An Enantioconvergent Synthesis of (*R*)-4-Aryloxy-1-butyne-3-ols for Prostanoid Side Chains

Martin E. Fox,[a] Mark Jackson,[a] Ian C. Lennon,[a,*] Raymond McCague,[a] Julian S. Parratt[a,b]

[a] Chirotech Technology Ltd, Unit 321, Cambridge Science Park, Milton Road, Milton, Cambridge, CB4 0WG, UK
Fax: (+44)-1223–506701, e-mail: ilennon@dow.com
[b] Current Address: Eastman Chemical (UK) Ltd., Llangefni, Anglesey, LL77 7YQ, UK

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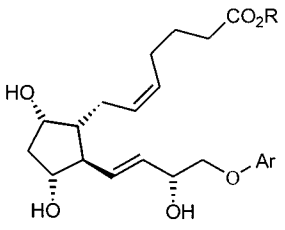
Abstract: The single enantiomer title alcohols, useful as ω-side chain precursors for pharmaceutically important prostaglandin analogues were synthesised from the corresponding racemic alcohols by a convenient 4-step sequence. After enzymatic acylation of the alcohol with a vinyl carboxylate, the residual (*S*)-alcohol in the mixture was converted to the mesylate. Subsequent displacement with the corresponding carboxylate anion, followed by enzymatic deacylation gave the desired (*R*)-alcohol. In this way, all of the starting alcohol was utilised without the need for separation of the starting material and product after the bioresolution.

Keywords: enzymatic resolution; nucleophilic substitution; propargylic compounds; prostanoids.

Introduction

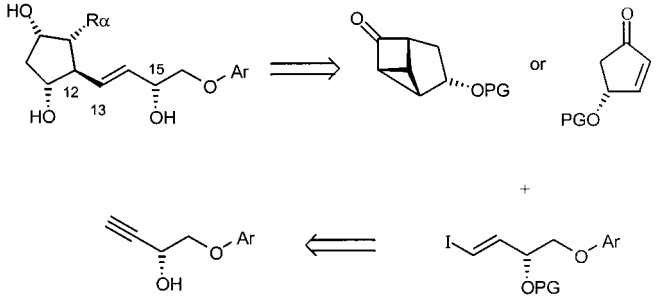
Prostaglandin analogues containing an (*R*)-3-hydroxy-4-aryloxy-1(*E*)-butene-1-yl ω-side chain are important pharmaceutical agents. Examples of such 17-oxaprostaglandin analogues include fluprostenol **1a**, cloprostenol **1c** and their various ester derivatives (Figure 1). Racemic fluprostenol (also known as equimate) was introduced as a veterinary contraceptive agent by ICI.[1] More recently, the single enantiomer isopropyl ester of fluprostenol, travoprost **1b**, has found application as a potent drug for the treatment of glaucoma and ocular hypertension.[2] Other prostaglandin analogues, useful as anti-glaucoma agents, with non-cyclopentanoid cores have also employed this type of ω-side chain.[3]

An attractive approach for the introduction of such side chains from the point of view of convergence and overall stereocontrol is to employ a C12–C13 bond forming step, since this allows the stereocentre at C15 to be defined in the side chain. This may be carried out by coupling of a cuprate reagent derived from an (*E*)-vinyl iodide to a suitable electrophilic cyclopentane core precursor such as a tricycloheptanone[4,5] or cyclopentenone (Scheme 1).[6,7,8] The vinyl iodide is most conveniently prepared from the corresponding suitably protected propargylic alcohol by hydrozirconation-iodination.



1a fluprostenol, Ar = 3-$CF_3C_6H_4$, R = H
1b travoprost, Ar = 3-$CF_3C_6H_4$, R = *i*-Pr
1c cloprostenol, Ar = 3-ClC_6H_4, R = H

Figure 1. Representative 17-oxaprostaglandin analogues.



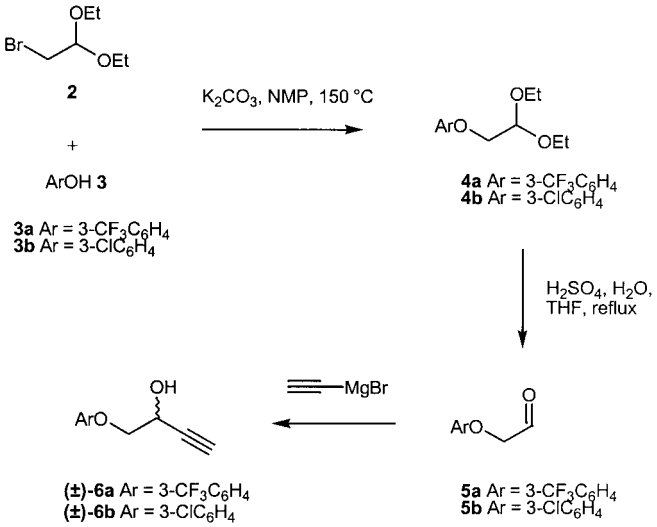
Scheme 1. Retrosynthetic analysis of prostaglandins by C12–C13 disconnection.

Addition of such a racemic cuprate reagent to a cyclopentenone has been used to prepare an 11-deoxy analogue of fluprostenol with a mixture of epimers in the ω-side chain at C15.[9,10] Gooding and coworkers describe the application of conjugate addition of a stannane-derived cuprate reagent to an enone, in a 3-component coupling, to the synthesis of prostaglandin analogues with (*E*)-CH = CHCH(OH)CH_2OPh as the ω-chain.[11]

In order to prepare single isomers of prostaglandin analogues we required a method suitable for the synthesis of large quantities of the single enantiomer ω-side chain propargylic alcohols. Since the racemic alcohols are readily available, the bioresolution of these compounds was an attractive option.[12] In a resolution, the undesired enantiomer is usually discarded. However by combining resolution with S_N2 inversion[13] of the undesired enantiomer, we were able to utilise all of the starting racemate. This approach also negates the need for a method to separate the alcohol from the carboxylate ester.[14]

