Highly Stereoselective Access to an (*E*)-Vinyl Bromide from an Aryl Ketone Leads to Short Syntheses of (*Z*)-Tamoxifen and Important Substituted Derivatives

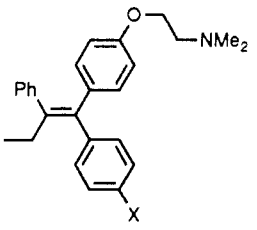
Gerard A. Potter and Raymond McCague*

Drug Development Section, Institute of Cancer Research, Sutton, Surrey, SM2 5NG, U.K.

Received April 4, 1990

The enol triflate derived from a 1-(4-alkoxyphenyl)-2-phenyl-1-butanone is unstable, fragmenting to a vinyl cation that can be trapped by bromide ion. The *E* isomer of the vinyl bromide which is formed in preference (20:1) gave, upon palladium-catalyzed coupling with phenylzinc chloride, an immediate precursor of (*Z*)-tamoxifen. Similarly, coupling with other aryl metal reagents led to the first stereoselective synthesis of the potent antiestrogen metabolite (*Z*)-4-hydroxytamoxifen and to (*E*)-4-bromotamoxifen. The alkoxy substituent assisted fragmentation of the enol triflate, but as a 1-phenyl group was sufficient to allow stereoselective vinyl bromide formation, the methodology could have generality in the stereoselective synthesis of tetrasubstituted olefins that are styrene derivatives.

Tamoxifen (1) (Citrate = ICI-Nolvadex) is a drug in clinical use for the treatment of hormone dependent breast cancer.[1] For this purpose, only the *Z* isomer of this tetrasubstituted olefin has the required antiestrogenic activity. The *E* isomer is contrastingly estrogenic[2] and consequently procedures for the stereoselective synthesis of tamoxifen are worthwhile. Amongst the metabolites of tamoxifen formed in patients, the 4-hydroxy derivative **2** (4-hydroxytamoxifen)[3] is of particular importance since it binds to the estrogen receptor with 100 times the affinity of tamoxifen.[4] Yet no stereoselective route to the preparation of **2** has been reported. Recently we have shown that there are other 4-substituted derivatives that also have greater in vitro potency than tamoxifen.[5]

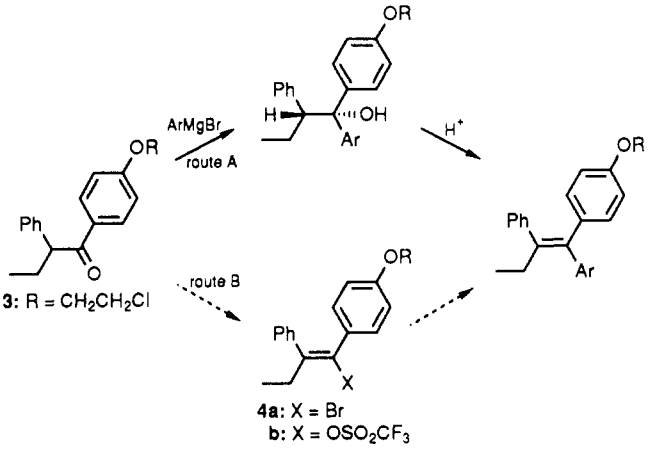


1: X = H
2: X = OH

Classically the synthesis of tamoxifen and its derivatives (Scheme I, route A) involves addition of an aryl Grignard reagent to a 1,2-diarylbutanone.[6] This addition is stereospecific, following Cram's rule, but the subsequent acid-promoted dehydration gives an isomer mixture.[7] A procedure for isolation of the required stereoisomer then needs to be found whenever a new product is prepared by this procedure.

