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A concise synthesis of honokiol

Ross M. Denton *, James T. Scragg, Adrià M. Galofré, Xiechao Gui, William Lewis †

School of Chemistry University of Nottingham, University Park, Nottingham NG7 2RD, UK

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ABSTRACT

Two approaches to the synthesis of the plant-derived biaryl neolignan honokiol are described. The second approach provided the natural product in either four steps with 34% overall yield or five steps and 55% overall yield.

1. Introduction

Honokiol-(**1**) (Fig. 1) is one of a family of biaryl neolignans originally isolated from *Magnoliae officinalis*[1] and more recently from *Magnoliae obovata*.[2] Honokiol-containing extracts of the stems and bark of these plants have long been used in traditional Chinese and Japanese medicine for the treatment of a variety of ailments. In 1975 the muscle relaxing properties of honokiol were described.[3] Since this time, a substantial body of literature describing the biological activity of the natural product in vitro and in vivo has appeared. Perhaps the most significant findings of these wide-ranging studies are concerned with honokiol's anticancer[4] and neurotrophic activity.[5] At present natural honokiol is obtained by extraction of magnolia bark; however, the isolation is complicated by the fact that the natural product is often isolated with its constitutional isomer magnolol-(**3**). Separation requires either HPLC,[6] electromigration[7] or chemical derivatisation.[8] Despite the considerable interest in the biological activity of honokiol in recent years there was, until recently, only two reported total syntheses of the natural product. The first,[9] reported in 1986, proceeds in four steps with an overall yield of 16% whilst the second reported synthesis proceeds in an improved 21% overall yield but required 14 steps.[5c] The recent report of a shorter and higher yielding route, 32%, which features a Suzuki cross-coupling as a key step[10] prompts us to report the results of our own studies pertaining to the development of a concise and robust synthesis of honokiol, which we developed to make material available for biological study.

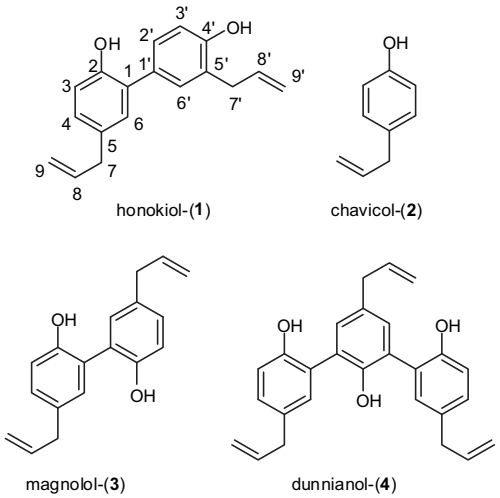

Figure 1. Honokiol-(**1**) and related neolignan natural products.

Our initial synthesis plan for honokiol is outlined in Scheme 1 in retrosynthetic form. The proposed route relies on the recently developed rhodium-catalysed direct arylation of phenols for the construction of the biaryl bond[11] (**7**+**8**→**6**) and Claisen and Claisen/Cope rearrangements to introduce the two allyl groups at the C5 and C5′ positions, respectively. The *ortho-tert*-butyl group present

* Corresponding author. Tel.: +44 115 9514194; fax: +44 115 9513564; e-mail address: ross.denton@nottingham.ac.uk (R.M. Denton).
† Corresponding author for X-ray crystal structures.

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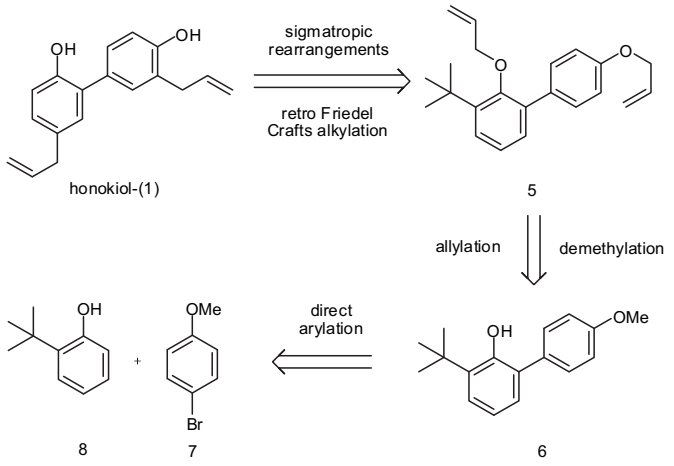
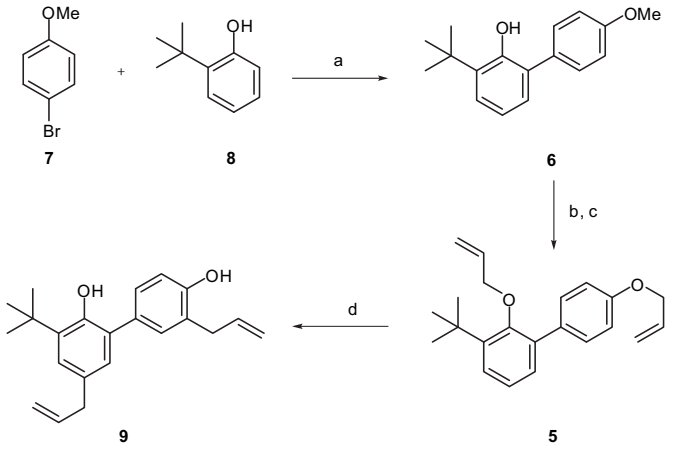
in starting material **6** is necessary to prevent both unwanted Claisen rearrangement occurring at C3 and to ensure mono-arylation during the direct arylation process.



Scheme 1. Synthesis plan for honokiol.

