Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3175–3182

TETRAHEDRON

The synthesis of *R*-3-alkoxy-1-(1′-hydroxyethyl)-4-methoxy-2-(1″-propenyl)benzenes utilizing Corey–Bakshi–Shibata asymmetric reductions

Charles B. de Koning,[a] Robin G. F. Giles,[b] Ivan R. Green[c,*] and Nazeem M. Jahed[c]

[a]*Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, P.O. Wits 2050, Johannesburg 2050, South Africa*
[b]*Department of Chemistry, Murdoch University, Murdoch, WA 6150, Australia*
[c]*Department of Chemistry, University of the Western Cape, Private Bag X17, Bellville 7530, South Africa*

Received 27 November 2002; revised 5 February 2003; accepted 28 February 2003

Abstract—Pyrolysis of the 3-*O*-allyl derivative **7** of isovanillin followed by alkylation of the derived allylphenol **8** afforded a series of benzaldehyde derivatives **9**–**11** each of which was transformed by initial treatment with methylmagnesium bromide followed by oxidation of the corresponding alcohols with activated manganese dioxide into a series of ketones **15**–**17**. Palladium(0) catalysed isomerization of the double bond in the prop-2′-enyl side-chain afforded ketones **36**–**38** which were subjected to the Corey–Bakshi–Shibata asymmetric reduction protocol to afford the *R*-3-alkoxy-1-(1′-hydroxyethyl)-4-methoxy-2-(1″-propenyl) benzenes **42**–**44** in yields of approximately 60% and with ee's of 75%.

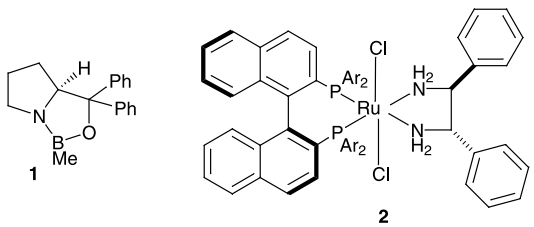
1. Introduction

Methods for the enantioselective reduction of benzylic carbonyl containing compounds are relatively well developed. A particularly useful method for achieving such reductions is by means of the Corey–Bakshi–Shibata (CBS) reduction.[1] This can be done in the presence of oxazaborolidines e.g. **1** (Fig. 1). However, other methods such as those developed by Noyori for asymmetric hydrogenation of ketones with BINAP-ruthenium catalysts such as **2** are also routinely employed,[2] even in industry.[3]

Earlier attempts by us[4] to employ the CBS enantioselective reduction protocol[5–8] to reduce the *ortho* allyl aryl ketones **3** and **4** were unsuccessful since reduction of the ketone carbonyl group did not occur. Instead the olefin bond reacted to produce the alcohols **5** and **6**, respectively (Fig. 2).

An argument put forward was that the methoxy group *ortho* to the carbonyl substituent of **3** and **4** caused the latter to be sterically inaccessible to the approach of the hydride from the well known oxazaborolidine catalyst.[9] Alternative oxazaborolidines derived from α-pinene[10,11] were not favoured due to their larger steric bulk and the low enantiomeric excess (ee) values of the desired product alcohols. The bifunctional ligands of Sibi et al.[12] were also unsuccessful due to similar low ee's of the derived alcohols.

In two major reviews on enantioselective reductions of carbonyl groups, it would appear that α,β-enones could be reduced to the correspondered α,β-enols in good yield and



1 2

Figure 1.

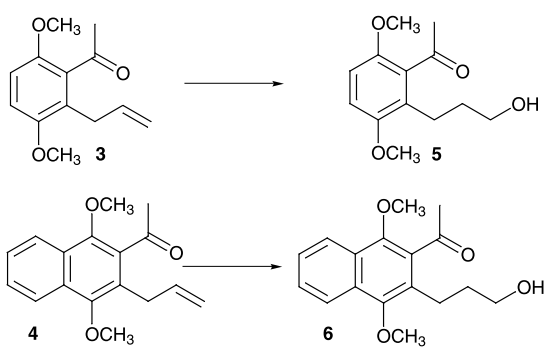
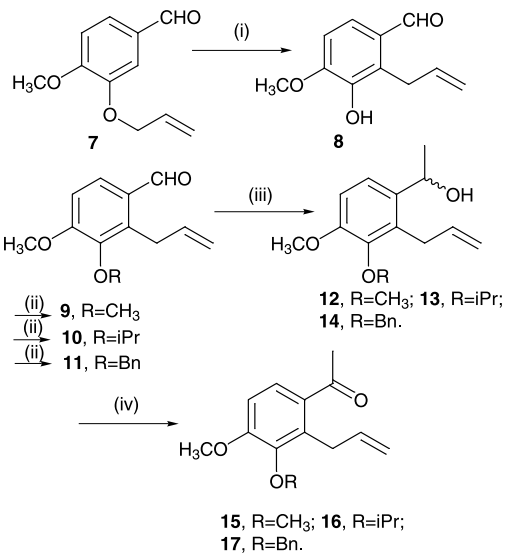


Figure 2.

Keywords: chiral reductions; benzylic alcohols.

* Corresponding author. Tel.: +27-21-959-2262; fax: +27-21-959-3055; e-mail: igreen@uwc.ac.za

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00328-4



Scheme 1. (i) 180°C/N_2. (ii) RBr, K_2CO_3, DMF, 80°C. (iii) MeMgBr, ether or THF, 25°C. (iv) MnO_2, benzene, reflux.

with high ee values using borane in conjunction with the CBS catalyst.[1,13] However, no examples resembling our system or simple examples of *ortho* allyl aryl ketones were apparent. Although the reviews indicated that reduction of moderately sterically crowded carbonyls could tolerate the above conditions, we decided to reduce the steric environment of the carbonyl group by moving the *ortho*-methoxy group of **1** to the *para*-position. In addition, the offending reactive *ortho*-allyl substituent was converted into the corresponding styrene. In this paper the enantioselective CBS reductions on these substrates is described. Preliminary results have been disclosed in a communication.[14]

2. Results and discussion

Pyrolysis of **7**[15] at 180°C for 12 h afforded phenol **8** which was without isolation immediately treated with 4 mole equivalents of the appropriate alkyl halide and potassium carbonate in hot (80°C) DMF to afford the *ortho*-allyl benzaldehydes **9**–**11** in yields of 77, 89 and 77%, respectively.

Each of the benzaldehydes was in turn treated with 1.5 mole equivalents of freshly prepared methylmagnesium iodide to produce the racemic alcohols **12**–**14** in yields of 93, 80, and 89%, respectively. It is interesting to note that when a larger excess of the Grignard reagent is used the yields are lowered with a concomitant increase in the production of a polymeric material. Oxidation of the racemic alcohols with activated manganese(IV) oxide in boiling benzene[16] afforded the corresponding ketones **15**–**17** in an average yield of 58% as illustrated in Scheme 1.

All three ketones **15**–**17** behaved analogously under the standard conditions of enantioselective reduction using the CBS catalyst and diborane dimethyl sulphide complex.[12,13] Very careful chromatographic separation of the products of the reaction revealed that apart from minor amounts of starting material each ketone afforded a similar range of three different undesired products (Fig. 3 and Table 1). For

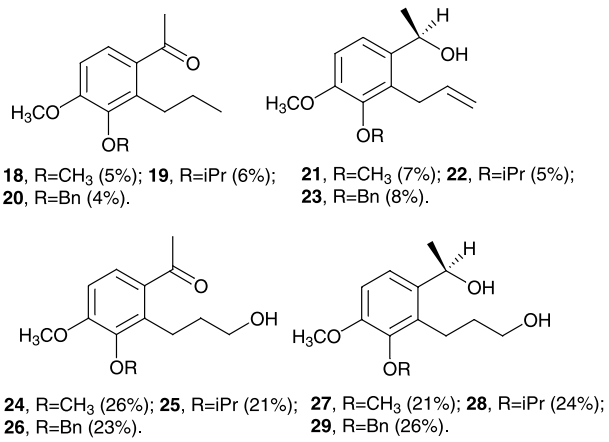


Figure 3.

