Complementary diastereoselectivity in the intermolecular addition of titanium and magnesium naphtholates to asymmetric lactaldehydes

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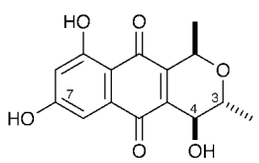
Addition of 7-benzyloxy-4,5-dimethoxy-1-naphthol **3** as its triisopropoxytitanium naphtholate to (2*R*, 1′*R* or *S*)-2-(1′-ethoxyethoxy)propanal **4** afforded solely (1*S*, 2*R*, 1″*R* or *S*)-1-(7′-benzyloxy-4′,5′-dimethoxy-1′-hydroxy-2′-naphthyl)-2-(1″-ethoxyethoxy)propan-1-ol **5**, being the *erythro* product arising from *anti* addition. Complementary reaction of the naphthol **3** as its bromomagnesium naphtholate with aldehyde **4** gave rise solely to the alternative (1*R*, 2*R*, 1″*R* or *S*) diastereomer **6** . The naphthol **3** was prepared through the completely regioselective addition of 2-methoxyfuran **9** to 5-benzyloxy-3-methoxydehydrobenzene **8**. This differentially protected bisalkoxybenzyne was conveniently prepared from vanillin.

We have previously reported[1] the synthesis in racemic form of the aphid pigment derivatives, quinone A **1** and quinone A′ **2**.[2]



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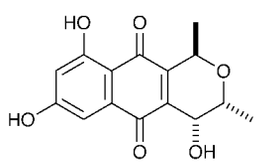

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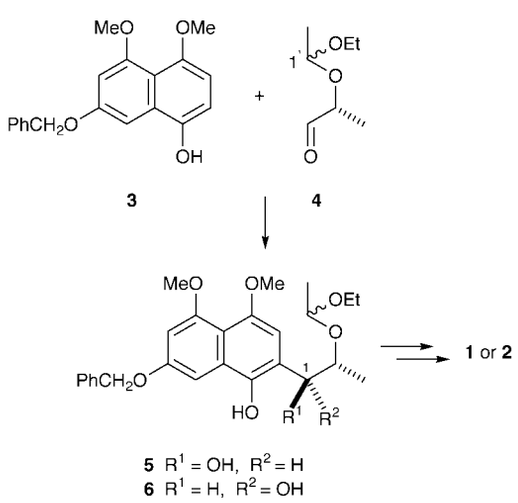
Among naturally occurring naphthopyranquinones,[3] these compounds are unusual in that the substituents at C-3 and C-4 are *trans* in the former and *cis* in the latter. In considering routes to asymmetric **1** and **2**, we recognised the potential of the discovery of Casiraghi and co-workers[4] that complementary highly diastereoselective C-arylations of asymmetric aldehydes can be achieved with the use of either titanium or magnesium phenolates. Since we have previously shown in the racemic syntheses of **1** and **2** that benzyl and methyl are convenient protecting groups for the phenolic oxygens at O-7 and O-9, respectively, the syntheses shown in Scheme 1 were considered.



5 R^1 = OH, R^2 = H
6 R^1 = H, R^2 = OH

Scheme 1

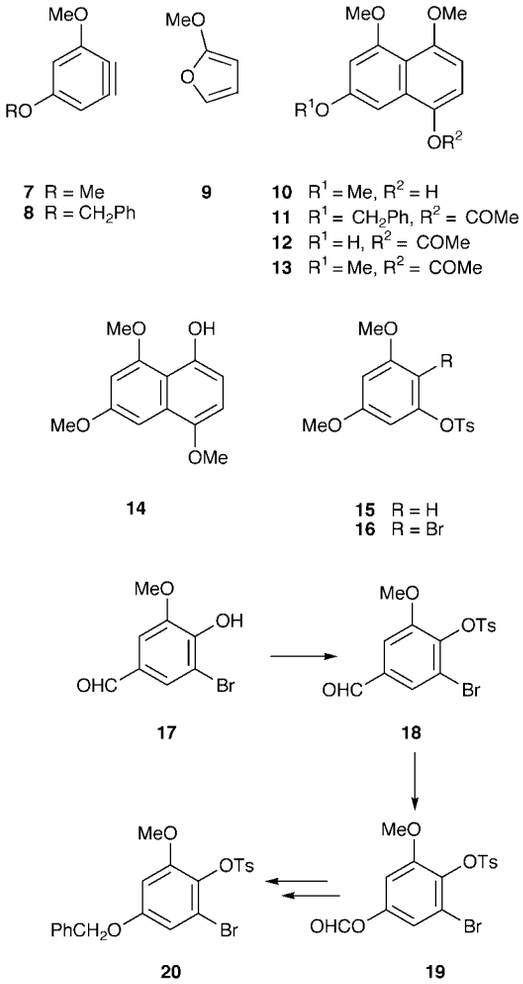
Alternative use of the titanium and magnesium naphtholates of **3** with the lactaldehyde derivative **4** would afford the products **5** and **6** of *anti* and *syn* addition respectively. Appropriate protection of the free hydroxy groups in **5** and **6**, followed by a Lewis acid-catalysed Mukaiyama reaction[5] of the aryl ether and acetal functions to achieve ring closure, should afford the asymmetric naphthopyran system. This type of cyclisation is related to methods used earlier for the formation of the racemates of the less highly substituted naphthopyranquinones eleutherin and isoeleutherin.[6] Standard manipulation of the individual diastereomers would then afford the asymmetric quinones **1** and **2**. This paper describes syntheses of the naphthol **3** and the aldehyde **4** and the completely diastereoselective reactions of this aldehyde with the titanium and magnesium naphtholates of **3** to form the respective individual adducts **5** and **6**.[7] In model studies, the C-2 epimeric aldehyde **35** reacted similarly with the respective naphtholates of the alternative naphthol **10** to afford the adducts **37** and **39** with analogous complete diastereoselectivity.[7]

Results and discussion

We have previously shown that 3,5-dimethoxybenzyne **7** adds to 2-methoxyfuran **9** to afford the two regioisomers, 4,5,7-trimethoxy-1-naphthol **10** and 4,6,8-trimethoxy-1-naphthol **14**, in a high combined yield (77%).[8] Importantly, the reaction was highly regioselective, giving the products **10** and **14** in a ratio of 10:1. For the monobenzyl analogue **3** of **10**, it was necessary to generate the differently protected 5-benzyloxy-3-methoxybenzyne **8** for use in a related reaction with 2-methoxyfuran.

Synthesis of precursors to 5-benzyloxy-3-methoxybenzyne 8

The generation of benzyne **7** had been simplified by the ready preparation of bromo tosylate **16** from the symmetrical tosylate **15**.[8] For unsymmetrical analogues, the related regioselective bromination could not be achieved in the desired sense.[9] Recognising the potential offered by the framework of the commercially available starting material vanillin, a five step route to the bromo tosylate **20** was investigated (Scheme 2). Vanillin was smoothly converted into 5-bromovanillin **17**,[10] from which the corresponding tosylate **18** was formed in high yield. Attempts to carry out the Baeyer–Villiger oxidation on

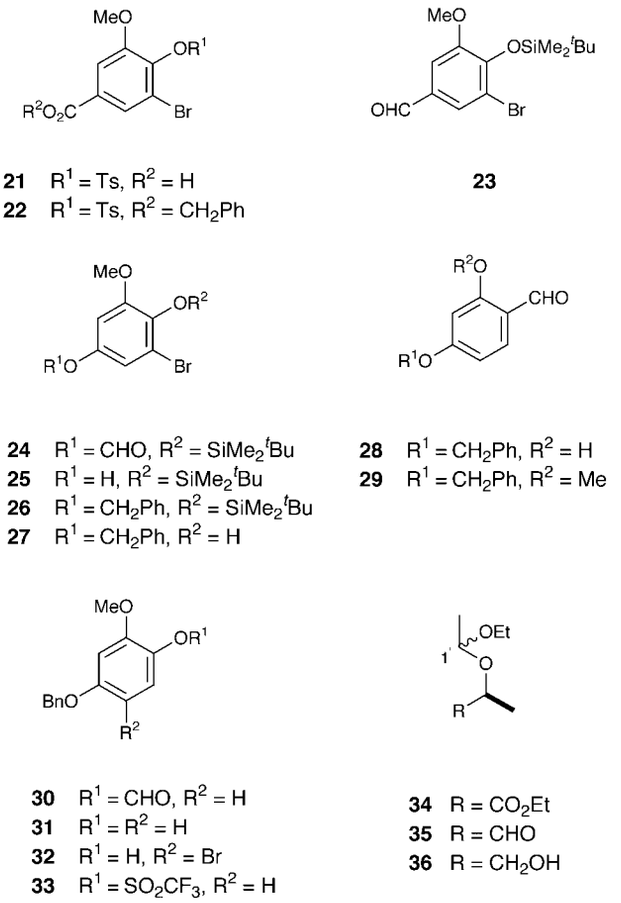


Scheme 2

tosylate **18** gave the acid **21**, characterised as its benzyl ester **22**, through migration of the hydride,[11] and related reactions occurred for the corresponding acetate and benzoate. Changing to a more electron donating silyl protecting group provided the *tert*-butyldimethylsilyl ether **23**, Baeyer–Villiger oxidation of which gave the desired formate **24**. The structural assignment was supported *inter alia* by the chemical shifts at δ 6.61 and 6.93 (J 2.6 Hz) of the two *meta*-coupled protons *ortho* to the formate substituent in the ^{1}H NMR spectrum, as well as the characteristic singlet at δ 8.25 for the formate proton. The corresponding aromatic resonances for the benzyl ester **22** were δ 7.56 and 7.87.

Since *tert*-butyldimethylsilyl ethers are stable to potassium carbonate in methanol,[12] the formate **24** was allowed to react under these conditions with the subsequent addition of benzyl bromide in a one pot reaction, affording the desired benzyl ether **26** together with the intermediate phenol **25**. The yields of the products **26** and **25** were 64 and 26%, respectively, and thus the desired benzyl ether **26** was obtained in a yield of 88% based on consumed phenol **25**. Furthermore, this phenol was recycled to increase the quantity of the required **26**.

Replacement of the silyl protecting group in **26** with tosyl was also best achieved in a one pot reaction. The silyl ether **26** was treated with tetra-*n*-butylammonium fluoride in tetrahydrofuran, with subsequent addition of tosyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene. This procedure furnished the required crystalline bromo tosylate **20** in a yield of 89%, which is an improvement over the yield for a two step procedure involving the isolation of intermediate phenol **27**. Thus, the bromo tosylate **20** was synthesised in four steps from the known and readily available 5-bromovanillin **17** in an overall yield of 59%.



The aryl triflate **33** was also investigated as a precursor to the benzyne **8** on the basis of a report[13] that aryl triflates react with lithium diisopropylamide to form intermediate benzynes. Aldehyde **29** was regarded as an appropriate precursor to triflate **33**, and this was obtained through methylation of the known[14] salicylaldehyde **28**. Baeyer–Villiger oxidation of the aldehyde **29** with *meta*-chloroperbenzoic acid gave the formate **30**, the product of aryl migration. The crude formate, which showed *inter alia* a characteristic resonance at δ 8.12 in its ^{1}H NMR spectrum for the formate proton, was hydrolysed to the corresponding phenol **31** using methanolic potassium hydroxide. The phenol **31** was prepared in a yield of 60% over the five steps from 2,4-dihydroxybenzaldehyde, the starting material for salicylaldehyde **28**, which is a significant improvement on literature methods[15,16] from a commercially available starting material.

