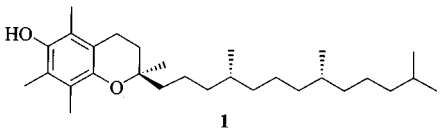
Enantioselective Synthesis of the Chromane Moiety of Vitamin E

Lutz F. Tietze,*[a] Jochen Görlitzer,[a] Ansgar Schuffenhauer,[a] and Matthias Hübner[a]

Keywords: Asymmetric synthesis / Atropisomerism / Bis(hydroxylation) / Conformational analysis / Palladium / Vitamin E

Several new approaches for the enantioselective synthesis of the chromane moiety of vitamin E are described. Sonogashira coupling of **3a** with the alkyne **4** and subsequent elimination gave **6**, which was bis(hydroxylated) in 93% yield and with 85% *ee*. Recrystallization gave enantiopure **7a**, which was hydrogenated and transformed into the vitamin E precursor **11**. The bis(hydroxylation) of **18** and **21** to give **9** and **22**, respectively, was less than satisfactory, proceeding with *ee* values of 28% and 18%. In contrast, stereoselective allylation of ketone **15** followed by removal of the protecting group or ozonolysis of the allyl moiety furnished the allyl alcohol **26** and the aldehyde **27**, respectively, in almost enantiopure form, which again could be used as precursors for vitamin E. Partial hydrogenation of **5a** gave the alkene **32a** and that of **28** the alkene **30b**, both of which show interesting atropisomerism.

Vitamin E is an important food supplement in the nutrition of humans and animals due to its radical quenching and cell-protecting properties.[1] Deficiency of this vitamin causes a degeneration of cells of the nervous system and muscles. Vitamin E is usually offered as a racemic mixture of diastereomers. Therefore, the development of methods for the preparation of enantiopure vitamin E is of considerable importance.[2] Methods used to date have included resolution of the products,[3] the use of auxiliaries[4] or of enantiopure building blocks,[5] as well as asymmetric oxidation.[6] In this paper, we describe the enantioselective bis(hydroxylation)[7] of the readily accessible enyne **6a** and of the alkene **21**, as well as the stereoselective allylation[8] of alkyl methyl ketone **15**. Some additional analogues have also been prepared.



1

Scheme 1. Tocopherol A

The synthesis of **6a** was performed by iodination of **2a** to give **3a**[9] in 78% yield, followed by quantitative Pd-catalyzed Sonogashira coupling[10] with the propargylic alcohol **4** and acid-catalyzed elimination in the presence of *p*-toluenesulfonic acid and acetic anhydride. The latter step could also be performed with the Burgess reagent.[11] Attempted use of sodium sulfate in place of acetic anhydride was not successful. In the presence of trimethyl orthoformate and *p*-toluenesulfonic acid, the methyl ether **8** was obtained. In a similar manner as that described for **6a**, but starting from **2b**, **6b** could be synthesized in 68% overall yield.

The bis(hydroxylation)[7] of **6a** and **6b** was accomplished under standard conditions using AD-Mix-α with [$(DHQ)_2PHAL$] in *t*BuOH/H_2O at 4°C, to give **7a** and **7b**, respectively, in yields of about 95% with 85% *ee*. The enantiomeric excess was determined by NMR spectroscopy using the monoester of Mosher's acid[12] (^1H and ^{19}F). Recrystallization of **7a** from hexane/*tert*-butyl methyl ether furnished the enantiopure compound.

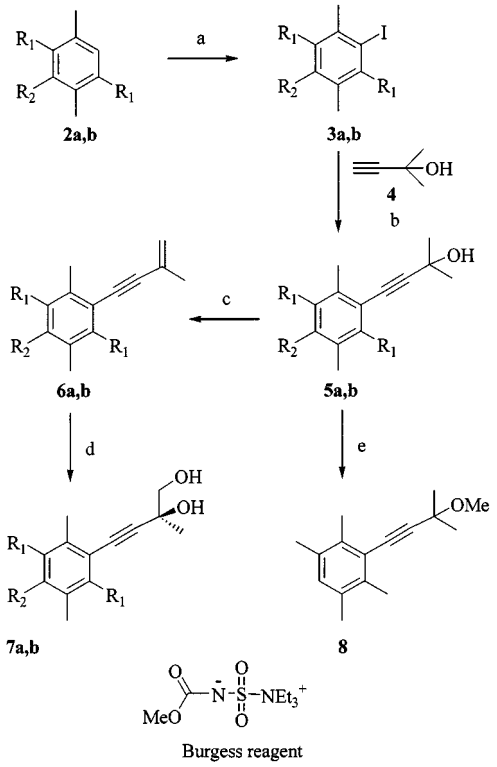
Hydrogenation of **7a** using Adams catalyst in methanol afforded **9** in 93% yield. Compounds **7a** and **9** were converted to the corresponding acetals **10** and **11**, respectively, in nearly quantitative yields by treatment with methyl isopropenyl ether (MIPE) in the presence of catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2. Both compounds have previously been used as vitamin E precursors.[4b,5] Hydrogenation of **10** to give **11** remained unsatisfactory, in spite of a broad variation of the conditions of solvent, catalyst, and pressure. The low reactivity of **10** can be attributed to a shielding of the triple bond by the acetal moiety.

In a second approach to enantiopure vitamin E, the ketone **15** was prepared by two routes and transformed into **18**, **21**, and **25**. Coupling of **3a** with **12** as described above, followed by hydrogenation with Pd/C and oxidation with Dess–Martin periodinane,[13] gave **15** in 57% overall yield. Somewhat unexpectedly, a highly efficient direct access to **15** in 82% yield could be achieved by reaction of **3a** with **16** in the presence of the Herrmann–Beller[14] catalyst **15a**.[15] Usually, Heck reactions of electron-rich and sterically hindered iodoarenes give only low yields. This was confirmed by performing a Heck reaction of **3a** and **16** in the presence of palladium acetate and silver carbonate, which led to the desired product **17** in only 31% yield under optimized conditions. The low reactivity of **3a** in Heck-type reactions has also been observed in other cases.[16] This gives a further indication that the reaction of haloarenes in the presence of the palladacene follows a different mechanistic course.

The ketone **15** was transformed into the alkene **18**, which was subjected to enantioselective Sharpless bis(hydroxylation). Since this reaction is sensitive to impurities, we prepared **18** by two different routes, namely by methylenation

[a] Institute of Organic Chemistry of the Georg-August-Universität,
Tammannstraße 2, D-37077 Göttingen, Germany
Fax: (internat.) + 49(0)551/399476
E-mail: ltietze@gwdg.de

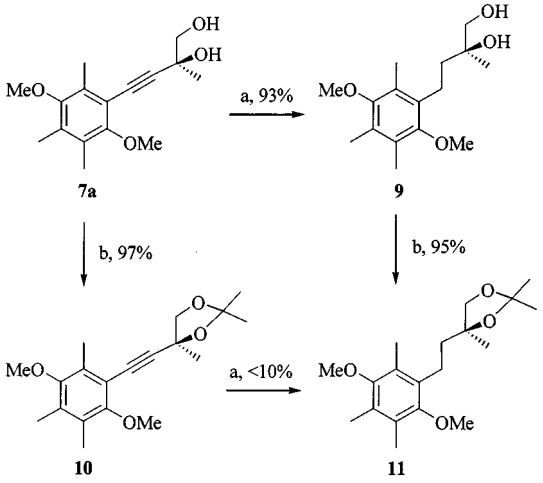
  1434–193X/99/0505–1075 $ 17.50+.50/0



Scheme 2. a: I_2, H_5IO_6, H_2O, AcOH, H_2SO_4; b: $PdCl_2(PPh_3)_2$, CuI, $NHEt_2$; c: PTS, Ac_2O, CH_2Cl_2 or Burgess reagent; d: *t*BuOH, H_2O, AD-Mix-α, [$(DHQ)_2PHAL$]; e: PTS, $HC(OMe)_3$, CH_2Cl_2, 95%

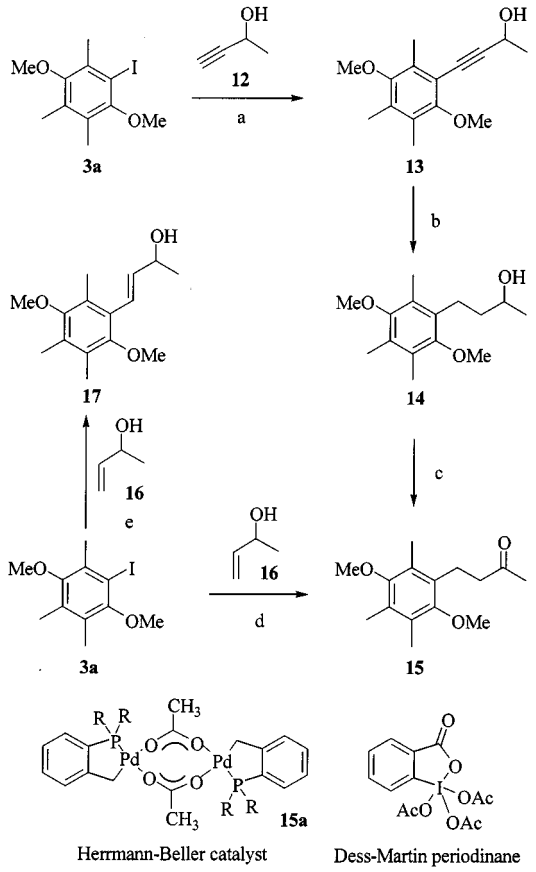
Table 1. Yields and enantiomeric excess values for compounds **3**–**7**

	R^1	R^2	**3**	**5**	**6**	**7**
a	OCH_3	CH_3	78%	72%	93%	93%, 84% *ee*
b	CH_3	H	79%	88%	98%	95%, 85% *ee*

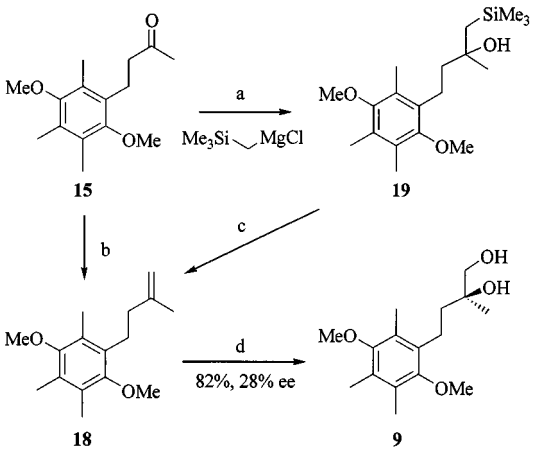


Scheme 3. a: PtO_2, MeOH, 3 atm H_2; b: MIPE, PPTS, CH_2Cl_2; MIPE = methyl isopropenyl ether; PPTS = pyridinium *p*-toluenesulfonate

of **15** in a Wittig reaction in 71% yield, and by a Grignard reaction of **15** with trimethylsilylmethylmagnesium chloride to give the alcohol **19** (78%). Upon treatment with potassium hydride, the latter underwent Peterson elimination[17] in 85% yield. The ketone **15** was also transformed into the unsaturated ester **20** in 83% yield by reaction with trimethyl phosphonoacetate. Subsequent reduction with DIBAH gave the allylic alcohol **21** in 93% yield as a second substrate for the enantioselective bis(hydroxylation).