Table 1. Yields of products for the reduction of ketones **15**–**17**

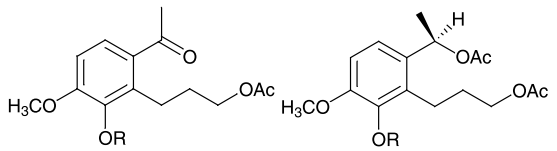
Starting material	Product			
	Yield (%)	Yield (%)	Yield (%)	Yield (%)
15, R=Me	**18**, 5	**21**, 7	**24**, 26	**27**, 21
16, R=*i*Pr	**19**, 6	**22**, 5	**25**, 21	**28**, 24
17, R=Bn	**20**, 4	**23**, 8	**26**, 23	**29**, 26

the purposes of brevity only the 3,4-dimethoxy analogue **15** will be discussed.

Typically the first product to elute after column chromatography was the saturated ketone **18**. A ν_{max} at 1688 cm^{-1} in the IR spectrum supported the presence of the aryl ketone functional group.[17] Support for the propanyl side-chain was clear from the ^1H NMR spectrum by a 3-proton triplet at 0.98 ppm (J=7.4 Hz), a 2-proton multiplet at 1.55 ppm and a 2-proton multiplet at 2.99 ppm. Signals at 14.6, 24.6 and 29.8 ppm in the ^{13}C NMR spectrum lent further credence to the proposed structure.

The next product to elute was assigned the structure **21** and is based, *inter alia*, on the following spectral data. A broad absorption band at 3404 cm^{-1} in the IR spectrum was assigned to the hydroxyl group. A sharp 3-proton doublet at 1.46 ppm (J=6.4 Hz) in the ^1H NMR spectrum was assigned to methyl group of the hydroxyethyl group while the corresponding 1-proton quartet at 5.06 ppm (J=6.4 Hz) was assigned to H-1 of the same side-chain. It is of interest to note that H-1′ of the 3-(2′-propenyl) side-chain appeared as a 2-proton ddt at 3.52 ppm (J=13.0, 5.6, 2.0 Hz) while the *trans* H-3′ appeared as a ddd at 4.90 ppm (J=17.0, 2.1, 2.0 Hz) and the *cis* H-3′ appeared as a ddd at 5.03 ppm (J=10.2, 2.1, 2.0 Hz).

Since alcohols **24** and **27** co-eluted, assignments were made by comparison and quantitative assessments were derived based on the relative integrations in the ^1H NMR spectra. In order to corroborate the structural assignments to the alcohols, the mixture was subjected to acetylation[18] and the derived acetates **30** and **33**, Figure 4, were separated and their structural assignments follow from an analysis of their spectral properties.



30, R=CH_3; **31**, R=iPr ; **32**, R=Bn.

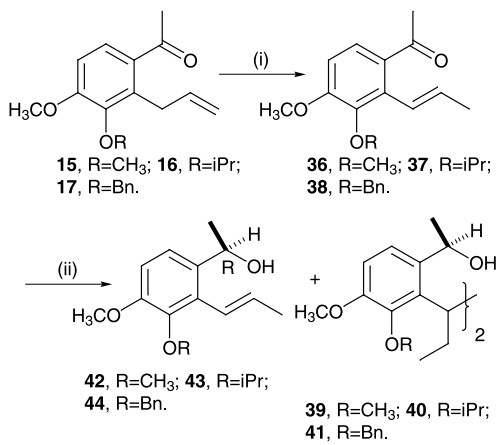
33, R=CH_3; **34**, R=iPr; **35**, R=Bn.

Figure 4.

As shown in Table 1 low yields (~7%) of the desired chiral alcohols **21**–**23**, were obtained and therefore, alternative routes were investigated in order to enhance the enantioselective reduction of the ketone function of **15**–**17**.

An analysis of the results in Figure 3 and Table 1 clearly indicates that the steric demand and possible electrophilic nature of the carbonyl in question for approach by the hydride from the oxazaborolidine catalyst is not still possible. It is suggested that the steric environment and electronic nature of the carbonyl group would be improved by moving the allyl double bond. Consequently, ketones **15**–**17** were treated with palladium dichloride bisacetonitrile[19] which caused the double bond in the side-chain to isomerize from the 2′- to the 1′-position thereby, producing ketones **36**–**38** in yields of 90%. Clear evidence for the *trans* geometry of the double bond was evident in the ^{1}H NMR spectrum in which H-3′ appeared as a 3-proton dd at ~1.88 ppm (J=6.7, 1.8 Hz), H-2′ appeared as a 1-proton dq at ~5.85 ppm (J=16.0, 6.7 Hz) while H-1′ appeared as a 1-proton dq at ~6.70 ppm (J=16.0, 1.8 Hz), Scheme 2.

Consequently, ketones **36**–**38** were subjected to the same enantioselective reduction protocol described earlier and in all cases two products were isolated. The first product (~18%), which interestingly had a similar R_F to the starting material, was assigned the dimeric diastereoisomeric structures **39**–**41**, respectively for the three analogues of the series. A strong absorption band at 3434 cm^{-1} in the IR spectrum demonstrated the presence of the hydroxyl groups. The mass spectra did not show the required molecular ion but rather evidence of the fragmentation pattern of the dimer. However, clear evidence for the diastereoisotopic nature of the molecule was provided by both the ^{1}H and ^{13}C NMR spectra since each H and C signal of the dimer could be identified and appeared as two sets of signals at slightly different δ values. Thus in dimer **39** there are *inter alia* two 3-proton triplets at 1.04 and 1.08 ppm (J=7.2 Hz) for H-3′ of the propano side-chain, two 3-proton doublets at 1.52 and 1.63 ppm (J=6.6 Hz) for H-2″ of the hydroxyethyl side-chain, two 1-proton multiplets at 2.43 and 2.62 ppm for H-1′ of the propano side-chain and four 3-proton singlets at 3.82, 3.84, 3.85 and 3.86 ppm for the methoxy groups. Interestingly the two hydroxy groups were evident as D_2O exchangeable signals at 4.28 and 4.38 ppm.



15, R=CH_3; **16**, R=iPr; **17**, R=Bn.

36, R=CH_3; **37**, R=iPr; **38**, R=Bn.

42, R=CH_3; **43**, R=iPr; **44**, R=Bn.

39, R=CH_3; **40**, R=iPr; **41**, R=Bn.

Scheme 2. (i) $PdCl_2(CH_3CN)_2$, CH_2Cl_2, 35°C, 72 h, 81–94%; (ii) $BH_3(CH_3)_2S$, THF, CBS catalyst, 25°C, 30 min, 55–61%, 74–75% ee.

The next products to elute were assigned as the desired chiral alcohols **42**–**44** (~60%). In the case of **42** a strong molecular ion at m/z 222 in the mass spectrum supported the expected molecular formula while in the IR spectrum a strong band at 3407 cm^{-1} confirmed the hydroxyl functionality. The following signals in the ^{1}H NMR spectrum support the assigned structure viz. a 3-proton doublet at 1.46 ppm (J=6.4 Hz) coupled to a 1-proton quartet at 5.13 ppm (J=6.4 Hz) supported the presence of the 1′-hydroxyethyl side-chain. A 3-proton dd at 1.92 ppm (J=6.4, 1.8 Hz) was assigned to the H-3″, while a 1-proton dq at 6.00 ppm (J=16.0, 6.4 Hz) was assigned to the *trans* H-2″ and a 1-proton dq at 6.4 ppm (J=16.0, 1.8 Hz) was assigned to H-1″ of the *trans* 1″-propenyl side-chain.

Three techniques were used to determine the enantiomeric excesses of the chiral alcohols **42**–**44**. In the classical Mosher ester methodology[20,21] it was found that the esters hydrolysed during chromatographic purification. However by employing the acid chloride methodology[22] the Mosher esters were stable. The methoxy signal of the Mosher ester moiety was used to determine the ee the *R* enantiomer being assigned at δ 3.55 while the *S* enantiomer being assigned at δ 3.48. In the case of ^{19}F NMR spectroscopy[23] a ^{19}F probe was used and the *R* and *S* enantiomers were assigned at 80.63 and 80.68 ppm, respectively. Excellent corroboration was obtained by the use of tris[3-heptafluoro-propylhydromethoxy methylene-(+)-camphorate], $Eu(hfc)_3$ in which the doublets for H-5 separated and were assigned as follows: **42** (*R*, 8.11; *S*, 8.02); **43** (*R*, 7.41; *S*, 7.77); and **44** (*R*, 8.09; *S*, 8.01), respectively.