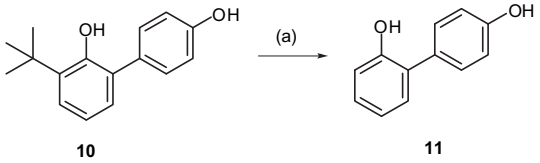
2. Results and discussion 1—Rhodium-catalysed direct arylation approach

The synthesis began with the rhodium-catalysed direct arylation of phenol **8** with bromide **7** according to the general protocol of Bedford and co-workers (Scheme 2) to afford the expected biaryl in 45% isolated yield.[11] Given that the reaction reaches full conversion with respect to the phenol the moderate yield obtained reflects the difficulty in separating the product from the excess bromide **7** used.



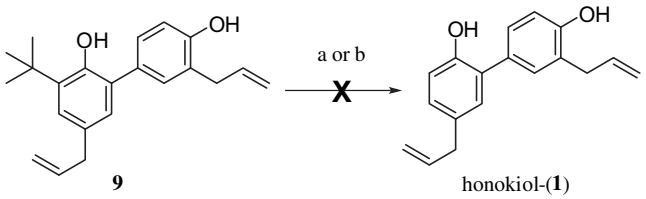
Scheme 2. Reagents and conditions: (a) $[RhCl(COD)]_2$ 10 mol %, $P(NMe_2)_3$ 30 mol %, Cs_2CO_3, toluene, reflux, 18 h, 45%. (b) $BCl_3{\cdot}SMe_2$, DCE, reflux, 18 h, 66%. (c) Allyl bromide, Cs_2CO_3, DMF, 15 h, 92%. (d) DMF, microwave, 200 °C, 50 min, 49%.

Demethylation of biaryl **6** was then effected using $BCl_3{\cdot}SMe_2$ affording the corresponding diol. Double allylation of this material was achieved in excellent yield using allyl bromide and Cs_2CO_3 in DMF affording rearrangement precursor **5**. We were pleased to observe that the latter compound underwent clean Claisen and Claisen/Cope rearrangements upon heating to 200 °C in the microwave to afford *tert*-butyl honokiol **9** in moderate yield. At this point of the synthesis all that remained was a retro Friedel–Crafts alkylation[12] reaction to remove the *tert*-butyl blocking group from C3. We were conscious of the lack of precedent for retro Friedel–Crafts alkylation in the presence of alkenes and of the possibility for nucleophilic capture of the derived *tert*-butyl carbocation by the adjacent aromatic ring. We therefore began by establishing that a retro alkylation reaction was viable on substrate **10**, which lacked the allyl groups.



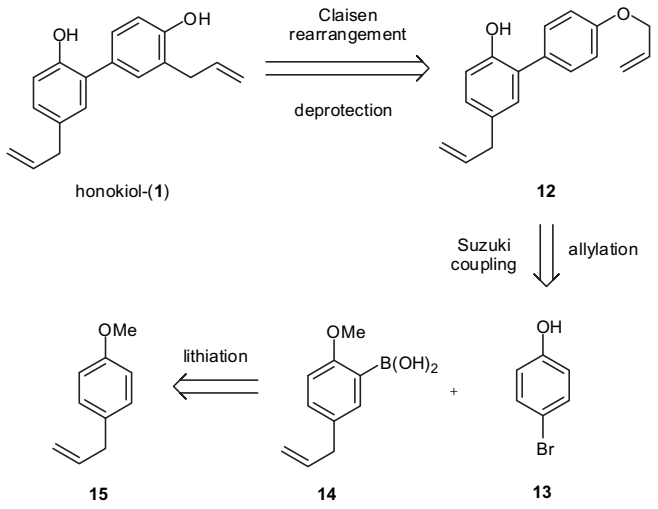
Scheme 3. Reagents and Conditions: (a) $AlCl_3$, toluene:CH_3NO_2 (10:1), 60 °C, 2 h 63%.

Heating a solution of **10** and $AlCl_3$ in toluene and nitromethane[13] to 60 °C afforded a good yield of biaryl **11**. No products arising from recapture of the *tert*-butyl group were observed in the ^1H NMR spectrum of the crude reaction mixture presumably because the solvent acts as an irreversible *tert*-butyl cation scavenger.[12] We then turned our attention to the removal of the *tert*-butyl blocking group from substrate **9** to complete the synthesis of honokiol (Scheme 4).



Scheme 4. Reagents and Conditions: (a) $AlCl_3$, toluene:CH_3NO_2 (10:1), 60 °C, 2 h. (b) $AlCl_3$, toluene, rt, 2 h.

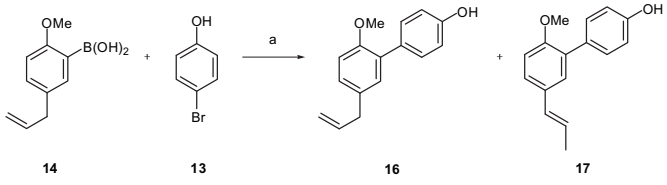
Unfortunately, repeated attempts under a variety of reaction conditions were uniformly unsuccessful. In the first instance the conditions depicted in Scheme 3 were employed. We were frustrated to observe that subjection of substrate **9** to the same conditions resulted in decomposition of **9**. Analysis of ^1H NMR and ^{13}C NMR spectra of the crude reaction mixture indicated that the *tert*-butyl group was intact but a complex mixture of products had formed. It was apparent from the spectra that a cyclisation had occurred between the hydroxyl group at position C4′and the allyl side chain at position C5′.[14] When **9** was subjected to the $AlCl_3$ in toluene at room temperature similar degradation was observed after 2 h. In a further experiment we examined the stability of commercial honokiol to $AlCl_3$ in toluene-d_8 at both room temperature and 60 °C. We were disappointed again to observe the disappearance of the CH_2 resonance for the C5′ allyl group suggesting that the unwanted cyclisation, as well as other reactions, had occurred at both room temperature and 60 °C. Given that honokiol was unstable to the initial reaction conditions employed for cleavage of the blocking group we returned to the $AlCl_3$ nitromethane complex, which is known to promote retro Friedel–Crafts alkylation under milder reaction conditions.[13] We began by establishing that honokiol was stable to this reagent for at least 16 h at room temperature in toluene-d_8. However, when **9** was treated with 1, 3 or 10 equiv of the $AlCl_3$ nitromethane complex at room temperature no reaction was observed. Frustratingly, heating the reaction mixture to 60 °C resulted in decomposition. Given these difficulties and the instability of the product above room temperature this route was abandoned and a revised synthesis plan was developed (Scheme 5).