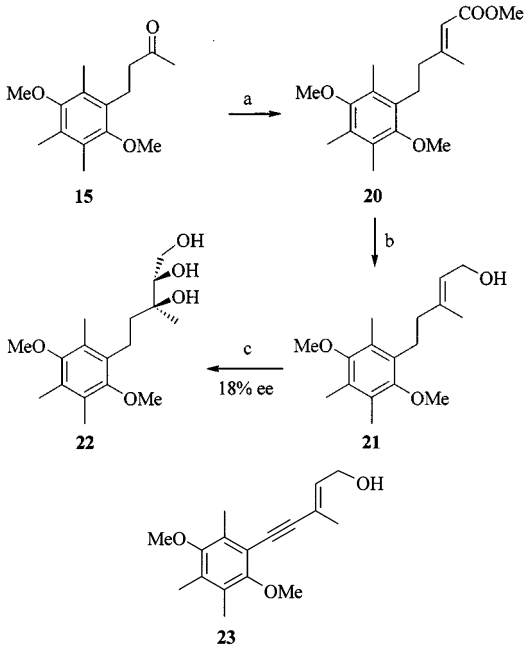
Scheme 4. a: $PdCl_2(PPh_3)_2$, CuI, $NHEt_2$, 67%; b: Pd/C, MeOH, 3 atm H_2, 96%; c: Dess–Martin periodinane, CH_2Cl_2, 89%; d: Herrmann–Beller catalyst, $NaHCO_3$, CH_3CN, DMF, H_2O, 70–120°C, 82%; e: $Pd(OAc)_2$, K_2CO_3, Ag_2CO_3, DMF, 40°C, 31%



Scheme 5. a: THF, 78%; b: $PPh_3CH_3^+Br^-$, *n*BuLi, THF, 71%; c: KH, THF, 85%; d: *t*BuOH, H_2O, AD-Mix-α, [$(DHQ)_2PHAL$]

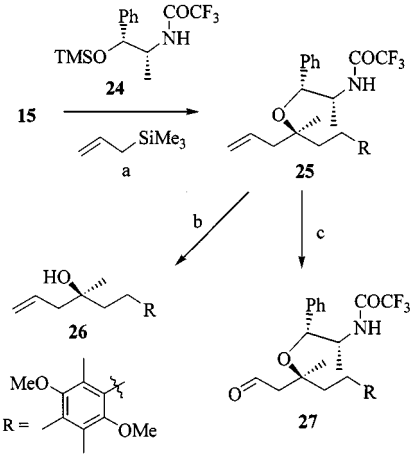
The bis(hydroxylation) of **18** and **21** was performed under standard conditions using AD-Mix-α with [$(DHQ)_2PHAL$]

in aqueous *t*BuOH solution at 4°C. The diol **9** and the triol **22**[6c] were obtained in good yields, but with low enantioselectivities (28% and 18% *ee*), which were again determined using the Mosher ester method[12] (^{1}H and ^{19}F). These results were somewhat unexpected since the enynes **6a** and **23**[6c] show good to excellent enantioselectivities upon bis(hydroxylation) under the same conditions (84% and > 95% *ee*, respectively). Thus, we assume that the observed differences in the enantioselectivities depend on the conformation of the side chain as well as on the distance between the aromatic ring and the alkene moiety, as we have previously shown for a different system.[6a] There is some evidence that in contrast to the slim arylalkynyl group in **6a** and **23**, the bulky arylalkyl group in **18** and **21** does not fit into the pocket of the catalyst and therefore does not allow a high facial discrimination of the alkene moiety in these compounds. These findings are underlined by force-field calculations,[18] which show a staggered conformation of the arylalkyl group in both **18** and **21**. Recently, Corey has pointed out that in substrates having three atoms between the alkene moiety and the aromatic ring, the side chain can adopt a suitable conformation in the pocket of the catalyst with little steric interaction.[19] The decrease in the enantioselectivity of the bis(hydroxylation) when using substrates with an *ortho* substituent at the aryl moiety is also in accordance with published results.[6a,20]



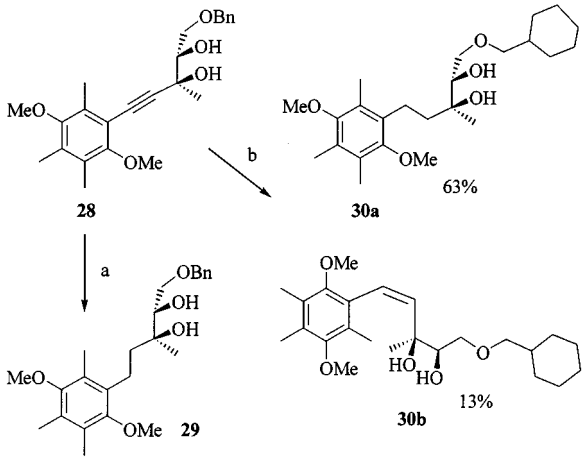
Scheme 6. a: LiHMDS, THF, $(MeO)_2P(O)CH_2CO_2Me$, 83%; b: DIBAH, THF, 93%, c: *t*BuOH, H_2O, AD-Mix-α, $[(DHQ)_2PHAL]$, 92%

As a third approach to the enantiopure chromane moiety of vitamin E, we employed a facial-selective allylation of the ketone **15**, which we had developed previously.[8] Reaction of **15**, allylsilane, and the norpseudoephedrine derivative **24** in the presence of a catalytic amount of TfOH led directly in a domino-type transformation[21] to a 53% yield of **25** (78% based on turnover), with a diastereoselectivity of 9:1 as determined by ^{13}C NMR and HPLC. Cleavage of the homoallylic ether moiety in **25** with sodium in liquid ammonia proceeded selectively, without reduction of the arene moiety, to give the corresponding alcohol **26** in almost quantitative yield. The arene moiety was also found to be stable under ozonolysis conditions; thus, treatment of **25** with ozone furnished the aldehyde **27** in 87% yield. Vitamin E may be obtained from **26** by a sequence of oxidative demethylation, rearomatization, introduction of the side chain according to established procedures, and finally cyclization.[4]

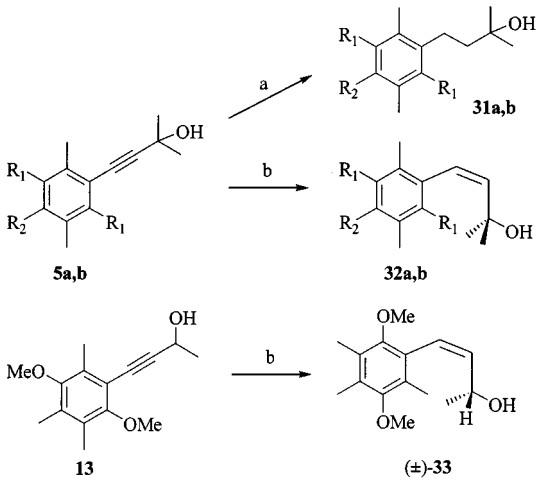


Scheme 7. a: CH_2Cl_2, TfOH, −78°C, 53%; b: Na, NH_3,THF, 94%; c: 1. O_3, CH_2Cl_2, 2. PPh_3, 87%

Hydrogenation of **28** in methanol in the presence of PtO_2 usually led to **29**.[6c] However, in one experiment under the same reaction conditions but with a different batch of PtO_2, we obtained 63% of **30a** and 13% of **30b** with a saturated benzyl moiety. In the hydrogenation of **5a** and **5b** with PtO_2 at a pressure of 3 atm, we obtained **31a** and **31b** in high yield; using only 1 atm of hydrogen, selective formation of **32a** and **32b** was observed. In the same way, **33** was obtained from **13**. Notably, using Pd or P2 nickel as the catalyst, selective reduction of the triple bond was not possible.



Scheme 8. a: PtO_2, MeOH, 3 atm H_2, 56%; b: PtO_2, MeOH, 3 atm H_2



Scheme 9. a: PtO_2, MeOH, 3 atm H_2; b: PtO_2, EtOAc, 1 atm H_2

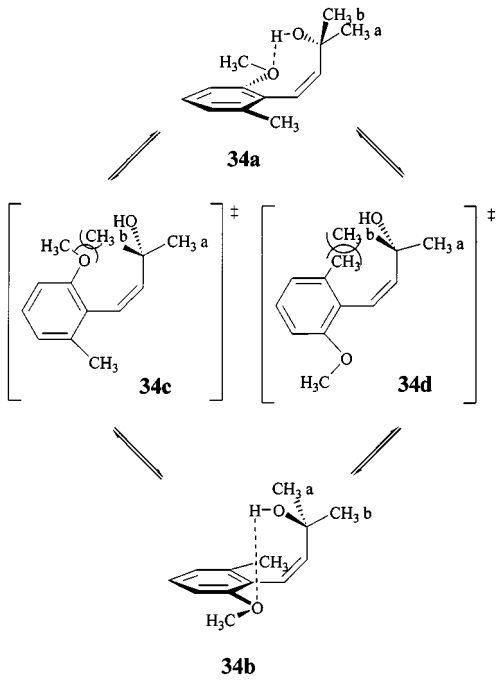
Table 2. Yields for compounds **31**–**33**

	R^1	R^2	**31**	**32**	**33**
a	OCH_3	CH_3	91%	95%	94%
b	CH_3	H	97%	87%	–

Compound **32a** exhibits some interesting dynamic properties, as revealed by temperature-dependent NMR investigations. In the ^{1}H-NMR spectrum of **32a** in $CDCl_3$ at room temperature, a very broad signal for the methyl groups in the allylic position is observed. In the ^{13}C-NMR spectrum under the same experimental conditions, the signal for the methyl groups is in fact absent. Further investigations showed that this phenomenon can be explained in terms of the existence of rotamers.[22] The same behaviour was observed, in an even more pronounced manner, in the case of compound **30b**. In contrast, in the case of **33**, which has only one methyl group in an allylic position, rotamers could not be detected at room temperature.

The height of the rotational barrier was determined by means of band-shape analysis. We recorded a series of ^{1}H-NMR spectra of **32a** and **30b** between −45°C and +60°C and −35°C and +80°C, respectively, in [D_8]toluene solution. The statistical parameters (chemical shifts [Hz], populations, relaxation times [s]: **32a**: 1. 429.2, 2. 367.2; 1. 3.48, 2. 3.55; 1. 0.262, 2. 0.279; **30b**: 1. 470.0, 2. 395.6; 1. 6.50, 2. 8.25; 1. 0.205, 2. 0.212) were taken from the spectra at −45°C and −35°C. The band shapes and the corresponding rate constants were calculated using the program DNMR5.[23] Insertion of the rate data into the Eyring equation and weighted least-squares adjustment with the program ACTPAR[24] yielded the activation parameters at 298 K for the conversion between the rotamers of **32a**: $\Delta H^{\neq}$ = (42.3 ± 1.3) kJ mol^{-1}, $\Delta S^{\neq}$ = (−53.6 ± 3.8) kJ mol^{-1} K^{-1}, and $\Delta G^{\neq}$ = (55.2 ± 2.5) kJ mol^{-1}; **30b**: $\Delta H^{\neq}$ = (42.7 ± 3.8) kJ mol^{-1}, $\Delta S^{\neq}$ = (−55.2 ± 14.2) kJ mol^{-1} K^{-1}, and $\Delta G^{\neq}$ = (59.0 ± 7.9) kJ mol^{-1}.