Further attempts to increase the enantiomeric excess of the chiral reductions using catecol–borane as reducing agent[24] did not lead to clean products and was not investigated further. Investigations of the temperature range[25] for the chiral reduction, demonstrated that 25°C was in fact the optimum temperature for the reduction.

In conclusion a method has been established for the asymmetric reduction of 4-methoxy-3-alkyloxy-2-(1′-propenyl)acetophenones using the CBS oxazaborolidine catalyst to form the corresponding (*R*)-alcohols in yields of 60% and with ee values of 75%.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR Spectra were recorded using a Varian

200 MHz spectrometer at 20°C in deuterochloroform and *J* values are given in Hz. Infrared spectra were measured as Nujol mulls or as thin films on a Perkin–Elmer FT-IR 1000 PC spectrometer. Melting points were recorded on a Fischer–John apparatus and are uncorrected. C and H Analyses were performed on a Carlo Erba NA 1500 Nitrogen analyser and GC-MS spectra were recorded on a Finnigan–Matt GCQ instrument. Column chromatography was carried out using Merck Kieselgel 60 (70–230 mesh) as dry columns. Hexane refers to that fraction boiling between 60–75°C. The residue obtained upon workup refers to material obtained from the dried ($MgSO_4$) organic extract after filtration and solvent removal.

3.1.1. 3,4-Dimethoxy-2-prop-2′-enylbenzaldehyde 9. Aldehyde **7**[15] (8.01 g; 41.7 mmol) was pyrolysed at 180°C (oil bath) under nitrogen for 12 h to afford the corresponding phenol **8** which without isolation was dissolved in dimethylformamide (80 mL) and treated with methyl iodide (23.7 g; 166 mmol) and potassium carbonate (23 g; 166 mmol) and vigorously stirred at 80°C for 24 h. The cooled reaction mixture was filtered and the filtrate was treated with water (600 mL) and the resulting solution was extracted with ether (4×150 mL). The residue obtained upon workup was chromatographed using EtOAc/hexane (1:4) as eluent to afford the aldehyde **9** (6.64 g; 77%) as a yellow oil. ν_{max} 1686 cm^{-1}; δ_H 3.81 (3H, s, OCH_3), 3.86 (2H, dt, *J*=5.8, 1.8 Hz, $-CH_2CH{=}CH_2$), 3.93 (3H, s, OCH_3), 4.91 (1H, dq, *J*=17.4, 1.8 Hz, *trans* $-CH_2CH{=}CH_2$), 5.01 (1H, dq, *J*=10.2, 1.8 Hz, *cis* $-CH_2CH{=}CH_2$), 6.00 (1H, m, $CH_2CH{=}CH_2$), 6.92 (1H, d, *J*=8.6 Hz, H-5), 7.64 (1H, d, *J*=8.6 Hz, H-6), and 10.05 (1H, s, CHO); δ_C 28.7, 55.8, 61.0, 110.0, 115.8, 128.1, 129.2, 136.3, 137.3, 147.4, 157.7, and 191.1. (Found: C, 69.7; H, 6.6%, M^+ 206. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.9%; M 206).

3.1.2. 3-Isopropoxy-4-methoxy-2-prop-2′-enylbenzaldehyde 10. Aldehyde **7** was similarly converted using isopropyl bromide into the corresponding aldehyde **10** (7.20 g; 90%) as a yellow oil. ν_{max} 1686 cm^{-1}; δ_H 1.28 [6H, d *J*=6.2 Hz, $CH(CH_3)_2$], 3.88 (2H, dt, *J*=5.8, 1.6 Hz, $CH_2CH{=}CH_2$), 3.90 (3H, s, OCH_3), 4.56 (1H, septet, *J*=6.2 Hz, $CH(CH_3)_2$), 4.88 (1H, ddd, *J*=17.2, 1.7, 1.5 Hz, *trans* $CH_2CH{=}CH_2$), 5.02 (1H, ddd, *J*=10.2, 1.7, 1.5 Hz, *cis* $CH_2CH{=}CH_2$), 6.00 (1H, m, $CH_2CH{=}CH_2$), 6.90 (1H, d, *J*=8.6 Hz, H-5), 7.61 (1H, d, *J*=8.6 Hz, H-6), and 10.07 (1H, s, CHO); δ_C 22.5 (×2), 29.0; 55.7, 75.0, 109.7, 115.7, 128.2 (×2), 136.6, 137.3, 145.1, 157.8 and 191.3. (Found: C, 71.7; H, 7.7%; M^+ 234. Calcd for $C_{14}H_{18}O_3$: C, 71.8; H, 7.8; M 234).

3.1.3. 3-Benzyloxy-4-methoxy-2-prop-2′-enylbenzaldehyde 11. Aldehyde **8** was similarly converted using benzyl bromide into the corresponding aldehyde **11** (9.05 g; 77%) as a yellow oil. ν_{max} 1686 cm^{-1}; δ_H 3.85 (2H, dt, *J*=5.6, 1.8 Hz, $CH_2CH{=}CH_2$), 3.97 (3H, s, OCH_3), 4.89 (1H, ddd, *J*=17.6, 1.9, 1.7 Hz, *trans* $CH_2CH{=}CH_2$), 4.98 (2H, s, CH_2Ph), 5.02 (1H, ddd, *J*=10.2, 1.9, 1.7 Hz, *cis* $CH_2CH{=}CH_2$), 6.00 (1H, m, $CH_2CH{=}CH_2$), 6.96 (1H, d, *J*=8.6 Hz, H-5), 7.37 (5H, m, Aryl-H), 7.67 (1H, d, *J*=8.6 Hz, H-6), and 10.06 (1H, s, CHO); δ_C 28.9, 56.0, 75.0, 110.0, 115.9, 128.2 (×2), 128.6 (×2), 129.2, 136.7, 137.3 (×2), 137.5, 140.7, 146.2, 157.8, and 191.2. (Found: C, 76.7; H, 6.3%; M^+ 282. Calcd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4%; M 282).

3.1.4. 3,4-Dimethoxy-1-(1′-hydroxyethyl)-2-prop-2′-enylbenzene 12. To a freshly prepared solution of methyl magnesium bromide [from magnesium turnings (730 mg; 30 mmol) and methyl iodide (4.26 g; 30 mmol) in ether (40 mL)] was added dropwise a solution of aldehyde **9** (4.12 g; 20 mmol) in ether (40 mL) at 20°C. After being stirred an additional 40 min, the solution was treated with saturated aqueous ammonium chloride to destroy excess Grignard reagent. The residue obtained upon ether extraction was chromatographed using EtOAc/hexane (1:4) initially and later (2:3) as eluent to afford the alcohol **12** (4.4 g; 93%) as a yellow oil. ν_{max} 3404 cm^{-1}; δ_H 1.46 (3H, d, *J*=6.4 Hz, $CH(OH)CH_3$), 1.58 (1H, bs, D_2O exchangeable, OH), 3.52 (2H, ddt, *J*=13.0, 5.6, 2.0 Hz, $CH_2CH{=}CH_2$), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.90 (1H, ddd, *J*=17.0, 2.1, 1.9 Hz, *trans* $CH_2CH{=}CH_2$), 5.03 (1H, ddd, *J*=10.2, 2.1, 1.9 Hz, *cis* $CH_2CH{=}CH_2$), 5.06 (1H, q, *J*=6.4 Hz, CH_3CHOH), 6.00 (1H, m, $CH_2CH{=}CH_2$), 6.86 (1H, d, *J*=8.2 Hz, H-5), and 7.24 (1H, d, *J*=8.2 Hz, H-6); δ_C 24.3, 29.7, 55.7, 60.9, 66.2, 110.8, 115.3, 121.0, 130.7, 137.2, 137.9, 147.1, and 152.1. (Found: C, 70.0; H, 8.1%; M^+ 222. Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222).