An ideal and versatile intermediate for the synthesis of tamoxifen and derivatives would be the vinyl bromide **4a** or triflate **4b**, since the bromide or triflate function should be replacable by an aryl group with retention of configuration in a palladium complex catalyzed coupling reaction (Scheme I, route B).[8,9] Indeed, such a coupling has been employed in a stereospecific synthesis of tamoxifen where a vinyl bromide was prepared following carbometalation of an appropriate alkyne.[10] Here, though, the alkoxy-bearing ring was introduced last. Carbometalation of an unsymmetrically diaryl-substituted alkyne could provide **4a** but would give predominantly the wrong regioisomer.[11]

Scheme I



We report here that the ketone **3** where R = CH_2CH_2Cl can be converted with a high degree of stereoselectivity into the (*E*)-vinyl bromide **4a**, which is a versatile precursor to tamoxifen and analogues, exemplified by the synthesis of 4-hydroxytamoxifen (**2**) and 4-bromotamoxifen.

Results and Discussion

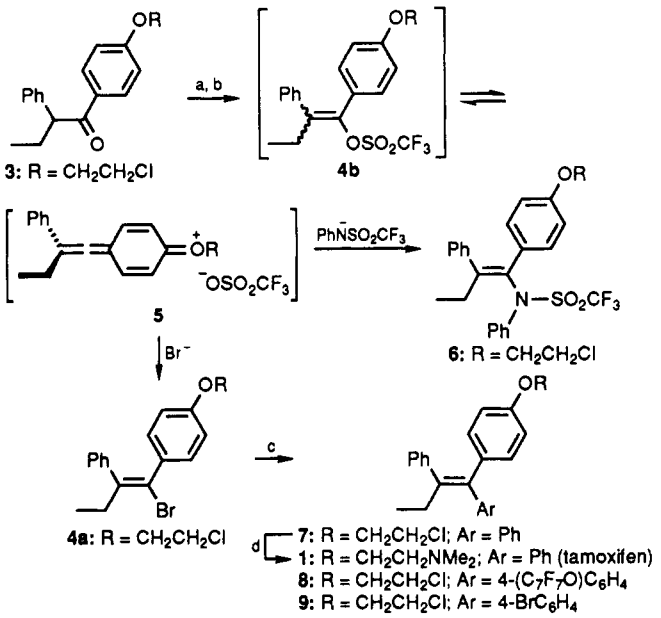
Preparation of the (*E*)-Vinyl Bromide 4a. The starting material for this study was the ketone **3**, readily preparable by Friedel-Crafts condensation between (2-chloroethoxy)benzene and 2-phenylbutyric acid.[12] Its chloroethoxy function is easily converted into the amino-alkoxy side chain of tamoxifen. Initially, an attempt was made to convert this ketone into its enol triflate **4b**, although no stereoselectivity was anticipated at this stage. Accordingly, **3** was deprotonated with potassium hydride

*To whom correspondence should be addressed; now at Enzymatic Ltd., Cambridge Science Park, CB4 4WE, U.K.

(1) Furr, B. J. A.; Jordan, V. C. *Pharmacol. Ther.* **1984**, *25*, 127.
(2) Harper, M. J. K.; Walpole, A. L. *Nature (London)* **1966**, *212*, 87.
(3) Daniel, C. P.; Gaskell, S. J.; Bishop, H.; Nicholson, R. I. *J. Endocrinol* **1979**, *83*, 401.
(4) Binart, N.; Catelli, M. G.; Geynet, C.; Puri, V.; Hahnel, R.; Mester, J.; Baulieu, E. E. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 812.
(5) McCague, R.; Leclercq, G.; Legros, N.; Goodman, J.; Blackburn, G. M.; Jarman, M.; Foster, A. B. *J. Med. Chem.* **1989**, *32*, 2527.
(6) Harper, M. J. K.; Richardson, D. N.; Walpole, A. L. British Patent, 1013907/1965.
(7) McCague, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1011.
(8) Yamamura, M.; Moritani, J.; Murahashi, S. I. *J. Organomet. Chem.* **1975**, *91*, C39.
(9) McCague, R. *Tetrahedron Lett.* **1987**, *28*, 701. For a review, see: Scott, S. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.
(10) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121.
(11) Eisch, J. J.; Hordis, C. K. *J. Am. Chem. Soc.* **1971**, *93*, 2974.
(12) McCague, R. *J. Chem. Res. Synop.* **1986**, 58; *J. Chem. Res. Miniprint* **1986**, 771.