The spectroscopic data were confirmed by PM3[25] calculations on the slightly simplified model compound **34**. As minimum energy structures, we found the two enantiomeric conformers **34a** and **34b**, with a torsion angle between the aromatic ring and the vinylic group of 90°. The distance between the hydrogen atom of the alcohol moiety and the oxygen atom of the methoxy group of 251 pm indicates that these conformers may be stabilized by a hydrogen bond. Conformers **34a** and **34b** may be interconverted by rotation about the single bond between the aromatic and the vinylic moieties, passing through structure **34c** or **34d**, in which the vinylic group and the aromatic ring are coplanar. Both structures correspond to stationary points on the rotational potential energy surface and have one precise imaginary vibrational frequency, and must thus represent transition structures. The energies of **34c** and **34d** relative to **34a/b** are 51.0 and 66.5 kJ mol^{-1}, respectively. A rotation of the allylic carbon atom completes the transformation of **34a** to **34b**. The activation enthalpy for this rotation is only small and the transition structure could not be localized with precision. Alternatively, rotation about the allylic bond might take place prior to the rotation of the aromatic ring and the process would then proceed via *ent*-**34c** or *ent*-**34d**. In both transition structures **34c** and **34d**, the Ar−*CH*=CH angle and the CH=*CH*−C(CH$_3$)$_2$OH angle are significantly widened in order to reduce steric repulsion. Clearly, with



Scheme 10. Atropisomerism of **34a**, **b**

Table 3. Results of PM3 calculations on **34a**–**d**

Structure	ΔH_f [kJ mol^{-1}]	Torsion angle Ar−CH=CH	Bond angle Ar−CH=CH	Bond angle CH=CH−C(CH$_3$)$_2$OH
34a/b	−263.6	±90°	128°	128°
34c	−212.5	0°	141°	138°
34d	−197.1	179°	144°	139°

an energy of 55.5 kJ mol^{-1} (relative to **34a/b**), **34d** is less stable than **34c** due to the greater steric demand of the methyl group compared to the methoxy group.

Since the ground-state structure of **34** is chiral, the two allylic methyl groups [CH_3(a) and CH_3(b)] are diastereotopic, and therefore they give rise to two signals in the low-temperature NMR spectra. When **34a** and **34b** interconvert, CH_3(a) and CH_3(b) are interchanged, and hence coalescence is observed at higher temperatures. The barrier to rotation in the model system **34**, via **34c**, amounts to 51.0 kJ mol^{-1}, which is only 8.8 kJ mol^{-1} higher than the experimental value of 42.2 kJ mol^{-1} observed for **32a**. This relatively small deviation may be attributable to the omission of the *m* and *p* substituents in the model system, thus lowering the electron density somewhat compared to that in **32a**. However, the semiempirical calculations clearly support the conformational analysis obtained by spectroscopic methods.

Experimental Section

General: Where appropriate, all reactions were carried out under inert atmosphere. − ^{1}H- and ^{13}C-NMR spectra: Varian XL-200, VXR-200, or Bruker AMX-300 spectrometers. − IR: Bruker IFS-25. − MS and HRMS: MAT 95. − Elemental analyses: Analytical laboratory of the University of Göttingen. − Column chromatography: Macherey−Nagel & Co. Kieselgel 60 (0.063−0.200 mm). − Analytical TLC: Macherey−Nagel & Co (SIL G/UV$_{254}$). − Solvents (distilled from): Et_2O (KOH or Na/benzophenone), petroleum ether 40−80°C (KOH), EtOAc (CaH_2), THF ($LiAlH_4$). − Satisfactory elemental analyses (C,H ±0.4%) or correct HRMS data were obtained for all new compounds.

1-Iodo-2,5-bis(methoxy)-3,4,6-trimethylbenzene (3a): The arene **2a** (13.0 g, 72.0 mmol) was dissolved in a mixture of glacial acetic acid (100 mL), water (30 mL), and concd. sulfuric acid (3.60 mL). After the addition of iodine (3.65 g, 14.4 mmol) and periodic acid (6.58 g, 28.9 mmol), the solution was stirred for 15 h under exclusion of light at 55°C. Water (150 mL) was then added and the aqueous phase was extracted with diethyl ether (2 × 200 mL). The combined organic phases were neutralized with satd. aqueous $NaHCO_3$ solution, washed with 0.1 N aqueous $Na_2S_2O_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification of the residue gave 17.1 g (78%) of the iodoarene **3a** as a crystalline solid. − ^{1}H NMR ($CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 3.62 (s, 3 H, 5-OCH_3), 3.68 (s, 3 H, 2-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 12.85, 13.90, 22.09 ($ArCH_3$), 60.23 (5-OCH_3), 60.26 (2-OCH_3), 96.52 (C-1), 128.6, 131.0, 132.7 (C-3, C-4, C-6), 152.8, 154.0 (C-2, C-5). − $C_{11}H_{15}O_2I$ (306.1).

General Procedure I: To a stirred solution of the iodoarene **3a** or **3b** (1.00 mmol) in Et_2NH (2 mL), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), CuI (20 mg, 0.10 mmol), and **4** (1.50 mmol) were added at room temp. and stirring was continued at 45°C for 4 h. Then, the solution was diluted with Et_2O (20 mL) and extracted with H_2O (2 × 50 mL). The organic phase was washed with brine, dried with Na_2SO_4, and the solvent was removed in vacuo. Chromatographic purification gave the desired propargylic alcohols **5a** and **5b**.

4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methyl-3-butyn-2-ol (5a): Reaction of **3a** (306 mg, 1.00 mmol) according to general procedure I gave 188 mg (72%) of **5a** as a crystalline solid; m.p. 61°C. − IR (KBr): $\tilde{\nu}$ = 3428 cm^{-1} (OH), 2248 (C≡C), 1088 (aryl ether). − UV (CH_3CN): λ_{max} (lg ε) = 214 nm (4.51), 248 (4.81), 258 (4.20). − ^{1}H NMR ($CDCl_3$): δ = 1.66 (s, 6 H, 2-CH_3), 1.86 (s, 3 H, 3′-CH_3), 2.20 (s, 3 H, 4′-CH_3), 2.33 (s, 3 H, 6′-CH_3), 3.64 (s, 3 H, 5′-OCH_3), 3.82 (s, 3 H, 2′-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 12.41, 12.96, 14.12 ($ArCH_3$), 31.52 (C-1, 2-CH_3), 60.07 (5′-OCH_3), 60.51 (2′-OCH_3), 65.73 (C-2), 77.46 (C-4), 101.3 (C-3), 114.9 (C-1′), 128.2, 131.2, 131.7 (C-3′, C-4′, C-6′), 152.7, 155.4 (C-2′, C-5′). − MS (70 eV); *m*/*z* (%) = 262 (100) [M$^+$], 247 (23) [M$^+$ − CH_3], 231 (20) [M$^+$ − OCH_3], 229 (10) [M$^+$ − CH_3 − H_2O]. − $C_{16}H_{22}O_3$ (262.3): calcd. C 73.25, H 8.45; found C 73.16, H 8.44.

General Procedure II: To a solution of the propargylic alcohol **5a** or **5b** (3.80 mmol) in CH_2Cl_2 (20 mL) were added acetic anhydride (0.8 mL, 8.00 mmol) and PTS (20 mg, 0.1 mmol). The reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (20 mL), washed with satd. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave the enynes **6a** and **6b**.

1,4-Dimethoxy-2,3,5-trimethyl-6-(3-methylbut-3-en-1-ynyl)-benzene (6a): Reaction of **5a** (1.00 g, 3.81 mmol) according to general procedure II gave 860 mg (93%) of the enyne **6a** as a crystalline solid, m.p. 48°C. − IR (KBr): $\tilde{\nu}$ = 3072 cm^{-1} (=CH), 2200 (C≡C), 1642 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 204 nm (4.42), 277 (4.31). − ^{1}H NMR ($CDCl_3$): δ = 2.04 (d, *J* = 1.0 Hz, 3 H, 3′-CH_3), 2.16 (s, 3 H, 2-CH_3), 2.20 (s, 3 H, 3-CH_3), 2.35 (s, 3 H, 5-CH_3), 3.64 (s, 3 H, 4-OCH_3), 3.83 (s, 3 H, 1-OCH_3), 5.28 (q, *J* = 1.0 Hz, 1 H, 4′-H_a), 5.39 (q, *J* = 1.0 Hz, 1 H, 4′-H_b). − ^{13}C NMR ($CDCl_3$): δ = 12.43, 12.99, 14.14 ($ArCH_3$), 23.53 (3′-CH_3), 60.04 (5-OCH_3), 60.53 (2-OCH_3), 84.02 (C-1′), 97.98 (C-2′), 115.4 (C-6), 121.0 (C-4′), 127.3 (C-3′), 128.2, 131.2, 131.7 (C-2, C-3, C-5), 152.7, 155.5 (C-1, C-4). − MS (70 eV); *m*/*z* (%) = 244 (100) [M$^+$], 229 (62) [M$^+$ − CH_3]. − $C_{16}H_{20}O_2$ (244.3): calcd. C 78.65, H 8.25; C 78.53, H 8.37.

General Procedure III: To a stirred ice-cooled suspension of AD-Mix-α [$(DHQ)_2PHAL$] (2.8 g) in *t*BuOH (10 mL) and H_2O (10 mL) was added the enyne **6a** or **6b** (2.00 mmol) and stirring was continued for 48 h at 4°C. After the addition of Na_2SO_3 (3 g) and stirring for 1 h at room temp., the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was removed in vacuo. Chromatographic separation gave the desired diols **7a** and **7b**, respectively.

(*S*)-4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methylbut-3-yne-1,2-diol (7a): Reaction of **6a** (732 mg, 3.00 mmol) according to general procedure III gave 730 mg (93%) of **7a** (84% *ee*) as colourless crystals. The *ee* could be improved to > 99% by recrystallization from *n*-hexane/*tert*-butyl methyl ether; m.p. 87°C. − $[\alpha]_D^{20}$ = +4.7 (*c* = 1.0, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3288 cm^{-1} (OH), 2224 (C≡C). − UV (CH_3CN): λ_{max} (lg ε) = 214 nm (4.56), 249 (4.25), 254 (4.26). − ^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 3 H, 2-CH_3), 2.15 (s, 3 H, 3′-CH_3), 2.19 (s, 3 H, 4′-CH_3), 2.23 (s, 3 H, 6′-CH_3), 2.51 (br. s, 1 H, 1-OH), 2.83 (s, 1 H, 2-OH), 3.58 (d, *J* = 12.0 Hz, 1 H, 1-H_a), 3.63 (s, 3 H, 5′-OCH_3), 3.77 (d, *J* = 12.0 Hz, 1 H, 1-H_b), 3.80 (s, 3 H, 2′-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 12.44, 12.99, 14.18 ($ArCH_3$), 25.24 (2-CH_3), 60.09 (5′-OCH_3), 60.67 (2′-OCH_3), 69.35 (C-2), 71.00 (C-1), 79.80 (C-4), 97.95 (C-3), 114.5 (C-1′), 128.3, 131.3, 132.2 (C-3′, C-4′, C-6′), 152.8, 155.4 (C-2′, C-5′). − MS (70 eV); *m*/*z* (%) = 278 (23) [M$^+$], 247 (100) [M$^+$ − CH_3O]. − $C_{16}H_{22}O_4$ (278.3): calcd. C 69.03, H 7.97; C 68.89, H 7.88.