3.1.5. 3-Isopropoxy-4-methoxy-1-(1′-hydroxyethyl)-2-prop-2′-enylbenzene 13. Conversion of aldehyde **10** by an analogous protocol described for **12** afforded alcohol **13** (4.01 g; 80%) as a yellow oil. ν_{max} 3396 cm^{-1}; δ_H 1.24 and 1.27 [each 3H, each d, *J*=6.2 Hz, $CH(CH_3)_2$], 1.44 [3H, d, *J*=6.4 Hz, $CH_3CH(OH)$], 1.75 (1H, bs, D_2O exchangeable, OH), 3.54 (2H, ddt, *J*=16.4, 5.8, 1.8 Hz, $CH_2CH{=}CH_2$), 3.82 (3H, s, OCH_3), 4.49 [1H, septet, *J*=6.2 Hz, $CH(CH_3)_2$], 4.95 (1H, ddd, *J*=17.2, 1.9, 1.7 Hz, *trans* $CH_2CH{=}CH_2$], 5.00 (1H, ddd, *J*=10.4, 1.9, 1.7 Hz, *cis* $CH_2CH{=}CH_2$), 5.08 [1H, q, *J*=6.4 Hz, $CH_3CH(OH)$], 5.95 (1H, m, $CH_2CH{=}CH_2$), 6.83 (1H, d, *J*=8.6 Hz, H-5), and 7.22 (1H, d, *J*=8.6 Hz, H-6); δ_C 22.6 (×2), 24.3, 30.2, 55.7, 66.1, 74.7, 110.7, 115.1, 120.4, 131.1, 137.3, 137.9, 144.8, and 152.1. (Found: C, 71.8; H, 8.9%; M^+ 250. Calcd for $C_{15}H_{22}O_3$: C, 71.9; H, 8.9%; M 250).

3.1.6. 3-Benzyloxy-4-methoxy-1-(1′-hydroxyethyl)-2-prop-2′-enylbenzene 14. Conversion of aldehyde **11** by an analogous protocol described for **12** afforded alcohol **14** (5.28 g; 89%) as a yellow oil. ν_{max} 3384 cm^{-1}; δ_H 1.46 [3H, d, *J*=6.4 Hz, $CH_3CH(OH)$], 1.68 (1H, bs, D_2O exchangeable, OH), 3.51 (2H, ddt, *J*=14.2, 5.8, 1.8 Hz, $CH_2CH{=}CH_2$), 3.88 (3H, s, OCH_3), 4.88 (1H, ddd, *J*=17.2, 1.9, 1.7 Hz, *trans* $CH_2CH{=}CH_2$), 4.98 (2H, s, CH_2Ph), 5.03 (1H, ddd, *J*=10.2, 1.9, 1.7 Hz, *cis* $CH_2CH{=}CH_2$), 5.06 [1H, q, *J*=6.4 Hz, $CH_3CH(OH)$], 5.97 (1H, m, $CH_2CH{=}CH_2$), 6.91 (1H, d, *J*=8.6 Hz, H-5), 7.31 (1H, d, *J*=8.6 Hz, H-6), and 7.40 (5H, m, Ph); δ_C 24.3, 29.9, 55.8, 66.2, 74.8, 110.9, 115.3, 121.1, 127.9, 128.1 (×2), 128.5 (×2), 131.0, 137.9, 137.3, 138.1, 145.0, and 152.2. (Found: C, 76.3; H, 7.5%; M^+ 298. Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%; M 298).

3.1.7. Acetyl-3,4-dimethoxy-2-prop-2′-enylbenzene 15. Alcohol **12** (2.16 g; 9.3 mmol) in benzene (150 mL) was

treated with activated manganese dioxide (21.6 g)[15] and the resulting mixture vigorously stirred and heated under reflux under nitrogen for 40 min. The warm mixture was filtered through Celite® and the residue obtained upon workup was chromatographed using EtOAc/hexane (1:4) as eluent to yield the ketone **15** (1.22 g; 57%) as a bright yellow oil. ν_{max} 1684 cm^{-1}; δ_H 2.52 (3H, s, CH_3CO), 3.76 (2H, dt, *J*=6.0, 1.8 Hz, $CH_2CH{=}CH_2$), 3.80 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.94 (1H, ddd, *J*=17.0, 1.9, 1.7 Hz, *trans* $CH_2CH{=}CH_2$), 4.95 (1H, ddd, *J*=10.2, 1.9, 1.7 Hz, *cis* $CH_2CH{=}CH_2$), 6.00 (1H, m, $CH_2CH{=}CH_2$), 6.80 (1H, d, *J*=8.8 Hz, H-5), and 7.50 (1H, d, *J*=8.8 Hz, H-6); δ_C 29.6, 30.4, 55.8, 60.9, 109.1, 114.9, 126.8, 131.5, 135.0, 137.8, 148.0, 155.7 and 200.5. (Found: C, 70.9; H, 7.2%; M^+ 220. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3%; M 220).

3.1.8. Acetyl-3-isopropoxy-4-methoxy-2-prop-2′-enylbenzene 16. Oxidation of alcohol **13** under the same conditions as **12** afforded ketone **16** (60%) as a bright yellow oil. ν_{max} 1688 cm^{-1}; δ_H 1.27 [6H, d, *J*=6.4 Hz, $CH(CH_3)_2$], 2.51 (3H, s, CH_3CO), 3.80 (2H, dt, *J*=6.0, 1.8 Hz, $CH_2CH{=}CH_2$), 3.87 (3H, s, OCH_3), 4.50 [1H, septet, *J*=6.4 Hz, $CH(CH_3)_2$], 4.93 (1H, ddd, *J*=17.0, 1.9, 1.7 Hz, *trans* $CH_2CH{=}CH_2$), 4.95 (1H, ddd, *J*=10.2, 1.9, 1.7 Hz, *cis* $CH_2CH{=}CH_2$), 5.91 (1H, m, $CH_2CH{=}CH_2$), 6.78 (1H, d, *J*=8.8 Hz, H-5), and 7.44 (1H, *J*=8.8 Hz, H-6); δ_C 22.6 (×2), 29.7, 30.6, 55.7, 75.0, 108.8, 114.9, 126.0, 131.9, 135.2, 137.6, 145.6, 155.7, and 201.0. (Found: C, 72.4; H, 8.2%; M^+ 248. Calcd for $C_{15}H_{20}O_3$: C, 72.5; H, 8.1%; M 248).

3.1.9. Acetyl-3-benzyloxy-4-methoxy-2-prop-2′-enylbenzene 17. Oxidation of alcohol **14** under the same conditions as **12** afforded ketone **17** (58%) as a bright yellow oil. ν_{max} 1684 cm^{-1}; δ_H 2.54 (3H, s, CH_3CO), 3.78 (2H, dt, *J*=5.8, 1.8 Hz, $CH_2CH{=}CH_2$), 3.93 (3H, s, OCH_3), 4.93 (1H, ddd, *J*=18.6, 1.9, 1.7 Hz, *trans* $CH_2CH{=}CH_2$), 4.95 (1H, ddd, *J*=10.1, 1.9, 1.7 Hz, *cis* $CH_2CH{=}CH_2$), 4.96 (2H, s, CH_2Ph), 5.98 (1H, m, $CH_2CH{=}CH_2$), 6.85 (1H, d, *J*=8.6 Hz, H-5), 7.41 (5H, m, Ph), and 7.53 (1H, d, *J*=8.6 Hz, H-6); δ_C 29.6, 30.6, 55.8, 78.4, 109.1, 115.0, 127.0, 128.1 (×3), 128.6 (×2), 131.7, 137.8, 135.3, 146.8, 147.1, 155.8, and 200.6. (Found: C, 76.9; H, 6.65%; M^+ 296. Calcd for $C_{19}H_{22}O_3$: C, 77.0; H, 6.8%; M 296).

3.2. The Corey–Bakshi–Shibata (CBS) reduction of acetyl-3,4-dimethoxy-2-prop-2′-enylbenzene 15

To an oven dried 3-necked flask was introduced the CBS catalyst[6] (0.1 mL, 0.05 mmol) under nitrogen at 25°C followed by the dropwise addition of borane/dimethyl sulphide complex in THF (0.33 mL, 0.33 mmol) and stirring was continued for 5 min. Ketone **15** (3.31 mmol) in THF (2.0 mL) was then introduced by syringe through one neck while additional borane/dimethyl sulphide complex in THF (1.99 mL; 1.99 mmol) was dripped in simultaneously by syringe through the other neck over a period of 10 min. After stirring for an additional 30 min, methanol (1.0 mL) was added and after stirring for 10 min more, the reaction mixture was extracted with dichloromethane and the residue was chromatographed using EtOAc/hexane (1:4) as eluent to yield the following products in order of elution. Ketone **15** (22 mg; 3%) identified by spectral comparison to pure ketone **15**.