0022-3263/90/1955-6184$02.50/0

Scheme II[a]



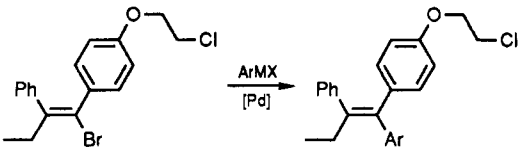
[a] (a) KH, THF, 25 °C; (b) Tf_2NPh (+LiBr), 25 °C; (c) ArMX, Pd catalyst—see Table I; (d) Me_2NH, EtOH, 100 °C.

and the enolate treated with *N*-phenyltrifluoromethanesulfonimide.[13] However, the only isolated product (29%) was an *N*-vinylsulfonamide. Significantly, though, it was formed with high stereoselectivity (20:1) for one geometric isomer (**6**) which can be assigned *E* stereochemistry since its proton NMR spectrum has signals for the chloroethoxy function at relatively low frequency owing to the shielding influence of the adjacent 2-phenyl ring.[14] This sulfonamide had presumably formed (Scheme II) following fragmentation of the enol triflate **4b** assisted by electron release from the alkoxy function, and trapping of the resultant vinyl cation **5** by the sulfonamide anion liberated from the reagent. The nucleophile had approached from the least hindered side of the cation, ethyl being of smaller steric bulk than phenyl. This size difference has previously been shown to provide complete Cram specificity in the addition of an aryl Grignard reagent to **3**.[7]

Apart from its formation in poor yield, **6** failed to show any synthetic utility being inert under the conditions of the palladium complex catalyzed coupling reactions described below. The low yield was presumably a consequence of the *N*-phenyltrifluoromethanesulfonamide anion being a particularly poor nucleophile. Consequently, the putative intermediate vinyl cation[15] should be interceptable by other nucleophilic sources present in the reaction mixture. Indeed, by the inclusion of lithium bromide (2.5 equiv), a vinyl bromide was formed (63%). Again the stereoselectivity was high (20:1 *E*:*Z*) and the pure *E* isomer **4a** was obtained after recrystallization.

A good comparison for this bromide trapping reaction is the known addition of carbanions to ketenes in a stereoselective manner,[16] as the cation **5** resembles a vinylogous ketene. The conversion of **3** into **4a** represents a direct (one-pot) conversion of a ketone into a vinyl bromide in good yield. In contrast, the classical approach of proceeding via a geminal dibromide gives very poor yields for ketones[17] and is not stereoselective.

Table I. Cross-Coupling Reactions of the Vinyl Bromide 4a with Various Aryl Organometallics



entry	ArMX	conditions[a]	isolated yield, %	de, %
1	$PhZnCl$[b]	A	99	90
2	PhZnCl	B	96	88
3	PhMgCl	A	98	88
4	PhMgCl	B	96	88
5	PhMgCl	C/25 °C/24 h	96	0
6	PhMgCl	C/70 °C/30 min	96	20
7	$PhSnBu_3$	D/Me_2NCOCH_3	94	43
8	$PhSnBu_3$	D/$(Me_2N)_3PO$	96	82
9	$4\text{-}(C_7F_7O)C_6H_4ZnCl$	A	99	90
10	$4\text{-}(C_7F_7O)C_6H_4MgCl$	A	96	88
11	BrC_6H_4ZnCl[c]	A	47	88
12	$4\text{-}BrC_6H_4B(OH)_2$[c]	E	56[d]	90

[a] Reactions were carried out using 4 equiv of ArMX and 0.5 mol % palladium catalyst unless otherwise stated under the following conditions: (A) $Pd(PPh_3)_4$, toluene, 110 °C, 1 h; (B) $Pd(PPh_3)_2Cl_2$, THF, 70 °C 1 h; (C) $Pd(PPh_3)_2(PhCH_2)Cl$, THF (see ref 23); (D) $(\eta^3\text{-}C_3H_5PdCl)_2$ (0.25 mol %), coordinating solvent indicated, LiBr (1 equiv), 25 °C, 24 h (see ref 23); (E) $Pd(PPh_3)_2Cl_2$, THF, Na_2CO_3 (aq, 2 M), 80 °C, 1 h (see ref 22). [b] A very slow nonstereoselective coupling reaction proceeded in the absence of palladium catalyst. [c] Two equivalents of ArMX were used. [d] 83% yield based on unrecovered vinyl bromide.