General Procedure IV: To a solution of the propargylic alcohol **5a**, **5b**, or **13**, or of the propargylic diol **7a** or **28** (1.00 mmol) in MeOH (4 mL) was added PtO_2 (23 mg, 0.10 mmol) and the solution was stirred under hydrogen for 18−24 h (TLC control). After removal

of the catalyst by filtration, the solvent was removed in vacuo and the residue was purified by column chromatography to give the alkenols **32a**, **32b**, **33**, the alcohols **14**, **31a**, and **31b**, and the diols **9**, **30a**, and **30b**, respectively.

(*S*)-4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methylbutane-1,2-diol (9): Reaction of **7a** (73 mg, 0.26 mmol) at a pressure of 3 atm H_2 according to general procedure IV gave 68 mg (93%) of the diol **9** as a crystalline solid; m.p. 42°C. − $[\alpha]_D^{20}$ = +3.4 (*c* = 2.2, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3380 cm^{-1} (OH). − UV (CH_3CN): λ_{max} (lg ε) = 200.5 (4.68). − ^1H NMR ($CDCl_3$): δ = 1.35 (s, 3 H, 2-CH_3), 1.67 (m_s, 3 H, 3-H, 1-OH), 2.17 (s, 6 H, 3′-CH_3, 4′-CH_3), 2.23 (s, 3 H, 6′-CH_3), 2.35 (br. s, 1 H, 2-OH), 2.68 (m_s, 3 H, 4-H), 3.44 (d, *J* = 11.0 Hz, 1 H, 1-H_a), 3.55 (d, *J* = 11.0 Hz, 1 H, 1-H_b), 3.64 (s, 3 H, 5′-OCH_3), 3.71 (s, 3 H, 2′-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 11.96, 12.69, 12.84 ($ArCH_3$), 21.49 (C-3), 23.26 (2-CH_3), 38.66 (C-4), 60.09 (5′-OCH_3), 60.94 (2′-OCH_3), 69.48 (C-2), 72.72 (C-1), 127.1, 128.0, 128.5, 132.0 (C-1′, C-3′, C-4′, C-6′), 152.4, 153.2 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 282 (24) [M^+], 193 (100) [$M^+ - C_4H_7O_2$].

General Procedure V: To a solution of diol **7a** or **9** (2.00 mmol) in CH_2Cl_2 (8 mL) were added methyl isopropenyl ether (0.47 mL, 5.00 mmol) and PPTS (25 mg, 0.1 mmol) and the reaction was monitored by TLC. The solution was then diluted with further CH_2Cl_2 (50 mL), washed with satd. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave the dioxolanes **10** and **11**, respectively.

(*S*)-4-(2,5-Dimethoxy-3,4,6-trimethylphenylethynyl)-2,2,4-trimethyl-[1,3]dioxolane (10): Reaction of **7a** (556 mg, 2.00 mmol) according to general procedure V gave 618 mg (97%) of the dioxolane **10** as a colourless oil. − $[\alpha]_D^{20}$ = +3.3 (*c* = 1.3, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2226 cm^{-1} (C≡C), 1374 [$C(CH_3)_2$]. − UV (CH_3CN): λ_{max} (lg ε) = 214 nm (4.56), 249 (4.27), 259 (4.28), 298 (3.29). − ^1H NMR ($CDCl_3$): δ = 1.45 (s, 3 H, 2-CH_{3a}), 1.60 (s, 3 H, 2-CH_{3b}), 1.70 (s, 3 H, 4-CH_3), 2.16 (s, 3 H, 3′′-CH_3), 2.20 (s, 3 H, 4′′-CH_3), 2.32 (s, 3 H, 6′′-CH_3), 3.32 (s, 3 H, 5′′-OCH_3), 3.81 (s, 3 H, 2′′-OCH_3), 3.92 (d, *J* = 9.0 Hz, 1 H, 1-H_a), 4.32 (d, *J* = 9.0 Hz, 1 H, 1-H_b). − ^{13}C NMR ($CDCl_3$): δ = 12.42, 12.99, 14.15 ($ArCH_3$), 26.15, 27.09 (2-CH_3), 27.02 (4-CH_3), 60.10 (5′′-OCH_3), 60.59 (2′′-OCH_3), 74.45 (C-4), 76.08 (C-5), 79.02 (C-2′), 98.51 (C-1′), 110.7 (C-2), 114.7 (C-1′′), 128.3, 131.4, 131.9 (C-3′′, C-4′′, C-6′′), 152.7, 155.7 (C-2′′, C-5′′). − MS (70 eV); *m/z* (%) = 318 (92) [M^+], 72 (100) [$C_4H_8O^+$]. − $C_{19}H_{26}O_4$ (318.2): calcd. C 71.66, H 8.24; found C 71.50, H 8.18.

(*S*)-4-[2-(2,5-Dimethoxy-3,4,6-trimethylphenyl)ethyl]-2,2,4-trimethyl[1,3]dioxolane (11): Reaction of **9** (135 mg, 0.48 mmol) according to general procedure V gave 147 mg (95%) of the dioxolane **11** as a colourless oil. − $[\alpha]_D^{20}$ = +4.7 (*c* = 1.0, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 1.40 (s, 3 H, 4-CH_3), 1.44 (s, 3 H, 2-CH_{3a}), 1.46 (s, 3 H, 2-CH_{3b}), 1.65 (dt, *J* = 14.0, 7.0 Hz, 1 H, 1′-H_a), 1.78 (dt, *J* = 14.0, 7.0 Hz, 1 H, 1′-H_b), 2.18 (s, 6 H, 3′′-CH_3, 4′′-CH_3), 2.23 (s, 3 H, 6′′-CH_3), 2.69 (m_c, 2 H, 2′-H), 3.65 (s, 3 H, 5′′-OCH_3), 3.69 (s, 3 H, 2′′-OCH_3), 3.78 (d, *J* = 9.0 Hz, 1 H, 1-H_a), 3.89 (d, *J* = 9.0 Hz, 1 H, 1-H_b). − ^{13}C NMR ($CDCl_3$): δ = 11.94, 12.70, 12.84 ($ArCH_3$), 22.27 (C-1′), 24.71 (4-CH_3), 27.11, 27.14 (2-CH_3), 40.26 (C-2′), 60.10 (5′′-OCH_3), 60.89 (2′′-OCH_3), 74.21 (C-5), 81.10 (C-4), 109.2 (C-2), 127.1, 128.0, 128.3, 131.9 (C-1′′, C-3′′, C-4′′, C-6′′), 152.8, 153.1 (C-2′′, C-5′′). − MS (70 eV); *m/z* (%) = 322 (100) [M^+], 193 (56). − $C_{19}H_{30}O_4$ (322.2).

Iododurene (3b): Durene (**2b**) (13.4 g, 0.10 mol), periodic acid dihydrate (4.56 g, 20.0 mmol), and iodine (10.2 g, 40 mmol) were dissolved in a mixture of concd. H_2SO_4 (3 mL), H_2O (20 mL), and glacial acetic acid (100 mL). The solution was heated at 65°C until the purple colour disappeared. H_2O (250 mL) was then added and the solid deposited was collected by filtration. Recrystallization from acetone gave 20.5 g (79%) of **3b** as a crystalline solid. − ^1H NMR ($CDCl_3$): δ = 2.32 (s, 6 H, 3′-CH_3, 5′-CH_3), 2.46 (s, 6 H, 2′-CH_3, 6′-CH_3), 6.89 (s, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$): δ = 21.64 (3′CH_3, 5′-CH_3), 26.59 (2′-CH_3, 6′-CH_3), 111.5 (C-1), 131.4 (C-4), 134.0 (C-3, C-5), 137.5 (C-2, C-6). − $C_{10}H_{13}I$ (260.1).

2-Methyl-4-(2,3,5,6-tetramethylphenyl)-3-butyn-2-ol (5b): Reaction of the iodoarene **3b** (5.20 g, 20.0 mmol) and **4** (2.93 mL, 30.0 mmol) according to general procedure I gave 3.81 g (88%) of the propargylic alcohol **5b** as a crystalline solid; m.p. 100°C. − IR (KBr): $\tilde{\nu}$ = 3352 cm^{-1} (OH), 2978 (CH), 2281 (C≡C). − UV (CH_3CN): λ_{max} (lg ε) = 213 nm (4.62), 246 (4.17), 255 (4.16). − ^1H NMR ($CDCl_3$): δ = 1.66 (s, 6 H, 1-H, 2-CH_3), 2.21 (s, 6 H, 3′-CH_3, 5′-CH_3), 2.34 (s, 6 H, 2-CH_3, 6′-CH_3), 6.90 (s, 1 H, 4′-H). − ^{13}C NMR ($CDCl_3$): δ = 17.50 (2′-CH_3, 6′-CH_3), 19.90 (3′-CH_3, 5′-CH_3), 31.73 (C-1, 2-CH_3), 65.92 (C-2), 80.97 (C-3), 101.4 (C-4), 122.5 (C-1′), 131.2 (C-4′), 133.2 (C-3′, C-5′), 135.8 (C-2′, C-6′). − MS (70 eV); *m/z* (%) = 216 (36) [M^+], 201 (100) [$M^+ - CH_3$]. − $C_{15}H_{20}O$ (216.2): calcd. C 83.29, H 9.32; found C 83.42, H 9.59.

1,2,4,5-Tetramethyl-3-(3-methylbut-3-en-1-ynyl)benzene (6b): Reaction of **5b** (650 mg, 3.00 mmol) according to general procedure II gave 579 mg (98%) of the enyne **6b** as a crystalline solid; m.p. 54°C. − IR (KBr): $\tilde{\nu}$ = 2940, 2920 cm^{-1} (CH), 2194 (C≡C), 1606 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 204 nm (4.41), 211 (4.42), 274 (4.29), 288 (4.20). − ^1H NMR ($CDCl_3$): δ = 2.07 (s, 3 H, 3′-CH_3), 2.24 (s, 6 H, 1-CH_3, 5-CH_3), 2.39 (s, 6 H, 2-CH_3, 4-CH_3), 5.31 (s, 1 H, 4′-H_a), 5.41 (s, 1 H, 4′-H_b), 6.93 (s, 1 H, 6-H). − ^{13}C NMR ($CDCl_3$): δ = 17.52 (2-CH_3, 4-CH_3), 19.91 (1-CH_3, 5-CH_3), 23.70 (3′-CH_3), 87.47 (C-2′), 98.13 (C-1′), 120.6 (C-4′), 123.11 (C-3), 127.4 (C-3′), 131.2 (C-6), 133.2 (C-1, C-5), 135.8 (C-2, C-4). − MS (70 eV); *m/z* (%) = 198 (100) [M^+], 183 (29) [$M^+ - CH_3$]. − $C_{15}H_{18}$ (198.2): calcd. C 90.85, H 9.15; found C 90.91, H 9.17.

2-Methyl-4-(2,3,5,6-tetramethylphenyl)-3-butyne-1,2-diol (7b): Reaction of **6b** (396 mg, 2.00 mmol) according to general procedure III gave 440 mg (95%) of the diol **7b** as a crystalline solid; m.p. 136°C. − $[\alpha]_D^{20}$ = +6.4 (*c* = 2.0, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3352 cm^{-1} (OH), 2974 (CH), 2272 (C≡C). − UV (CH_3CN): λ_{max} (lg ε) = 213 nm (4.62), 246 (4.19), 260 (4.16). − ^1H NMR ($CDCl_3$): δ = 1.60 (s, 3 H, 2-CH_3), 2.10 (dd, *J* = 5.0, 3.3 Hz, 1 H, 1-OH), 2.20 (s, 6 H, 3′-CH_3, 5′-CH_3), 2.36 (s, 6 H, 2′-CH_3, 6′-CH_3), 2.64 (s, 1 H, 2-OH), 3.61 (dd, *J* = 8.0, 5.0 Hz, 1 H, 1-H_a), 3.79 (dd, *J* = 6.0, 3.3 Hz, 1 H, 1-H_b), 6.90 (s, 1 H, 4′-H). − ^{13}C NMR ($CDCl_3$): δ = 17.60 (2′-CH_3, 6′-CH_3), 19.89 (3′-CH_3, 5′-CH_3), 25.61 (2-CH_3), 69.42 (C-2), 71.05 (C-1), 83.43 (C-3), 97.96 (C-4), 122.1 (C-1′), 131.6 (C-4′), 133.4 (C-3′, C-5), 136.0 (C-2′, C-6). − MS (70 eV); *m/z* (%) = 232 (17) [M^+], 201 (100) [$M^+ - OCH_3$]. − $C_{15}H_{20}O_2$ (232.2): calcd. C 77.55, H 8.68; found C 77.45, H 8.74.