3.2.1. 1-Acetyl-3,4-dimethoxy-2-propylbenzene 18. (38 mg; 5%) as an oil. ν_{max} 1688 cm^{-1}; δ_H 0.98 (3H, t, *J*=7.4 Hz, H-3′), 1.55 (2H, m, H-2′), 2.54 (3H, s, CH_3CO), 2.90 (2H, m, H-1′), 3.81 and 3.91 (each 3H, s, OCH_3), 6.78 (1H, d, *J*=8.8 Hz, H-5), and 7.48 (1H, d, *J*=8.8 Hz, H-6); δ_C 14.6, 24.6, 28.6, 29.8, 55.8, 60.9, 108.6, 126.8, 131.5, 138.4, 147.8, 155.5, and 200.7. (Found: C, 70.15; H, 8.3%; M^+ 222. Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222).

Alcohol **21** (51 mg; 7%) as an oil. ν_{max} 3404 cm^{-1}; δ_H 1.46 (3H, d, *J*=6.3 Hz, CH_3CHOH), 1.58 (1H, bs, D_2O exchangeable, OH), 3.52 (2H, ddt, *J*=13.0, 5.6, 2.0 Hz, $CH_2CH{=}CH_2$), 3.80 and 3.86 (each 3H, s, OCH_3), 4.90 (1H, ddd, *J*=17.0, 2.1, 1.9 Hz, *trans* $CH_2CH{=}CH_2$), 5.03 (1H, ddd, *J*=10.2, 2.1, 1.9 Hz, *cis* $CH_2CH{=}CH_2$), 5.06 (1H, q, *J*=6.4 Hz, CH_2CHOH), 6.00 (1H, m, $CH_2CH{=}CH_2$), 6.86 (1H, d, *J*=8.8 Hz, H-5), and 7.24 (1H, d, *J*=8.8 Hz, H-6); δ_C 24.3, 29.7, 55.7, 60.9, 66.2, 110.8, 115.3, 121.0, 130.7, 137.2, 137.9, 147.1 and 152.1. (Found: C, 70.1; H, 8.2%; M^+ 222. Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222).

3.2.2. 1-Acetyl-2-(3′-hydroxypropyl)-3,4-dimethoxybenzene 24. (205 mg; 26%) as an oil. ν_{max} 3348 and 1680 cm^{-1}; δ_H 1.81 (2H, m, H-2′), 2.56 (3H, s, CH_3CO), 3.03 (2H, t, *J*=6.2 Hz, H-1′), 3.54 (2H, t, *J*=6.0 Hz, H-3′), 3.83 and 3.92 (each 3H, s, OCH_3), 6.82 (1H, d, *J*=8.8 Hz, H-5), and 7.50 (1H, d, *J*=8.8 Hz, H-6).

3.2.3. 1-(1′-Hydroxyethyl)-2-(3″-hydroxypropyl)-3,4-dimethoxybenzene 27. (167 mg; 21%) an an oil. ν_{max} 3350 cm^{-1}; δ_H 1.49 (3H, d, *J*=6.4 Hz, CH_3CHOH), 1.81 (2H, m, H-2″), 2.82 (2H, m, H-1″), 3.54 (2H, t, *J*=6.1 Hz, H-3″), 3.83 and 3.92 (each 3H, s, OCH_3), 5.10 (1H, q, *J*=6.4 Hz, CH_3CHOH), 6.80 (1H, d, *J*=8.8 Hz, H-5), and 7.24 (1H, d, *J*=8.8 Hz, H-6).

The mixture of alcohols **24** and **27** was acetylated[18] and the acetates were purified by chromatographic separation using EtOAc/hexane (1:4) as eluent to yield 2-(3′-acetoxypropyl)-1-acetyl-3,4-dimethoxybenzene **30** (217 mg; 90%) as an oil. ν_{max} 1742 and 1688 cm^{-1}; δ_H 1.86 (2H, m, H-2′), 2.06 (3H, s, CH_3COO), 2.54 (3H, s, CH_3CO), 3.00 (2H, m, H-1′), 3.81 and 3.91 (each 3H, s, OCH_3), 4.13 (2H, t, *J*=8.6 Hz, H-3′), 6.80 (1H, d, *J*=8.6 Hz, H-5), and 7.53 (1H, d, *J*=8.6 Hz, H-6); δ_C 21.0, 23.3, 29.6, 29.8, 55.8, 60.8, 64.8, 108.9, 127.2, 131.1, 137.3, 147.9, 155.7, 171.5, and 200.5. (Found: 64.1; H, 7.1%; M^+ 280. Calcd for $C_{15}H_{20}O_5$: C, 64.3; H, 7.2%, M 280). Further elution afforded 1-(1′-acetoxyethyl)-2-(3″-acetoxypropyl)-3,4-dimethoxy-benzene **33** (192 mg; 85%) as an oil. ν_{max} 1752 cm^{-1}; 1.51 (3H, d, *J*=6.6 Hz, CH_3CHOAc), 1.75 (2H, m, H-2″), 2.04 and 2.08 (each 3H, s, CH_3COO), 2.75 (2H, m, H-1″), 3.82 and 3.85 (each 3H, s, OCH_3), 4.13 (2H, t, *J*=6.4 Hz, H-3″), 6.02 (1H, q, *J*=6.6 Hz, CH_3CHOAc), 6.82 (1H, d, *J*=8.6 Hz, H-5), and 7.15 (1H, d, *J*=8.6 Hz, H-6); δ_C 21.0, 21.4, 22.2, 22.7, 29.7, 55.7, 60.7, 64.4, 68.9, 110.6, 121.8, 132.9, 133.3, 147.1, 152.3, 170.5, and 171.5. (Found: C, 62.9; H, 7.4%; (M^+-60) 264. Calcd for $C_{17}H_{24}O_6$: C, 63.0; H, 7.4%; M 324).

3.3. The CBS reduction of acetyl-3-isopropoxy-4-methoxy-2-prop-2′-enylbenzene 16

By an analogous procedure described above ketone **16** (850 mg; 3.43 mmol) was reduced to give:

Ketone **16** (51 mg; 6%) by comparison of spectra.

3.3.1. 1-Acetyl-3-isopropoxy-2-propyl-4-methoxybenzene 19. (51 mg; 6%) as an oil. ν_{max} 1686 cm^{-1}; δ_H 0.93 (3H, t, J=7.4 Hz, H-3′), 1.26 [6H, d, J=6.0 Hz, CH(CH_3)$_2$], 1.52 (2H, m, H-2′), 2.52 (3H, s, CH_3CO), 2.92 (2H, m, H-1′), 3.85 (3H, s, OCH_3), 4.46 [1H, septet, J=6.0 Hz, CH(CH_3)$_2$], 6.71 (1H, d, J=8.6 Hz, H-5), and 7.42 (1H, d, J=8.6 Hz, H-6); δ_C 12.6, 20.6 (×2), 22.1, 27.0, 27.8, 53.6, 72.9, 106.3, 124.2, 129.7, 136.8, 143.5, 153.6 and 199.1. (Found: C, 71.8; H, 8.8%; M^+ 250. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.9%; M 250).

3.3.2. 3-Isopropoxy-4-methoxy-1-(1′-hydroxyethyl)-2-prop-2″-enylbenzene 22. (43 mg; 5%) as an oil. ν_{max} 3396 cm^{-1}; δ_H 1.24 and 1.27 [each 3H, d, J=6.2 Hz, CH(CH_3)$_2$], 1.44 (3H, d, J=6.4 Hz, CH_3CHOH), 1.75 (1H, bs, D_2O exchangeable, OH), 3.54 (2H, ddt, J=16.4, 5.8, 1.8 Hz, CH_2CH=CH_2), 3.82 (3H, s, OCH_3), 4.49 [1H, septet, J=6.2 Hz, CH(CH_3)$_2$], 4.95 (1H, ddd, J=17.2, 1.9, 1.7 Hz, *trans* $CH_2CH=CH_2$), 5.00 (1H, ddd, J=10.4, 1.9, 1.7 Hz, *cis* $CH_2CH=CH_2$), 5.08 (1H, q, J=6.4 Hz, CH_3CHOH), 5.95 (1H, m, $CH_2CH=CH_2$), 6.83 (1H, d, J=8.6 Hz, H-5), and 7.22 (1H, d, J=8.6 Hz, H-6); δ_C 22.6 (×2), 24.3, 30.2, 55.7, 66.1, 74.7, 110.7, 115.1, 120.4, 131.1, 137.3, 137.9, 144.8, and 152.1. (Found: C, 71.8; H, 8.9%; M^+ 250. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.9%; M 250).