The monobromination of phenol **31** was investigated in the hope that this might be achieved *ortho* to the phenolic substituent, as this would provide an alternative route, after tosylation, to the previously prepared bromo tosylate **20**. Methods[17,18] for exclusive *ortho* bromination of phenols gave mixtures with **31**. Bromination in glacial acetic acid containing sodium acetate provided the *meta*-bromophenol **32** in a yield of 60%. The structure **32** was assigned on the basis of the ^{1}H NMR spectrum, which showed the two *para* aromatic protons as two singlets at δ 6.48 and 7.07, whereas for the isomeric *ortho*-bromophenol **27** mentioned above, the two *meta* aromatic protons appeared as two doublets (J 2.7 Hz) at δ 6.51 and 6.69.

The phenol **31** was then converted into the triflate **33** in high yield. This triflate was therefore available in six simple steps from commercially available 2,4-dihydroxybenzaldehyde in an overall yield of 55%.

Regioselective Diels–Alder additions

Generation of the required 5-benzyloxy-3-methoxybenzyne **8** in the presence of 2-methoxyfuran **9** was then investigated. Thus,

a solution of the bromo tosylate **20** and 2-methoxyfuran **9** in dry tetrahydrofuran at −78 °C was treated with *n*-butyllithium. Acid-induced ring-opening of the derived adduct afforded the naphthol **3** as a single regioisomer. Since this naphthol **3** was unstable on standing, it was stored as the stable acetate **11**, isolated in a yield of 46%, or 56% based on consumed starting material **20**.

The triflate **33** was then examined as an alternative source of the desired benzyne **8**. A cooled (−78 °C) solution of lithium diisopropylamide in tetrahydrofuran was added to a mixture of the triflate **33** and 2-methoxyfuran **9** in the same solvent at the same temperature. The derived naphthol **3** was converted into its acetate **11**, which was obtained in an optimised yield of 32% over the two steps from triflate **33**. The use of *n*-butyllithium in place of lithium diisopropylamide reduced the overall yield of **11** to 11%.

Confirmation of the regiochemistry of the cycloaddition reaction to form naphthol **3** was obtained through hydrogenolysis of the benzyl ether **11** to form the naphthol **12**, which was in turn methylated to form the known trimethoxynaphthyl acetate **13**.[19]

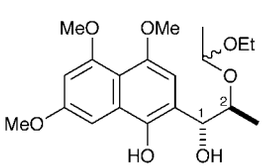
The acetate **11** was reconverted into the naphthol **3** by reduction with lithium aluminium hydride immediately prior to its use in diastereoselective additions.

Diastereoselective additions of asymmetric aldehydes to naphthols

In preliminary investigations into the proposed diastereoselective additions of the aldehyde **4** to the naphthol **3** to afford the complementary adducts **5** or **6** (Scheme 1), use was made of the C-2 epimeric aldehyde **35** and the more readily accessible naphthol **10**.[8] The protected lactaldehyde **35** was obtained from commercially available (*S*)-ethyl lactate, which is cheaper than esters of the enantiomeric (*R*)-lactate.

Protection of the (*S*)-lactate with ethyl vinyl ether afforded the ester **34** as a mixture of C-1′ diastereomers.[20]† Reduction of this mixture with diisobutylaluminium hydride afforded predominantly the aldehyde **35**[21] as a 55:45 mixture of C-1′ diastereomers, together with some of the diastereomeric alcohols **36**, which did not interfere with the subsequent reactions.

With some modifications to the literature method,[4b] the aldehyde **35** was added to a toluene solution of the triisopropoxytitanium naphtholate of **10** with the application of ultrasonic irradiation. The required product **37** was obtained with complete diastereoselectivity at the newly formed asymmetric centre C-1, in a yield of 63%. This product was an inseparable mixture of diastereomers at the acetal carbon.



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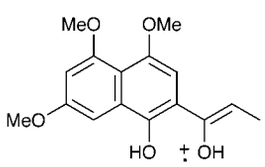

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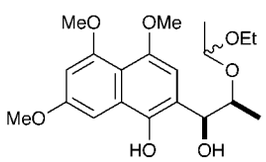

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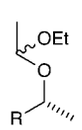


40 R = CO_2Me
41 R = CH_2OH

The mass spectrum of compound **37** gave a molecular ion at *m*/*z* 380 and a fragment ion **38** at *m*/*z* 290. In the ^{1}H NMR spectrum of **37**, the major and minor diastereomers showed vicinal coupling constants between the protons 1-H and 2-H of 4.3 and 4.0 Hz, respectively, and the corresponding 1-H chemical shifts were δ 4.86 and 4.94. A comparison of these with the related data for the two diastereomers of **39** (*vide infra*) showed the compounds **37** to have smaller coupling constants and lower field chemical shifts than those observed for compounds **39**.[4b,24] These values confirmed an *anti* arrangement of the two hetero atoms at C-1 and C-2 in **37**, *i.e.*, compound **37** was the *erythro* diastereomer.

Use of the alternative magnesium naphtholate[4b] of **10** with the same aldehyde **35**, once again under ultrasonication, afforded the complementary *threo* product **39**, *i.e.*, the product of solely *syn* addition. In this case, the yield was 73% and the mixture of diastereomers at the acetal carbon was separable by chromatography. The ^{1}H NMR spectra showed vicinal coupling between 1-H and 2-H for the major and minor diastereomers as 7.8 and 8.5 Hz, for which the 1-H chemical shifts were δ 4.57 and 4.56. These larger coupling constants and higher field chemical shifts were diagnostic[4b,24] of a C-1/C-2 *threo* arrangement for the adduct.

In the complementary reactions of the titanium and magnesium naphtholates of **10** with aldehyde **35**, each process was shown to be completely diastereoselective since neither **37** nor **39** could be detected in the ^{1}H NMR spectrum of the other crude product.

The success of these model reactions encouraged the investigation of the related diastereoselective reactions proposed in Scheme 1 which would provide the correct absolute stereochemistry for, and ultimately the total synthesis of, asymmetric quinones A **1** and A′ **2**.

In a series of transformations related to the conversion of (*S*)-ethyl lactate into the diastereomeric aldehydes **35** above, the more expensive (*R*)-methyl lactate was similarly transformed, *via* its ethoxyethyl derivative **40**, into the aldehyde **4**, contaminated with some alcohol **41**, both as mixtures of diastereomers at the acetal carbon. Reaction of the triisopropoxytitanium naphtholate of **3** with the aldehyde **4** under ultrasonication led to the isolation of the *erythro* product **5** in an unoptimised yield of 43%. Once again, it was not possible to separate the mixture of diastereomeric acetals. Confirmation that arylation of the aldehyde had proceeded in the *anti* mode was provided by the ^{1}H NMR spectrum of adduct **5**, in which the chemical shifts of 1-H for the major and minor diastereomers were δ 4.92 and 4.98, with respective 1-H–2-H coupling constants of 4.1 and 3.7 Hz. These chemical shifts were downfield of the corresponding signals for the C-1 epimer **6** (*vide infra*) and the coupling constants were smaller. Both these factors are once again diagnostic[4b,24] of *anti* diastereoselectivity for the product **5**.

Alternative addition of the bromomagnesium naphtholate of **3** to the aldehyde **4** with ultrasonication afforded only the *threo* adduct **6** in a yield of 78%. In this instance, the individual diastereomers of **6** (~1:1) arising from the ethoxyethyl protecting group were separated by chromatography. In the ^{1}H NMR spectra, the vicinal coupling constants (8.5 and 8.0 Hz) were again larger and the chemical shifts (δ 4.57 and 4.58 respectively) were further upfield than for the corresponding diastereomers of adduct **5**. These data confirmed **6** as the products of *syn* addition.

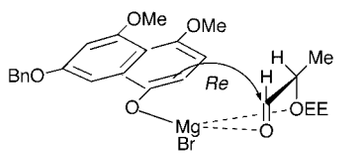
Once again, the use of the complementary titanium and magnesium naphtholates of **3** with the aldehyde **4** was completely diastereoselective, leading to the *anti* and *syn* adducts, **5** and **6**, respectively. The absence of the product **6** in the titanium-mediated reaction and the alternative product **5** in the magnesium-mediated reaction was confirmed by the lack of the diagnostic 1-H signals of the alternative diastereomer in the ^{1}H NMR spectrum of each product.

The mechanistic aspects of this process of diastereoselective

† Since the resolution achieved in our ^{1}H and ^{13}C NMR spectra was far superior to that previously reported,[21–23] the details of these spectra are provided in the Experimental section.

arylation of asymmetric α-alkoxy aldehydes by metal phenolates have been discussed in some depth in the literature.[4b,c,25–27] The phenolates of certain coordinating metals are known to possess the advantages of being Lewis acids and of providing an activated nucleophilic aromatic ring with a reactive *ortho*-carbon.[4b,27] This allows the direct regioselective arylation of carbonyl electrophiles, with the metal ion involved determining the stereoselectivity with respect to the neighbouring chiral centre.

When the metal ion is capable of bis-ligation with the aldehydic reactant, *i.e.*, it is capable of chelation with both the aldehydic oxygen and the α-oxygen of the reactant, a double-chelate "Cram cyclic" transition-state pertains.[4c,25] This is the case with the highly oxygenophilic MgBr ion in the magnesium naphtholate of **3** leading to a transition state **42** with the aldehyde **4**,



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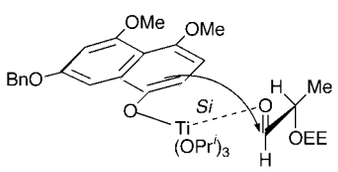

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where the *Si* face of the aldehyde is shielded by the methyl group and nucleophilic attack occurs solely from the *Re* face resulting in the 1,2-*syn* product **6**.

To achieve the alternative 1,2-*anti* selectivity, a metal ion incapable of additional chelation to the α-oxygen, in this case titanium, must be used, and reaction then occurs *via* a non-cyclic "Felkin–Anh" transition state **43**,[4c,25] where steric and/or electronic factors predominate. In this complex, the *Re* face is shielded by the methyl substituent and arylation occurs solely from the *Si* face, leading to the 1,2-*anti* product **5** of non-chelation control.

Conclusions

The bromo tosylate **20** was synthesised in four steps from the known 5-bromovanillin **17** in an overall yield of 59%. The naphthyl acetate **11** was derived from the bromo tosylate **20** in a reasonable yield of 46% (approximately 56% based on consumed **20**). Preparation of the aryl triflate **33** required six steps from commercially available 2,4-dihydroxybenzaldehyde and proceeded in an overall yield of 55%. By contrast, the best yield of the naphthyl acetate **11** produced from the aryl triflate **33** was 32%. Of the two methods investigated, the synthetic route of choice for the preparation of the naphthyl acetate **11**, from aspects of both overall yield and number of synthetic steps, is from vanillin *via* the bromo tosylate **20**. Whereas the formation of the naphthol **10** from the bromo tosylate **16** also produced the regioisomer **14** in low yield,[8] the naphthol **3** was the only regioisomer isolated from either the bromo tosylate **20** or the triflate **33**.

Complete and complementary diastereoselectivity can be achieved in the addition of naphthol **3** to aldehyde **4** through the appropriate choice of metal as the naphtholate counterion. Thus, the reactions of the titanium naphtholates of **3** and **10** with the aldehydes **4** and **35** separately afforded the *anti* 1,2-addition products **5** and **37** as the sole adducts. Conversely, the complementary magnesium naphtholates of **3** and **10** with the same aldehydes respectively formed the corresponding diastereomers **6** and **39** of *syn* 1,2-addition as the sole adducts.