3-(3-Methoxy-3-methylbut-1-ynyl)-1,2,4,5-tetramethylbenzene (8): To a solution of the propargylic alcohol **5b** (216 mg, 1.00 mmol) and trimethyl orthoformate (0.27 mL, 2.50 mmol) in dry CH_2Cl_2 (5 mL) was added *p*-toluenesulfonic acid (25 mg, 0.10 mmol) and stirring was continued for 4 h at room temperature. The solution was then diluted with CH_2Cl_2 (10 mL), washed with satd. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 241 mg (93%) of the *O*-methylated product **8** as a crystalline solid; m.p. 58°C. − IR (KBr): $\tilde{\nu}$ = 2984, 2936 cm^{-1} (CH), 2216 (C≡C). − UV (CH_3CN): λ_{max} (lg ε) = 213 nm (4.59), 246 (4.16), 255 (4.14). − ^1H NMR ($CDCl_3$): δ = 1.58 (s, 6 H, 4′-H, 3′-CH_3), 2.21 (s, 6 H, 1-CH_3, 5-CH_3), 2.36 (s, 6 H, 2-CH_3, 4-CH_3), 3.47 (s, 3 H, OCH_3), 6.90 (s, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$): δ = 17.54 (2-CH_3, 4-CH_3), 19.91

(1-CH_3, 5-CH_3), 28.67 (C-4′, 3′-CH_3), 51.80 (C-3′), 83.10 (C-2′), 98.67 (C-1′), 122.8 (C-3), 131.2 (C-6), 133.2 (C-1, C-5), 135.8 (C-4, C-6). − MS (70 eV); *m/z* (%) = 230 (11) [M^+], 215 (100) [$M^+ - CH_3$]. − $C_{16}H_{22}O$ (230.2): calcd. C 83.43, H 9.63; found C 83.32, H 9.57.

4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)but-3-yn-2-ol (13): Reaction of **3a** (306 mg, 1.00 mmol) with **12** (0.09 mL, 1.25 mmol) according to general procedure I gave, after recrystallization from *n*-hexane/*tert*-butyl methyl ether, 166 mg (67%) of the propargylic alcohol **13** as a crystalline solid; m.p. 65°C. − IR (KBr): $\tilde{\nu}$ = 3410 cm^{-1} (OH), 2222 (C≡C). − UV (CH_3CN): λ_{max} (lg ε) = 214 nm (4.55), 249 (4.24), 259 (4.25), 298 (3.31). − ^1H NMR ($CDCl_3$): δ = 1.59 (d, *J* = 7.0 Hz, 3 H, 1-H), 2.09 (d, *J* = 5.0 Hz, 1 H, OH), 2.15 (s, 3 H, 3′-CH_3), 2.18 (s, 3 H, 4′-CH_3), 2.33 (s, 3 H, 6′-CH_3), 3.63 (s, 3 H, 5′-OCH_3), 3.80 (s, 3 H, 2′-OCH_3), 4.83 (dq, *J* = 7.0, 5.0 Hz, 1 H, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 12.41, 12.94, 14.12 ($ArCH_3$), 24.52 (C-1), 58.76 (5′-OCH_3), 60.02 (2′-OCH_3), 60.56 (C-2), 79.01 (C-4), 98.75 (C-3), 114.9 (C-1′), 128.2, 131.3, 131.7 (C-3′, C-4′, C-6′), 152.6, 155.5 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 248 (100) [M^+], 233 (32) [$M^+ - CH_3$], 217 (41) [$M^+ - OCH_3$]. − $C_{15}H_{20}O_3$ (248.2): calcd. C 72.54, H 8.12; found C 72.73, H 8.02.

4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)butan-2-ol (14): Reaction of **13** (248 mg, 1.00 mmol) at a pressure of 3 atm H_2 according to general procedure IV gave 242 mg (96%) of the alcohol **14** as a crystalline solid; m.p. 80°C. − IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1} (OH). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.64). − ^1H NMR ($CDCl_3$): δ = 1.16 (d, *J* = 7.0 Hz, 3 H, 1-H), 1.57−1.65 (m, 2 H, 3-H), 2.17 (s, 3 H, 3′-CH_3, 4′-CH_3), 2.23 (s, 3 H, 6′-CH_3), 2.63−2.87 (m, 2 H, 4-H), 3.55−3.62 (m, 1 H, 2-H), 3.64 (s, 3 H, 5′-OCH_3), 3.68 (s, 3 H, 2′-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 11.46, 12.15, 12.32 ($ArCH_3$), 24.59 (C-1), 22.59 (C-3), 38.72 (C-4), 59.37, 60.32 (OCH_3), 66.25 (C-2), 126.7, 127.1, 127.7, 131.0 (C-1′, C-3′, C-4′, C-6′), 152.2, 152.8 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 252 (100) [M^+], 193 (45), 179 (49). − $C_{15}H_{24}O_3$ (252.2): calcd. C 71.38, H 9.59; found C 71.50, H 9.53.

4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)butan-2-one (15). − Method A: To a solution of alcohol **14** (506 mg, 2.00 mmol) in CH_2Cl_2 (10 mL) at 0°C, a solution of Dess−Martin periodinane (1.10 g, 2.58 mmol) in CH_2Cl_2 (10 mL) was added over a period of 2 h. The solution was subsequently diluted with Et_2O (50 mL) and 1.3 N NaOH was slowly added, which resulted in the formation of a cloudy white suspension. The mixture was stirred at room temperature until it became clear, and was then washed with 1.3 N NaOH (2 × 20 mL) and brine, dried with Na_2SO_4, and concentrated. Chromatographic separation gave 444 mg (89%) of the ketone **15**. − **Method B:** To a stirred solution of the iodoarene **3a** (612 mg, 2.00 mmol), $NaHCO_3$ (184 mg, 2.2 mmol), and tetrabutylammonium chloride (556 mg, 2.00 mmol) in DMF/CH_3CN/H_2O (5:5:1; total volume 2 mL) at 70°C, 3-buten-2-ol (**16**) (0.35 mL, 4.00 mmol) followed by the Herrmann−Beller catalyst (2 mol-%, 938 mg) were added. The temperature was raised to 120°C and stirring was continued for a further 2 h. After cooling, the solution was diluted with Et_2O (10 mL), washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 405 mg (82%) of the coupled product **15** as a crystalline solid. − ^1H NMR ($CDCl_3$): δ = 2.16 (s, 9 H, 1-H, 3′-CH_3, 4′-CH_3), 2.55−2.66 (m, 2 H, 3-H), 2.79−2.92 (m, 2 H, 4-H), 3.62 (s, 3 H, 5′-OCH_3), 3.66 (s, 3 H, 2′-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 12.03, 12.71, 12.80 ($ArCH_3$), 21.47 (C-4), 29.79 (C-1), 43.88 (C-3), 60.09, 60.82 (OCH_3), 127.0, 128.1, 128.7, 130.6 (C-1′, C-3′, C-4′, C-6′), 152.8, 153.1 (C-2′, C-5′), 208.5 (C=O).

(*E*)-4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)but-3-en-2-ol (17): To a stirred mixture of the iodoarene **3a** (630 mg, 2.05 mmol), K_2CO_3 (130 mg, 1.00 mmol), Ag_2CO_3 (298 mg, 1.08 mmol), and $Pd(OAc)_2$ (20 mg, 50 μmol) in degassed DMF (5 mL) was added 3-buten-2-ol (**16**) (0.35 mL, 4.00 mmol) and the mixture was heated at 40°C for 5 h. Then, H_2O (10 mL) was added and the solution was extracted with *tert*-butyl methyl ether (2 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was subjected to column chromatography, which furnished 198 mg (31%) of **17** as a colourless oil. − IR (film): $\tilde{\nu}$ = 3416 cm^{-1} (OH), 1654 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 207 nm (4.47). − ^1H NMR ($CDCl_3$): δ = 1.39 (d, *J* = 7.0 Hz, 3 H, 1-H), 2.16 (s, 3 H, 3′-CH_3), 2.20 (s, 3 H, 4′-CH_3), 2.25 (s, 3 H, 6′-CH_3), 3.59 (s, 3 H, 5′-OCH_3), 3.64 (s, 3 H, 2′-OCH_3), 4.50 (dd, *J* = 7.0, 7.0 Hz, 1 H, 2-H), 5.72 (dd, *J* = 16.0, 7.0 Hz, 1 H, 3-H), 6.57 (d, *J* = 16.0 Hz, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$): δ = 12.49, 12.87, 13.38 ($ArCH_3$), 23.47 (C-1), 59.80 (5′-OCH_3), 60.05 (2′-OCH_3), 69.55 (C-2), 123.6 (C-4), 127.1, 128.1, 128.2, 129.6 (C-1′, C-3′, C-4′, C-6′), 138.8 (C-3), 152.4, 153.0 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 250 (100) [M^+], 235 (14), 193 (47). − $C_{15}H_{22}O_3$ (250.2): calcd. C 71.97, H 8.86; found C 71.99, H 8.76.

1,4-Dimethoxy-2,3,5-trimethyl-6-(3-methylbut-3-enyl)benzene (18). − Method A (Peterson Olefination): To a stirred suspension of potassium hydride (320 mg, 8.00 mmol) in THF (20 mL) was added a solution of the alcohol **19** (676 mg, 2 mmol) in THF (6 mL). After 1.5 h, the mixture was poured into a cold ammonium chloride solution (10%, 50 mL) and covered with a layer of Et_2O (20 mL). The organic layer was subsequently washed with satd. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 420 mg (85%) of the alkene **17**. − **Method B (Wittig Reaction):** Methyltriphenylphosphonium iodide (404 mg, 1.00 mmol) in THF (2 mL) was allowed to react with butyllithium (1.6 M in hexane, 0.66 mL, 1.05 mmol) for 1 h at −78°C and then the mixture was slowly warmed to room temperature. After 20 min, the solution was cooled to −40°C once more and a solution of ketone **15** (250 mg, 1.00 mmol) in THF (2.5 mL) was added dropwise. The resulting mixture was stirred at room temperature; if after 3 h the substrate had not been fully consumed (TLC control, petroleum ether/ethyl acetate, 4:1), the solution was heated for a further 30 min at 45°C. The solvent was then removed in vacuo and the residue was taken up in a mixture of H_2O (10 mL) and pentane (20 mL). The organic layer was washed with satd. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 176 mg (71%) of the alkene **18** as a crystalline solid; m.p. 53°C. − IR (KBr): $\tilde{\nu}$ = 1644 cm^{-1} (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.65). − ^1H NMR ($CDCl_3$): δ = 1.82 (s, 3 H, 3′-CH_3), 2.10−2.21 (m, 2 H, 2′-H), 2.18 (s, 6 H, 2-CH_3, 3-CH_3), 2.23 (s, 3 H, 5-CH_3), 2.68−2.81 (m, 2 H, 1′-H), 3.65 (s, 3 H, 4-OCH_3), 3.70 (s, 3 H, 1-OCH_3), 4.82 (br. s, 2 H, 4′-H). − ^{13}C NMR ($CDCl_3$): δ = 11.84, 12.55, 12.70 ($ArCH_3$), 22.39 (3′-CH_3), 26.07 (C-2′), 38.21 (C-1′), 59.83 (5-OCH_3), 60.75 (2-OCH_3), 109.6 (C-4′), 127.0, 127.7, 128.1, 131.9 (C-1, C-3, C-4, C-6), 145.9 (C-3′), 152.7, 152.9 (C-2, C-5). − MS (70 eV); *m/z* (%) = 248 (37) [M^+], 193 (100). − $C_{16}H_{24}O_2$ (248.2): calcd. C 77.38, H 9.74; found C 77.11, H 9.61.