3.3.3. 1-Acetyl-2-(3′-hydroxypropyl)-3-isopropoxy-4-methoxybenzene 25. (163 mg; 21%) as an oil. ν_{max} 3346 and 1682 cm^{-1}; δ_H 1.28 [6H, d, J=6.2 Hz, CH(CH_3)$_2$], 1.83 (2H, m, H-2′), 2.56 (3H, s, CH_3CO), 3.10 (2H, t, J=6.2 Hz, H-1′), 3.46 (2H, t, J=6.2 Hz, H-3′), 3.89 (3H, s, OCH_3), 4.50 [1H, septet, J=6.2 Hz, CH(CH_3)$_2$], 6.80 (1H, d, J=8.6 Hz, H-5), and 7.54 (1H, d, J=8.6 Hz, H-6).

3.3.4. 1-(1′-Hydroxyethyl)-2-(3″-hydroxypropyl)-3-isopropoxy-4-methoxybenzene 28. (188 mg; 24%) as an oil. ν_{max} 3345 cm^{-1}; δ_H 1.25 [6H, d, J=6.2 Hz, CH(CH_3)$_2$], 1.45 (3H, d, J=6.4 Hz, CH_3CHOH), 1.75 (2H, m, H-2″), 2.83 (2H, t, J=6.2 Hz, H-1″), 3.43 (2H, t, J=6.0 Hz, H-3″), 3.81 (3H, s, OCH_3), 4.50 [1H, septet, J=6.2 Hz, CH(CH_3)$_2$], 6.79 (1H, d, J=8.6 Hz, H-5), and 7.21 (1H, d, J=8.6 Hz, H-6).

The above mixture of alcohols **25** and **28** (351 mg) was acetylated and the acetates were purified as described earlier to yield 2-(3′-acetoxypropyl)-1-acetyl-3-isopropoxy-4-methoxy-benzene **31** (188 mg; 85%) as an oil. ν_{max} 1734 and 1688 cm^{-1}; δ_H 1.27 [6H, d, J=6.2 Hz, CH(CH_3)$_2$], 1.89 (2H, m, H-2′), 2.06 (3H, s, CH_3COO), 2.55 (3H, s, CH_3CO), 3.08 (2H, t, J=8.5 Hz, H-1′), 3.88 (3H, s, OCH_3), 4.10 (2H, t, H-3′), 4.56 [1H, septet, J=6.2 Hz, CH(CH_3)$_2$), 6.77 (1H, d, J=8.8 Hz, 5-H), and 7.49 (1H, d, J=8.8 Hz, H-6); δ_C 21.2, 22.7 (×2), 23.8, 29.5, 29.7, 55.7, 64.9, 74.8, 108.7, 126.5, 131.2, 137.6, 145.5, 155.6, 171.4 and 200.3. (Found: C, 66.3; H, 7.8%; M^+ 308. Calcd for $C_{17}H_{24}O_5$: C, 66.2; H, 7.9%; M 308). Next to elute from the column was 1-(1′-acetoxyethyl)-2-(3″-acetoxypropyl)-3-isopropoxy-4-methoxybenzene **34**. (247 mg; 85%) as an oil. ν_{max} 1766 cm^{-1}; δ_H 1.27 [6H, d, J=6.2 Hz, CH(CH_3)$_2$], 1.51 (3H, d, J=6.6 Hz, CH_3CHOAc), 1.86 (2H, m, H-2″), 2.05 and 2.08 (each 3H, s, CH_3COO), 2.80 (2H, t, J=6.4 Hz, H-1″), 3.82 (3H, s, OCH_3), 4.12 (2H, t, J=6.4 Hz, H-3″), 4.52 [1H, septet, J=6.2 Hz, CH(CH_3)$_2$], 6.08 (1H, q, J=6.6 Hz, CH_3CHOAc), 6.80 (1H, d, J=8.6 Hz, H-5), and 7.12 (1H, d, J=8.6 Hz, H-6); δ_C 21.1, 21.5 (×2), 22.3, 22.8, 23.3, 29.3, 55.7, 64.6, 69.1, 74.5, 110.4, 121.2, 132.8, 133.8, 144.8, 152.2, 170.4 and 171.4. (Found: C, 64.6; H, 8.1%; M^+ 352. Calcd for $C_{19}H_{28}O_6$: C, 64.7; H, 8.0%; M 352).

3.4. The CBS reduction of acetyl-3-benzyloxy-4-methoxy-2-prop-2′-enylenzene 17

By an analogous procedure describe above ketone **17** (980 mg; 3.31 mmol) was reduced to give:

Ketone **17** (39 mg; 4%) identified by spectral comparisons.

3.4.1. 1-Acetyl-3-benzyloxy-2-propyl-4-methoxybenzene 20. (39 mg; 4%) as an oil. ν_{max} 1677 cm^{-1}; δ_H 0.95 (3H, t, J=7.4 Hz, H-3′), 1.54 (2H, m, H-2′), 2.56 (3H, s, CH_3CO), 2.92 (2H, t, J=8.8 Hz, H-1′), 3.93 (3H, s, OCH_3), 4.98 (2H, s, OCH_2Ph), 6.81 (1H, d, J=8.6 Hz, H-5), 7.41 (5H, m, aryl-H) and 7.49 (1H, d, J=8.6 Hz, H-6); δ_C 14.5, 24.5, 28.9, 29.7, 55.7, 74.8, 108.6, 127.0, 127.9 (×3), 128.2 (×2), 130.9, 131.4, 138.6, 146.7, 155.6 and 200.6. (Found: C, 76.4; H, 7.55%; M^+ 298. Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%; M 298).

3.4.2. 3-Benzyloxy-4-methoxy-1-(1′-hydroxyethyl)-2-prop-2″-enylbenzene 23. (79 mg; 8%) as an oil. ν_{max} 3384 cm^{-1}; δ_H 1.46 (3H, d, J=6.4 Hz, CH_3CHOH), 1.68 (1H, bs, D_2O exchangeable, OH), 3.51 (2H, ddt, J=14.2, 5.8, 1.8 Hz, $CH_2CH=CH_2$), 3.88 (3H, s, OCH_3), 4.88 (1H, ddd, J=17.2, 1.9, 1.7 Hz, *trans* $CH_2CH=CH_2$), 4.98 (2H, s, CH_2Ph), 5.03 (1H, ddd, J=10.2, 1.9, 1.7 Hz, *cis* $CH_2CH=CH_2$), 5.06 (1H, q, J=6.4 Hz, CH_3CHOH), 5.97 (1H, m, $CH_2CH=CH_2$), 6.91 (1H, d, J=8.6 Hz, H-5), 7.31 (1H, d, J=8.6 Hz, H-6), and 7.40 (5H, m, aryl-H); δ_C 24.3, 29.9, 55.8, 66.2, 74.8, 110.9, 115.3, 121.1, 127.9, 128.1 (×2), 128.5 (×2), 131.0, 137.3, 137.9, 138.1, 145.0 and 152.2. (Found: C, 76.3; H, 7.5%; M^+ 298. Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%; M 298).

3.4.3. 1-Acetyl-2-(3′-hydroxypropyl)-3-benzyloxy-4-methoxybenzene 26. (239 mg; 23%) as an oil. δ_H 1.83 (2H, m, H-2′), 2.57 (3H, s, CH_3CO), 3.03 (2H, t, J=6.0 Hz, H-1′), 3.48 (2H, t, J=6.0 Hz, H-3′), 3.95 (3H, s, OCH_3), 4.98 (2H, s, CH_2Ph), 6.85 (1H, d, J=8.6 Hz, H-5), 7.39 (5H, m, aryl-H), and 7.55 (1H, d, J=8.6 Hz, H-6).

3.4.4. 1-(1′-Hydroxyethyl)-2-(3″-hydroxypropyl)-3-benzyloxy-4-methoxybenzene 29. (272 mg; 26%) as an oil. δ_H 1.49 (3H, d, J=6.4 Hz, CH_3CHOH), 1.81 (2H, m, H-2″), 2.79 (2H, t, J=6.0 Hz, H-1″), 3.47 (2H, t, J=6.0 Hz, H-3″), 3.89 (3H, s, OCH_3), 4.98 (2H, s, CH_2Ph), 5.10 (1H, d, J=6.4 Hz, CHCHOH), 6.87 (1H, d, J=8.8 Hz, H-5), 7.28 (1H, d, J=8.8 Hz, H-6), and 7.41 (5H, m, aryl-H).