Results and Discussion

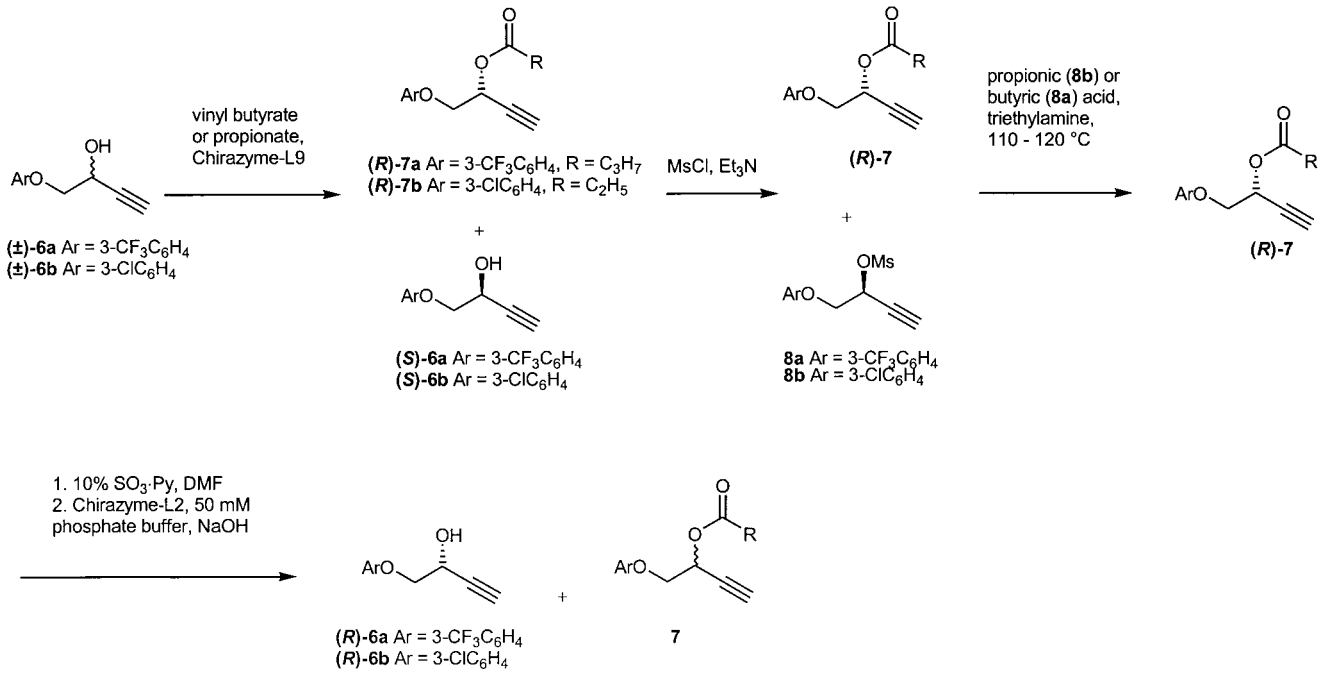
The literature route[9,10] to racemic propargylic alcohols **6** involves a DIBAL-H reduction of carboxylic esters to provide the aldehydes **5.** This process requires a low reaction temperature and a highly exothermic low-temperature quench, and hence is difficult to scale up. Therefore, we employed an alternative route starting with inexpensive bromoacetaldehyde diethyl acetal **2** and the required phenols **3** (Scheme 2). Nucleophilic substitution gave the aryloxyacetaldehyde diethyl acetals **4**,[15] which were hydrolysed to the corresponding aldehydes **5** with aqueous sulfuric acid.[16] Addition of ethynylmagnesium bromide gave the desired racemic alcohols **6** in high overall yield.



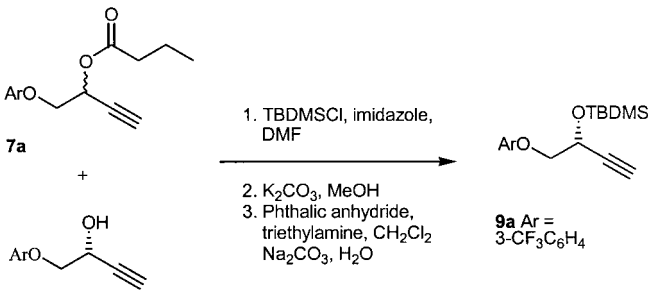
Scheme 2. Synthesis of racemic alcohols **6.**

The racemic alcohols **6** were resolved by Chirazyme L-9-catalysed transesterification[17] with vinyl butyrate **6a** or propionate **6b**, to give a mixture of ester (*R*)-**7** (>90% ee) and alcohol (*S*)-**6** (~90% ee) (Scheme 3).[18] This mixture was treated with methanesulfonyl chloride and triethylamine, converting the alcohol (*S*)-**6** to the mesylate (*S*)-**8.** Heating the mixture of ester (*R*)-**7** and mesylate (*S*)-**8** with either butyric or propionic acid and triethylamine afforded the esters (*R*)-**7** in ~90% ee. The reduction in enantiomeric excess can be attributed to the displacement proceeding *via* a non-S_N2 pathway, some deacylation of (*R*)-**7** under the mesylation conditions, or subsequent racemisation of the product. Indeed, small amounts of alcohol **6** were also present (<5%), presumably generated by ester hydrolysis. This residual alcohol **6** was removed by treatment of the crude ester with 10% sulfur trioxide-pyridine complex to form the hydrogen sulfate ester, which was extracted into the aqueous phase. Further enhancement of the optical purity was accomplished by Chirazyme L-2-catalysed hydrolysis of ester (*R*)-**7** to give the desired alcohol (*R*)-**6** (>99% ee). A screen of the commercially available lipases identified Chirazyme L-9 has the best enzyme for transesterification and Chirazyme L-2 as the optimum enzyme for the ester hydrolysis, in terms of selectivity and reactivity. For the transesterification of 2,5-hexanediol with vinyl butyrate, Chirazyme L-2 was shown to be the most selective enzyme.[19] This demonstrates that each different substrate needs to be screened against the available enzymes, as selectivity and reactivity will vary dramatically.

The (*R*)-3-chlorophenoxy substituted alcohol (*R*)-**6b** is a crystalline solid (mp 48 °C) and was readily separated from residual ester **7b** by crystallisation, to provide the pure alcohol with high enantiomeric purity (>99% ee). This could be converted into the desired *tert*-butyldimethylsilyl ether **9b.** However the (*R*)-3-trifluoromethylphenoxy-substituted alco-



Scheme 3. Bioresolution-inversion sequence.

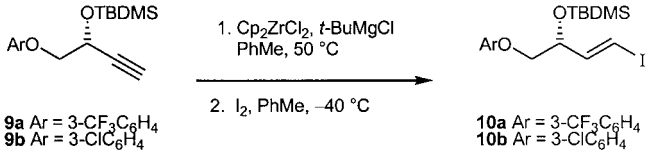


(*R*)-**6a** Ar = 3-$CF_3C_6H_4$

Scheme 4. Silylation of (*R*)-alcohol **10a.**

hol (*R*)-**6a** is a liquid at room temperature, therefore a method had to be developed to remove the residual ester **7a.** This was achieved by silylation of the alcohol (*R*)-**6a** and transesterification of the residual ester **7a**, providing a mixture of **9a** and the alcohol **6a.** Formation of the hemiphthalate ester and washing with aqueous base afforded the pure silyl ether **9a** (Scheme 4). For both examples, overall yields of 58 – 65% were achieved for the conversion of the racemic propargylic alcohols **6** into their respective single enantiomer silyl-protected alcohols **9.**

Hydrozirconation of the silyl-protected alcohols **9** with Schwartz's reagent[20] formed *in situ* and subsequent addition of iodine gave (*E*)-vinyl iodides **10** required for prostanoid synthesis (Scheme 5). Confirmation of the absolute configuration of vinyl iodide **10a** and hence alcohol **6a**, was obtained by transformation to travoprost.[21]



Scheme 5. Hydrozirconation-iodination.