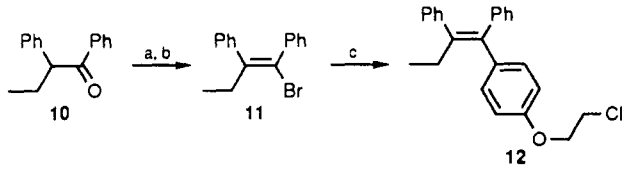
Conversion of the (*E*)-Vinyl Bromide 4a into Tamoxifen and Derivatives. Reaction of the (*E*)-vinyl bromide **4a** with phenylzinc chloride (4 equiv) under catalysis by tetrakis(triphenylphosphine)palladium(0) in toluene at reflux gave triarylbutenes in 99% yield. These reaction conditions, which are essentially the same as those used by Miller and Al-Hassan in their tamoxifen synthesis[10] resulted in some loss of stereochemical integrity as 5% of the product was *E* isomer. However, the *Z* isomer **7** was obtained pure by a single recrystallization.

Stereochemical assignments in substituted triphenylbutenes are readily established since shielding by the 2-phenyl ring causes shifts to lower frequency of the protons in the cis substituent.[12,14] In this case, the product **7** is known anyway.[18] Since related coupling reactions have been shown to proceed with retention of configuration,[8,10] the assigned stereochemistry can be confirmed. Conversion of **7** into (*Z*)-tamoxifen is a known reaction which has been accomplished in 93% yield.[18]

The formation of some unwanted *E* isomer prompted us to try different aryl nucleophiles and coupling conditions. These are summarized in Table I. The best procedure found (entry 1) is that already described although phenylmagnesium chloride was almost as effective. Curiously, conditions giving reaction at lower temperature, i.e. using a catalyst reducable in situ to the especially active dicoordinate species. "$Pd(PPh_3)_2$"[19] (entry 5) caused considerable loss of stereoretention. Also, when using the same catalyst and reagent at a different temperature, the higher reaction temperature gave the better stereoretention

(13) McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(14) Collins, D. J.; Hobbs, J. J.; Emmens, C. W. *J. Med. Chem.* **1971**, *14*, 952.
(15) Stang, P. J.; Rappoport, Z.; Hanack, M. C.; Subramanian, L. R. *Vinyl Cations*; Academic: New York, 1979.
(16) Baigne, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391. Häner, R.; Laube, T.; Seebach, D. *Ibid.* **1985**, *107*, 5396.
(17) Lasinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341.
(18) Jarman, M.; McCague, R. *J. Chem. Res. Synop.* **1985**, 116; *J. Chem. Res. Miniprint* **1985**, 1342.
(19) Negichi, E.-i.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338.

Scheme III[a]



[a] (a) KH, THF, 25 °C; (b) LiBr, Tf_2NPh, 70 °C, 12 h; (c) $ClCH_2CH_2O\text{-}C_6H_4ZnCl$, $Pd(PPh_3)_4$, PhMe, 110 °C.

(entries 1, 3, 6 vs 2, 4, 5 respectively). The imperfect stereocontrol is attributed to the lability of the oxidative addition product of the vinyl bromide onto the palladium since when this product was prepared by treating the vinyl bromide with stoichiometric $Pd(PPh_3)_4$ in benzene at ambient temperature,[20] NMR spectroscopy revealed that a 1:2 mixture of *E* [$\delta(CDCl_3)$ of OCH_2 = 4.08] and *Z* [δ 4.18] isomers had formed. Presumably, when the reaction was carried out at the relatively high temperature of boiling toluene, this intermediate is short lived relative to the rate of nucleophilic attack on palladium and final reductive elimination.