Corresponding intramolecular diastereoselective control is discussed in the accompanying paper.[28]

Experimental

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity PolAAr 2001 polarimeter for chloroform solutions of *c* 1.0 at 20 °C unless otherwise stated and are given in 10^{-1} deg cm^2 g^{-1}. The ultrasonication bath used was a Branson B3200-E4, operating at a frequency of 44–50 kHz. GC analyses employed a Hewlett Packard 5790A Series Gas Chromatograph, with flame ionization detection. Electron impact mass spectra were obtained on a Hewlett Packard 5986 spectrometer or on a Perkin-Elmer ITD Ion Trap Detector spectrometer. High resolution mass spectra were measured on an AEI MS 902 high resolution mass spectrometer. NMR spectra were recorded using a Hitachi R-24B spectrometer (^{1}H, 60 MHz), a Bruker AM-300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz) or a Bruker ARX-500 spectrometer (^{1}H, 500 MHz; ^{13}C, 126 MHz). Unless otherwise stated, all spectra of purified products were measured on the Bruker AM-300 spectrometer in [^{2}H]chloroform with tetramethylsilane as internal reference. *J* Values are given in Hz. In the ^{13}C NMR spectra, assignments of signals with the same superscripts are interchangeable. Normal work-up (A) refers to extraction with an organic solvent, then washing of the organic extracts with aqueous hydrochloric acid (1 M), water, saturated aqueous sodium hydrogen carbonate solution, water and brine. Normal work-up (B) refers to addition of an organic solvent and water, removal of the water layer and the organic layer was then washed with water and brine. In each case, the organic phase was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Hexane refers to the hydrocarbon fraction with bp 65–70 °C. Column chromatography was performed on Merck silica gel 60 (70–230 mesh) and rapid filtration chromatography on Fluka silica gel 60 (230 mesh). Preadsorption was carried out on Merck silica gel 60 (35–70 mesh). The adsorbent for radial chromatography was Merck silica gel 60 PF_{254}.

2-Bromo-4-formyl-6-methoxyphenyl toluene-*p*-sulfonate 18

A stirred solution of 5-bromovanillin **17**[10] (1.00 g, 4.33 mmol) and triethylamine (0.90 cm^3, 6.5 mmol) in dry tetrahydrofuran (22 cm^3) was treated portionwise at 0 °C with tosyl chloride (0.91 g, 4.8 mmol). After 26 h at room temperature, water was added and the mixture stirred (1 h). Extraction into ether was followed by washing of the organic layers with aqueous sodium hydroxide (1 M), water and brine, drying and evaporation under reduced pressure to yield a yellow solid (1.58 g). This was preadsorbed on silica gel and then subjected to rapid filtration through a plug of silica gel (gradient elution: 20 and 50% ethyl acetate–hexane) to provide the tosylate **18** as a yellow solid (1.37 g, 82%). Recrystallisation from methylene chloride–hexane gave needles, mp 118–9 °C (Found: C, 46.8; H, 3.1. $C_{15}H_{13}BrO_5S$ requires C, 46.8; H, 3.4%); ν_{max}/cm^{-1} 1701 (C=O), 1593, 1576 and 1470 (C=C); δ_H 2.49 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 7.38 (1H, d, *J* 1.8, 5-H), 7.38 and 7.89 (4H, AA′BB′, ArH), 7.67 (1H, d, *J* 1.8, 3-H) and 9.88 (1H, s, CHO); δ_C 21.7 (CH_3), 56.2 (OCH_3), 110.2 (C-5), 119.2 (C-2), 128.0 (C-3), 128.4 (C-2′ and C-6′),[a] 129.5 (C-3′ and C-5′),[a] 134.5 (C-4), 135.5 (C-4′),[b] 142.1 (C-1), 145.4 (C-1′),[b] 154.0 (C-6) and 189.54 (CHO); *m*/*z* 386 (M$^+$ {^{81}Br}, 4%), 384 (M$^+$ {^{79}Br}, 4), 231 (5), 229 (5), 155 (100), 91 (91) and 65 (17).

Benzyl 3-bromo-5-methoxy-4-(*p*-tolylsulfonyloxy)benzoate 22

A solution of the tosyl aldehyde **18** (250 mg, 0.65 mmol) and *m*-chloroperbenzoic acid (231 mg of 85%, 1.14 mmol) in methylene chloride (passed through basic alumina before use) (5 cm^3) was heated under reflux (4 h). During this time, a

sample was removed and concentrated, the ^{1}H NMR spectrum (60 MHz) of which showed approximately 30% of starting material remained (by integration of the aldehydic proton) with signals for *m*-chloroperbenzoic acid and *m*-chlorobenzoic acid obscuring some regions of the spectrum. The reaction mixture was then concentrated and the residue dissolved in ethyl acetate. The organic solution was washed a number of times with saturated sodium hydrogen carbonate solution and then brine, and dried and concentrated to a yellow solid (150 mg). The crude product (142 mg) was dissolved in dry *N*,*N*-dimethylformamide (4 cm^3) and an excess of benzyl bromide (0.091 cm^3, 0.76 mmol) and anhydrous potassium carbonate (105 mg, 0.76 mmol) added with stirring under nitrogen. After 17 h, thin layer chromatography (TLC) indicated consumption of the lower R_f component of the initial crude product, the continued presence of the tosyl aldehyde **18** and a new, higher R_f product. The reaction mixture was then quenched with water and normal work-up (A) with ether yielded an orange oil (201 mg). This oil was preadsorbed on silica gel and subjected to rapid filtration through a plug of silica gel (20% ethyl acetate–hexane), from which the higher R_f product **22** was obtained as an orange oil (114 mg, 36%‡ over two steps). Further gradient elution column chromatography of this oil with 10 and 20% ethyl acetate–hexane as eluent gave an oil (Found: M$^+$, 490.0086. $C_{22}H_{19}{}^{79}BrO_6S$ requires M, 490.0086); ν_{max} (film)/cm^{-1} 1724 (C=O), 1596, 1497 and 1463 (C=C); δ_H 2.47 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 5.36 (2H, s, OCH_2), 7.33–7.45 (5H, m, C_6H_5), 7.39 and 7.88 (4H, AA′BB′, ArH), 7.56 (1H, d, *J* 1.9, 6-H) and 7.87 (1H, d, *J* 1.9, 2-H); δ_C 21.7 (CH_3), 56.3 (OCH_3), 67.4 (OCH_2), 112.8 (C-6), 118.4 (C-3), 126.5 (C-2), 128.4 (C-2′ and C-6′),[a] 128.5 (C-3′ and C-5′),[a] 128.5 (C-4′), 128.7 (C-2″ and C-6″),[a] 129.5 (C-3″ and C-5″),[a] 129.9 (C-1), 134.7 (C-1′), 135.5 (C-4″),[b] 141.0 (C-4), 145.3 (C-1″),[b] 153.5 (C-5) and 164.5 (C=O); *m*/*z* 492 (M$^+$ {^{81}Br}, 1%), 490 (M$^+$ {^{79}Br}, 1), 337 (2), 335 (2), 230 (1), 228 (2), 203 (3), 201 (3), 155 (7) and 91 (100).

3-Bromo-4-(*tert*-butyldimethylsilyloxy)-5-methoxybenzaldehyde 23

Solid *tert*-butylchlorodimethylsilane (3.79 g, 25.2 mmol) was added to a stirred solution of 5-bromovanillin **17** (4.00 g, 17.3 mmol) and imidazole (2.90 g, 42.5 mmol) in dry *N*,*N*-dimethylformamide (100 cm^3) under argon. After 4 h, the reaction mixture was poured into water and extracted with ether. The organic extracts were washed with water and brine, dried and concentrated to an orange oil (6.57 g). Filtration through a pad of silica gel with 20% ethyl acetate–hexane as eluent afforded the silyl ether **23** as a yellow oil (5.33 g, 89%). A portion of this was subjected to a further chromatographic separation with 10% ethyl acetate–hexane to give a yellow oil which crystallised and was then recrystallised from methanol to furnish plates, mp 58–59.5 °C (Found: C, 48.3; H, 6.0. $C_{14}H_{21}BrO_3Si$ requires C, 48.7; H, 6.1%); ν_{max}/cm^{-1} 1687 (C=O), 1586, 1567, 1489 and 1462 (C=C); δ_H 0.23 (6H, s, $SiCH_3$), 1.02 (9H, s, CCH_3), 3.85 (3H, s, OCH_3), 7.31 (1H, d, *J* 1.9, 6-H), 7.62 (1H, d, *J* 1.9, 2-H) and 9.76 (1H, s, CHO); δ_C −3.8 ($SiCH_3$), 18.9 (CCH_3), 25.8 (CCH_3), 55.3 (OCH_3), 108.7 (C-6), 115.3 (C-3), 129.6 (C-2), 130.3 (C-1), 148.6 (C-4), 151.3 (C-5) and 189.7 (CHO); *m*/*z* 289 [(M − ^{t}Bu) {^{81}Br}, 97%], 287 [(M − ^{t}Bu) {^{79}Br}, 100], 274 (80), 273 (44), 272 (80), 271 (32), 245 (4), 243 (6), 73 (19) and 59 (14).

3-Bromo-4-(*tert*-butyldimethylsilyloxy)-5-methoxyphenyl formate 24

A solution of the silyl ether **23** (4.77 g, 13.8 mmol) and *m*-chloroperbenzoic acid (4.39 g, 20.4 mmol) in methylene chloride (100 cm^3) was heated under reflux (2 h) and then left overnight at room temperature. The progress of the reaction at this point was observed by ^{1}H NMR spectroscopy (60 MHz) of a concentrated sample which showed complete consumption of the aldehydic starting material and a singlet at δ 8.15 indicative of a formate proton. The reaction mixture was therefore worked-up as described for the Baeyer–Villiger rearrangement of **18** to give an orange oil (4.81 g, 96%) of the formate **24**; ν_{max} (film)/cm^{-1} 1744 (C=O), 1585 and 1491 (C=C); δ_H 0.21 (6H, s, $SiCH_3$), 1.03 (9H, s, CCH_3), 3.78 (3H, s, OCH_3), 6.61 (1H, d, *J* 2.6, 6-H), 6.93 (1H, d, *J* 2.6, 2-H) and 8.25 (1H, s, OCHO); δ_C −3.9 ($SiCH_3$), 18.8 (CCH_3), 25.9 (CCH_3), 55.3 (OCH_3), 104.5 (C-6), 114.7 (C-3), 117.0 (C-2), 143.2 (C-1), 147.2 (C-4), 151.0 (C-5) and 159.2 (OCHO); *m*/*z* 305 [(M − ^{t}Bu) {^{81}Br}, 84%], 303 [(M − ^{t}Bu) {^{79}Br}, 79], 290 (45), 288 (46), 262 (100), 260 (99), 247 (21), 245 (22), 89 (18), 73 (45), 59 (15) and 57 (14).