Conclusion

A scaleable and high-yielding synthesis of (*R*)-4-aryloxy-1-butyne-3-ols starting from the corresponding racemic alcohols has been developed. These compounds are precursors to the ω-side chains of commercially important prostaglandin analogues. Utilisation of both enantiomers of the starting racemic alcohol was achieved through inversion of the (*S*)-enantiomer by a 4-step resolution and inversion sequence, providing the products in 58 – 65% yield, as opposed to the theoretical maximum of 50% for a resolution alone.

Experimental Section

General Methods

Melting points were determined on an Electrothermal capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz (Bruker AM200), or 400 MHz (Bruker DPX 400). ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are quoted in ppm. Optical rotations were determined using a Perkin Elmer 341 Polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded using a Perkin Elmer 1600 Series FTIR. Mass spectra were recorded using a Navigator LC/MS system, or a Hewlett Packard GC-MS. Analytical thin layer chromatography was performed on Merck silica gel precoated plates and visualised using ceric ammonium molybdate or potassium permanganate solution. Chirazyme L-9 (Roche Molecular Biochemicals, *Rhizomucor*) and Chirazyme L-2 (Roche Molecular Biochemicals, *Candida antarctica*) were used as supplied.

(3-Trifluoromethylphenoxy)acetaldehyde Diethyl Acetal (4a)[15]

A 20-L flange flask was charged with anhydrous K_2CO_3 (3.14 kg, 22.72 mol, 1.2 equivalents) and 1-methyl-2-pyrrolidinone (5 L, 1.7 volumes). The suspension was stirred under nitrogen, 3-hydroxybenzotrifluoride (**3a**; 2.98 kg, 18.4 mol, 1 equivalent), and bromoacetaldehyde diethyl acetal (**2**; 3.66 kg, 18.6 mol, 1 equivalent) were added. The mixture was stirred at 140 – 150 °C for 8 h. The mixture was cooled to room temperature overnight and then split into two batches for work-up. H_2O (7.5 L) was added to each aliquot in 20-L reaction flasks, leading to two batches, 1 and 2. When the solids had dissolved, the biphasic mixture was extracted with heptane (5 L each). The organic phases were washed with 2 M NaOH (3.75 L each) and H_2O (2 × 4 L each) and dried ($MgSO_4$, 700 g each). The organic phases were filtered and concentrated under reduced pressure. This afforded the acetal **4a** as a brown mobile oil; yields: 2.46 kg (48%) and 1.86 kg, (36.3%); 84.3% overall; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4 (1H, t, *J* = 7.7 Hz), 7.3 – 7.0 (3H, m), 4.85 (1H, t, *J* = 5.5 Hz), 4.05 (2H, d, *J* = 5.5 Hz), 3.85 – 3.55 (4H, m), 1.3 (6H, t, *J* = 7.0 Hz).

(3-Trifluoromethylphenoxy)acetaldehyde (5a)[9,10]

A 20-L flask was charged with the acetal **4a** (1.2 kg, 4.33 mol, 1 equivalent), THF (6 L, 5 volumes) and 2 M H_2SO_4 (6 L, 12 mol, 2.78 equivalents). The biphasic mixture was heated to reflux (65 – 68 °C) under nitrogen, and stirred at reflux for 4 to 5 h. The mixture was cooled to room temperature before toluene (2.5 L) was added, and the lower aqueous phase was removed. The organic phase was evaporated to remove the bulk of the THF. The aqueous phase was extracted with toluene (2.5 L). The combined organic phases were washed with H_2O (3 × 3.5 L), dried over ($MgSO_4$, 634 g), filtered and concentrated under reduced pressure to afford the crude aldehyde as a brown oil (989.6 g). The crude product was purified by wiped film distillation (oil jacket: 150 °C, cold finger 0 °C, vacuum 8 mm Hg). This afforded the product, a 3:1 mixture of aldehyde **5a** and its ethyl hemiacetal, as a pale yellow oil; yield: 799 g (90%). ^{1}H NMR (200 MHz $CDCl_3$): δ = 9.9 (1H, s), 7.4 (1H, t, *J* = 7.7 Hz), 7.3 (1H, d, *J* = 7.7 Hz), 7.2 – 7.0 (2H, m), 4.4 (2H, s).

(±)-4-(3-Trifluoromethylphenoxy)-1-butyne-3-ol (6a)[9,10]

A 20-L flask was fitted with an overhead stirrer, a 500-mL dropping funnel, a nitrogen inlet and outlet and a temperature probe. The flask was charged with ethynylmagnesium bromide (1.22 equivalents, 0.5 M in THF, 9600 mL, 4.8 mol) under a nitrogen atmosphere. The solution was cooled to 15 – 18 °C using an H_2O/ice bath. The neat aldehyde **5a** (799 g, a 3:1 mixture of aldehyde and ethyl hemiacetal, approximately 3.91 mol) was added dropwise over 1 h, maintaining the temperature below 20 °C. Residual aldehyde in the dropping funnel was washed in with additional THF (50 mL). The reaction mixture was stirred at 20 °C for further 2.5 h. Saturated NH_4Cl solution (2 L) was added dropwise to quench the reaction at such a rate that the temperature was maintained below 25 °C. A white precipitate formed and the mixture was stirred for 10 min. H_2O (2 L) was added to dissolve the precipitate, and two layers separated out after 30 – 45 min. The organic layer was removed and was concentrated under reduced pressure. Toluene (1 L) was added to the aqueous layer, followed by 6 M HCl (1.2 L) with vigorous stirring to dissolve the suspended $Mg(OH)_2$. The layers were allowed to

separate, the organic layer was removed and the aqueous layer was extracted with toluene (1 L). The concentrated THF layer was dissolved in toluene (500 mL) and the solution was combined with the two toluene extracts. The combined toluene solution was washed with H_2O (3 L) and brine ($2\times$ 500 mL), dried ($MgSO_4$, 288 g), filtered and concentrated under reduced pressure. This afforded the crude product as a brown oil (867 g). The crude material was purified by wiped film distillation (oil jacket: 150 °C, cold finger +5 °C, vacuum 0.4 mm Hg). This afforded the product **6a** as a yellow oil, which crystallised slowly on standing; yield: 778 g (78% from the acetal **4a** over 2 steps); IR (film): $\nu_{max}=3306$, 3300 (br), 2941, 2880, 2122, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.41$ (1H, t, $J=8.0$ Hz), 7.25 (1H, d, $J=8.5$ Hz), 7.18 (1H, s), 7.11 (1H, dd, $J=8.5$ and 2.5 Hz), 4.80–4.77 (1H, m), 4.18 (1H, dd, $J=9.5$ and 4.0 Hz), 4.13 (1H, dd, $J=9.5$ and 7.0 Hz), 2.73 (1H, br s), 2.54 (1H, d, $J=2.0$ Hz); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta=156.6$, 130.3 (q, $J=32$ Hz), 128.4, 124.8 (q, $J=271$ Hz), 116.5 (q, $J=4$ Hz), 116.4, 109.9 (q, $J=4$ Hz), 79.1, 72.9, 69.8, 59.4.