4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methyl-1-trimethylsilylbutan-2-ol (19): Magnesium turnings (486 mg, 20.0 mmol) in Et_2O (6 mL) were activated with iodine and chloromethyltrimethylsilane (one tenth of 2.78 mL, 20.0 mmol) under stirring. Once the reaction had started, the remaining chloromethyltrimethylsilane in Et_2O (8 mL) was added dropwise. After stirring for 30 min at room temperature, a solution of ketone **15** (2.50 g, 10.0 mmol) in 8 mL Et_2O was added and the resulting mixture was heated to reflux for

2 h. The solution was then cooled, diluted with *tert*-butyl methyl ether (30 mL), and hydrolysed with satd. ammonium chloride solution. The organic layer was washed with satd. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 2.63 g (78%) of the silylated alcohol **19** as a colourless oil. − IR (film): $\tilde{\nu}$ = 3470 cm^{-1} (OH). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.71). − ^1H NMR ($CDCl_3$): δ = 0.07 [s, 9 H, $Si(CH_3)_3$], 1.04 (s, 2 H, 1-H), 1.29 (s, 3 H, 2-CH_3), 1.59−1.68 (m, 2 H, 3-H), 2.16 (s, 6 H, 3′-CH_3, 4′-CH_3), 2.21 (s, 3 H, 6′-CH_3), 2.77 (m_c, 2 H, 4-H), 3.63 (s, 3 H, 5′-OCH_3), 3.67 (s, 3 H, 2′-OCH_3). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.46 ($SiCH_3$), 11.96, 12.60, 12.77 ($ArCH_3$), 21.97 (C-3), 26.90 (2-CH_3), 32.19 (C-1), 45.42 (C-4), 59.94 (5′-OCH_3), 60.76 (2′-OCH_3), 73.35 (C-2), 127.0, 127.8, 128.0, 132.2 (C-1′, C-3′, C-4′, C-6′), 152.5, 153.0 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 338 (61) [M^+], 320 (25), 193 (100). − $C_{19}H_{34}O_3Si$ (338.2): calcd. 338.2277; found 338.2277 (HRMS).

Methyl(*E*)-5-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methyl-2-pentenoate (20): To a solution of trimethyl phosphonoacetate (0.17 mL, 1.20 mmol) in THF (2 mL) at 0°C was added lithium hexamethyldisilazide (1 M in THF, 1.2 mL) and the mixture was stirred for 30 min. After the addition of a solution of ketone **15** (250 mg, 1.00 mmol) in THF (2 mL), the mixture was heated at 45°C for 3 h. The solution was subsequently diluted with Et_2O (20 mL), washed with H_2O (20 mL) and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 254 mg of the α,β-unsaturated ester **20** [83% pure (*E*) product] as a crystalline solid. − IR (KBr): $\tilde{\nu}$ = 1720 cm^{-1} (C=O), 1648 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.68). − ^1H NMR ($CDCl_3$): δ = 2.17 (s, 6 H, 3′-CH_3, 3-CH_3), 2.21 (s, 3 H, 4′-CH_3), 2.23−2.33 (m, 2 H, 4-H), 2.25 (s, 3 H, 6′-CH_3), 2.72−2.78 (m, 2 H, 5-H), 3.64 (s, 3 H, 5′-OCH_3), 3.67 (s, 3 H, 2′-OCH_3), 3.70 (s, 3 H, OCH_3), 5.76 (s, 1 H, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 11.67, 12.35, 12.50 ($ArCH_3$), 18.54 (3-CH_3), 25.64 (C-4), 41.02 (C-5), 50.36 (CO-O*C*H_3), 59.62 (5′-OCH_3), 60.48 (2′-OCH_3), 114.8 (C-3), 126.7, 127.7, 128.3, 130.6 (C-1′, C-3′, C-4′, C-6′), 152.5, 152.8 (C-2′, C-5′), 159.8 (C-2), 166.8 (C=O). − MS (70 eV); *m/z* (%) = 306 (42) [M^+], 193 (100). − $C_{18}H_{26}O_4$ (306.2): calcd. C 70.56, H 8.55; found C 70.47, H 8.49.

(*E*)-5-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methylpent-2-en-1-ol (21): To a solution of the α,β-unsaturated ester **20** in THF (4 mL) at 0°C was added DIBAH (1 M in hexane, 2.0 mL) and stirring was continued at room temperature for 6 h. The mixture was then diluted with *tert*-butyl methyl ether (20 mL) and H_2O (20 mL) and titrated with 2 N HCl until the formed aluminium hydroxide redissolved. The organic layer was washed with H_2O (2 × 20 mL) and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 238 mg (93%) of the allylic alcohol **21** as a crystalline solid. − IR (KBr): $\tilde{\nu}$ = 3416 cm^{-1} (OH), 1654 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 207 nm (4.47). − ^1H NMR ($CDCl_3$): δ = 1.78 (s, 3 H, 3-CH_3), 2.15−2.20 (m, 2 H, 4-CH_2), 2.17 (s, 6 H, 3′-CH_3, 4′-CH_3), 2,23 (s, 3 H, 6′-CH_3), 2.68−2.75 (m, 2 H, 5-CH_2), 3.64 (s, 3 H, 5′-OCH_3), 3.68 (s, 3 H, 2′-OCH_3), 4.17 (dd, *J* = 7.0, 4.5 Hz, 2 H, 1-CH_2), 5.46 (t, *J* = 7.0, 1 H, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 12.49, 12.87, 13.38 ($ArCH_3$), 23.47 (C-1), 59.80, 60.05 (OCH_3), 69.55 (C-2), 123.6 (C-3), 127.1, 128.1, 128.2, 129.6 (C-1′, C-3′, C-4′, C-6′), 138.8 (C-2), 152.4, 153.0 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 250 (100) [M^+], 235 (14), 193 (47). − $C_{17}H_{26}O_3$ (278.2): calcd. C 73.35, H 9.41; found C 73.20, H 9.38.

(3*S*,1′*R*,2′*R*)-1-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methyl-3-(1′-phenyl-2′-trifluoroacetamido-1′-propyloxy)hex-5-ene (25): To a stirred solution of ketone **15** (1.00 g, 4.00 mmol), (*R*,*R*)-2-trifluoroacetylamino-1-trimethylsilyloxy-1-phenylpropane (**24**) (620 mg, 2.00 mmol), and allyltrimethylsilane (456 mg, 4.00 mmol) in CH_2Cl_2 (8 mL) at −78°C was added either a 1:1 mixture of TfOH (20 μL, 0.2 mmol) and TMSOTf (36 μL, 0.2 mmol) or pure TfOH (40 μL, 0.4 mmol) and stirring was continued at this temperature. After quenching the reaction by the addition of triethylamine (320 μL), the mixture was poured into water (20 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. Chromatographic purification of the residue gave 554 mg of the homoallylic ether **25** (53%) as a colourless oil. The diastereoselectivity was estimated to be 9:1 (^{13}C NMR). − $[\alpha]_D^{20}$ = −28.0 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3318 cm^{-1} (NH), 1720 (C=O), 1638 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 191 nm (4.86). − ^1H NMR ($CDCl_3$): δ = 0.98 (s, 3 H, 3-CH_3), 1.26 (d, *J* = 7.0 Hz, 3 H, 3′-H), 1.56−1.73 (m, 2 H, 2-H), 2.17 (s, 9 H, 3′′-CH_3, 4′′-CH_3, 6′′-CH_3), 2.46 (d, *J* = 7.0 Hz, 2 H, 4-H), 2.61−2.82 (m, 2 H, 1-H), 3.63 (s, 3 H, 5′′-OCH_3), 3.65 (s, 3 H, 2′′-OCH_3), 4.08−4.21 (m, 1 H, 2-H), 4.67 (d, *J* = 4.5 Hz, 1 H, 1′-H), 5.10−5.21 (m, 2 H, 6-H), 5.88 (ddd, *J* = 16.5, 10.0, 7.0 Hz, 1 H, 5-H), 6.50 (br. d, *J* = 8.0 Hz, 1 H, NH), 7.22−7.34 (m, 5 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = 11.86, 12.71, 12.86 ($ArCH_3$), 17.63 (C-3′), 21.59 (3-CH_3), 23.63 (C-2), 40.37 (C-1), 43.00 (C-4), 51.91 (C-2′), 60.07 (5′′-OCH_3), 60.87 (2′′-OCH_3), 74.26 (C-1′), 78.84 (C-3), 115.5 (q, $^1J_{CF}$ = 288 Hz, CF_3), 126.5 (C-6), 127.1, 127.7, 127.9, 128.3, 131.9, 132.0 (C-1′′, C-3′′, C-4′′, C-6′′, Ph-C-2,6), 134.0 (C-5), 141.5 (Ph-C-1), 152.8, 153.0 (C-2′′, C-5′′), 156.4 (q, $^2J_{CF}$ = 39 Hz, C=O). − MS (70 eV); *m/z* (%) = 521 (31) [M^+], 230 (35), 193 (100). − $C_{29}H_{38}F_3NO_4$ (521.3): calcd. 521.2752; found 521.2752 (HRMS).

1-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methylhex-5-en-3-ol (26): To a stirred solution of sodium (60 mg, 2.60 mmol) in liquid ammonia (100 mL) at −78°C was slowly added the homoallylic ether **25** (240 mg, 0.46 mmol). Stirring was continued for 25 min at this temperature and then solid ammonium chloride was added in small portions until the blue colour disappeared. After evaporation of the ammonia, the residue was taken up in *tert*-butyl methyl ether (50 mL). The organic layer was washed with H_2O (2 × 20 mL), satd. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatographic purification gave 126 mg (94%) of the homoallylic alcohol **26** as a colourless solid; m.p. 39°C. − $[\alpha]_D^{20}$ = +6.0 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3438 cm^{-1} (OH), 1640 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.60). − ^1H NMR ($CDCl_3$): δ = 1.26 (s, 3 H, 3-CH_3), 1.55−1.68 (m, 2 H, 2-H), 2.16 (s, 6 H, 3′-CH_3, 4′-CH_3), 2.19 (s, 3 H, 6′-CH_3), 2.30 (d, *J* = 7 Hz, 2 H, 4-H), 2.64−2.77 (m, 2 H, 1-H), 3.64 (s, 3 H, 5′-OCH_3), 3.77 (s, 3 H, 2′-OCH_3), 5.07−5.19 (m, 2 H, 6-H), 5.81−6.02 (m, 1 H, 5-H). − ^{13}C NMR ($CDCl_3$): δ = 11.85, 12.56, 12.71 ($ArCH_3$), 21.52 (C-2), 26.43 (3-CH_3), 41.59 (C-1), 46.28 (C-4), 59.89 (5′-OCH_3), 60.75 (2′-OCH_3), 71.97 (C-3), 118.3 (C-6), 127.0, 127.7, 128.1, 132.0 (C-1′, C-3′, C-4′, C-6′), 134.1 (C-5), 152.5, 152.9 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 292 (28) [M^+], 193 (100). − $C_{18}H_{28}O_3$ (292.2): calcd. C 73.93, H 9.65; found C 73.69, H 9.52.