The target potent antiestrogen metabolite 4-hydroxytamoxifen (**2**) suffers a facile geometric isomerization in the presence of acid or radical sources as a result of conjugation between the hydroxyl group and olefinic bond,[21] so any procedure for its stereoselective preparation needs to avoid this. Accordingly, the Grignard reagent derived from the heptafluoro-*p*-tolyl ether of 4-bromophenol was chosen as the nucleophilic coupling partner, since the resulting product **8** is known and has been shown to be convertable into 4-hydroxytamoxifen without isomerization.[12] Using the arylzinc reagent (Table I, entry 9) formed from the Grignard, the reaction was as efficient as with phenylzinc chloride. This route to **8** formally represents the first stereoselective synthesis of **2**.

4-Bromotamoxifen is a useful precursor to other 4-substituted tamoxifen derivatives through bromine–lithium exchange followed by electrophile treatment.[5] The preparation of its chloroethoxy precursor **9** from **4a** (Table I, entries 11 and 12) proceeded with good stereocontrol, but the yield was only moderate due to competing coupling of the 4-bromine atom in the product. The best method was using the arylboronic acid as a source of the nucleophilic coupling partner.[22]

Role of the Alkoxy Group. In order to determine whether the alkoxy group is a requirement in allowing vinyl bromide formation, 1,2-diphenylbutan-1-one (**10**) was used as substrate. The isomeric enol triflates were now more stable as they could be observed by proton NMR spectroscopy as a 1:2 mixture of *E* and *Z* geometric isomers but were unstable with respect to hydrolysis since attempted column chromatography on silica returned the ketone. Heating of the solution with lithium bromide still formed the vinyl bromide, 36% and 5% yields of *E* and *Z* isomers, respectively, but neither the yield of the wanted *E* isomer **11** nor the stereoselectivity of its formation were as good as for the conversion of **3** into **4a**. The reduced selectivity can be attributed to the higher energy of the carbocation intermediate. Coupling of **11** with the appropriate arylzinc chloride (Scheme III) gave **12**, an immediate precursor of the *E* isomer of tamoxifen.[18] This coupling proceeded with very high retention of stereochemistry, the *E*:*Z* product ratio was 100:1. Therefore in the conversion of **4a** into **7**, the alkoxy group was reducing the stereocontrol. As the oxidative addition product of **4a** to the palladium species is the likely labile intermediate, we propose that loss of stereochemical integrity proceeds via reversible unimolecular fragmentation of this intermediate to an ion pair with the vinyl carbocation stabilized by the alkoxy group.

The finding that the phenyl group is just sufficient to allow stereoselective olefin formation renders the synthetic approach used here potentially versatile for the stereoselective synthesis of tetrasubstituted olefins where at least one aryl substituent is present (i.e styrene derivatives) since aryl ketones are readily available and methodology exists for the palladium complex catalyzed replacement of vinylic bromide for alkyl as well as aryl groups.[24,25]

Experimental Section

Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker AC250 instrument with tetramethylsilane as internal reference and mass spectra (MS, electron impact, 70 eV) on a VG7070H spectrometer with a VG2235 data station. High-resolution mass spectra were calibrated against perfluorokerosene. Melting points were determined on a hot stage apparatus and are uncorrected. All reactions were performed under an atmosphere of argon and manipulations carried out using standard syringe/septa/Schlenk line techniques. Lithium bromide was dried by heating to 600 °C and cooling under vacuum. Dry tetrahydrofuran (THF) refers to the commercially available anhydrous grade. Chromatography refers to column chromatography on silica gel (Merck 15111) with the eluant indicated applied at a positive pressure of 0.5 atm.