Bioresolution of (±)-4-(3-Trifluoromethylphenoxy)-1-butyne-3-ol (6a)

The racemic alcohol 6a (843 g, 3.66 mol) was placed in a 10-L jacketed vessel. Heptane (4.3 L) and vinyl butyrate (580 mL, 4.82 mol) were added and the mixture was equilibrated to 22 °C, with efficient stirring under an atmosphere of nitrogen. Chirazyme L-9 (171 g) was added to the mixture, which was then stirred for 45 h at 22 °C. The suspension was filtered, and the residues were washed with heptane (1.5 L) and the washings were combined with the filtrate before evaporating the solvent under reduced pressure. The isolated material was dissolved in toluene (1.7 L) and washed with saturated aqueous $NaHCO_3$ solution (2×550 mL) to remove any remaining butyric acid. The combined aqueous washings were extracted with toluene (330 mL). The combined toluene solutions were washed with saturated aqueous NaCl solution (440 mL), dried ($MgSO_4$, 95 g), filtered and the solvent was removed under reduced pressure to afford an equimolar mixture (993.4 g) of the (*S*)-alcohol (*S*)-6a (>90% ee) and the corresponding (*R*)-butyrate ester (*R*)-7a (>98% ee) in quantitative yield. The mixture was analysed for enantiomeric excess of the starting alcohol and butyrate ester by derivatisation of remaining starting material (pyridine/propionic anhydride) then analysis by chiral GC using a Chirasil DEX-CB column. 150 °C isothermal for 12 min. Butyrate ester, RT (*S*) = 7.6 min, RT (*R*) = 7.9 min. Alcohol (unresolved) RT = 6.1 min. Propionate ester, RT (*S*) = 5.5 min, RT (*R*) = 5.7 min.

In-situ Mesylation of (*S*)-4-(3-Trifluoromethylphenoxy)-1-butyne-3-ol (*S*)-(6a)

The (1:1) alcohol (*S*)-**6a**/butyrate (*R*)-**7a** ester mixture (993 g, 1.83 mol in alcohol) from the Chirazyme L-9-mediated transesterification reaction was dissolved in CH_2Cl_2 (4 L) and added to a 10-L flask fitted with a thermometer, overhead stirrer and pressure equalising dropping funnel under an atmosphere of nitrogen. The mixture was equilibrated to 2 °C (ice/salt bath, temperature −10 °C) with efficient stirring and triethylamine (650 mL, 4.7 mol) was added. The mixture was allowed to return to 0 °C before a solution of methanesulfonyl chloride (200 mL, 2.59 mol) in CH_2Cl_2 (400 mL) was added dropwise over 2 h, maintaining a reaction temperature of <2 °C. Upon complete addition, the reaction was stirred for a further 30 min at <2 °C. When the reaction was complete by TLC (40% EtOAc/heptane), ice-cold H_2O (1.5 L) was added with rapid stirring for 15 min at ~3 °C. After allowing the two layers to partition over the course of 10 min, the two phases were separated. The organic phase was washed with 1.5 N HCl (1.5 L). The CH_2Cl_2 layer was again separated, recharged to the vessel and then washed with saturated aqueous $NaHCO_3$ solution (0.7 L) with rapid stirring. The organic solution was dried ($MgSO_4$, 195 g), filtered and the solvent was removed under reduced pressure to afford a viscous orange oil (1093.9 g, 112.6 wt %). GC analysis indicated that the mesylate **8a**/butyrate **7a** mixture contained no residual alcohol **6a.**

(*R*)-4-[3-(Trifluoromethyl)phenoxy]-1-butyne-3-yl Butyrate (*R*)-(7a)

Butyric acid (230 mL, 2.51 mol) was charged into a 10-L flange flask, fitted with an overhead stirrer, thermometer and pressure equalising dropping funnel. The flask was cooled to 0–5 °C, under a nitrogen atmosphere. Triethylamine (330 mL, 2.37 mol) was added over 1 hour, maintaining an internal temperature below 5 °C. Upon complete addition, the butyrate ester (*R*)-**7a**/mesylate **8a** (1:1) mixture (1093 g, 1.83 mol in mesylate) was added and the reaction mixture was heated to 110–120 °C for 2 h. The mixture was allowed to cool to room temperature overnight. The dark brown reaction mixture was diluted with heptane (1.6 L) and transferred to a 10-L jacketed vessel. A mixture of H_2O (0.8 L) and saturated aqueous $NaHCO_3$ solution (0.8 L) was added and the mixture was vigorously stirred for 15 min. The aqueous phase was separated and extracted with heptane (300 mL). The organic phases were combined and washed with 1.2 N HCl (0.8 L), and saturated aqueous $NaHCO_3$ solution (0.8 L). The organic phase was dried over $MgSO_4$ (100 g), filtered and the solvent was removed under reduced pressure to yield the butyrate **7a** as a brown liquid; yield: 891.4 g (83%). GC analysis using a Chirasil DEX-CB column indicated that the enantiomeric excess was 90%. Some alcohol **6a** was present in the crude product.

Removal of Residual Alcohol 7a from Butyrate (*R*)-(7a)

The crude butyrate **7a** was added to a 5-L flange flask, fitted with an overhead stirrer and nitrogen inlet. DMF (0.9 L) was added, then sulfur trioxide-pyridine complex (45 g, 0.32 mol) was added in approximately 10-g portions until GC showed no alcohol **6a** present, the reaction mixture was stirred for additional 80 min. The reaction mixture was diluted with heptane (1.8 L) and saturated aqueous $NaHCO_3$ solution (2.3 L) was added. The mixture was stirred for 10 min, the aqueous phase was separated and extracted with heptane (0.5 L). The combined organic extracts were washed with 10% aqueous $KHSO_4$ solution (0.9 L), saturated aqueous $NaHCO_3$ solution (0.9 L) and then dried with $MgSO_4$ (50 g). The solution was filtered and evaporated to give butyrate **7a** as a yellow oil; yield: 851 g (96% by weight), 90% ee by chiral GC analysis using a Chirasil DEX-CB column.); IR (film): $\nu_{max}=3306$, 2969, 2938, 2879, 2128, 1747, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.40$ (1H, t, $J=8.0$ Hz), 7.24 (1H, d, $J=7.5$ Hz), 7.16 (1H, s), 7.09 (1H, dd, $J=8.5$ and 2.5 Hz), 5.79–5.76 (1H, m), 4.30–4.23 (2H, m), 2.55 (1H, d, $J=2.0$ Hz); 2.35 (2H, quintet, $J=7.4$ Hz), 0.96 (3H, t, $J=7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=172.8$, 158.6, 132.0 (q, $J=32$ Hz), 130.5, 124.2 (q, $J=271$ Hz), 118.6, 112.0 (q, $J=4$ Hz), 78.2, 75.5, 69.4, 62.1, 36.3, 18.7, 13.9. MS (APCI): $m/z=301$ (M + H, 100%), 213 (M − $C_4H_7O_2$, 74); anal. found: C 60.09, H 5.14%; $C_{15}H_{15}F_3O_3$ requires C 60.00, H 5.03%.