(3*S*,1′*R*,2′*R*)-1-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-3-methyl-3-(1′-phenyl-2′-trifluoroacetamido-1′-propyloxy)-1-pentanal (27): Ozone was bubbled through a solution of **25** (250 mg, 0.48 mmol) in CH_2Cl_2 (15 mL) at −78°C until a blue colour persisted. After purging with nitrogen, triphenylphosphane (177 mg, 0.68 mmol) was added and stirring was continued at this temperature for 30 min. The mixture was slowly allowed to warm to room temperature and then concentrated in vacuo. The residue was purified by column chromatography to give 219 mg (87%) of the aldehyde **27** as

a colourless oil. − $[\alpha]_D^{20}$ = +1.4 (*c* = 0.5, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3308 cm^{-1} (NH), 1708 (C=O), 1670 (C=O), 1670 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 199 nm (4.71). − ^1H NMR ($CDCl_3$): δ = 1.18 (d, *J* = 7.0 Hz, 3 H, 3′-H), 1.23 (s, 3 H, 3-CH_3), 1.56−1.75 (dd, *J* = 6.5, 6.5 Hz, 2 H, 4-H), 2.10 (s, 3 H, 3′′-CH_3), 2.16 (s, 3 H, 4′′-CH_3), 2.17 (s, 3 H, 6′′-CH_3), 2.57−2.71 (m, 2 H, 5-H), 2.76 (d, *J* = 2.5 Hz, 2 H, 2-H), 3.62 (s, 3 H, 5′′-OCH_3), 3.63 (s, 3 H, 2′′-OCH_3), 4.14−4.21 (m, 1 H, 2′-H), 4.69 (d, *J* = 5.0 Hz, 1 H, 1′-H), 6.42 (br. d, *J* = 8.0 Hz, 1 H, NH), 7.22−7.34 (m, 5 H, arom. H), 9.90 (d, *J* = 2.5 Hz, 1 H, 1-H). − ^{13}C NMR ($CDCl_3$): δ = 11.85, 12.70, 12.85 ($ArCH_3$), 16.25 (C-3′), 21.90 (3-CH_3), 24.31 (C-4), 40.98 (C-5), 51.56 (C-2), 51.79 (C-2′), 60.07 (5′′-OCH_3), 60.81 (2′′-OCH_3), 74.87 (C-1′), 78.35 (C-3), 115.8 (q, $^1J_{CF}$ = 287 Hz, CF_3), 126.7, 126.8, 127.0, 128.1, 128.5, 128.6, 131.1 (C-1′′, C-3′′, C-4′′, C-6′′, Ph-C-2,6), 140.4 (Ph-C-1), 152.8, 153.1 (C-2′′, C-5′′), 156.4 (q, $^2J_{CF}$ = 39 Hz, C=O), 210.7 (C=O). − MS (70 eV); *m*/*z* (%) = 523 (45) [M^+], 193 (100). − $C_{28}H_{36}F_3NO_5$ (523.5): calcd. 523.2545; found 523.2545 (HRMS).

(2*S*,3*S*)-1-Cyclohexylmethyloxy-5-(2,5-dimethoxy-3,4,6-trimethylphenyl)-3-methylpentane-2,3-diol (30a): Reaction of **28** (190 mg, 0.48 mmol) in methanol at a pressure of 3 atm H_2 according to general procedure IV gave 123 mg (63%) of the alkenol **30a** as a white solid; m.p. 85°C. − $[\alpha]_D^{20}$ = −4.0 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3384 cm^{-1} (OH), 2934 (CH). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.69). − ^1H NMR ($CDCl_3$): δ = 0.87−1.02, 1.13−1.27, 1.61−1.79 (3 m, 12 H, 4-CH_2, 2′′-H, 3′′-H, 4′′-H, 5′′-H, 6′′-H), 1.27 (s, 3 H, 3-CH_3), 2.16 (s, 6 H, 3′-CH_3, 4′-CH_3), 2.23 (s, 3 H, 6′-CH_3), 2.64−2.73 (m_c, 2 H, 5-CH_2), 2.81 (d, *J* = 6.0 Hz, 1 H, 2-OH), 2.98 (s, 1 H, 3-OH), 3.22−3.33 (dd, *J* = 7.0, 7.0 Hz, 2 H, cyclohexyl-CH_2), 3.58−3.68 (m, 3 H, 1-H, 2-H), 3.63 (s, 3 H, 5′-OCH_3), 3.69 (s, 3 H, 2′-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 11.94, 12.68, 12.83 (3′-CH_3, 4′-CH_3, 6′-CH_3), 21.46 (C-5), 22.32 (3-CH_3), 25.84 (C-3′′, C-5′′), 26.57 (C-4′), 30.05 (C-2′′, C-6′′), 38.01 (C-1′′), 39.19 (C-4), 60.05 (5′-OCH_3), 60.96 (2′-OCH_3), 72.21 (C-1), 73.80 (C-3), 74.03 (C-2), 77.68 (cyclohexyl-CH_2), 127.3, 127.9, 128.9, 132.2 (C-1′, C-3′, C-4′, C-6′), 152.9 (C-5′), 153.2 (C-2′). − MS (70 eV); *m*/*z* (%) = 408 (12) [M^+], 251 (41) [$M^+ - C_9H_{17}O_2$], 193 (100) [$C_{12}H_{17}O_2$]. − $C_{24}H_{40}O_5$ (408.3): calcd. C 70.55, H 9.87; found C 70.75, H 9.76.

(2*S*,3*S*)-1-Cyclohexylmethyloxy-5-(2,5-dimethoxy-3,4,6-trimethylphenyl)-3-methylpent-4-ene-2,3-diol (30b): As a by-product of the above reaction, 25 mg (13%) of the alkenol **30b** was obtained as a colourless oil. − $[\alpha]_D^{20}$ = −36.0 (*c* = 1.0, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3452 cm^{-1} (OH). − UV (CH_3CN): λ_{max} (lg ε) = 202 (4.50). − ^1H NMR ($CDCl_3$): δ = 0.86−1.36, 1.53−1.76 (2 m, 9 H, cyclohexyl-H), 1.56 (s, 3 H, 3-CH_3), 2.16 (s, 3 H, 3′-CH_3), 2.17 (s, 3 H, 4′-CH_3), 2.19 (s, 3 H, 6′-CH_3), 3.06 (br. s, 1 H, 2-H), 3.23 (br. s, 2 H, cyclohexyl-CH_2), 3.62 (s, 3 H, 5′-OCH_3), 3.64 (s, 3 H, 2′-OCH_3), 4.18 (br. s, 2 H, 1-H) 5.92 (br. s, 1 H, 5-H), 6.24 (d, *J* = 12.0 Hz, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$): δ = 12.6, 12.7 13.4 ($ArCH_3$), 23.5 (br. s, 3-CH_3), 25.8, 26.5, 30.0 (C-2′′, C-3′′, C-4′′, C-5′′, C-6′′), 37.9 (C-1′′), 59.8, 60.0 (OCH_3), 72.0 (br. s, C-3), 72.2 (br. s, C-2), 77.3 (cyclohexyl-CH_2), 124.1 (C-5), 126.9, 127.9, 129.2, 129.6 (C-1′, C-3′, C-4′, C-6′), 136.9 (C-4), 149.7 (C-2′), 153.1 (C-5′). − MS (70 eV); *m*/*z* (%) = 406 (3), 249 (100). − $C_{24}H_{38}O_5$ (406.2): calcd. 406.2719; found 406.2719 (HRMS).

4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methylbutan-2-ol (31a): Reaction of **5a** (65 mg, 0.25 mmol) at a pressure of 3 atm H_2 according to general procedure IV gave 60 mg (91%) of the alcohol **31a** as a crystalline solid; m.p. 55°C. − IR (KBr): $\tilde{\nu}$ = 3444 cm^{-1} (OH), 1088 (aryl ether). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.63). − ^1H NMR ($CDCl_3$): δ = 1.29 (s, 6 H, 1-H, 2-CH_3), 1.64 (t, *J* = 7.0 Hz, 2 H, 3-H), 2.17 (s, 6 H, 3′-CH_3, 4′-CH_3), 2.20 (s, 3 H, 6′-CH_3), 2.71 (t, *J* = 7.0 Hz, 2 H, 4-H), 3.64 (s, 3 H, 5′-OCH_3), 3.70 (s, 3 H, 2′-OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 11.95, 12.68, 12.81 ($ArCH_3$), 22.05 (C-3), 29.09 (C-1, 2-CH_3), 43.80 (C-4), 60.03 (5′-OCH_3), 60.88 (2′-OCH_3), 70.97 (C-2), 127.1, 127.9, 128.2, 132.2 (C-1′, C-3′, C-4′, C-6′), 152.6, 153.1 (C-2′, C-5′). − MS (70 eV); *m*/*z* (%) = 266 (100) [M^+], 248 (34), 233 (41). − $C_{16}H_{26}O_3$ (266.3): calcd. C 72.14, H 9.84; found C 72.27, H 9.76.

2-Methyl-4-(2,3,5,6-tetramethylphenyl)-3-butan-2-ol (31b): Reaction of **5b** (108 mg, 0.50 mmol) at a pressure of 3 atm H_2 according to general procedure IV gave 100 mg (97%) of the alcohol **31b** as a crystalline solid; m.p. 112°C. − IR (KBr): $\tilde{\nu}$ = 3365cm^{-1} (OH). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.68). − ^1H NMR ($CDCl_3$): δ = 1.21 (s, 6 H, 1-H, 2-CH_3), 1.65 (s, 1 H, OH), 2.17 (s, 6 H, 3′-CH_3, 5′-CH_3), 2.20 (s, 6 H, 2′-CH_3, 6′-CH_3), 5.77 (d, *J* = 12.5 Hz, 1 H, 3-H), 6.27 (d, *J* = 12.5 Hz, 1 H, 4-H), 6.88 (s, 1 H, 4′-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.12 (2′-CH_3, 6′-CH_3), 20.46 (3′-CH_3, 5′-CH_3), 24.88 (C-3), 28.97 (C-1, 2-CH_3), 43.09 (C-4), 70.91 (C-2), 129.3 (C-4′), 131.8 (C-3′, C-5), 133.6 (C-2′, C-6), 138.4 (C-1′). − MS (70 eV); *m*/*z* (%) = 220 (43) [M^+], 202 (21), 146 (100). − $C_{15}H_{24}O$ (220.2): calcd. C 81.76, H 10.98; found C 81.65, H 10.99.