Scheme 5. Revised synthesis plan for honokiol.

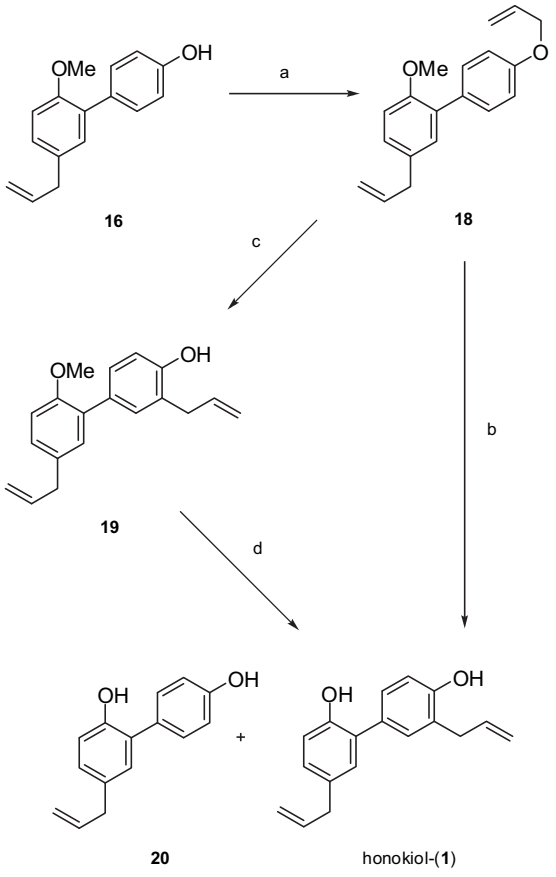
3. Results and discussion 2—Suzuki coupling approach

The revised synthesis plan relies on a Suzuki cross-coupling between boronic acid **14** and bromophenol **13**. We recognized that this strategy was dependant on the identification of cross-coupling conditions that would not isomerise the potentially sensitive allyl group. However, in our previous synthesis of dunnianol-(**4**)[15] we established that Suzuki couplings with **14** were possible without isomerisation of the C5 allyl group (Scheme 6). Boronic acid **14** was prepared from commercially available **15** via directed *ortho*-lithiation.[16] This high yielding procedure is convenient and should find application in the synthesis of other oligomeric natural products derived from chavicol-(**2**). With the boronic acid in hand we focused on the Suzuki cross-coupling of **14** with bromophenol **13** (see Scheme 7). Given our previous success in a similar system[15] we were surprised and frustrated to discover that the Suzuki cross-coupling of **13** and **14** under identical conditions was met with substantial alkene isomerisation (Table 1, entry 1).



Scheme 6. Reagents and conditions: (a) For conditions see entry 12 of Table 1, 15 h, 94%.

Initial changing of solvents to either DMF or acetonitrile did not suppress isomerisation (entries 2 and 3). However, reactions carried out in the absence of $Pd(OAc)_2$ (entries 5 and 6) resulted in markedly less isomerised product. For this reason $Pd(PPh_3)_4$ was next examined (entries 7 and 8); unfortunately, the isomerised alkene was still obtained under these conditions. Changing the palladium source to $Pd_2(dba)_3$ was also ineffective with both sodium and potassium carbonate (entries 9 and 10). Work carried out by Liu and Chen on the cross-coupling of 4-hydroxyboronic acid and 4-allyl-2-bromo-1-methoxybenzene[10] identified conditions using *S*-Phos[17] and KF combined with $Pd_2(dba)_3$ (entry 11); a modification of the solvent system afforded a slight increase in the yield (entry 12). Efforts to switch to a cheaper phosphine ligand and a cheaper base (entries 13 and 14, respectively) both resulted in isomerisation of the product. The data shows that *S*-Phos, KF and $Pd_2(dba)_3$ are required for efficient cross-coupling without isomerisation of the sensitive alkene.[10] Under these conditions **16** was obtained in 94% isolated yield with no detectable isomerisation.



Scheme 7. Reagents and conditions: (a) Allyl bromide, K_2CO_3, acetone, reflux, 18 h, 99%. (b) $BCl_3{\cdot}SMe_2$, DCE, reflux, 18 h, 47%. (c) 1,2-Dichlorobenzene, microwave, 200 °C, 15 min, 86%. (d) $BCl_3{\cdot}SMe_2$, DCE, reflux, 18 h, 91%.

Table 1
Conditions screened for Suzuki coupling of **16** and **17**

Entry	Pd source 10 mol %	Ligand 30 mol %	Base 5 equiv	Solvent (10:1)	Ratio **16**:**17**[a]
1	$Pd(OAc)_2$	PPh_3	Na_2CO_3	^{i}PrOH/H_2O	3:2
2	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF/H_2O	3:10
3	$Pd(OAc)_2$	PPh_3	Na_2CO_3	CH_3CN/H_2O	3:8
4	$Pd(OAc)_2$	PPh_3	K_2CO_3	^{i}PrOH/H_2O	3:4
5	—	PPh_3	Na_2CO_3	^{i}PrOH/H_2O	Trace[b]
6	—	PPh_3	K_2CO_3	^{i}PrOH/H_2O	Trace[b]
7	$Pd(PPh_3)_4$	—	Na_2CO_3	^{i}PrOH/H_2O	1:6
8	$Pd(PPh_3)_4$	—	K_2CO_3	^{i}PrOH/H_2O	9:2
9	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	^{i}PrOH/H_2O	3:2
10	$Pd_2(dba)_3$	PPh_3	K_2CO_3	^{i}PrOH/H_2O	3:2
11	$Pd_2(dba)_3$	*S*-Phos	KF	1,4-Dioxane/H_2O	1:0[c]
12	$Pd_2(dba)_3$	*S*-Phos	KF	THF/H_2O	1:0
13	$Pd_2(dba)_3$	PPh_3	KF	THF/H_2O	9:4
14	$Pd_2(dba)_3$	*S*-Phos	Na_2CO_3	THF/H_2O	3:2