(*R*)-4-(3-Trifluoromethylphenoxy)-1-butyne-3-ol (*R*)-(6a)

KH_2PO_4 solution (30.9 g in 4.4 L H_2O) was added to a 10-L jacketed vessel. The solution was equilibrated to 28–32 °C. KOH solution (12.2 g in 109 mL H_2O) was titrated in until pH 6.9–7.1 was reached. The butyrate ester (*R*)-**7a** (851.4 g, 2.84 mol) was dissolved in heptane (850 mL) and this solution was added to the buffer solution. The mixture was equilibrated to 28–32 °C. Chirazyme L-2 (19.2 g) was added and the reaction mixture stirred at 30 °C while titrating to pH 7 (actual 6.9–7.1) using 4 N NaOH solution. After 3 h the reaction reached 90% conversion (according to base uptake – 570 mL). Toluene (0.7 L) was added, and the catalyst was removed by suction filtration. The organic phase was separated and the aqueous phase was extracted with toluene (0.4 L). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ solution (2×0.7 L), dried ($MgSO_4$, 50 g), filtered and the filter cake was washed with additional toluene (0.6 L). The solvent was evaporated under reduced pressure to afford crude (*R*)-alcohol (*R*)-**6a**; yield: 716 g (84%), >99% ee by derivatisation with pyridine/propionic anhydride and chiral GC analysis using a Chirasil DEX-CB column) containing butyrate ester **7a** [8–10%, 90% ee (*S*)] as a brown oil.

(*R*)-4-(3-Trifluoromethylphenoxy)-3-(*tert*-butyldimethylsilyloxy)-1-butyne (9a)

Crude alcohol (*R*)-**6a** (740 g, about 75% pure, 2.41 mmol) was dissolved in DMF (1 L) and the solution was placed in a nitrogen-purged flask. Imidazole (214 g, 3.14 mol) was added. The solution was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (364 g, 2.41 mol) was added in portions, maintaining the internal temperature below 10 °C. The reaction mixture was allowed to warm to room temperature, and stirred for 15 h. H_2O (2.2 L) was added over 30 min. The mixture was extracted with heptane (2.2 L + 0.6 L). The combined organic phases were washed with H_2O (2 × 1 L), dried ($MgSO_4$) filtered and concentrated under reduced pressure to provide the crude (*R*)-silyl ether **9a**; yield: 988 g.

Removal of Residual Butyrate Ester 7a from (*R*)-4-(3-Trifluoromethylphenoxy)-3-(*tert*-butyldimethylsilyloxy)-1-butyne (9a)

Crude silyl ether (*R*)-**9a** (988 g, about 75% pure, 2.15 mmol) was dissolved in MeOH (1.5 L) and K_2CO_3 (37 g, 0.27 mol) was added. The mixture was stirred for 3 h, after which the methanol was removed under reduced pressure. H_2O (1.5 L) and heptane (1.5 L) were added to the residue, the mixture was stirred, and the layers were separated. The organic layer was washed with H_2O (0.7 L), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.5 L), phthalic anhydride (78 g, 0.53 mol) and NEt_3 (87 mL, 0.63 mol) were added. The solution was stirred for 2 h, after which the solvent was removed under reduced pressure and 10% aqueous Na_2CO_3 solution (0.7 L), heptane (2.2 L), H_2O (4.5 L) and NaCl (500 g) were added. After stirring vigorously the mixture was allowed to partition. The heptane layer was separated, the aqueous layer was extracted with heptane (0.5 L), and the combined organic layers were washed with H_2O (1.5 L). The heptane solution was dried over $MgSO_4$ and passed through a silica plug (321 g). The compound was eluted with heptane (1.5 L), and after evaporation of the solvent, the (*R*)-silyl ether **9a** was obtained as a light yellow mobile liquid; yield: 740 g (58% overall from the racemic propargylic alcohol (±)-**6a**); $[\alpha]_D^{23}$: −28.2 (*c* 0.98, CH_2Cl_2); IR (film): ν_{max} = 3310, 1329, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (1H, t, *J* = 8.0 Hz), 7.08 (1H, d, *J* = 7.5 Hz), 7.00 (1H, s), 6.95 (1H, dd, *J* = 8.5 and 2.5 Hz), 4.61 (1H, td, *J* = 6.0 and 2.0 Hz), 3.97 (2H, d, *J* = 6.0 Hz), 2.35 (1H, d, *J* = 2.0 Hz), 0.78 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 132.2 (q, *J* = 32 Hz), 130.4, 127.0, (q, *J* = 271 Hz), 118.6, 118.1, 111.9 (q, *J* = 4 Hz), 82.4, 74.1, 72.6, 62.4, 26.0, 18.7, −4.4, and −4.6; MS (APCI); *m/z* = 345 (M + H, 32%) 279 (15), 213 (M − $C_6H_{15}SiO$, 73), 179 (100), 147 (83); anal. found: C 59.27, H 6.79%; $C_{17}H_{23}F_3SiO_2$ requires C 59.28, H 6.73%. After removal of the TBDMS group from a small sample with HCl in MeOH, chiral HPLC analysis of the propargylic alcohol (*R*)-**6a** using a Chiralpak AD column, UV 210 nm, 1.0 mL/min, elution solvent 96:4 heptane:isopropanol showed the enantiomeric excess to be > 99%.

(*R*)-4-(3-Trifluoromethylphenoxy)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-1*E*-butene (10a)