5-Benzyloxy-1-bromo-2-(*tert*-butyldimethylsilyloxy)-3-methoxybenzene 26

Potassium carbonate (1.28 g, 9.31 mmol) was added to a stirred solution of the formate **24** (3.36 g, 9.31 mmol) in methanol (70 cm^3) under nitrogen. After 10 min, the wine-red solution was examined by TLC, which showed complete consumption of the formate **24** and production of a lower R_f spot. Therefore, after 20 min, benzyl bromide (1.67 cm^3, 14.0 mmol) was added. After 6 h, the reaction mixture was reduced in volume, water added and the solution acidified with aqueous hydrochloric acid (1 M). It was extracted with ether and the ether extracts treated as in normal work-up (B) to give a red oil (3.99 g). Gradient elution dry column chromatography with 2 to 80% ethyl acetate–hexane as eluents gave the title compound **26** as an oil (2.53 g, 64% basic yield, 88% yield based on consumed phenol **25**), further purified by dry column chromatography with 5% ethyl acetate–hexane and distillation to produce an oil, bp 160 °C/0.025 mmHg (Kugelrohr) (Found: C, 57.1; H, 6.8. $C_{20}H_{27}BrO_3Si$ requires C, 56.7; H, 6.4%); ν_{max} (film)/cm^{-1} 1602, 1572, 1491 and 1468 (C=C); δ_H 0.21 (6H, s, $SiCH_3$), 1.05 (9H, s, CCH_3), 3.76 (3H, s, OCH_3), 4.97 (2H, s, OCH_2), 6.50 (1H, d, *J* 2.9, 4-H), 6.74 (1H, d, *J* 2.9, 6-H) and 7.31–7.46 (5H, m, C_6H_5); δ_C −3.9 ($SiCH_3$), 18.9 (CCH_3), 26.0 (CCH_3), 55.2 (OCH_3), 70.7 (OCH_2), 100.2 (C-4), 109.0 (C-6), 114.8 (C-1), 127.7 (C-2′ and C-6′),[a] 128.1 (C-4′), 128.6 (C-3′ and C-5′),[a] 136.6 (C-1′),[b] 137.2 (C-2),[b] 151.5 (C-5)[c] and 153.2 (C-3);[c] *m*/*z* 424 (M$^+$ {^{81}Br}, 0.3%), 422 (M$^+$ {^{79}Br}, 0.3), 367 (13), 365 (13), 352 (7), 350 (6), 271 (8), 91 (100) and 73 (50). This was followed by 3-bromo-4-(*tert*-butyldimethylsilyloxy)-5-methoxyphenol **25** as a red oil (0.81 g, 26% yield from the formate **24**), further purified by column chromatography (10 and 20% ethyl acetate–hexane) to provide a red oil, still containing some trace impurities; ν_{max} (film)/cm^{-1} 3416 (OH), 1605, 1587 and 1493 (C=C); δ_H 0.16 (6H, s, $SiCH_3$), 1.00 (9H, s, CCH_3), 3.73 (3H, s, OCH_3), 4.81 (1H, br s, OH), 6.34 (1H, d, *J* 2.8, 6-H) and 6.56 (1H, d, *J* 2.8, 2-H); δ_C −3.9 ($SiCH_3$), 18.9 (CCH_3), 26.0 (CCH_3), 55.2 (OCH_3), 99.6 (C-6), 110.7 (C-2), 114.9 (C-3), 137.0 (C-4), 149.8 (C-5)[a] and 151.5 (C-1);[a] *m*/*z* 334 (M$^+$ {^{81}Br}, 1%), 332 (M$^+$ {^{79}Br}, 1), 319 (1), 317 (1), 304 (2), 302 (2), 277 (50), 275 (48), 262 (100), 260 (99), 182 (10), 73 (27) and 59 (12).

Recycling of 3-bromo-4-(*tert*-butyldimethylsilyloxy)-5-methoxyphenol 25

Potassium carbonate (46 mg, 0.33 mmol) was added to a stirred solution of the phenol **25** (100 mg, 0.30 mmol) in methanol (3 cm^3) under argon. After 15 min, benzyl bromide (0.072 cm^3, 0.60 mmol) was added. After 3 days, work-up as described for the preparation above produced an orange oil (117 mg). Filtration through a pad of silica with 5 and

‡ The low yield of the benzyl ester **22** arose from sodium hydrogen carbonate washes to remove *m*-chlorobenzoic acid produced in the Baeyer–Villiger reaction.

10% ethyl acetate–hexane as eluents yielded 5-benzyloxy-1-bromo-2-(*tert*-butyldimethylsilyloxy)-3-methoxybenzene **26** as a yellow oil (81 mg, approx. 80% pure, 51% yield), probably contaminated by residual benzyl bromide.

4-Benzyloxy-2-bromo-6-methoxyphenol 27

A solution of the benzyl ether **26** (118 mg, 0.28 mmol) in tetrahydrofuran (4 cm^3) was treated with tetra-*n*-butylammonium fluoride trihydrate (220 mg, 0.70 mmol). After 3.5 h, water and ether were added. The aqueous layer was acidified with aqueous hydrochloric acid (1 M) and re-extracted with ether. The organic extracts were then treated as in normal work-up (B) to give a dark orange oil (87 mg). Filtration through a plug of silica gel (20% ethyl acetate–hexane) produced a pale yellow oil (79 mg, 92%). This oil crystallised after trituration with hexane while cooling in an acetone–dry ice bath. Recrystallisation from methylene chloride–hexane afforded the phenol **27** as spears, mp 55–6 °C (Found: C, 54.15; H, 3.9. $C_{14}H_{13}BrO_3$ requires C, 54.4; H, 4.2%); ν_{max}/cm^{-1} 3507 (OH), 1607, 1588, 1498 and 1451 (C=C); δ_H 3.83 (3H, s, OCH_3), 4.95 (2H, s, OCH_2), 5.51 (1H, br s, OH), 6.51 (1H, d, *J* 2.7, 5-H), 6.69 (1H, d, *J* 2.7, 3-H) and 7.28–7.42 (5H, m, C_6H_5); δ_C 56.3 (OCH_3), 70.9 (OCH_2), 100.1 (C-5), 107.6 (C-2), 109.0 (C-3), 127.6 (C-2′ and C-6′),[a] 128.1 (C-4′), 128.6 (C-3′ and C-5′),[a] 136.6 (C-1′),[b] 137.7 (C-1),[b] 147.6 (C-4)[c] and 152.5 (C-6);[c] *m*/*z* 310 (M^+ {^{81}Br}, 2%), 308 (M^+ {^{79}Br}, 3), 92 (10), 91 (100), 65 (12) and 53 (6).

4-Benzyloxy-2-bromo-6-methoxyphenyl toluene-*p*-sulfonate 20

Solid tetra-*n*-butylammonium fluoride trihydrate (4.97 g, 15.7 mmol) was added to a stirred solution of the benzyl ether **26** (5.55 g, 13.1 mmol) in tetrahydrofuran (100 cm^3) under nitrogen. After 45 min, TLC showed consumption of the benzyl ether **26** and production of the phenol **27**. Therefore, after 1 h, tosyl chloride (3.00 g, 15.7 mmol) was added. Since TLC after 4.5 h indicated the presence of a significant amount of tosyl chloride, an aliquot of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.35 cm^3, 15.7 mmol) was added, followed by a repeat addition of tosyl chloride (3.00 g, 15.7 mmol) after 5 h. This was necessary to ensure complete reaction of the phenol **27**, since this phenol and the bromo tosylate **20** have identical R_f's (30% ethyl acetate–hexane as eluent) and are very difficult to separate chromatographically. After 7 h, work-up was by concentration of the suspension, addition of water and ethyl acetate and then as described in the preparation of **27** above using ethyl acetate. Two purifications of the red solid (9.82 g) by gradient elution dry column chromatography (using 10 to 100% ethyl acetate–hexane) yielded the bromo tosylate **20** as a light pink solid (5.42 g, 89%). Recrystallisation from methanol furnished slightly hygroscopic, fine plates, mp 140.5–143 °C (Found: C, 54.35; H, 3.9. $C_{21}H_{19}BrO_5S$ requires C, 54.4; H, 4.1%); ν_{max}/cm^{-1} 1594, 1484 and 1455 (C=C); δ_H 2.45 (3H, s, CH_3), 3.55 (3H, s, OCH_3), 4.98 (2H, s, OCH_2), 6.47 (1H, d, *J* 2.8, 5-H), 6.74 (1H, d, *J* 2.8, 3-H), 7.30–7.42 (5H, m, C_6H_5) and 7.33 and 7.86 (4H, AA′BB′, ArH); δ_C 21.6 (CH_3), 55.8 (OCH_3), 70.6 (OCH_2), 100.3 (C-5), 109.4 (C-3), 118.3 (C-2), 127.6 (C-2″ and C-6″),[a] 128.3 (C-4″), 128.4 (C-2′ and C-6′),[b] 128.6 (C-3″ and C-5″),[a] 129.3 (C-3′ and C-5′),[b] 131.8 (C-1), 134.8 (C-4′),[c] 135.9 (C-1″),[c] 144.8 (C-1′),[c] 153.9 (C-4)[d] and 157.8 (C-6);[d] *m*/*z* 464 (M^+ {^{81}Br}, 0.1%), 462 (M^+ {^{79}Br}, 0.1), 309 (2), 307 (3), 155 (1), 92 (8), 91 (100) and 65 (2).

4-Benzyloxy-2-methoxybenzaldehyde 29

The monobenzyl ether **28**[14] (1.16 g, 5.09 mmol) was dissolved in dry *N*,*N*-dimethylformamide (35 cm^3) and methyl iodide (0.64 cm^3, 10.2 mmol), followed by anhydrous potassium carbonate (0.84 g, 6.11 mmol), added with stirring. The suspension was heated (4 h, 80 °C) and then cooled and poured into water. Extraction with ether, washing of the organic layer with water, aqueous sodium hydroxide (1 M), water and brine, drying and concentrating gave the methoxy compound **29** (1.23 g, 100%) as a cream crystalline solid. Recrystallisation from methanol yielded cream plates, mp 92–94.5 °C [lit.,[29] 95 °C (ethanol–water)]; ν_{max}/cm^{-1} 1664 (C=O), 1596, 1503 and 1475 (C=C); δ_H 3.88 (3H, s, OCH_3), 5.12 (2H, s, OCH_2), 6.53 (1H, d, *J* 2.2, 3-H), 6.62 (1H, ddd, *J* 0.7, 2.2 and 8.7, 5-H), 7.32–7.51 (5H, m, C_6H_5), 7.80 (1H, d, *J* 8.7, 6-H) and 10.29 (1H, d, *J* 0.7, CHO); δ_C 55.6 (OCH_3), 70.3 (OCH_2), 98.8 (C-3), 106.4 (C-5), 119.2 (C-1), 127.5 (C-2′ and C-6′),[a] 128.3 (C-4′), 128.7 (C-3′ and C-5′),[a] 130.7 (C-6), 135.9 (C-1′), 163.5 (C-2),[b] 165.2 (C-4)[b] and 188.3 (CHO); *m*/*z* 242 (M^+, 37%), 92 (48), 91 (100) and 65 (50).

