 (2H, m), 7.76−7.66 (1H, m), 7.05 (1H, t, J = 8.1), 6.73 (1H, d, J = 8.0), 6.55 (1H, d, J = 8.2), 5.18 (1H, t, J = 8.7), 5.05 (1H, s), 4.90 (1H, s), 3.44 (1H, dd, J = 16.3 and 9.6), 3.03 (1 H, dd, J = 16.3 and 7.9), 1.71 (3H, s). δ_C/ppm (100 MHz): 161.8, 145.6, 143.2, 135.4, 132.0, 132.0, 129.3, 128.9, 124.9, 120.8, 113.9, 112.6, 108.7, 86.5, 32.7, 17.0. ν_{max}/cm^{-1} (film): 2924, 1654, 1621, 1594, 1192, 1006. HRMS: calcd for $C_{17}H_{15}NO_6S$ 361.0620; found 361.0627. MS: *m*/*z* 361.0627 (100), 346.0342 (41), 264.9931 (8), 175.0756 (70), 159.0790 (82). X-ray data for **25**: $C_{17}H_{15}NO_6S$; M = 361.36; orthorhombic; 0.71073 Å; *P*2(1)2(1)2(1); a = 5.7422(8) Å, b = 13.106(2) Å, c = 22.274(3) Å, U = 1676.3(4) Å;^{3} 173(2) K, space group, *P*2-(1)2(1)2(1), Z = 4;. μ(Mo Kα) = 0.073 mm^{-1}; 13 907 reflections measured, 4041 unique [R(int) = 0.0355], which were used in all calculations. Final R indices [$I > 2\sigma(I)$] R_1 = 0.0382, w$R(F^2)$ = 0.0916. CCDC number 616088.

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Supporting Information Available: ^{1}H and ^{13}C NMR of **9**−**14**, **17**, **19**−**27**, **1e**, and **1f**. This material is available free of charge via the Internet at http://pubs.acs.org. X-ray crystallographic data for compounds **16** and **27** have been deposited into the CCDC.

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