A dry, 5-L, three-necked flask was purged with nitrogen, and bis(cyclopentadienyl)zirconium dichloride (459 g, 1.57 mol) and toluene (2 L) were added. The vessel was covered with aluminium foil to exclude light, evacuated and purged with nitrogen. *tert*-Butylmagnesium chloride (2 M in ether, 785 mL) was added over 30 min. The mixture was heated at 50 °C for 1 hour. During this time gas evolution was observed (isobutylene). The alkyne **9a** (450 g, 1.31 mol) in toluene (500 mL) was added, and heating was continued between 50–60 °C for 5 h. The reaction mixture was cooled to −40 °C and a solution of iodine (497 g, 1.96 mol) in THF (600 mL) was added over 35 min. The mixture was warmed to room temperature over one hour, then 1 M aqueous $Na_2S_2O_5$ (2 L) was added. Heptane (3 L) was added and a dense bright yellow precipitate formed. The mixture was filtered, and the filter cake was washed with heptane (1 L). The organic layer was separated, the aqueous phase was extracted with heptane (1 L), and the combined organic phases were washed with 1 M aqueous $Na_2S_2O_5$ solution (3 L), saturated aqueous $NaHCO_3$ solution (2 L) and brine (2 L). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was passed through a pad of activated aluminium oxide (Neutral Brockmann 1, 150 mesh, 750 g) eluting with heptane (6 L). The solution was concentrated under reduced pressure, the residue was dissolved in heptane (1 L) and filtered through a Celite pad. The solution was concentrated to provide the iodide **10a** as a red/brown oil; yield: 441 g (71.5%); $[\alpha]_D^{23}$: −15.5 (*c* 0.96, CH_2Cl_2); IR (film): ν_{max} = 1609, 1592, 1329, 1130 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.11 (6H, s, 2), 0.92 (9H, s), 3.91 (2H, d, *J* = 6.0 Hz), 4.51 (1H, m, CH), 6.50 (1H, dd, *J* = 14.0 and 1.0 Hz), 6.68 (1H, dd, *J* = 14.0 and 5.0 Hz), 7.04–7.11 (2H, m), 7.24 (1H, m), 7.40 (1H, t, *J* = 8.0 Hz). GC analysis showed 5–10% of the alkene 4-(3-trifluoromethylphenoxy)-3-(*tert*-butyldimethylsilyloxy)-1-butene to be present.

(3-Chlorophenoxy)acetaldehyde Diethyl Acetal (4b)[15,16]

A mixture of bromoacetaldehyde diethyl acetal **2** (61.6 g, 313 mmol), 3-chlorophenol **3b** (40.2 g, 313 mmol), and K_2CO_3 (47.5 g, 344 mmol) in *N*-methylpyrrolidinone (80 mL) was heated to 140 °C under a nitrogen atmosphere overnight then to 150 °C for further 4 h. The mixture was allowed to cool to room temperature and partitioned between heptane (300 mL) and H_2O (300 mL). The organic phase was washed with 2 M aqueous NaOH solution (200 mL) and H_2O (2 × 200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give acetal **4b** as a pale brown liquid; yield: 55.9 g (73%). IR (film): ν_{max} = 2976, 2931, 2880, 1594, 1478, 1307, 1286 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (1 H, t, *J* = 8.4 Hz), 6.95–6.93 (2H, m), 6.81 (1H, ddd, *J* = 8.2, 2.4 and 1.0 Hz), 4.82 (1H, t, *J* = 5.2 Hz), 3.98 (2H, d, *J* = 5.2 Hz), 3.80–3.73 (2H, m), 3.67–3.59 (2H, m), 1.25 (6H, t, *J* = 7.0 Hz); GCMS (EI): *m/z* = 155 (9%), 153 (25%), 103 (93), 75 (77), 47 (100); anal. found: C 58.76, H 6.87, Cl 14.52%; $C_{12}H_{17}ClO_3$ requires C 58.90, H 7.00, Cl 14.49%.

(3-Chlorophenoxy)acetaldehyde (5b)[16]

A 2 M solution of H_2SO_4 was added to the acetal **4b** (55.5 g, 227 mmol), dissolved in THF (550 mL). The H_2SO_4 solution was added to the acetal solution and the mixture was heated at reflux under nitrogen while stirring vigorously for 20 h. The solution was allowed to cool to room temperature then diluted with toluene (500 mL). The aqueous layer was removed and the organic layer was washed with H_2O (3 × 250 mL), dried ($MgSO_4$), filtered, and the solvent was concentrated under reduced pressure. Kugelrohr distillation (150–175 °C at 0.5–1 mm Hg) gave the aldehyde **5b** as a pale yellow mobile oil; yield: 34.9 g (90%). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.86 (1H, s), 7.23 (1H, t), 7.02 (1H, d), 6.91 (1H, t), 6.85–6.75 (1H, m), 4.59 (2H, s); GCMS (EI): *m/z* = 172 ($M^{37}Cl$, 15%), 170 ($M^{35}Cl$, 46), 143 (25), 141 (69), 113 (57), 111 (100).

(±)-4-(3-Chlorophenoxy)-1-butyne-3-ol (6b)

Ethynylmagnesium bromide (0.5 M in THF, 530 mL, 265 mmol) was transferred to a nitrogen-purged flask. The Grignard solution was cooled to +4 °C, then the aldehyde **5b** (34.9 g, 205 mmol) was added over 15 min. Residual aldehyde was washed in with THF (10 mL). The solution was stirred for 1 h at 0–10 °C, then allowed to warm to room temperature and stirred at room temperature for 15 h. The reaction was quenched with H_2O (250 mL), then the mixture was acidified with 2 M HCl (250 mL). The layers were separated and the aqueous layer was extracted with toluene (250 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (250 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated to give the crude acetylenic alcohol **6b** as a brown oil, which solidified slowly on storage; yield: 38.7 g (96%). The crude product (37 g) was recrystallised as follows: The solid was dissolved in toluene (100 mL) and heptane (200 mL) was added. The solution was cooled to 10 °C, then cooled to 0 °C in stages over 2–3 h, and stirred at 0 °C for 1 h. The solid was

collected by filtration, washed with ice-cold heptane-toluene (2:1) and dried to give the pure alcohol as a buff powder; yield: 24.7 g. A second crop was obtained after combining the mother liquors from the two recrystallisations; yield: 4.9 g; total yield: 29.6 g (85%); mp 38 °C; IR (KBr): $\nu_{max} = 3300$ (br), 3263, 1598, 1477, 1450, 1287, 1229, 1096, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.21$ (1H, t, $J = 8.1$ Hz), 6.98 (1H, dt, $J = 7.9$ and 1.0 Hz), 6.95 (1H, t, $J = 2.2$ Hz), 6.83 (1H, ddd, $J = 8.4$, 2.5 and 1.0 Hz), 4.79 – 4.74 (1H, m), 4.13 (1H, dd, $J = 9.4$ and 3.5 Hz), 4.07 (1H, dd, $J = 9.4$ and 6.9 Hz), 2.55 (1H, d, $J = 2.0$ Hz), 2.49 (1H, d, $J = 5.4$ Hz); GCMS (EI): $m/z = 198$ ($M^{37}Cl$, 8%), 196 ($M^{35}Cl$, 24), 181 (11), 143 (19), 141 (56), 128 (90), 113 (50), 111 (100), 105 (19).

Bioresolution of (±)-4-(3-Chlorophenoxy)-1-butyne-3-ol (6b)

The racemic alcohol **6b** (19.1 g, 97 mmol) was placed in a jacketed flask, and MTBE (17 mL) and heptane (95 mL) were added. The mixture was equilibrated to 22 °C and vinyl propionate (13.2 mL, 121 mmol) and Chirazyme-L-9 (4.46 g) were added. The mixture was stirred at 22 °C for 46.5 h, after which time chiral GC analysis showed the starting alcohol to be 87% ee (*S*) and the propionate to be 92% ee (*R*), a conversion of 48.6%. The solution was filtered and the solvent was evaporated to give the alcohol (*S*)-**6b**/propionate (*R*)-**7b** mixture as a pale yellow oil. Analysis for enantiomeric excess was by derivatisation with pyridine/butyric anhydride then analysis by chiral GC using a Chirasil DEX-CB column. 120 °C for 15 min, ramp to 165 °C at 3 °C/min, hold for 10 min. Alcohol (TFA derivative), RT (*S*) = 22.3 min, RT (*R*) = 22.5 min. Alcohol (unresolved), RT = 35.2 min. Propionate ester, RT (*S*) = 33.5 min, RT (*R*) = 34.2 min. Butyrate ester, RT (*S*) = 38.6 min, RT (*R*) = 39.3 min.