4-Benzyloxy-2-methoxyphenol 31

Following the method described above for the Baeyer–Villiger rearrangement of silyl ether **23**, the methoxy compound **29** (2.18 g, 9.01 mmol) was transformed into a mixture of 4-benzyloxy-2-methoxyphenyl formate **30** and 4-benzyloxy-2-methoxyphenol **31** as a red oil (2.22 g); ν_{max} (film)/cm^{-1} 3464 (OH), 1743 (C=O), 1613, 1508 and 1452 (C=C). The mixture of predominantly formate **30** with some phenol **31** (2.22 g) was dissolved in methanol (20 cm^3) and a solution of potassium hydroxide (1.45 g, 25.8 mmol) in water (20 cm^3) added under nitrogen. After 1.5 h, aqueous hydrochloric acid (1 M) (40 cm^3) was added, followed by extraction into ethyl acetate. The organic layers were washed as in normal work-up (B) to give a red oil (2.07 g). Column chromatography with 10 and 20% ethyl acetate–hexane as eluents gave the phenol **31** as a red oil (1.58 g, 76% yield over two steps). Further column chromatography with the same eluents gave an orange solid which was then recrystallised from ether–hexane to furnish spears, mp 38–40 °C (lit.,[30] 35–7 °C); ν_{max} /cm^{-1} 3446 (OH), 1512 and 1452 (C=C); δ_H 3.85 (3H, s, OCH_3), 5.00 (2H, s, OCH_2), 5.24 (1H, s, OH), 6.46 (1H, dd, *J* 2.8 and 8.6, 5-H), 6.57 (1H, d, *J* 2.8, 3-H), 6.82 (1H, d, *J* 8.6, 6-H) and 7.31–7.45 (5H, m, C_6H_5); δ_C 55.9 (OCH_3), 70.8 (OCH_2), 100.4 (C-3), 105.5 (C-5), 114.0 (C-6), 127.6 (C-2′ and C-6′),[a] 127.9 (C-4′), 128.6 (C-3′ and C-5′),[a] 137.2 (C-1′), 140.0 (C-1), 147.0 (C-2) and 152.7 (C-4); *m*/*z* 230 (M^+, 88%), 153 (6), 139 (7), 111 (9), 92 (15), 91 (100) and 65 (17).

Examples of attempted bromination at C-6 of phenol 31

A. A solution (0.94 cm^3) of bromine (23 mg, 0.14 mmol) in glacial acetic acid was added dropwise to a stirred solution of the phenol **31** (30 mg, 0.13 mmol) and sodium acetate (11 mg, 0.13 mmol) in glacial acetic acid (2 cm^3). After 3 h, the reaction mixture was poured into an excess of saturated aqueous sodium hydrogen carbonate solution. Normal work-up (A) with ethyl acetate (minus the acid wash) then gave a red oil (38 mg), the ^{1}H NMR spectrum (60 MHz) of which appeared to show the presence of one predominant product. Column chromatography with 10 and 20% ethyl acetate–hexane gave 4-benzyloxy-5-bromo-2-methoxyphenol **32** as a red oil (24 mg, 60%); δ_H (60 MHz) 3.70 (3H, s, OCH_3), 4.95 (2H, s, OCH_2), 5.15 (1H, br s, OH), 6.48 (1H, s, 3-H), 7.07 (1H, s, 6-H) and 7.20–7.55 (5H, m, C_6H_5); *m*/*z* 310 (M^+ {^{81}Br}, 4%), 308 (M^+ {^{79}Br}, 5), 229 (8), 91 (100) and 65 (24).

B. Using the original method for *ortho*-bromination described by Pearson *et al.*,[17] with quantities of reagents as follows: *tert*-butylamine (0.055 cm^3, 0.52 mmol) in dry toluene (2 cm^3) and bromine (42 mg, 0.26 mmol) in dry methylene chloride (1.13 cm^3), the phenol **31** (50 mg, 0.22 mmol) added in dry methylene chloride (3 cm^3) yielded a pink–red oil (52 mg). Examination by TLC, GCMS and ^{1}H NMR spectroscopy (60 MHz) indicated a complex mixture.

C. Following the adaptation of the original method for *ortho*-bromination of phenols published by Sargent and co-

workers[18] with bromine (0.22 mmol) in dry methylene chloride (0.86 cm^3) in the presence of isopropylamine (0.028 cm^3, 0.33 mmol) in dry toluene (3 cm^3), the phenol **31** (50 mg, 0.22 mmol) in dry methylene chloride (2 cm^3) was converted to a crude red oil (57 mg). Analysis by TLC, GCMS and ^1H NMR spectroscopy (60 MHz) indicated a mixture containing starting material as the major component.

(4-Benzyloxy-2-methoxy)phenyl trifluoromethanesulfonate 33

Following a literature procedure for the preparation of aryl triflates,[31] except that 2 equiv. (0.585 cm^3, 3.48 mmol) of trifluoromethanesulfonic (triflic) anhydride was used, the phenol **31** (400 mg, 1.74 mmol) was transformed into its triflate as a crude orange oil (593 mg). Column chromatography with 10% ethyl acetate–hexane as eluent gave the triflate **33** as a pale yellow crystalline solid (570 mg, 91%). Recrystallisation of a portion of this (170 mg) from methylene chloride–hexane afforded needles (111 mg), mp 66–68 °C (Found: C, 50.0; H, 3.6. $C_{15}H_{13}F_3O_5S$ requires C, 49.7; H, 3.6%); ν_{max}/cm^{-1} 1609 and 1509 (C=C); δ_H 3.86 (3H, s, OCH_3), 5.04 (2H, s, OCH_2), 6.51 (1H, dd, *J* 2.8 and 8.9, 5-H), 6.64 (1H, d, *J* 2.8, 3-H), 7.12 (1H, d, *J* 8.9, 6-H) and 7.32–7.44 (5H, m, C_6H_5); δ_C 56.1 (OCH_3), 70.6 (OCH_2), 101.3 (C-3), 105.0 (C-5), 118.7 (q, *J* 321, CF_3), 122.8 (C-6), 127.5 (C-2′ and C-6′),[a] 128.3 (C-4′), 128.7 (C-3′ and C-5′),[a] 132.8 (C-1), 136.1 (C-1′), 152.2 (C-2) and 159.2 (C-4); *m/z* 362 (M^+, 2%), 229 (5), 197 (7), 91 (100) and 65 (9).

1-Acetoxy-7-benzyloxy-4,5-dimethoxynaphthalene 11

A. Following the procedure described by Giles, Hughes and Sargent for the preparation of 4,5-dimethoxy-1-naphthol,[8] except that the temperature of the reaction was −80 °C, the bromotosylate **20** (500 mg) gave a red oil (452 mg) as the crude product.

The crude product was immediately dissolved in dry pyridine (5 cm^3) and acetic anhydride (0.20 cm^3, 2.12 mmol) added with stirring under argon. After 16 h, ether and water were added. The water layer was removed and the organic layer was subjected to a normal work-up (A) (ether) to give a red solid (393 mg). Dry column chromatography with 10 and 20% ethyl acetate–hexane as eluents gave a green solid (218 mg) of predominantly R_f 0.27 (30% ethyl acetate–hexane) material, being the required product **11** [purified further by radial chromatography with the same eluents to give orange needles (176 mg, 46%)], and an orange oil (89 mg, approx. 18% recovery) of predominantly R_f 0.34 material, identified by ^1H NMR spectroscopy (60 MHz) as the starting material bromo tosylate **20** and a small amount of debrominated starting material.

In order to successfully purify the required product **11**, the green solid was dissolved in a mixture of dry ether and dry tetrahydrofuran and the solution added to an excess of lithium aluminium hydride in dry ether with stirring under nitrogen. After 1.5 h, work-up was by the dropwise addition of saturated ammonium chloride solution, the addition of anhydrous magnesium sulfate and filtration of the resultant suspension through Celite. Concentration of the filtrate was followed by dry column chromatography (20 and 40% ethyl acetate–hexane). The fractions containing 7-benzyloxy-4,5-dimethoxy-1-naphthol **3**, R_f 0.20 (30% ethyl acetate–hexane), were collected to give a cream solid, δ_H (60 MHz) 3.80 and 3.90 (each 3H, s, OCH_3), 5.10 (2H, s, OCH_2), 6.54 and 6.75 (2H, AB, *J* 8, 3- and 2-H), 6.56 (1H, d, *J* 2, 6- or 8-H), 7.20–7.50 (6H, m, C_6H_5 and 6- or 8-H) and 8.00 (1H, br s, OH).

This solid was dissolved in dry pyridine and an excess of acetic anhydride added. Work-up as described directly above for the same reaction gave a yellow solid. Dry column chromatography (20 and 30% ethyl acetate–hexane) yielded a pale green crystalline solid. Recrystallisation from methylene chloride–hexane afforded fine needles of the naphthalene **11**, mp 109–109.5 °C (Found: C, 71.7; H, 5.8. $C_{21}H_{20}O_5$ requires C, 71.6; H, 5.7%); ν_{max}/cm^{-1} 1754 (C=O), 1625, 1612 and 1589 (C=C); δ_H 2.39 (3H, s, $COCH_3$), 3.936 and 3.941 (each 3H, s, OCH_3), 5.15 (2H, s, OCH_2), 6.62 and 6.73 (each 1H, d, *J* 2.3, 6- and 8-H), 6.67 (1H, d, *J* 8.5, 3-H), 7.10 (1H, d, *J* 8.5, 2-H) and 7.32–7.50 (5H, m, C_6H_5); δ_C 21.0 ($COCH_3$), 56.4 and 56.6 (OCH_3), 70.1 (OCH_2), 93.5 (C-6),[a] 99.6 (C-8),[a] 103.3 (C-3),[a] 114.1 (C-4a), 119.2 (C-2), 127.7 (C-2′ and C-6′),[b] 128.2 (C-4′), 128.7 (C-3′ and C-5′),[b] 130.7 (C-8a), 136.6 (C-1),[c] 139.2 (C-1′),[c] 155.4 (C-4),[d] 158.0 (C-7),[d] 158.8 (C-5)[d] and 169.7 ($COCH_3$); *m/z* 352 (M^+, 19%), 310 (56), 281 (7), 219 (28), 191 (27), 91 (100) and 65 (21).

B. Dry diisopropylamine (0.187 cm^3, 1.33 mmol) in dry tetrahydrofuran (4 cm^3) was cooled to 0 °C under an atmosphere of argon and a solution of *n*-butyllithium in hexane (0.61 cm^3, 2.2 M, 1.34 mmol) was added. After stirring for 15 min, the mixture was cooled to −78 °C. In a separate round-bottomed flask, under argon, the aryl triflate **33** (100 mg, 0.28 mmol) was dissolved in dry tetrahydrofuran (2 cm^3) and an excess of 2-methoxyfuran (0.30 cm^3) added. This solution was also cooled to −78 °C. The lithium diisopropylamide (LDA) solution was then added dropwise *via* syringe to the aryl triflate solution over 10 min. After stirring for 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature over a further 2.5 h. It was then acidified with concentrated hydrochloric acid, stirred for 15 min and poured into water. Extraction with ethyl acetate and washing of the organic phase as in normal work-up (B) gave a red oil (254 mg). Radial chromatography (10 and 20% ethyl acetate–hexane) gave only one identifiable product: 7-benzyloxy-4,5-dimethoxy-1-naphthol **3**, R_f 0.20 (30% ethyl acetate–hexane), as a green oil (29 mg). This oil was dissolved in dry pyridine (2 cm^3) and acetic anhydride (0.3 cm^3) added under nitrogen. After 2 days, normal work-up (B) (ether), with an additional dilute aqueous hydrochloric acid (1 M) wash, gave the naphthalene **11** as an orange crystalline solid (31 mg, 32% over two steps), R_f 0.27 (30% ethyl acetate–hexane). Recrystallisation from methylene chloride–hexane produced pale orange, fine needles of naphthalene **11** (24 mg, 25%), mp 107–9 °C.