[a] Ratio determined by integration of C7 and C9 resonances of **16** and **17**, respectively from the ^{1}H NMR spectrum of the crude reaction mixture.
[b] As no source of palladium was added to the reaction mixture no coupling occurred, however, trace amounts of **14** with isomerisation of the double bond were visible on the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Protocol of Liu and Chen.[10]

The synthesis of honokiol was then completed as follows. The free hydroxyl group of **16** was allylated and ether **18** underwent Claisen-rearrangement and deprotection on treatment with $BCl_3{\cdot}SMe_2$ to afford honokiol in moderate yield with the remainder of the mass-balance being **20**. This procedure, although slightly

lower yielding than an existing method, benefits from the use of 2.5 equiv of single boron halide reagent.[18] Alternatively, if a higher yield is desired the thermal Claisen rearrangement provided product **19** in 86% yield. Conversion of **19** to honokiol was achieved in excellent yield using $BCl_3 \cdot SMe_2$. The synthetic material (Fig. 2) was identical to a natural sample in all respects.[19]

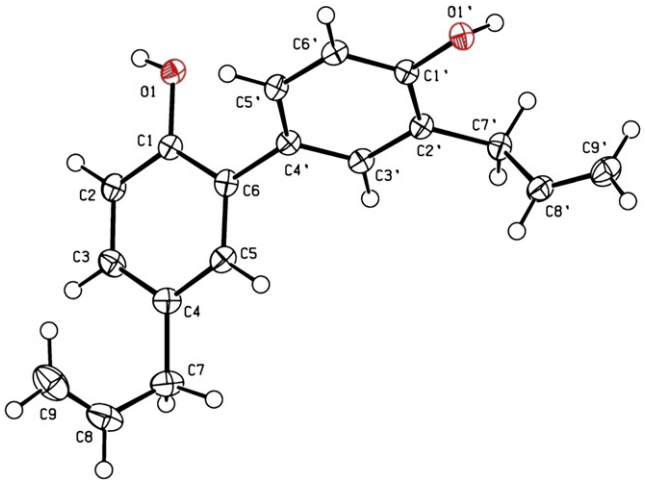


Figure 2. Crystal structure representation of honokiol.[20]

4. Conclusion

In conclusion we have developed a short (four steps) route to honokiol-(**1**) that proceeds in 34% overall yield from commercially available starting materials. We have prepared ca. 100 mg of honokiol-(**1**) in a single run using this route. Finally, if a higher overall yield is required the thermal rearrangement of **20** can be performed resulting in 55% overall yield, the highest yielding route to date, at the cost of one additional step to the synthesis.

5. Experimental

5.1. General

All glassware were flame-dried or oven-dried and allowed to cool under a stream of nitrogen before use. Cooling to −78 °C was effected using dry ice-acetone mixtures. Degassing was achieved by purging nitrogen through the appropriate solution for 10 min. The petrol used refers to the fraction with bp 40–60 °C. Commercial solvents and reagents were used as supplied with the following exceptions. Tetrahydrofuran (THF) was pre-dried over sodium wire and distilled under an atmosphere of nitrogen from sodium benzophenone ketyl or obtained from a solvent tower, where degassed THF was passed through two columns of activated alumina and a 7 μ filter under a 4 bar pressure. Diethyl ether (Et_2O) was pre-dried over sodium wire and distilled under an atmosphere of nitrogen from sodium benzophenone ketyl or obtained from a solvent tower, where degassed ether was passed through two columns of activated alumina and a 7 μ filter under a 4 bar pressure. Toluene was pre-dried over sodium wire and distilled under an atmosphere of nitrogen from sodium benzophenone ketyl or obtained from a solvent tower, where degassed toluene was passed through two columns of activated alumina and a 7 μ filter under a 4 bar pressure. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride powder or purchased as analytical grade and stored over activated 4 Å molecular sieves. Dimethylformamide (DMF) was dried over calcium hydride powder, filtered and distilled under reduced pressure onto activated 4 Å molecular sieves. Trimethylborate ($B(OMe)_3$) was dried over sodium wire, filtered and distilled and stored over activated 4 Å molecular sieves. *N*,*N*,*N*′,*N*′-Tetramethylethylene-1,2-diamine (TMEDA) was dried over calcium hydride powder, filtered and distilled and stored over activated 4 Å molecular sieves. Activation of 4 Å molecular sieves was achieved by heating to 200 °C under high vacuum for 15 h. Microwave reactions were carried out on a CEM Explorer microwave. Reactions were monitored using thin layer chromatography (TLC) on Polygram® SIL G/UV_{254} 0.25 mm silica gel precoated sheets with fluorescent indicator. Sheets were visualised using ultra-violet light (254 nm) and/or anisaldehyde or $KMnO_4$ solutions, as appropriate. Flash chromatography was performed using Fluorochem silica gel 60, 35–70 μ, unless otherwise noted. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR instrument as dilute chloroform solutions or as neat solids using an ATR accessory. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 as dilute solutions in the indicated deuterated solvent. All chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. All chemical shifts are reported relative to chloroform (δ_H=7.27 ppm, δ_C=77.0 ppm). Coupling constants (J) are reported in hertz and are recorded after averaging. The multiplicity of a ^1H NMR signal is designated by one of the following abbreviations: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad signal. ^{13}C multiplicities were assigned using a DEPT sequence. Where appropriate; HMQC, HMBC and NOE experiments were performed to aid assignment. Assignments of protons (e.g., *ortho*, *para*) are made with respect to the hydroxyl or methoxy groups. Mass spectra were acquired on a VG micromass 70E, VG Autospec or Micromass LCTOF. Melting points were acquired on a Stuart® SMP3 melting point apparatus.