The mixture of alcohols **26** and **29** (511 mg) was acetylated to yield the pure acetates as described earlier. 2-(3′-Acetoxypropyl)-1-acetyl-3-benzyloxy-4-methoxybenzene **32** (238 mg; 88%) as an oil. ν_{max} 1750 and 1684 cm^{-1}; δ_H 1.89 (2H, m, H-2′), 1.96 (3H, s, CH_3COO), 2.55 (3H, s, CH_3CO), 3.08 (2H, t, J=7.8 Hz, H-1′), 3.93 (3H, s, OCH_3), 4.08 (2H, t, J=6.6 Hz, H-3′), 4.97 (2H, s, CH_2Ph), 6.84 (1H, d, J=8.6 Hz, H-5), 7.39 (5H, m, aryl-H), and 7.56 (1H, d, J=8.6 Hz, H-6); δ_C 20.9, 23.6, 29.5, 29.7, 55.8, 64.7, 74.6, 108.9, 127.4, 128.0 (×3), 128.5 (×2), 131.1, 135.7, 137.7, 146.7, 155.7, 171.4 and 200.1. (Found: C, 70.7; H, 6.7%; M^+-60=296. Calcd for $C_{21}H_{24}O_5$: C, 70.8; H, 6.8%; M 356).

3.4.5. 1-(1′-Acetoxyethyl)-2-(3″-acetoxypropyl)-3-benzyloxy-4-methoxybenzene 35. (294 mg; 85%) as an oil. ν_{max} 1734cm^{-1}; δ_H 1.52 (3H, d, J=6.6 Hz, CH_3CHOAc), 1.86 (2H, m, H-2″), 2.00 and 2.06 (each 3H, s, CH_3COO), 2.75 (2H, t, J=7.0 Hz, H-1″), 3.88 (3H, s, OCH_3), 4.06 (2H, t, J=7.0 Hz, H-3″), 5.01 (2H, s, CH_2Ph), 6.08 (1H, q, J=6.6 Hz, CH_3CHOAc), 6.85 (1H, d, J=8.6 Hz, H-5), 7.11 (1H, d, J=8.6 Hz, H-6), and 7.39 (5H, m, aryl-H); δ_C 20.9, 21.4, 22.1, 23.0, 29.6, 55.7, 64.3, 68.9, 74.7, 110.6, 121.9, 127.9 (×3), 128.5 (×2), 132.9, 133.5, 138.1, 145.0, 152.4, 170.4, and 171.4. (Found: C, 79.5; H, 7.8%; M^+-60=340. Calcd for $C_{23}H_{28}O_6$: C, 79.5; H, 7.9%; M 400).

3.4.6. Acetyl-3,4-dimethoxy-2-prop-1′-enylbenzene 36. Acetyl-3,4-dimethoxy-2-prop-2′-enylbenzene **15** (1.00 g; 4.45 mmol) in dichloromethane (50 mL) was treated with palladium dichloride bis-acetonitrile (100 mg) and the mixture stirred under gentle reflux for 72 h. Flash chromatography using EtOAc/hexane (1:9) as eluent afforded the conjugated product **36** (940 mg; 94%) as a yellow oil. ν_{max} 1684 cm^{-1}; δ_H 1.90 (3H, dd, J=6.6, 1.8 Hz, H-3′), 2.41 (3H, s, CH_3CO), 3.75 and 3.89 (each 3H, s, OCH_3), 5.85 (1H, dq, J=16.0, 6.6 Hz, H-2′), 6.73 (1H, dq, J=16.0, 1.8 Hz, H-1′), 6.82 (1H, d, J=8.6 Hz, H-5), and 7.25 (1H, d, J=8.6 Hz, H-6); δ_C 19.3, 30.6, 55.9, 60.3, 110.0, 124.7, 124.8, 132.4, 133.4, 133.8, 146.5, 154.9, and 203.4. (Found: C, 70.8; H, 7.4%; M^+ 220. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3%; M 220).

3.4.7. Acetyl-3-isopropoxy-4-methoxy-2-prop-1′-enylbenzene 37. By an analogous protocol alkene **16** (1.22 g; 4.0 mmol) was isomerised to alkene **37** (989 mg; 81%) as a yellow oil. ν_{max} 1694 cm^{-1}; δ_H 1.23 [6H, d, J=6.2 Hz, $CH(CH_3)_2$], 1.88 (3H, dd, J=6.6, 1.8 Hz, H-3′), 2.34 (3H, s, CH_3CO), 3.86 (3H, s, OCH_3), 4.38 (1H, septet, J=6.2 Hz, $CH(CH_3)_2$], 5.82 (1H, q, J=8.8 Hz, H-5), and 7.18 (1H, d, J=8.8 Hz, H-6); δ_C 19.2, 22.6 (×2), 30.7, 55.9, 75.5, 110.0, 124.3, 125.7, 125.9, 128.8, 133.1, 144.6, 155.9, and 203.9. (Found: C, 72.4; H, 8.2%; M^+ 248. Calcd for $C_{15}H_{20}O_3$: C, 72.5; H, 8.1%; M 248).

3.4.8. Acetyl-3-benzyloxy-4-methoxy-2-prop-1′-enylbenzene 38. Alkene **17** (1.33 g; 4.55 mmol) was isomerised by an analogous protocol to alkene **38** (1.16 g; 87%) as a yellow oil. ν_{max} 1684 cm^{-1}; δ_H 1.84 (3H, dd, J=6.6 Hz, 1.8 Hz, H-3′), 2.40 (3H, s, CH_3CO), 3.90 (3H, s, OCH_3), 4.89 (2H, s, CH_2Ph), 5.82 (1H, dq, J=16.0, 6.6 Hz, H-2′), 6.63 (1H, dq, J=16.0, 1.8 Hz, H-1′), 6.84 (1H, d, J=8.6 Hz, H-5), 7.28 (1H, d, J=8.6 Hz, H-6), and 7.37 (5H, m, aryl-H); δ_C 19.2, 30.6, 56.0, 74.0, 110.1, 125.1, 128.1, 128.4 (×3), 128.5 (×2), 133.0, 133.5, 133.8, 137.5, 145.3, 155.1, and 203.3. (Found: C, 76.8; H, 6.9%; M^+ 296. Calcd for $C_{19}H_{22}O_3$: C, 77.00; H, 6.8%; M 296).

3.4.9. (*R*)-3,4-Dimethoxy-1-(1′-hydroxyethyl)-2-prop-1″-enylbenzene 42. The residue obtained from the CBS-catalysed enantiomeric reduction of ketone **36** (1.00 g; 4.55 mmol) as described earlier was chromatographed using EtOAc/hexane (1:4) as eluent to yield firstly the dimeric diastereoisomer **39** (365 mg; 18%) as a viscous oil. ν_{max} 3434 cm^{-1}; δ_H 1.04 and 1.08 (each 3H, t, J=7.2 Hz, H-3′), 1.52 and 1.63 [each 3H, d, J=6.6 Hz, CH_3CH(OH)], 1.82 (4H, m, H-2′), 2.43 and 2.62 (each 1H, m, H-1′), 3.82, 3.84, 3.85, and 3.86 (each 3H, s, OCH_3), 4.28 and 4.38 (each 1H, bs, D_2O exchangeable, OH), 5.20 [2H, q, J=6.6 Hz, CH(OH)CH_3], 6.75 (3H, m, 2×H-5 and H-6) and 6.93 (1H, d, J=8.8 Hz, H-6); δ_C 14.1, 14.3, 22.5, 23.8, 27.3, 27.6, 55.6, 55.7, 60.5, 60.7, 70.1 (×2), 73.9 (×2), 109.3, 110.2, 119.3, 120.4, 133.1, 133.4, 133.6, 134.8, 146.8, 147.4, 154.4 and 155.0. (Found: C, 70.0; H, 8.6%. Calcd for $C_{26}H_{38}O_6$: C, 69.9; H, 8.6%). Further elution afforded the *R*-alcohol **42** (590 mg; 59%) as an oil. ν_{max} 3407 cm^{-1}; δ_H 1.46 (3H, d, J=6.4 Hz, CH_3CHOH), 1.64 (1H, bs, D_2O exchangeable, OH), 1.92 (3H, dd, J=6.4, 1.8 Hz, H-3″), 3.72 and 3.86 (each 3H, s, OCH_3), 5.13 (1H, q, J=6.4 Hz, CH_3CHOH), 6.00 (1H, dq, J=16.0, 6.4 Hz, H-2″), 6.42 (1H, dq, J=16.0, 1.8 Hz, H-1″), 6.82 (1H, d, J=8.6 Hz, H-5), and 7.26 (1H, d, J=8.6 Hz, H-6); δ_C 19.4, 24.4, 55.9, 60.2, 66.4, 111.0, 120.7, 123.5, 131.2, 132.3, 136.7, 146.5, and 151.5. $[\alpha]_D$=+32.2° (c=0.785, CH_2Cl_2); ee via Mosher ester 75% and via Eu(hfc)$_3$ reagent 75%. (Found: C, 70.2; H, 8.1%; M^+ 222. Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222).