Mesylation of alcohol (*S*)-(6b)/Propionate (*R*)-(7b) Mixture

The alcohol **6b**/propionate **7b** mixture was dissolved in MTBE (100 mL) and the solution was cooled to 5 °C. NEt_3 (10.8 mL, 78 mmol) was added. The solution was cooled to 0 – 2 °C and methanesulfonyl chloride (3.75 mL, 48.5 mmol) was added over 30 min, maintaining the internal temperature at 0 – 2 °C. The suspension was stirred at 0 – 2 °C for 15 min then extra methanesulfonyl chloride (0.2 mL, 2.6 mmol) was added. The suspension was stirred at 0 – 2 °C for 5 min then the reaction was quenched with H_2O (85 mL). The aqueous layer was removed, and the organic layer was washed with a mixture of saturated aqueous $KHSO_4$ solution and H_2O (1:1, 80 mL), saturated aqueous $NaHCO_3$ solution (80 mL) and brine (40 mL). After drying ($MgSO_4$), filtration and evaporation of the solvent, the mesylate **8b**/propionate **7b** mixture was obtained as a yellow oil; yield: 26 g. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.27 - 6.92$ (4H total, m), 6.84 – 6.78 (2H, m) 5.74 (1H propionate, td, $J = 5.8$ and 2.3 Hz), 5.51 (1H mesylate, td, $J = 5.6$ and 2.4 Hz), 4.25 (2H, mesylate, d, $J = 4.9$ Hz), 4.19 (1H propionate, d, $J = 5.5$ Hz), 3.16 (3H mesylate, s), 2.79 (1H mesylate, d, $J = 2.4$ Hz), 2.53 (1H propionate, d, $J = 2.1$ Hz), 2.39 (2H propionate, q, $J = 7.6$ Hz), 1.16 (3H propionate, t, $J = 7.5$ Hz).

(*R*)-4-(3-Chlorophenoxy)-1-butyne-3-yl Propionate (*R*)-(7b)

NEt_3 (12 mL, 86 mmol) was added to propionic acid (7.2 mL, 97 mmol) over 15 min. The mesylate **8b**/propionate (*R*)-**7b** mixture (26 g) was added, washing in with NEt_3 (1.5 mL, 11 mmol). The reaction flask was purged with nitrogen, and the mixture was heated to 110 – 120 °C for 4 h, allowed to cool to room temperature. The mixture was diluted with heptane (80 mL) and saturated aqueous $NaHCO_3$ solution (80 mL) was added cautiously while stirring. The layers were separated and the aqueous layer was extracted with heptane (20 mL). The combined organic layers were washed with saturated aqueous $KHSO_4/H_2O$ (1:1, 80 mL), saturated aqueous $KHSO_4$ solution (80 mL) and saturated aqueous $NaHCO_3$ solution (80 mL), dried ($MgSO_4$) and filtered. The solvent was concentrated under reduced pressure to afford the crude propionate (*R*)-**7b** as a brown oil; yield: 20.3 g.

Removal of Residual Alcohol from Crude Propionate (*R*)-(7b)

The crude propionate (20.3 g, 80.3 mmol) was dissolved in anhydrous DMF (20 mL). Sulfur trioxide-pyridine complex (1.28 g, 8.03 mmol) was added. The solution was stirred at room temperature for 1 h. The solution was diluted with heptane (80 mL) then saturated aqueous $NaHCO_3$ solution (40 mL) was added cautiously while stirring. H_2O (40 mL) was added and the layers were separated. The organic layer was washed with saturated $KHSO_4$ solution/H_2O (1:1, 80 mL), dried ($MgSO_4$) and filtered. After evaporation of the solvent, the alcohol-free propionate (*R*)-**7b** was obtained as a brown oil; yield: 19.3 g (79% from the racemic alcohol **6b**), enantiomeric excess 79% by chiral GC using a Chirasil DEX-CB column; IR (film): $\nu_{max} =$ 3293, 2942, 2882, 2127, 1747, 1594, 1428, 1362, 1284 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.21$ (1H, t, $J = 8.1$ Hz), 6.98 (1H, dt, $J = 7.9$ and 1.0 Hz), 6.95 (1H, t, $J = 2.2$ Hz), 6.83 (1H, ddd, $J = 8.4$, 2.5 and 1.0 Hz), 4.76 – 5.73 (1H, m), 4.23 – 4.10 (2H, m), 2.53 (1H, d, $J = 2.4$ Hz), 2.47 – 2.32 (2H, m); 1.16 (3H, t, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.2$, 158.8, 135.0, 130.3, 122.3, 115.4, 113.2, 77.9, 75.1, 69.0, 61.9, 27.4, 8.9; GCMS (EI): $m/z =$ 180 ($M^{37}Cl$-propionate, 3%), 178 ($M^{35}Cl$-propionate, 8), 125 (35), 57 (100).

(*R*)-4-(3-Chlorophenoxy)-1-butyne-3-ol (*R*)-(6b)