5.2. Honokiol 1

To a solution of **18** (200 mg, 0.713 mmol) in DCE (5 mL) was added $BCl_3 \cdot SMe_2$ (1.12 mL, 1.78 mmol of a 2.00 M solution in CH_2Cl_2) and the solution was heated to reflux for 18 h. The reaction was cooled to room temperature and H_2O (5 mL) was added. The reaction was stirred for a further 15 min before being diluted with CH_2Cl_2 (20 mL), washed with brine (3×20 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 3:1) gave **1** (89.5 mg, 47%) as a colourless solid, mp 85–87 °C, literature mp 84–86 °C9, R_f 0.32 (petrol/EtOAc, 3:1). A crystal suitable for X-ray analysis was obtained by slow evaporation from a petrol/EtOAc solution. IR: ν_{max} ($CHCl_3$) 3595, 3550, 3081, 3010, 2979, 5960, 2927, 2855, 1638, 1609, 1588, 1490, 1261, 1177, 998, 910 cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.24 (1H, dd, J=7.4, 2.4, ArH_{meta}), 7.22 (1H, d, J=2.4, ArH_{meta}), 7.07 (1H, dd, J=7.7, 2.2, ArH_{meta}), 7.04 (1H, d, J=2.2, ArH_{meta}), 6.93 (1H, J=7.4, ArH_{ortho}), 6.91 (1H, J=7.7, ArH_{ortho}), 6.05 (1H, ddt, J=17.1, 10.1, 6.4, $ArCH_2CHCH_2$), 5.98 (1H, ddt, J=17.0, 9.9, 6.8, $ArCH_2CHCH_2$), 5.24 (1H, dd, J=10.1, 1.6, $ArCH_2CHCH_{2cis}$), 5.23 (1H, dd, J=17.1, 1.6, $ArCH_2CHCH_{2trans}$), 5.10 (1H, dd, J=9.9, 1.6, $ArCH_2CHCH_{2cis}$), 5.08 (1H, dd, J=17.0, 1.6, $ArCH_2CHCH_{2trans}$), 5.07 (1H, br s, ArO*H*), 5.06 (1H, br s, ArO*H*), 3.48 (2H, d, J=6.4, $ArCH_2CHCH_2$), 3.36 (2H, d, J=6.8, $ArCH_2CHCH_2$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 153.9 (Cq), 150.7 (Cq), 137.8 (CH), 135.9 (CH), 132.2 (Cq), 131.1 (CH), 130.2 (Cq), 129.6 (CH), 128.8 (CH), 128.5 (CH), 127.7 (Cq), 126.3 (Cq), 116.9 (CH_2), 116.6 (CH), 115.6 (CH), 115.5 (CH_2), 39.4 (CH_2), 35.2 (CH_2). HRMS: (ESI^+) m/z calculated for $C_{18}H_{18}O_2Na$ 289.1191, m/z found 289.1199.

To a solution of **19** (28.0 mg, 0.100 mmol) in DCE (1 mL) was added $BCl_3 \cdot SMe_2$ (0.100 mL, 0.200 mmol of a 2.00 M solution in CH_2Cl_2) and the solution was heated to reflux for 18 h. The reaction was cooled to room temperature and H_2O (5 mL) was added. The reaction was stirred for a further 15 min before being diluted with CH_2Cl_2 (10 mL), washed with brine (3×10 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 3:1) gave **1** (24.2 mg, 91%) as a colourless solid. Data matched that previously recorded.

5.3. 2-4′-Bis(allyloxy)-3-*tert*-butylbiphenyl 5

To a solution of **10** (100 mg, 0.413 mmol) in DMF (5 mL) was added Cs_2CO_3 (269 mg, 0.826 mmol), allyl bromide (71.9 μL, 0.826 mmol) and the solution was stirred at room temperature for 15 h. MeOH (5 mL) was added and the reaction was stirred for a further 15 min. The reaction was diluted with H_2O (20 mL), washed with Et_2O (3×20 mL), the organics were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 5:1) gave **5** (122 mg, 92%) as a colourless solid, mp 56–58 °C, R_f 0.73 (petrol/EtOAc, 5:1). IR: ν_{max} ($CHCl_3$) 3084, 3010, 2961, 2873, 1648, 1608, 1513, 1485, 1463, 1433, 1405, 1287, 1239, 1178, 1059, 995, 833 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 7.51 (2H, d, J=9.0, ArH_{meta}), 7.31 (1H, dd, J=7.6, 1.8, ArH_{meta}), 7.17 (1H, dd, J=7.6, 1.8, ArH_{meta}), 7.08 (1H, dd, J=7.6, 7.6, ArH_{para}), 6.97 (2H, d, J=9.0, ArH_{ortho}), 6.10 (1H, ddt, J=17.6, 10.6, 1.6, ArOCH$_2$CHCH$_2$), 5.77 (1H, ddt, J=17.4, 10.4, 1.6, ArOCH$_2$CHCH$_2$), 5.45 (1H, dd, J=17.6, 1.6, ArOCH$_2$CHCH_{2trans}), 5.32 (1H, dd, J=10.6, 1.6, ArOCH$_2$CHCH_{2cis}), 5.18 (1H, dd, J=17.4, 1.6, ArOCH$_2$CHCH_{2trans}), 5.09 (1H, dd, J=10.4, 1.6, ArOCH$_2$CHCH_{2cis}), 4.59 (2H, d, J=5.2, ArOCH_2CHCH$_2$), 3.93 (2H, d, J=5.2, ArOCH_2CHCH$_2$), 1.44 (9H, s, ArC(CH_3)$_3$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 157.6 (Cq), 155.4 (Cq), 143.1 (Cq), 133.7 (CH), 133.7 (Cq), 133.1 (CH), 132.2 (Cq), 129.7 (CH), 129.4 (CH), 125.8 (CH), 123.2 (CH), 117.5 (CH_2), 116.3 (CH_2), 114.5 (CH), 72.5 (CH_2), 68.7 (CH_2), 35.0 (Cq), 30.6 (CH_3). HRMS: (ESI^+) m/z calculated for $C_{22}H_{26}O_2Na$ 345.1825, m/z found 345.1830.