3.4.10. (*R*)-3-Isopropoxy-4-methoxy-1-(1′-hydroxyethyl)-2-prop-1″-enylbenzene 43. The residue obtained from the CBS-catalysed enantiomeric reduction of ketone **37** (1.01 g; 4.07 mmol) as described earlier was chromatographed using EtOAc/hexane (1:4) as eluent to yield firstly the dimeric diastereoisomer **40** (415 mg; 20%) as a viscous oil. ν_{max} 3428 cm^{-1}; δ_H 0.97 and 1.04 (each 3H, t, J=7.2 Hz, H-3′), 1.20 and 1.37 [each 6H, d, J=6.4 Hz, $CH(CH_3)_2$], 1.51 and 1.63 (each 3H, d, J=6.8 Hz, CH_3CHOH), 1.80 (4H, m, H-2′), 2.52 and 2.70 (each 1H, m, H-1′), 3.82 and 3.83 (each 3H, s, OCH_3), 4.30 and 4.39 (each 1H, bs, D_2O exchangeable, OH), 4.52 [2H, m, $CH(CH_3)_2$], 5.20 (2H, q, J=6.8 Hz, CH_3CHOH), 6.73 (3H, m, 2×H-5 and H-6), and 6.88 (1H, d, J=8.8 Hz, H-6); δ_C 14.0, 14.4, 21.1, 22.2, 22.3, 22.9, 23.0, 23.3, 26.7, 27.8, 55.5, 55.6, 70.2 (×2), 74.0 (×2), 74.1, 74.4, 109.0, 110.0, 118.7, 119.8, 133.1, 133.5, 133.6, 135.4, 144.6, 145.1, 151.4, and 152.1. (Found: C, 71.5, H, 9.2%. Calcd for $C_{30}H_{46}O_6$: C, 71.7; H, 9.2%). Further elution afforded the (*R*)-alcohol **43** (590 mg; 58%) as a pale yellow oil. ν_{max} 3400 cm^{-1}; δ_H 1.22 [6H, d, J=6.2 Hz, $CH(CH_3)_2$], 1.45 (3H, d, J=6.2 Hz, CH_3CHOH), 1.66 (1H, bs, D_2O exchangeable, OH), 1.91 (3H, dd, J=6.4, 1.6 Hz, H-3″), 3.82 (3H, s, OCH_3), 4.29 (1H, septet, J=6.2 Hz, $CH(CH_3)_2$], 5.13 (1H, q, J=6.4 Hz, CH_3CHOH), 5.98 (1H, dq, J=16.0, 6.4 Hz, H-2″), 6.41 (1H, dq, J=16.0, 1.6 Hz, H-1″), 6.82 (1H, d, J=8.6 Hz, H-5), and 7.26 (1H, d, J=8.6 Hz, H-6); δ_C 19.2, 22.6 (×2), 24.0, 55.2, 66.5, 75.4, 110.8, 120.2, 124.5, 132.0, 132.2, 136.5, 144.6, and 152.5. $[\alpha]_D$=+28.3° (c=0.755 in CH_2Cl_2); ee via Mosher ester and Eu(hfc)$_3$

was 75%. (Found: C, 71.9; H, 8.9%; M^+ 250. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.9%; M 250).

3.4.11. (*R*)-3-Benzyloxy-4-methoxy-1-(1′-hydroxyethyl)-2-prop-1″-enylbenzene 44. The residue obtained by the CBS-catalysed enantiomeric reduction of ketone **38** (980 mg; 3.31 mmol) as described earlier was chromatographed using EtOAc/hexane (1:4) as eluent to yield firstly the dimeric diastereoisomer **41** (370 mg; 19%) as a viscous oil. ν_{max} 3407 cm^{-1}; δ_H 0.97 and 1.02 (each 3H, t, J=7.4 Hz, H-3′), 1.53 and 1.64 (each 3H, d, J=6.6 Hz, CH_3CHOH), 1.62 (4H, m, H-2′), 2.44 and 2.60 (each 1H, m, H-1′), 3.88 and 3.89 (each 3H, s, OCH_3), 4.38 and 4.40 (each 1H, bs, D_2O exchangeable, OH), 5.10 (6H, m, CH_3C*H*OH and CH_2Ph), 6.80 (3H, m, 2×H-5 and H-6), 6.95 (1H, d, J=8.8 Hz, H-6), and 7.40 (10H, m, aryl-H); δ_C 14.1, 14.4, 21.5, 24.0, 27.4, 28.0, 55.9, 56.0, 70.1 (×2), 74.0, 74.6, 74.8 (×2), 109.5, 110.4, 119.6, 120.7, 127.8 (×4), 128.5 (×4), 128.6 (×2), 133.5, 133.7 (×2), 133.9, 135.2, 138.2, 145.9, 146.5, 151.6, and 152.2. (Found: C, 76.1; H, 7.7%. Calcd for C_{38} $H_{46}O_6$: C, 76.2; H, 7.8%). Further elution afforded the (*R*)-alcohol **44** (610 mg; 62%) as a pale yellow oil. ν_{max} 3396 cm^{-1}; δ_H 1.46 (3H, d, J=6.2 Hz, CH_3CHOH, 1.70 (1H, bs, D_2O exchangeable, OH), 1.89 (3H, dd, J=6.5, 1.8 Hz, H-3″), 3.87 (3H, s, OCH_3), 4.88 (2H, s, CH_2Ph), 5.11 (1H, q, J=6.2 Hz, CH_3C*H*OH), 5.97 (1H, dq, J=16.0, 6.5 Hz, H-2″), 6.39 (1H, dq, J=16.0, 1.8 Hz, H-1″), 6.87 (1H, d, J=8.4 Hz, H-5), 7.31 (1H, d, J=8.4 Hz, H-6), and 7.38 (5H, m, aryl-H); δ_C 19.2, 24.4, 56.0, 66.5, 74.6, 111.1, 120.8, 123.7, 128.3 (×3), 128.4 (×2), 131.1, 132.4, 136.7, 138.0, 145.5, and 152.1. $[\alpha]_D$=+21.9° (c=0.755, CH_2Cl_2); ee via Mosher ester and Eu(hfc)$_3$ was 75%. (Found: C, 76.5; H, 7.4%; M^+ 298. Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%; M 298).

Acknowledgements

This work was supported by the National Research Foundation, and the Universities of the Western Cape and Witwatersrand.

References

1. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.
2. (a) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40. (b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931.
3. Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055.
4. Giles, R. G. F.; Green, I. R. *Synth. Commun.* **1996**, *26*, 3161.
5. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
6. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, J.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
7. Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.
8. Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.
9. Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429.
10. Masui, M.; Shiori, T. *Tetrahedron* **1995**, *51*, 8363.
11. Masui, M.; Shiori, T. *Synlett* **1996**, 49.
12. Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett.* **1999**, *40*, 2477.
13. Sing, V. K. *Synthesis* **1992**, 605.
14. de Koning, C. B.; Giles, R. G. F.; Green, I. R.; Jahed, N. M. *Tetrahedron Lett.* **2001**, *43*, 4199.
15. de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 787.
16. Mancera, O.; Rosenkrantz, G.; Sondheimer, F. *J. Chem. Soc.* **1953**, 2190.
17. Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*; 5th ed. McGraw-Hill, 1995.
18. Nagabhushana, K. S.; Ameer, F.; Green, I. R. *Synth. Commun.* **2001**, *31*, 719.
19. Giles, R. G. F.; Lee Son, V. R.; Sargent, M. V. *Aust. J. Chem.* **1990**, *43*, 777.
20. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
21. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
22. Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763.
23. Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.
24. Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028.
25. Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465.