A 50 mM phosphate buffer was prepared in a jacketed flask by dissolving KH_2PO_4 (1.04 g, 7.63 mmol) in H_2O (150 mL). The solution was equilibrated to 30 °C then titrated to pH 7 with aqueous 2 M KOH solution. A solution of NaOH (3.24 g, 81 mmol) in H_2O (20 mL) was also prepared. A solution of the (*R*)-propionate (*R*)-**7b** (24.1 g, 95 mmol) in heptane (22 mL) was added to the buffer solution. Chirazyme L-2 (440 mg) was added and the mixture was stirred vigorously at 30 °C for 4 h while titrating to pH 7 with the NaOH solution [19 mL (approximately 77 mmol) of NaOH solution was used]. The mixture was diluted with toluene (50 mL), filtered through Celite, washing the bed with toluene (30 mL) and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 80 mL), dried ($MgSO_4$), and filtered through a silica plug (20 g), eluting with heptane-MTBE (2:1, 200 mL). After evaporation of the solvent, toluene (50 mL) and heptane (150 mL) were added. The solution was cooled to −10 °C over 30 min while stirring. Crystallisation began at 10 °C. The suspension was stirred at −10 °C for 30 min and filtered. The crystals were washed with cold (−20 °C) heptane-toluene (3:1) and dried to give the alcohol (*R*)-**6b** as a fine white solid; yield: 10.9 g (58.1%), enantiomeric excess >99% by chiral GC. Analysis for enantiomeric excess was by derivatisation with trifluoroacetic anhydride then analysis by chiral GC using a Chirasil DEX-CB column. 120 °C for 15 min, ramp to 165 °C at 3 °C/min, hold for 10 min. Alcohol (TFA derivative), RT (*S*) = 22.3 min, RT (*R*) = 22.5 min. Alcohol (underivatised), RT = 35.2 min; mp 48 °C; $[\alpha]_D^{25}$: −24.4 (*c* 1.0, $CHCl_3$); IR (KBr): $\nu_{max} = 3300$ (br), 3285, 1598, 1481, 1431, 1312, 1275, 1255, 1232, 1095, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.20 (1H, t, $J = 8.1$ Hz), 6.96 (1H, dt, $J = 7.9$ and 1.0 Hz), 6.93 (1H, t, $J =$ 2.2 Hz), 6.81 (1H, ddd, $J = 8.4$, 2.5 and 1.0 Hz), 4.77 – 4.73 (1H, m), 4.11 (1H, dd, $J = 9.4$ and 3.9 Hz), 4.06 (1H, dd, $J = 9.9$ and 6.9 Hz), 2.65 (1H, d, $J =$ 5.4 Hz), 2.53 (1H, d, $J = 2.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.8$, 135.0, 130.4, 121.7, 115.3, 113.2, 80.8, 74.6, 71.5, 61.1; GCMS (EI): $m/z = 198$ ($M^{37}Cl$, 8%), 196 ($M^{35}Cl$, 24), 181 (11), 143 (19), 141 (56), 128 (90), 113 (50), 111 (100) and 105 (19); anal. found: C 61.09, H 4.64, Cl 17.91%; $C_{10}H_9ClO_2$ requires C 61.08, H 4.61, Cl 18.03%.

(*R*)-4-(3-Chlorophenoxy)-3-tert-butyldimethylsilyloxy-1-butyne (9b)

Imidazole (7.86 g, 115 mmol) was added to a solution of alcohol (R)-**6b** (10.8 g, 55 mmol) in DMF (11 mL). When the solution was homogeneous, it was cooled in an ice/H_2O bath and tert-butyldimethylsilyl chloride (8.70 g, 57.7 mmol) was added over 15 min. The solution was allowed to warm to room temperature and stirred at room temperature for 2 h. The reaction was quenched cautiously by addition of H_2O (75 mL) over 15 min, then heptane (75 mL) was added. The organic layer was separated and washed (H_2O, 2 ×

75 mL), dried ($MgSO_4$), then filtered through a silica pad (5 g), eluting with heptane (75 mL) to give the silyl ether **9b** as a colourless, mobile oil; yield: 17.0 g (99.5%); $[\alpha]_D^{25}$: −30.7 (c 1.2, $CHCl_3$); IR (film): ν_{max} = 3305, 2953, 2929, 2857, 1594, 1476, 1429, 1362, 1287, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (1H, t, J = 8.1 Hz), 6.95 – 6.91 (2H, m), 6.80 (1H, ddd, J = 8.4, 2.5 and 1.0 Hz), 4.72 (1H, td, J = 5.9 and 2.5 Hz), 4.08 – 4.01 (2H, m), 2.47 (1H, d, J = 2.0 Hz), 0.91 (9H, s), 0.16 (3H, s), 0.13 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 134.8, 130.2, 121.2, 115.2, 113.1, 82.0, 73.6, 72.2, 62.0, 25.7, 18.3, −4.8, −5.0; GCMS (EI): m/z = 255 ($M^{37}Cl$ − 57, 10%), 253 ($M^{35}Cl$ − 57), 213 (31), 187 (32), 185 (100), 75 (40); anal. found: C 61.78, H 7.39, Cl 11.45%; $C_{16}H_{23}ClO_2Si$ requires C 61.81, H 7.46, Cl 11.40%. After removal of the TBDMS group with HCl/MeOH and derivatisation with trifluoroacetic anhydride, the enantiomeric excess was found to be > 99% by chiral GC analysis using a Chirasil DEX-CB column.

(*E*)-1-Iodo-4-(3-chlorophenoxy)-3(*R*)-*tert*-butyldimethylsilyloxy-1-butene (10b)

Zirconocene dichloride (9.35 g, 32.0 mmol) and toluene (50 mL) were added to a 250-mL, three-necked flask, which was then flushed with nitrogen and maintained under a nitrogen atmosphere. The flask was covered with foil to exclude light. The mechanical stirrer was started and *tert*-butylmagnesium chloride (2 M, Et_2O, 16.0 mL, 32.0 mmol) was added. The mixture was heated to 50 °C for 1 h. The alkyne **9b** (8.29 g, 26.66 mmol) in toluene (20 mL) was added and heating was continued for a further 5 h. The heating mantle was removed and the reaction allowed to cool to room temperature. The flask was then cooled in a CO_2/acetone bath to −40 °C. A solution of iodine (10.15 g, 40.0 mmol) in tetrahydrofuran (20 mL) was added over 10 min (maximum temperature reached −33 °C). The cold bath was removed and the mixture was allowed to warm to 20 °C. After 20 min, the reaction mixture was re-cooled to 10 °C and aqueous 1 M $Na_2S_2O_5$ (100 mL) was added (temperature increased to 18 °C). The mixture was poured into a mixture of heptane (100 mL) and aqueous $Na_2S_2O_5$ (1 M, 100 mL) and then filtered to remove a dense yellow precipitate. The filter cake was washed with heptane (100 mL). The organic phase was separated and the aqueous layer was extracted with heptane (100 mL). The combined organic phases were washed with aqueous 1 M $Na_2S_2O_5$ (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by filtration through a pad of neutral alumina (40 g), eluting with heptane (300 mL) and then 5% MTBE in heptane (100 mL). The solvent was evaporated to give a slightly cloudy yellow/orange oil. The purification step was repeated using a pad of alumina (10 g) over a bed of Celite and eluting with heptane (250 mL). Evaporation of solvent afforded the vinyl iodide **10b** as a clear yellow/orange oil; yield: 8.77 g (20.2 mmol, 75%); $[\alpha]_D^{30}$: −13.8 (*c* 1.0, CH_2Cl_2); IR (film): ν_{max} = 1595, 1475 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.20 (1 H, t, *J* = 8.0 Hz), 6.97 – 6.88 (2H, m), 6.80 – 6.74 (1H, m), 6.67 (1H, dd, *J* = 14.5 and 5.0 Hz), 6.48 (1H, dd, *J* = 14.0 and 7.0 Hz), 4.51 – 4.43 (1H, m), 3.85 (2H, d, *J* = 6.0 Hz), 0.91 (9H, s), 0.10 (6H, s); GCMS (EI): *m*/*z* = 381 (M − *t*-Bu, 9%), 185 (100). GC analysis showed 5 – 10% of the alkene 4-(3-chlorophenoxy)-3-(*tert*-butyldimethylsilyloxy)-1-butene to be present.

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