5.4. 3-*tert*-Butyl-4′-methoxybiphenyl-2-ol 6[11b]

To a solution of **8** (0.102 mL, 0.666 mmol) in toluene (10 mL) were added **7** (0.125 mL, 0.999 mmol), Cs_2CO_3 (368 mg, 1.70 mmol), P(NMe$_2$)$_3$ (36.3 μL, 0.200 mmol) and [RhCl(COD)]$_2$ (32.8 mg, 66.6 μmol) and the solution was heated to reflux for 18 h. The reaction was cooled to room temperature, acidified (1 M HCl to pH 5), diluted with CH_2Cl_2 (20 mL), washed with brine (3×20 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 9:1) gave **6** (76.8 mg, 45%) as a colourless solid, mp 118–120 °C, R_f 0.48 (petrol/EtOAc, 9:1). IR: ν_{max} ($CHCl_3$) 3693, 3541, 3000, 2960, 2912, 2875, 2839, 1711, 1609, 1513, 1609, 1512, 1434, 1247, 1178, 1031, 909, 892 cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.38 (2H, d, J=8.8, ArH_{meta}), 7.29 (1H, dd, J=7.7, 1.6, ArH_{ortho}), 7.07 (1H, dd, J=7.7, 1.6, ArH_{meta}), 7.04 (2H, d, J=8.8, ArH_{meta}), 6.91 (1H, dd, J=7.7, 7.7, ArH_{para}), 5.43 (1H, br s, ArOH), 3.88 (3H, s, ArOCH_3), 1.45 (9H, s, ArC(CH_3)$_3$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 159.3 (Cq), 151.0 (Cq), 135.9 (Cq), 130.6 (CH), 129.1 (Cq), 128.3 (Cq), 127.8 (CH), 126.1 (CH), 119.6 (CH), 114.7 (CH), 55.2 (CH_3), 34.7 (Cq), 29.4 (CH_3). HRMS: (ESI^+) m/z calculated for $C_{17}H_{20}O_2Na$ 279.1356, m/z found 279.1325.

5.5. 3,5′-Diallyl-3-*tert*-butylbiphenyl-2,4′-diol 9

A solution of **5** (30.0 mg, 93.1 μmol) in DMF (1.5 mL) was heated at 200 °C for 50 min using a microwave. The reaction was diluted with H_2O (5 mL) and, washed with Et_2O (3×5 mL). The organics were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 3:1) gave **9** (14.7 mg, 49%) as a colourless solid, mp 73–75 °C, R_f 0.26 (petrol/EtOAc, 3:1). IR: ν_{max} ($CHCl_3$) 3595, 3543, 3081, 3009, 2961, 2916, 2872, 1730, 1638, 1611, 1502, 1485, 1432, 1258, 1171, 997, 918 cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.22 (1H, dd, J=7.9, 2.4, ArH_{meta}), 7.18 (1H, d, J=2.1, ArH_{meta}), 7.07 (1H, d, J=2.1, ArH_{meta}), 6.91 (1H, d, J=7.9, ArH_{ortho}), 6.86 (1H, d, J=2.4, ArH_{meta}), 6.06 (1H, ddt, J=17.4, 10.1, 6.4, ArCH$_2$CHCH$_2$), 5.96 (1H, ddt, J=18.0, 10.7, 6.9, ArCH$_2$CHCH$_2$), 5.33 (1H, br s, ArOH), 5.21 (1H, d, J=18.0, 1.6, ArCH$_2$CHCH_{2trans}), 5.19 (1H, dd, J=10.7, 1.6, ArCH$_2$CHCH_{2cis}), 5.09 (1H, dd, J=17.4, 1.6, ArCH$_2$CHCH_{2trans}), 5.09 (1H, br s, ArOH), 5.04 (1H, dd, J=10.1, 1.6, ArCH$_2$CHCH_{2cis}), 3.45 (2H, d, J=6.4, ArCH_2CHCH$_2$), 3.33 (2H, d, J=6.9, ArCH_2CHCH$_2$), 1.41 (9H, s, ArC(CH_3)$_3$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.0 (Cq), 149.4 (Cq), 138.0 (CH), 135.0 (CH), 131.6 (CH), 130.9 (Cq), 129.7 (Cq), 129.0 (CH), 128.4 (Cq), 127.8 (CH), 126.5 (Cq), 126.5 (CH), 119.7 (Cq), 116.9 (CH_2), 116.7 (CH), 115.4 (CH_2), 39.8 (CH_2), 35.2 (CH_2), 34.9 (Cq), 29.6 (CH_3). HRMS: (ESI^+) m/z calculated for $C_{22}H_{26}O_2Na$ 345.1825, m/z found 345.1830.

5.6. 3-*tert*-Butylbiphenyl-2,4′-diol 10

To a solution of **6** (100 mg, 0.390 mmol) in DCE (5 mL) was added $BCl_3 \cdot SMe_2$ (0.293 mL, 0.585 mmol of 2.00 M solution in CH_2Cl_2) and the solution was heated to reflux for 18 h. The reaction was cooled to room temperature and H_2O (5 mL) was added. The reaction was stirred for a further 15 min before being diluted with CH_2Cl_2 (20 mL), washed with brine (3×20 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 9:1) gave **10** (62.3 mg, 66%) as a colourless solid, mp 100–102 °C, R_f 0.13 (petrol/EtOAc, 9:1). IR: ν_{max} ($CHCl_3$) 3595, 3543, 3154, 2960, 1514, 1171, 888 cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.34 (2H, d, J=8.6, ArH_{meta}), 7.29 (1H, dd, J=7.8, 1.6, ArH_{meta}), 7.05 (1H, dd, J=7.8, 1.6, ArH_{meta}), 6.97 (2H, d, J=8.6, ArH_{meta}), 6.91 (1H, dd, J=7.8, 7.8, ArH_{para}), 5.40 (1H, br s, ArOH), 4.83 (1H, br s, ArOH), 1.45 (9H, s, ArC(CH_3)$_3$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.5 (Cq), 151.2 (Cq), 136.1 (Cq), 131.0 (CH), 129.5 (Cq), 128.4 (Cq), 128.1 (CH), 126.4 (CH), 119.8 (CH), 116.3 (CH), 34.9 (Cq), 29.6 (CH_3). HRMS: (ESI^+) m/z calculated for $C_{16}H_{18}O_2Na$ 265.1199, m/z found 265.1198.