C. Following the procedure described by Giles, Hughes and Sargent for the preparation of 4,5-dimethoxy-1-naphthol,[8] except that an aryl triflate was used instead of a bromo tosylate, 1.1 equiv. of *n*-butyllithium (0.19 cm^3, 2.3 M, 0.46 mmol) and 10 equiv. of 2-methoxyfuran (0.38 cm^3, 4.1 mmol) were used and the addition was carried out at −78 °C followed by immediately allowing the mixture to warm to room temperature, the aryl triflate **33** (150 mg, 0.41 mmol) gave a brown oil (296 mg) as the crude product. Column chromatography (10–30% ethyl acetate–hexane) gave the naphthol **3** as a purple oil (38 mg). This oil was dissolved in dry pyridine and acetic anhydride. After 20 h, water and ether were added and stirring continued for 3 h. Normal work-up (A) (ether) then gave a red oil (23 mg). Column chromatography with 10 and 20% ethyl acetate–hexane produced the naphthalene **11** as an orange solid (16 mg, 11% over two steps).

Conversion of naphthalene 11 to 1-acetoxy-4,5,7-trimethoxynaphthalene 13

To a stirred solution of the naphthalene **11** (95 mg, 0.27 mmol) in ethyl acetate (12 cm^3) was added 10% palladium on carbon catalyst (120 mg). The suspension was then subjected to an atmosphere of hydrogen for 2.5 h. Filtration through a pad of Celite and concentration of the filtrate gave 1-acetoxy-4,5-dimethoxy-7-hydroxynaphthalene **12** as an orange solid (68 mg, 96%), R_f 0.06 (30% ethyl acetate–hexane), δ_H (60 MHz) 2.25 (3H, s, $COCH_3$), 3.80 and 3.85 (each 3H, s, OCH_3), 5.90 (1H, br s, OH), 6.38 and 6.58 (each 1H, d, *J* 2, 6- and 8-H), 6.51 (1H, d, *J* 8, 3-H) and 6.96 (1H, d, *J* 8, 2-H). Naphthol **12** (68 mg, 0.26 mmol) was dissolved in dry *N*,*N*-dimethylformamide (5 cm^3) and methyl iodide (0.041 cm^3, 0.65 mmol), followed by anhydrous potassium carbonate (43 mg, 0.31 mmol) were

added with stirring. The suspension was heated (17 h, 60 °C) and then cooled and poured into water. Extraction with ether, washing of the organic layer with water and brine, drying and concentrating gave the naphthalene **13** as an orange solid (65 mg, 91%). Recrystallisation from methylene chloride–hexane furnished pale orange crystals (38 mg), mp 110.5–113 °C (lit.,[19] 110–2 °C; lit.,[8] 114–5 °C); δ_H 2.41 (3H, s, $COCH_3$), 3.88 (3H, s, OCH_3), 3.92 (6H, s, OCH_3), 6.52 and 6.63 (each 1H, d, *J* 2.3, 6- and 8-H), 6.65 (1H, d, *J* 8.4, 3-H) and 7.09 (1H, d, *J* 8.4, 2-H).

Conversion of naphthalene 11 to naphthol 3

The naphthalene **11** (370 mg, 1.05 mmol) was dissolved in dry tetrahydrofuran (10 cm^3) and the solution added dropwise to an excess of lithium aluminium hydride (81 mg, 2.10 mmol) in dry ether (8 cm^3) with stirring. After 1 h, saturated ammonium chloride solution was added dropwise, followed by anhydrous magnesium sulfate and the resultant suspension was filtered through Celite. Concentration of the filtrate gave the naphthol **3** as a yellow solid (326 mg, 100%).

(2*S*, 1′*R* or *S*)-Ethyl 2-(1′-ethoxyethoxy)propanoate 34

Pyridinium toluene-*p*-sulfonate (PPTS; Aldrich) (1.26 g, 5.00 mmol) was added to a solution of (*S*)-ethyl lactate [Fluka Chemie AG; measured $[\alpha]_D$ −11.0 (neat)] (5.72 cm^3, 50.0 mmol) and ethyl vinyl ether (as supplied by Aldrich) (12.0 cm^3, 125 mmol) in dry methylene chloride (170 cm^3). After standing for 17 h, the solution was washed with water (three times), brine, dried and concentrated to a yellow oil (10.52 g), $[\alpha]_D$ −65.9. Kugelrohr distillation gave, after the forerun was discarded, compound **34** as a pale yellow liquid (6.54 g, 69%), bp 105–130 °C/approx. 18 mmHg (Kugelrohr) (lit.,[23] 80 °C/20 mmHg; lit.,[22] 74 °C/12 mmHg); $[\alpha]_D$ −67.1 [lit.,[23] −68.7 (*c* 5, $CHCl_3$); lit.,[22] −78.9 (*c* 4.4, $CHCl_3$)]; ν_{max} (film)/cm^{-1} 1751 (C=O); δ_H (major diastereomer) 1.19 (3H, t, *J* 7.1, 1″-CH_3), 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.37 (3H, d, *J* 5.4, 1′-CH_3), 1.42 (3H, d, *J* 7.0, 2-CH_3), 3.49 and 3.62 (each 1H, dq, *J* 9.3 and 7.1, 1′-OCH_2), 4.20 (2H, q, *J* 7.1, CO_2CH_2), 4.34 (1H, q, *J* 7.0, 2-H) and 4.78 (1H, q, *J* 5.4, 1′-H); δ_H (minor diastereomer) 1.17 (3H, t, *J* 7.1, 1″-CH_3), 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.32 (3H, d, *J* 5.4, 1′-CH_3), 1.39 (3H, d, *J* 7.0, 2-CH_3), 3.53 and 3.70 (each 1H, dq, *J* 9.4 and 7.1, 1′-OCH_2), 4.188 (1H, q, *J* 7.0, 2-H), 4.195 (2H, q, *J* 7.1, CO_2CH_2) and 4.79 (1H, q, *J* 5.4, 1′-H); δ_C (major diastereomer) 14.2 ($CH_3CH_2O_2C$), 15.3 (C-3), 18.9 (C-2″), 20.0 (C-2′), 60.2 (C-1″), 60.8 (CH_2O_2C), 69.9 (C-2), 99.3 (C-1′) and 173.4 (C-1); δ_C (minor diastereomer) 14.2 ($CH_3CH_2O_2C$), 15.1 (C-3), 18.9 (C-2″), 19.7 (C-2′), 60.8 (CH_2O_2C), 61.1 (C-1″), 69.6 (C-2), 99.4 (C-1′) and 173.7 (C-1); *m*/*z* 145 [(M − OEt), 22%], 101 (10), 73 (99), 69 (29), 57 (14), 55 (15), 45 (100) and 43 (21).

(2*S*, 1′*R* or *S*)-2-(1′-Ethoxyethoxy)propanal 35

Neat diisobutylaluminium hydride (1.69 cm^3, 9.5 mmol) was added to dry hexane (6 cm^3) in a pressure-equalising dropping funnel. This solution was then added dropwise to a cooled (−70 °C) solution of the ester **34** (1.50 g, 7.9 mmol) in dry ether (12 cm^3) under argon. After stirring for 1 h, saturated sodium sulfate solution (3.2 cm^3) was added dropwise. The mixture was then allowed to warm to room temperature over 2 h, after which time a gelatinous precipitate had formed. The mixture was filtered through a pad of Celite and the residues washed with ether. The filtrate was concentrated and the residue subjected to Kugelrohr distillation to produce an oil (0.79 g), bp 100–115 °C/approx. 18 mmHg (Kugelrohr) [lit.,[27] (pure aldehyde **35**) 53–4 °C/17 mmHg], being a mixture of aldehyde **35** and alcohol **36** [(2*S*, 1′*R* or *S*)-2-(1′-ethoxyethoxy)propan-1-ol], in an approximate ratio 7:3 (yields approx. 48 and 20%), estimated by comparison of the integration of the aldehydic proton signal with that of the multiplet for the acetal proton (1′-H; δ 4.70) in the ^{1}H NMR spectrum (60 MHz); δ_H (aldehyde **35**; Major diastereomer) 1.19 (3H, t, *J* 7.1, 1″-CH_3), 1.32 (3H, d, *J* 7.0, 2-CH_3), 1.38 (3H, d, *J* 5.4, 1′-CH_3), 3.45–3.75 (2H, m, OCH_2), 4.15 (1H, dq, *J* 1.7 and 7.0, 2-H), 4.83 (1H, q, *J* 5.4, 1′-H) and 9.62 (1H, d, *J* 1.7, 1-H); δ_H (aldehyde **35**; Minor diastereomer) 1.17 (3H, t, *J* 7.1, 1″-CH_3), 1.27 (3H, d, *J* 7.0, 2-CH_3), 1.36 (3H, d, *J* 5.3, 1′-CH_3), 3.45–3.75 (2H, m, OCH_2), 3.94 (1H, dq, *J* 2.7 and 7.0, 2-H), 4.74 (1H, q, *J* 5.3, 1′-H) and 9.59 (1H, d, *J* 2.7, 1-H); *m*/*z* (aldehyde **35**) 145 [(M − H), 0.4%], 131 (4), 117 (10), 101 (42), 73 (100), 57 (70) and 45 (100).

(1*R*,2*S*,1″*R* or *S*)-2-(1″-Ethoxyethoxy)-1-(1′-hydroxy-4′,5′,7′-trimethoxynaphthalene-2′-yl)propan-1-ol 37

The published method of Casiraghi *et al.*[4b] was modified as follows:

Freshly prepared naphthol **10**[8] (500 mg, 2.14 mmol) was dissolved in toluene (approx. 70 cm^3, AR grade) in a 3-necked round-bottomed flask. Water was then removed as its azeotrope by distillation, using a gentle flame to heat the solution. The system was then flushed with argon and fresh, neat titanium tetraisopropoxide (0.748 cm^3, 2.51 mmol) was added, producing a red solution. The propan-2-ol–toluene azeotrope was removed by distillation and then the distillation apparatus was replaced by a septum. The solution was cooled in an ice bath and the aldehyde **35** (1.03 g, approx. 4.23 mmol, 60% pure; prepared the previous day) added *via* a syringe. After 40 min, the flask was transferred to the ultrasonication bath for a further 10 h (bath temperature range: 10–40 °C). The reaction mixture was then diluted with ether (200 cm^3) and stirred vigorously overnight with saturated sodium fluoride solution (200 cm^3). Filtration of the mixture through a pad of Celite was followed by separation of the ether layer. The aqueous layer was re-extracted with ether and the combined organic layers were washed with brine, dried and concentrated to a low volume. Column chromatography with 20–40% ethyl acetate–hexane gave:

1. Of R_f 0.30 (30% ethyl acetate–hexane), a bright yellow oil (16 mg), a decomposition product of compound **37**.

2. Of R_f 0.12 (30% ethyl acetate–hexane), the required product compound **37** as a mixture of diastereomers at C-1″, a red oil (512 mg, 63%). This compound was reasonably stable, but soon after chromatography always underwent a small amount of decomposition to by-products at R_f 0.30 and baseline material. Compound **37**: (Found: M^+, 380.1834. $C_{20}H_{28}O_7$ requires M, 380.1835); $[\alpha]_D$ +15.9 (*c* 0.9, $CHCl_3$) (mixture of diastereomers at C-1″); ν_{max} (film)/cm^{-1} 3349 (OH), 1612, 1516, 1471 and 1453 (C=C); δ_H (major diastereomer; 500 MHz) 1.19 (3H, t, *J* 7.1, CH_3CH_2), 1.20 (3H, d, *J* 6.4, 2-CH_3), 1.30 (3H, d, *J* 5.3, 1″-CH_3), 3.50 and 3.63 (each 1H, dq, *J* 9.2 and 7.1, CH_2), 3.70 (1H, s, 1-OH), 3.83, 3.91 and 3.92 (each 3H, s, OCH_3), 4.07 (1H, dq, *J* 4.3 and 6.4, 2-H), 4.76 (1H, q, *J* 5.3, 1″-H), 4.86 (1H, d, *J* 4.3, 1-H), 6.24 (1H, s, 3′-H), 6.51 and 7.13 (each 1H, d, *J* 2.3, 6′- and 8′-H) and 8.82 (1H, s, 1′-OH); δ_H (minor diastereomer; 500 MHz) 1.14 (3H, d, *J* 6.6, 2-CH_3), 1.15 (3H, t, *J* 7.0, CH_3CH_2), 1.35 (3H, d, *J* 5.3, 1″-CH_3), 3.43 and 3.56 (each 1H, dq, *J* 9.2 and 7.0, CH_2), 3.70 (1H, s, 1-OH), 3.83, 3.91 and 3.92 (each 3H, s, OCH_3), 4.11 (1H, dq, *J* 4.0 and 6.6, 2-H), 4.82 (1H, q, *J* 5.3, 1″-H), 4.94 (1H, d, *J* 4.0, 1-H), 6.26 (1H, s, 3′-H), 6.51 and 7.15 (each 1H, d, *J* 2.3, 6′- and 8′-H) and 8.81 (1H, s, 1′-OH); δ_C (major diastereomer; 126 MHz) 15.2 (C-3), 17.7 (CH_3CH_2), 20.3 (C-2″), 55.2, 56.1 and 57.5 (OCH_3), 60.3 (CH_2), 76.2 (C-2), 78.3 (C-1), 93.2 (C-1″), 99.4 (C-6′),[a] 99.6 (C-3′),[a] 105.3 (C-8′),[a] 113.5 (C-8′a),[b] 117.1 (C-4′a),[b] 129.6 (C-2′), 144.5 (C-1′), 149.9 (C-4′), 157.7 (C-7′)[c] and 157.9 (C-5′);[c] δ_C (minor diastereomer; 126 MHz) 15.3 (C-3), 17.7 (CH_3CH_2), 20.5 (C-2″), 55.2, 56.2 and 57.5 (OCH_3), 60.6 (CH_2), 76.0 (C-2), 78.4 (C-1), 93.3 (C-1″), 98.9 (C-6′),[a] 99.4 (C-3′),[a] 105.5 (C-8′),[a] 113.5 (C-8′a),[b] 117.1 (C-4′a),[b] 129.6 (C-2′), 144.5 (C-1′), 149.9 (C-4′), 157.7 (C-7′)[c] and 157.9 (C-5′);[c] *m*/*z* 380 (M^+, 2%), 334 (4), 306 (5), 290 (64), 288 (19), 273 (14), 247 (29), 233 (16), 73 (65) and 45 (100).

(1*S*,2*S*,1″*R*)- and (1*S*,2*S*,1″*S*)-2-(1″-Ethoxyethoxy)-1-(1′-hydroxy-4′,5′,7′-trimethoxynaphthalen-2′-yl)propan-1-ol 39

Using the method of Casiraghi *et al.*[4b] as follows:

A solution of the Grignard reagent ethylmagnesium bromide in dry ether was prepared and an aliquot (1.16 cm^3, containing 2.94 mmol) was transferred to a round-bottomed flask which was then flushed with argon. A solution of the freshly prepared naphthol **10**[8] (550 mg, 2.35 mmol) in dry ether (25 cm^3) was added, leading to a heavy suspension. The ether was removed under vacuum and dry methylene chloride (22 cm^3) added to the cream solid. The resulting suspension was cooled in an ice bath and the aldehyde **35** (1.29 g, approx. 5.30 mmol, 60% pure; prepared the previous day) added. After 20 min, the flask was transferred to the ultrasonication bath for a further 7.5 h (bath temperature range: 10–30 °C). The deep orange reaction mixture was then poured into methylene chloride and saturated ammonium chloride solution and stirred vigorously. After 1 day, the organic layer was separated and the aqueous layer re-extracted with methylene chloride. The combined organic layers were washed with water and brine, dried, filtered through Celite and concentrated to a green oil (1.46 g). TLC (30% ethyl acetate–hexane) showed minor spots at R_f 0.25 and on the baseline, which were minor decomposition products seen repeatedly, and two major spots at R_f 0.15 and 0.10 for the two diastereomers (at C-1″) of **39**. These two diastereomers were separable by chromatography and column chromatography with 10–40% ethyl acetate–hexane gave:

1. Of R_f 0.15, one diastereomer of product **39**, as a light green solid (269 mg, 30%). Recrystallisation of a portion (100 mg) from methylene chloride–hexane afforded small, light green needles (87 mg), mp 124–127.5 °C (Found: M^+ 380.1834. $C_{20}H_{28}O_7$ requires M, 380.1835); $[\alpha]_D$ +57.0 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 3431 and 3244 (OH), 1609, 1515, 1470 and 1450 (C=C); δ_H (500 MHz) 1.03 (3H, d, *J* 6.3, 2-CH_3), 1.30 (3H, t, *J* 7.1, C$H_3$$CH_2$), 1.39 (3H, d, *J* 5.2, 1″-CH_3), 3.621 and 3.625 (each 1H, dq, *J* 7.0 and 7.1, CH_2), 3.86, 3.92 and 3.94 (each 3H, s, OCH_3), 4.02 (1H, dq, *J* 8.5 and 6.3, 2-H), 4.56 (1H, d, *J* 8.5, 1-H), 4.72 (1H, q, *J* 5.2, 1″-H), 5.09 (1H, s, 1-OH), 6.34 (1H, s, 3′-H), 6.53 and 7.16 (each 1H, d, *J* 2.4, 6′- and 8′-H) and 8.87 (1H, s, 1′-OH); δ_C (126 MHz) 15.3 (C-3), 17.8 (*C*$H_3$$CH_2$), 20.7 (C-2″), 55.3, 56.1 and 57.5 (OCH_3), 62.2 (CH_2), 78.3 (C-2), 80.0 (C-1), 92.8 (C-1″), 99.3 (C-6′),[a] 100.6 (C-3′),[a] 106.5 (C-8′),[a] 113.7 (C-8′a),[b] 116.7 (C-4′a),[b] 129.3 (C-2′), 144.8 (C-1′), 149.9 (C-4′), 157.8 (C-7′)[c] and 158.0 (C-5′);[c] *m*/*z* 380 (M^+, 3%), 334 (7), 318 (11), 290 (100), 273 (26), 247 (50), 233 (11), 73 (8) and 57 (6).

2. Of R_f 0.10, after further chromatography, the other diastereomer of product **39** as a deep green oil (contaminated with some inseparable impurities) (520 mg, approx. 74% pure, approx. 43% yield) (Found: M^+ 380.1834. $C_{20}H_{28}O_7$ requires M, 380.1835); $[\alpha]_D$ +12.4 (*c* 0.2, $CHCl_3$; purity of sample: 74%); ν_{max} (film)/cm^{-1} 3333 (OH), 1610, 1516, 1471 and 1451 (C=C); δ_H (500 MHz) 1.10 (3H, d, *J* 6.2, 2-CH_3), 1.20 (3H, t, *J* 7.1, C$H_3$$CH_2$), 1.38 (3H, d, *J* 5.3, 1″-CH_3), 3.50 and 3.70 (each 1H, dq, *J* 9.2 and 7.1, CH_2), 3.83, 3.90 and 3.92 (each 3H, s, OCH_3), 3.99 (1H, dq, *J* 7.8 and 6.2, 2-H), 4.28 (1H, s, 1-OH), 4.57 (1H, d, *J* 7.8, 1-H), 4.79 (1H, q, *J* 5.3, 1″-H), 6.31 (1H, s, 3′-H), 6.51 and 7.13 (each 1H, d, *J* 2.1, 6′- and 8′-H) and 8.54 (1H, s, 1′-OH); δ_C (126 MHz) 15.1 (C-3), 17.7 (*C*$H_3$$CH_2$), 20.2 (C-2″), 55.2, 56.1 and 57.5 (OCH_3), 61.7 (CH_2), 75.4 (C-2), 79.6 (C-1), 92.9 (C-1″), 99.4 (C-6′),[a] 100.1 (C-3′),[a] 106.1 (C-8′),[a] 113.6 (C-8′a),[b] 117.1 (C-4′a),[b] 129.4 (C-2′), 144.5 (C-1′), 149.9 (C-4′), 157.8 (C-7′)[c] and 158.0 (C-5′);[c] *m*/*z* 380 (M^+, 15%), 362 (9), 334 (29), 318 (35), 291 (37), 290 (100), 273 (39), 261 (21), 247 (50), 233 (26), 73 (40) and 57 (7).

(2*R*, 1′*R* or *S*)-Methyl 2-(1′-ethoxyethoxy)propanoate 40

Following the method described above for the preparation of compound **34**, (*R*)-methyl lactate (6.20 cm^3, 65.0 mmol) was converted into the diastereomeric esters **40** as a pale yellow oil (12.50 g). Kugelrohr distillation gave the title compound as a liquid (11.58 g, 100%), bp 110–130 °C/approx. 18 mmHg (Kugelrohr) (Found: C, 54.1; H, 9.2. $C_8H_{16}O_4$ requires C, 54.55; H, 9.1%); $[\alpha]_D$ +77.8 (*c* 1.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 1756 (C=O); δ_H (major diastereomer) 1.18 (3H, t, *J* 7.0, 1″-CH_3), 1.35 (3H, d, *J* 5.3, 1′-CH_3), 1.41 (3H, d, *J* 6.9, 2-CH_3), 3.52 and 3.67 (each 1H, dq, *J* 9.4 and 7.0, 1′-OCH_2), 3.74 (3H, s, CO_2CH_3), 4.35 (1H, q, *J* 6.9, 2-H) and 4.78 (1H, q, *J* 5.3, 1′-H); δ_H (minor diastereomer) 1.16 (3H, t, *J* 7.0, 1″-CH_3), 1.31 (3H, d, *J* 5.4, 1′-CH_3), 1.39 (3H, d, *J* 6.8, 2-CH_3), 3.49 and 3.61 (each 1H, dq, *J* 9.3 and 7.0, 1′-OCH_2), 3.74 (3H, s, CO_2CH_3), 4.20 (1H, q, *J* 6.8, 2-H) and 4.77 (1H, q, *J* 5.3, 1′-H); δ_C (major diastereomer) 15.3 (C-3), 19.0 (C-2″), 20.0 (C-2′), 51.9 (*C*H_3O_2C), 60.3 (C-1″), 69.8 (C-2), 99.4 (C-1′) and 173.9 (C-1); δ_C (minor diastereomer) 15.1 (C-3), 18.9 (C-2″), 19.7 (C-2′), 51.9 (*C*H_3O_2C), 61.1 (C-1″), 69.9 (C-2), 99.6 (C-1′) and 174.1 (C-1); *m*/*z* 131 [(M − OEt), 3%], 101 (20), 88 (19), 73 (100) and 70 (34).

(2*R*,1′*R* or *S*)-2-(1′-Ethoxyethoxy)propanal 4

According to the procedure described above for the preparation of aldehyde **35**, (2*R*,1′*R* or *S*)-methyl 2-(1′-ethoxyethoxy)-propanoate (1.40 g, 7.9 mmol) was reduced with diisobutylaluminium hydride (1.84 cm^3, 10.3 mmol) to give an oil (1.55 g). Kugelrohr distillation yielded an oil (0.90 g), bp 105–115 °C/approx. 18 mmHg (Kugelrohr), being a mixture of aldehyde **4** and alcohol **41** [(2*R*,1′*R* or *S*)-2-(1′-ethoxyethoxy)propan-1-ol], in an approximate ratio 7:3 (yields approx. 54 and 23%), estimated by comparison of the integration of the aldehydic proton signal with that of the multiplet for the acetal proton (1′-H) in the ^1H NMR spectrum (60 MHz); $[\alpha]_D$ +35.6 (*c* 1.5, $CHCl_3$) (aldehyde:alcohol, 6:4); ν_{max} (film)/cm^{-1} (aldehyde **4**) 1735 (C=O); the ^1H NMR spectrum (300 MHz) was identical to that reported above for the pair of diastereomeric aldehydes **35**, since these are enantiomeric to the aldehyde pair **4**.