(*Z*)-4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methyl-3-buten-2-ol (32a): Reaction of **5a** (65 mg, 0.25 mmol) in ethyl acetate at a pressure of 1 atm H_2 according to general procedure IV gave 63 mg (95%) of the alkenol **32a** as a crystalline solid; m.p. 63°C. − IR (KBr): $\tilde{\nu}$ = 3280 cm^{-1} (OH), 1088 (aryl ether). − UV (CH_3CN): λ_{max} (lg ε) = 205 nm (4.51). − ^1H NMR ($C_2D_2Cl_4$): δ = 1.18 (s, 6 H, 1-H, 2-CH_3), 2.10 (s, 3 H, 3′-CH_3), 2.13 (s, 3 H, 4′-CH_3), 2.16 (s, 3 H, 6′-CH_3), 3.61 (s, 3 H, 5′-OCH_3), 3.63 (s, 3 H, 2′-OCH_3), 5.81 (d, *J* = 10.0 Hz, 1 H, 3-H), 6.12 (d, *J* = 10.0 Hz, 1 H, 4-H). − ^{13}C NMR ($C_2D_2Cl_4$): δ = 12.57, 12.74, 13.42 ($ArCH_3$), 29.92 (C-1, 2-CH_3), 59.74 (5′-OCH_3), 59.94 (2′-OCH_3), 70.81 (C-2), 122.0 (C-3), 126.9, 128.0, 129.5, 129.6 (C-1′, C-3′, C-4′, C-6′), 140.2 (C-4), 150.6, 153.4 (C-2′, C-5′). − MS (70 eV); *m*/*z* (%) = 264 (100) [M^+], 249 (42). − $C_{16}H_{24}O_3$ (264.3): calcd. C 72.69, H 9.15; found C 72.45, H 8.94.

2-Methyl-4-(2,3,5,6-tetramethylphenyl)-3-buten-2-ol (32b): Reaction of **5b** (216 mg, 1.00 mmol) in ethyl acetate at a pressure of 1 atm H_2 according to general procedure IV gave 192 mg (87%) of the alcohol **32b** as a crystalline solid; m.p. 65°C. − IR (KBr): $\tilde{\nu}$ = 3276 cm^{-1} (OH), 1646 (C=C), 1602 (arom. C=C). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.54). − ^1H NMR ($CDCl_3$): δ = 1.21 (s, 6 H, 1-H, 2-CH_3), 1.65 (s, 1 H, OH), 2.17 (s, 6 H, 3′-CH_3, 5′-CH_3), 2.20 (s, 6 H, 2′-CH_3, 6′-CH_3), 5.77 (d, *J* = 12.5 Hz, 1 H, 3-H), 6.27 (d, *J* = 12.5 Hz, 1 H, 4-H), 6.88 (s, 1 H, 4′-H). − ^{13}C NMR ($CDCl_3$): δ = 17.22 (2′-CH_3, 6′-CH_3), 20.03 (3′-CH_3, 5′-CH_3), 29.78 (C-1, 2-CH_3), 72.48 (C-2), 125.9 (C-4), 130.3 (C-4′), 131.3 (C-3′, C-5), 133.5 (C-2′, C-6), 136.2 (C-1′), 138.3 (C-3). − MS (70 eV); *m*/*z* (%) = 218 (28) [M^+], 203 (42), 185 (100). − $C_{15}H_{22}O$ (218.2): calcd. C 82.52, H 10.16; found C 82.67, H 10.13.

(*Z*)-4-(2,5-Dimethoxy-3,4,6-trimethylphenyl)but-3-en-2-ol [(±)-33)]: Reaction of **13** (372 mg, 1.50 mmol) in ethyl acetate at a pressure of 1 atm H_2 according to general procedure IV gave 352 mg (94%) of the alkenol **33** as a crystalline solid; m.p. 66°C. − IR (KBr): $\tilde{\nu}$ = 3406 cm^{-1} (OH), 1658 (C=C). − UV (CH_3CN): λ_{max} (lg ε) = 207 nm (4.47). − ^1H NMR ($CDCl_3$): δ = 1.19 (d, *J* = 7.0 Hz, 3 H, 1-H), 2.12 (s, 6 H, 3′-CH_3), 2.19 (s, 3 H, 4′-CH_3), 2.22 (s, 3 H, 6′-CH_3), 3.41 (br. s, 1 H, OH), 3.56 (s, 3 H, 5′-OCH_3), 3.66 (s, 3 H, 2′-OCH_3), 4.08−4.19 (m, 1 H, 2-H), 5.72 (dd, *J* = 11.8, 9.1 Hz, 1 H, 3-H), 6.27 (d, *J* = 11.8 Hz, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$): δ = 12.30, 12.43, 12.86 ($ArCH_3$), 21.85 (C-1), 59.63 (5′-OCH_3),

64.17 (2′-OCH_3), 64.17 (C-2), 123.99 (C-3), 127.0, 127.6, 127.8, 129.4 (C-1′, C-3′, C-4′, C-6′), 137.1 (C-4), 151.0, 152.7 (C-2′, C-5′). − MS (70 eV); *m/z* (%) = 250 (100) [M^+], 235 (26), 193 (42). − $C_{15}H_{22}O_3$ (250.2): calcd. C 71.97, H 8.86; found C 71.99, H 8.81.

Acknowledgments

This work was supported by the state of Lower Saxony, the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 416), and the Fonds der Chemischen Industrie. We thank the BASF AG and Degussa AG for generous gifts of chemicals.

[1] [1a] L. J. Machlin, "Vitamin E" in *Handbook of Vitamins*, 2nd ed. (Ed.: L. J. Machlin), Marcel Dekker Inc., New York, **1991**, p. 99−144. − [1b] G. W. Burton, K. U. Ingold, *J. Am. Chem. Soc.* **1981**, *103*, 6472−6477.
[2] T. Netscher, *Chimia* **1996**, *50*, 563−567.
[3] [3a] E. Mizugushi, T. Suzuki, K. Achiwa, *Synlett* **1994**, 929−930. − [3b] N. Cohen, J. W. Scott, F. T. Bizzaro, R. J. Lopresti, W. F. Eichel, G. Saucy, *Helv. Chim. Acta* **1978**, *61*, 837−843. − [3c] J. W. Scott, F. T. Bizzaro, D. R. Parrish, G. Saucy, *Helv. Chim. Acta* **1976**, *59*, 290−306. − [3d] J. A. Hyatt, C. Skelton, *Tetrahedron: Asymmetry* **1997**, *8*, 523−526.
[4] [4a] J. Hübscher, R. Barner, *Helv. Chim. Acta* **1990**, *73*, 1068−1086. − [4b] Y. Sakito, G. Suzukamo, *Tetrahedron Lett.* **1982**, *23*, 4953−4954.
[5] [5a] R. Barner, M. Schmid, *Helv. Chim. Acta* **1979**, *62*, 2384−2399. − [5b] N. Cohen, R. J. Lopresti, G. Saucy, *J. Am. Chem. Soc.* **1979**, *101*, 6710−6716.
[6] [6a] L. F. Tietze, J. Görlitzer, *Synthesis* **1998**, 873−878. − [6b] L. F. Tietze, J. Görlitzer, *Liebigs Ann.* **1997**, 2221−2225. − [6c] L. F. Tietze, J. Görlitzer, *Synlett* **1997**, 1049−1050. − [6d] L. F. Tietze, J. Görlitzer, *Synthesis* **1997**, 873−878. − [6e] L. F. Tietze, J. Görlitzer, *Synlett* **1996**, 1041−1042. − [6f] E. Mizuguchi, K. Achiwa, *Synlett* **1995**, 1255−1056. − [6g] S. Takano, T. Sugihara, K. Ogasawara, *Synlett* **1990**, 451−452. − [6h] K. Takabe, K. Okisaka, Y. Uchiyama, T. Katagiri, H. Yoda, *Chem. Lett.* **1985**, 561−562.
[7] [7a] D. W. Nelson, A. Gypser, P. T. Ho, H. C. Kolb, T. Kondo, H.-L. Kwong, D. V. McGrath, A. E. Rubin, P.-O. Norrby, K. P. Gable, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 1840−1858. − [7b] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483−2547.
[8] [8a] L. F. Tietze, K. Schiemann, C. Wegner, *J. Am. Chem. Soc.* **1995**, *117*, 5851−5852. − [8b] L. F. Tietze, K. Schiemann, C. Wegner, C. Wulff, *Chem. Eur. J.* **1996**, *2*, 1164−1172. − [8c] L. F. Tietze, C. Wegner, C. Wulff, *Synlett* **1996**, 471−472. − [8d] L. F. Tietze, C. Wulff, C. Wegner, A. Schuffenhauer, K. Schiemann, *J. Am. Chem. Soc.* **1998**, *120*, 4276−4280. − [8e] L. F. Tietze, C. Wegner, C. Wulff, *Eur. J. Org. Chem.* **1998**, 1639−1644.
[9] H. Suzuki, *Org. Synth. Coll. Vol.* **1988**, *6*, 700−701.
[10] [10a] K. Sonogashira, Y. Thoda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467−4470. − [10b] R. Rossi, A. Carpita, F. Bellina, *Org. Prep. Proc. Int.* **1995**, *27*, 127−160.
[11] E. M. Burgess, H. R. Penton Jr., E. A. Taylor, *J. Org. Chem.* **1973**, *38*, 26−31.
[12] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543−2549.
[13] [13a] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4156−4159. − [13b] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. − [13c] R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899−2903.
[14] W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T. H. Riermeier, K. Öfele, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357−1364.
[15] [15a] C. Lilibris, B. Resul, U. Hacksell, *Tetrahedron* **1995**, *51*, 9139−9154. − [15b] J.-M. Gaudin, *Tetrahedron Lett.* **1991**, *32*, 6113−6116.
[16] L. F. Tietze, J. Görlitzer, unpublished results.
[17] D. J. Ager, *Synthesis* **1984**, 384−398.
[18] L. F. Tietze, A. Schuffenhauer, J. Görlitzer, unpublished results.
[19] See, for example: [19a] H.-S. Byun, E. R. Kumar, R. Bittman, *J. Org. Chem.* **1994**, *59*, 2630−2633. − [19b] C. Vilcheze, R. Bittman *J. Lipid Res.* **1994**, *35*, 734−738. − [19c] E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1995**, *117*, 10805−10816. − [19d] E. J. Corey, A. Guzman-Perez, M. Noe, *Tetrahedron Lett.* **1995**, *36*, 3481−3484.
[20] Z.-M. Wang, X.-L. Zhang, K. B. Sharpless, *Tetrahedron Lett.* **1993**, *34*, 2267−2270.
[21] [21a] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115−136. − [21b] U. Beifuss, L. F. Tietze, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131−170.
[22] [22a] I. Petterson, U. Berg, *J. Chem. Res (S)* **1984**, 208−209. − [22b] J. E. Anderson, *Tetrahedron* **1987**, *43*, 3041−3046. − [22c] C. S. C. Yang, R. S. H. Liu, *Tetrahedron Lett.* **1973**, *14*, 4811−4814. − [22d] J. E. Anderson, D. J. D. Barkel, C. J. Cooksey, *Tetrahedron Lett.* **1983**, *24*, 1077−1080.
[23] [23a] D. S. Stephenson, G. Binsch, *J. Magn. Reson.* **1978**, *32*, 145−152. − [23b] D. S. Stephenson, G. Binsch, *Quantum Chem. Progr. Exch.* **1978**, *11*, 365.
[24] G. Binsch, H. Kessler, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 411−428.
[25] [25a] The PM3 calculations were performed with a PC using a 32-bit version of the program package MOPAC 6.0 by J. J. P. Stewart, **1990**. − [25b] J. J. P. Stewart, *J. Comp. Chem.* **1989**, *10*, 108.

Received September 24, 1998
[O98434]