5.7. Biphenyl-2,4′-diol 11[21]

To a solution of **10** (50.0 mg, 0.207 mmol) in toluene (1 mL) and CH_3NO_2 (0.1 mL) was added $AlCl_3$ (136 mg, 1.03 mmol) and the solution was heated to 60 °C for 2 h. The reaction was diluted with EtOAc (5 mL), washed with H_2O (3×5 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 3:1) gave **11** (24.2 mg, 63%) as a colourless solid, mp 161–163 °C, literature mp 162–163 °C[21], R_f 0.33 (petrol/EtOAc, 3:1). IR: ν_{max} ($CHCl_3$) 3478, 3357, 2925, 2923, 2853, 1593, 1494, 1477, 1274, 1196, 1175, 1101, 812 cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.36 (2H, d, J=8.5, ArH_{meta}), 7.25–7.21 (2H, m, ArH), 7.00–6.95 (4H, m, ArH), 5.31 (1H, br s, ArOH), 5.16 (1H, br s, ArOH). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.4 (Cq), 152.5 (Cq), 130.5 (CH), 130.2 (CH), 129.3 (Cq), 128.8 (CH), 127.7 (Cq), 120.8 (CH), 116.2 (CH), 115.7 (CH). HRMS: (ESI^+) m/z calculated for $C_{12}H_{10}O_2Na$ 209.0573, m/z found 209.0583.

5.8. 5′-Allyl-2′-methoxybiphenol-4-ol 16

To a solution of **13** (199 mg, 1.15 mmol) in THF (10 mL) and H_2O (1 mL) were added **14** (330 mg, 1.72 mmol), KF (300 mg, 5.75 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (142 mg, 0.345 mmol) and $Pd_2(dba)_3$ (66.1 mg, 0.115 mmol) and the solution was heated to reflux and stirred for 15 h. The reaction was cooled to room temperature, diluted with EtOAc (25 mL) and washed with 1 M HCl (2×25 mL) and brine (2×25 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 3:1) gave **16** (259 mg, 94%) as a yellow oil, R_f 0.48 (petrol/EtOAc, 3:1). IR: ν_{max} ($CHCl_3$) 3596, 3082, 3009, 2935, 2837, 1731, 1639, 1613, 1591, 1518, 1496, 1256, 1174, 1044, 1029, 835 cm^{-1}. ^1H MNR: (400 MHz, $CDCl_3$) δ 7.43 (2H, d, J=8.8, ArH_{meta}), 7.13 (1H, s, ArH_{meta}), 7.12 (1H, d, J=7.4, ArH_{meta}), 6.92 (1H, d, J=7.4, ArH_{ortho}), 6.88 (2H, d, J=8.8, ArH_{ortho}), 5.99 (1H, ddt, J=17.0, 11.5, 6.7, ArCH$_2$CHCH$_2$), 5.11 (1H, dd, J=17.0, 1.9, ArCH$_2$CHCH_{2trans}), 5.07 (1H, dd, J=11.5, 1.9, ArCH$_2$CHCH_{2cis}), 4.80 (1H, br s, ArOH), 3.80 (3H, s,

ArOCH_3), 3.38 (2H, d, J=6.7, ArCH_2CHCH$_2$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.9 (Cq), 154.5 (Cq), 137.8 (CH), 132.3 (Cq), 131.2 (Cq), 131.0 (CH), 130.8 (CH), 130.2 (Cq), 128.1 (CH), 115.6 (CH_2), 114.9 (CH), 111.3 (CH), 55.7 (CH_3), 39.4 (CH_2). HRMS: (ESI$^+$) m/z calculated for $C_{16}H_{16}O_2Na$ 263.1039, m/z found 263.1043.

5.9. 5-Allyl-4′-(allyloxy)-2-methoxybiphenyl 18

To a solution of **16** (250 mg, 1.04 mmol) in acetone (5 mL) were added K_2CO_3 (216 mg, 1.56 mmol) and allyl bromide (0.996 mL, 1.14 mmol) and the solution was heated to reflux for 18 h. The reaction was cooled to room temperature and MeOH (10 mL) was added. The reaction was stirred for a further 15 min before the reaction was diluted with EtOAc (20 mL), washed with brine (3×20 mL), dried over $MgSO_4$ and concentrated in vacuo giving **18** (278 mg, 99%) as a colourless oil, R_f 0.68 (petrol/EtOAc, 3:1). IR: ν_{max} ($CHCl_3$) 3072, 3009, 2960, 2938, 1736, 1670, 1639, 1515, 1495, 1266, 1240, 1179, 1029, 997, 834 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.49 (2H, d, J=8.8, ArH_{meta}), 7.16 (1H, d, J=2.0, ArH_{meta}), 7.13 (1H, dd, J=8.4, 2,0, ArH_{meta}), 6.99 (2H, d, J=8.8, ArH_{ortho}), 6.93 (1H, d, J=8.4, ArH_{ortho}), 6.11 (1H, ddt, J=17.2, 10.4, 5.2, ArOCH$_2$CHCH$_2$), 6.00 (1H, ddt, J=16.8, 10.0, 6.8, ArCH$_2$CHCH$_2$), 5.47 (1H, dd, J=17.2, 1.2, ArOCH$_2$CHCH_{2trans}), 5.33 (1H, dd, J=10.4, 1.2, ArOCH$_2$CHCH_{2cis}), 5.12 (1H, dd, J=16.8, 1.6, ArCH$_2$CHCH_{2trans}), 5.09 (1H, dd, J=10.0, 1.6, ArCH$_2$CHCH_{2cis}), 4.60 (2H, d, J=5.2, ArOCH_2CHCH$_2$), 3.84 (3H, s, ArOCH_3), 3.40 (2H, d, J=6.8, ArCH_2CHCH$_2$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 157.7 (Cq), 154.9 (Cq), 137.8 (CH), 133.5 (Cq), 132.3 (Cq), 131.2 (Cq), 131.0 (CH), 130.6 (CH), 130.3 (Cq), 128.0 (CH), 117.7 (CH_2), 115.6 (CH_2), 114.3 (CH), 111.4 (CH), 68.9 (CH_2), 55.7 (CH_3), 39.5 (CH_2). HRMS: (ESI$^+$) m/z calculated for $C_{19}H_{20}O_2H$ 286.1536, m/z found 286.1522.