(1*S*,2*R*,1″*R* or *S*)-1-(7′-Benzyloxy-1′-hydroxy-4′,5′-dimethoxy-2′-naphthyl)-2-(1″-ethoxyethoxy)propan-1-ol 5

Following the procedure described above for the preparation of **37**, freshly prepared naphthol **3** (199 mg, 0.64 mmol) was treated with titanium tetraisopropoxide (0.229 cm^3, 0.77 mmol) and the aldehyde **4** (375 mg, approx. 1.54 mmol, 60% pure) was added. Column chromatography with 30–50% ethyl acetate–hexane gave:

1. Of R_f 0.26 (30% ethyl acetate–hexane), a bright yellow band containing a decomposition product.

2. Of R_f 0.08 (30% ethyl acetate–hexane), the required product **5** as a mixture of diastereomers at C-1″, a deep red oil (126 mg, 43%). This compound was reasonably stable, but soon after chromatography always underwent a small amount of decomposition to by-products at R_f 0.26 and baseline material. Compound **5** (Found: M^+, 456.2131. $C_{26}H_{32}O_7$ requires M, 456.2148); $[\alpha]_D$ −8.6 (*c* 0.3, $CHCl_3$) (mixture of diastereomers at C-1″); ν_{max} (film)/cm^{-1} 3339 (OH), 1624, 1608, 1516, 1499 and 1454 (C=C); δ_H (major diastereomer; 500 MHz) 1.216 (3H, t, *J* 7.1, C$H_3$$CH_2$), 1.217 (3H, d, *J* 6.5, 2-CH_3), 1.34 (3H, d, *J* 5.3, 1″-CH_3), 3.53 and 3.65 (each 1H, dq, *J* 9.2 and 7.1, CH_2), 3.56 (1H, br s, 1-OH), 3.86 and 3.93 (each 3H, s, OCH_3), 4.09 (1H, dq, *J* 4.1 and 6.5, 2-H), 4.81 (1H, q, *J* 5.3, 1″-H), 4.92 (1H, d, *J* 4.1, 1-H), 5.17 (2H, s, $C_6H_5CH_2$), 6.29 (1H, s, 3′-H), 6.62 and 7.29 (each 1H, d, *J* 2.3, 6′- and 8′-H), 7.32–7.51 (5H, m, C_6H_5) and 8.86 (1H, s, 1′-OH); δ_H (minor diastereomer; 500 MHz) 1.15 (3H, d, *J* 5.7, 2-CH_3), 1.18 (3H, t, *J* 7.0, C$H_3$$CH_2$), 1.37 (3H, d, *J* 5.3, 1″-CH_3), 3.47 and 3.59 (each 1H, dq, *J* 9.2 and 7.0, CH_2), 3.56 (1H, br s, 1-OH), 3.86 and 3.93 (each 3H, s, OCH_3), 4.12 (1H, dq, *J* 3.7 and 5.7, 2-H), 4.84 (1H, q, *J* 5.3, 1″-H), 4.98 (1H, d, *J* 3.7, 1-H), 5.17 (2H, s, $C_6H_5CH_2$), 6.31 (1H, s, 3′-H), 6.62 and 7.31 (each 1H, d, *J* 2.3, 6′- and 8′-H), 7.32–7.51 (5H, m, C_6H_5) and 8.83 (1H, s, 1′-OH); δ_C (major diastereomer; 126

MHz) 15.1 (C-3), 15.2 (CH_3CH_2), 20.3 (C-2″), 56.2 and 57.5 (OCH_3), 60.4 (CH_3CH_2), 70.0 ($C_6H_5CH_2$), 76.3 (C-2), 78.3 (C-1), 94.2 (C-1″), 99.5 (C-6′),[a] 99.7 (C-3′),[a] 105.1 (C-8′),[a] 113.6 (C-8′a),[b] 116.9 (C-4′a),[b] 127.9 (C-2‴ and C-6‴),[c] 128.0 (C-4‴), 128.6 (C-3‴ and C-5‴),[c] 129.6 (C-2′), 136.8 (C-1‴), 144.5 (C-1′), 150.1 (C-4′), 157.2 (C-7′)[d] and 157.8 (C-5′);[d] δ_C (minor diastereomer; 126 MHz) 14.4 (C-3), 15.2 (CH_3CH_2), 20.6 (C-2″), 56.2 and 57.6 (OCH_3), 60.7 (CH_3CH_2), 70.0 ($C_6H_5CH_2$), 76.1 (C-2), 78.4 (C-1), 94.3 (C-1″), 99.0 (C-6′),[a] 99.7 (C-3′),[a] 105.4 (C-8′),[a] 113.6 (C-8′a),[b] 116.9 (C-4′a),[b] 127.9 (C-2‴ and C-6‴),[c] 128.0 (C-4‴), 128.6 (C-3‴ and C-5‴),[c] 129.6 (C-2′), 136.8 (C-1‴), 144.5 (C-1′), 150.1 (C-4′), 157.2 (C-7′)[d] and 157.8 (C-5′);[d] *m/z* 456 (M^+, 3%), 438 (4), 410 (5), 394 (18), 366 (52), 350 (18), 275 (15), 247 (38), 231 (23), 91 (100) and 73 (18).

(1*R*, 2*R*, 1″*R*)- and (1*R*, 2*R*, 1″*S*)-1-(7′-Benzyloxy-1′-hydroxy-4′,5′-dimethoxy-2′-naphthyl)-2-(1″-ethoxyethoxy)propan-1-ol 6

Following the method described above for the preparation of **39**, the freshly prepared naphthol **3** (326 mg, 1.05 mmol) in dry ether (10 cm^3) and dry tetrahydrofuran (4 cm^3) was added to an aliquot (0.43 cm^3, containing 1.31 mmol) of ethylmagnesium bromide in dry ether, resulting in a green solution, with further treatment with the aldehyde **4** (0.63 g, approx. 3.02 mmol, 70% pure). The crude product was obtained as a red oil (0.79 g). TLC (30% ethyl acetate–hexane) showed minor spots at R_f 0.29 and on the baseline, which were minor decomposition products seen repeatedly, and two major spots at R_f 0.14 and 0.09 for the two diastereomers (at C-1″) of **6**. These two diastereomers were separable by chromatography and column chromatography with 20–50% ethyl acetate–hexane gave:

1. Of R_f 0.14, one of the diastereomeric products **6**, as a light green solid (190 mg, 40%). Recrystallisation from methylene chloride–hexane afforded deep cream needles (159 mg), mp 95–96.5 °C (Found: C, 68.2; H, 7.7%; M^+ 456.2169. $C_{26}H_{32}O_7$ requires C, 68.4; H, 7.1%; M, 456.2148); $[a]_D$ −40.4 (*c* 0.3, $CHCl_3$); ν_{max}/cm^{-1} 3356 (OH), 1615, 1522, 1499, 1473 and 1456 (C=C); δ_H (500 MHz) 1.04 (3H, d, *J* 6.4, 2-CH_3), 1.30 (3H, t, *J* 7.0, CH_3CH_2), 1.39 (3H, d, *J* 5.2, 1″-CH_3), 3.62 and 3.64 (each 1H, dq, *J* 9.2 and 7.0, CH_3CH_2), 3.87 and 3.94 (each 3H, s, OCH_3), 4.03 (1H, dq, *J* 8.5 and 6.4, 2-H), 4.57 (1H, d, *J* 8.5, 1-H), 4.73 (1H, q, *J* 5.2, 1″-H), 5.10 (1H, s, 1-OH), 5.18 (2H, s, $C_6H_5CH_2$), 6.36 (1H, s, 3′-H), 6.62 and 7.29 (each 1H, d, *J* 2.4, 6′- and 8′-H), 7.32–7.52 (5H, m, C_6H_5) and 8.88 (1H, s, 1′-OH); δ_C (126 MHz) 15.3 (C-3), 17.8 (CH_3CH_2), 20.8 (C-2″), 56.2 and 57.6 (OCH_3), 62.2 (CH_3CH_2), 70.0 ($C_6H_5CH_2$), 78.3 (C-2), 80.0 (C-1), 93.9 (C-1″), 99.7 (C-6′),[a] 100.6 (C-3′),[a] 106.6 (C-8′),[a] 113.9 (C-8′a),[b] 116.7 (C-4′a),[b] 127.9 (C-2‴ and C-6‴),[c] 128.0 (C-4‴), 128.6 (C-3‴ and C-5‴),[c] 129.3 (C-2′), 136.8 (C-1‴), 144.9 (C-1′), 149.9 (C-4′), 157.2 (C-7′)[d] and 157.9 (C-5′);[d] *m/z* 456 (M^+, 1%), 438 (1), 410 (2), 394 (11), 366 (24), 349 (10), 275 (20), 247 (34), 149 (12), 91 (100) and 65 (11).

2. Of R_f 0.09, one of the diastereomeric products **6**, as an unstable thick, red oil (183 mg, 38%); $[a]_D$ −8.4 (*c* 0.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 3430 (OH), 1609, 1516, 1499 and 1454 (C=C); δ_H (500 MHz) 1.12 (3H, d, *J* 6.2, 2-CH_3), 1.23 (3H, t, *J* 7.1, CH_3CH_2), 1.42 (3H, d, *J* 5.3, 1″-CH_3), 3.53 and 3.74 (each 1H, dq, *J* 9.2 and 7.1, CH_3CH_2), 3.86 and 3.94 (each 3H, s, OCH_3), 4.01 (1H, dq, *J* 8.0 and 6.2, 2-H), 4.22 (1H, s, 1-OH), 4.58 (1H, d, *J* 8.0, 1-H), 4.83 (1H, q, *J* 5.3, 1″-H), 5.17 (2H, s, $C_6H_5CH_2$), 6.34 (1H, s, 3′-H), 6.62 and 7.28 (each 1H, d, *J* 2.3, 6′- and 8′-H), 7.32–7.51 (5H, m, C_6H_5) and 8.55 (1H, s, 1′-OH); δ_C (126 MHz) 15.2 (C-3), 17.7 (CH_3CH_2), 20.3 (C-2″), 56.2 and 57.5 (OCH_3), 61.9 (CH_3CH_2), 70.0 ($C_6H_5CH_2$), 75.3 (C-2), 79.8 (C-1), 94.0 (C-1″), 99.8 (C-6′),[a] 100.1 (C-3′),[a] 106.3 (C-8′),[a] 113.8 (C-8′a),[b] 117.0 (C-4′a),[b] 127.9 (C-2‴ and C-6‴),[c] 128.1 (C-4‴), 128.6 (C-3‴ and C-5‴),[c] 129.4 (C-2′), 136.8 (C-1‴), 144.7 (C-1′), 150.0 (C-4′), 157.3 (C-7′)[d] and 157.9 (C-5′);[d] *m/z* 456 (M^+, 1%), 438 (2), 410 (2), 394 (19), 366 (31), 349 (18), 275 (28), 247 (51), 229 (19), 91 (100) and 65 (12).

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