5.10. 3,5′-Diallyl-2′-methoxybiphenyl-4-ol 19[2]

A solution of **18** (20.0 mg, 71.3 μmol) in 1,2-dichlorobenzene (1.5 mL) was heated at 200 °C for 15 min using a microwave. Purification by flash chromatography (gradial elution starting with petrol increasing to petrol/EtOAc, 5:1) gave **19** (17.2 mg, 86%) as a colourless oil, R_f 0.36 (petrol/EtOAc, 4:1). IR: ν_{max} ($CHCl_3$) 3599, 3080, 3010, 2955, 2936, 2908, 2838, 1639, 1611, 1585, 1512, 1466, 1435, 1301, 1247, 1176, 1035, 919 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.32 (1H, dd, J=8.2, 2.1, ArH_{meta}), 7.29 (1H, d, J=2.0, ArH_{meta}), 7.12 (1H, s, ArH_{meta}), 7.11 (1H, dd, J=8.1, 2.4, ArH_{meta}), 6.91 (1H, d, J=8.1, ArH_{ortho}), 6.86 (1H, d, J=8.2, ArH_{ortho}), 6.12–5.94 (2H, m, ArCH$_2$CHCH$_2$), 5.23 (1H, dd, J=17.3, 1.6, ArCH$_2$CHCH_{2trans}), 5.19 (1H, dd, J=11.5, 1.6, ArCH$_2$CHCH_{2cis}), 5.11 (1H, dd, J=17.2, 1.6, ArCH2-CHCH_{2trans}), 5.07 (1H, dd, J=11.3, 1.6, ArCH$_2$CHCH_{2cis}), 5.04 (1H, br s, ArOH), 3.80 (3H, s, ArOCH_3), 3.47 (2H, d, J=6.4, ArCH_2CHCH$_2$), 3.38 (2H, d, J=6.8, ArCH_2CHCH$_2$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 154.8 (Cq), 153.3 (Cq). 137.8 (CH), 136.5 (CH), 132.3 (Cq), 131.5 (CH), 131.2 (Cq), 131.0 (CH), 130.4 (Cq), 129.0 (CH), 128.0 (CH), 124.7 (Cq), 116.6 (CH_2), 115.5 (CH_2), 115.4 (CH), 111.3 (CH), 55.7 (CH_3), 39.4 (CH_2), 35.4 (CH_2). HRMS: (ESI$^+$) m/z calculated for $C_{19}H_{20}O_2Na$ 303.1356, m/z found 303.1356.

5.11. 5-Allylbiphenyl-2,4′-diol 20

To a solution of **18** (200 mg, 0.713 mmol) in DCE (5 mL) was added $BCl_3{\cdot}SMe_2$ (1.12 mL, 1.78 mmol of a 2.00 M solution in CH_2Cl_2) and the solution was heated to reflux for 18 h. The reaction was cooled to room temperature and H_2O (5 mL) was added. The reaction was stirred for a further 15 min before being diluted with CH_2Cl_2 (20 mL), washed with brine (3×20 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (petrol/EtOAc, 3:1) also gave **22** (94.9 mg, 49%) as a colourless solid, mp 104–106 °C, R_f 0.22 (petrol/EtOAc, 3:1). IR: ν_{max} ($CHCl_3$) 3594, 3556, 3082, 3060, 2979, 2905, 1639, 1611, 1516, 1493, 1331, 1260, 1171, 911, 839 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.36 (2H, d, J=8.4, ArH_{meta}), 7.07 (1H, dd, J=8.0, 2.0, ArH_{meta}), 7.04 (1H, d, J=2.0, ArH_{meta}), 6.95 (2H, d, J=8.4, ArH_{meta}), 6.92 (1H, d, J=8.0, ArH_{ortho}), 5.99 (1H, ddt, J=16.8, 10.0, 6.8, ArCH$_2$CHCH$_2$), 5.21 (1H, br s, ArOH), 5.10 (1H, dd, J=16.8, 1.6, ArCH$_2$CHCH_{2trans}), 5.07 (1H, dd, J=10.0, 1.6, ArCH$_2$CHCH_{2cis}), 3.36 (2H, d, J=6.8, ArCH_2CHCH$_2$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 39.4 (CH_2), 115.6 (CH), 115.7 (CH_2), 116.1 (CH), 127.7 (Cq), 128.9 (CH), 129.5 (Cq), 130.3 (CH), 130.5 (CH), 132.4 (Cq), 137.8 (CH), 150.8 (Cq), 155.3 (Cq). HRMS: (ESI$^+$) m/z calculated for $C_{15}H_{14}O_2Na$ 249.0891, m/z found 249.0907.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.08.005.

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18. Previous workers have used 2.0 equiv of BCl_3 to effect the Claisen rearrangement and then a further 2.5 equiv of BBr_3 for cleavage of the methylether in 64% yield. In our experience the use of commercial BBr_3 results in some bromination of the C5 allyl group.
19. Natural honokiol was purchased from Aldrich. Examination of the ^1H NMR data for the synthetic material (Ref. 5c,10) and natural material revealed a discrepancy. Fukuyma and co-workers (Ref. 5c) report a peak at 7.20 ppm, which given the other data we assume is a typographical error.
20. Crystallographic data (excluding structure factors) for **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 778234. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or by visiting www.ccdc.cam.ac.uk/data_request/cif.
21. Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299–308.