(*E*)-1-Bromo-1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butene (4a). 1-[4-(2-Chloroethoxy)phenyl]-2-phenyl-1-butanone[12] (**3**; 3.03 g, 10 mmol) was added to a stirred suspension of potassium hydride (from 1.72 g of a 35 wt % dispersion in mineral oil, 15 mmol) in dry THF (40 mL). After 1 h, a solution of anhydrous lithium bromide (2.17 g, 25 mmol) in dry THF (10 mL) was added to the yellow enolate solution, followed by a solution of *N*-phenyltrifluoromethanesulfonimide (3.57 g, 10 mmol) in dry THF (10 mL), and the mixture was stirred for 4 h. After addition of 2-propanol (1 mL) to destory excess hydride, the mixture was poured into water (100 mL) and extracted with ether (3 × 75 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude product as an oil. ^1H NMR analysis at this stage showed an isomer ratio, *E*:*Z*, of 20:1. Chromatography gave, on elution with 20:1 petroleum ether (bp 60–80 °C)-dichloromethane, **4a** (2.3 g, 63%) as crystals. The pure isomer obtained by recrystallization from *n*-pentane had mp 84–85 °C: ^1H NMR ($CDCl_3$) δ 1.04 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2), 2.79 (q, *J* = 7.5 Hz, 2 H, CH_3CH_2), 3.75 (t, *J* = 5.9 Hz, 2 H, CH_2CH_2Cl), 4.13 (t, *J* = 5.9 Hz, CH_2CH_2Cl), 6.63 (d, *J* = 8.9 Hz, 2 H, Ar*H* ortho to OR), 6.99–7.15 (m, 7 H, remaining Ar*H*) [the minor *Z* isomer gave inter alia δ 3.84 (t, *J* = 5.9 Hz, CH_2CH_2Cl) and 4.25 (t, *J* = 5.9 Hz, CH_2CH_2Cl)]; ^{13}C NMR ($CDCl_3$) δ 11.6 (q, CH_2CH_3), 33.2 (t, CH_2CH_3), 41.7 (t, CH_2CH_2Cl), 67.7 (t, CH_2CH_2Cl), 113.6 (d, ArC ortho to OR), 120.3 (s), 126.6 (d), 127.9 (d), 129.0 (d), 131.5 (d), 134.1 (s), 140.5 (s), 143.9 (s), and 157.0 (s, ArC-OR); MS *m*/*z* 366 (M^+, ^{81}Br), 364 (M^+, ^{79}Br, 100). Anal. Calcd for $C_{18}H_{18}BrClO$: C, 59.12; H, 4.96; Br, 21.85; Cl, 9.69. Found: C, 59.26; H, 5.08; Br, 21.97; Cl, 9.58.

***N*-[(*E*)-1-[4-(2-Chloroethoxy)phenyl]-2-phenyl-1-butenyl]-*N*-phenyltrifluoromethanesulfonamide (6).** The ketone **3** (1.51 g, 5.0 mmol) was converted into its potassium enolate in dry THF (20 mL) as described above and treated with a solution of *N*-phenyltrifluoromethanesulfonimide (1.79 g, 5.0 mmol) in dry THF (5 mL). After 2 h, workup followed the procedure used in the preparation of **4a**, but the chromatographic eluant was 10:1

(20) Fitton, P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 4.
(21) Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1982**, *47*, 287.
(22) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
(23) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551.
(24) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
(25) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

petroleum ether (bp 60–80 °C)-dichloromethane. The sulfonamide **6** was obtained (0.74 g, 29%) as a colorless oil in an isomer ratio (*E*/*Z*) of 20:1, ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 2.88 (q, J = 7.4 Hz, 2 H, CH_3CH_2), 3.71 (t, J = 6.0 Hz, 2 H, CH_2CH_2Cl), 4.11 (t, J = 6.0 Hz, 2H, CH_2CH_2Cl), 6.59 (d, J = 8.8 Hz, 2 H, Ar*H* ortho to OR), 6.93–7.39 (m, 12 H, remaining Ar*H*) [the minor *Z* isomer gave inter alia δ 3.84 (t, J = 6.0 Hz, CH_2CH_2Cl) and 4.30 (t, J = 6.0 Hz, CH_2CH_2Cl)]; high-resolution MS calcd for $C_{25}H_{23}{}^{35}ClF_3NO_3{}^{32}S$ m/z 509.1039, found m/z 509.1039.

(*Z*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-1-butene (7). A solution of phenylzinc chloride was prepared by adding a solution of *n*-butyllithium in pentane (2.0 M; 1 mL, 2 mmol) to a stirred solution of bromobenzene (314 mg, 2 mmol) in dry THF (2 mL) at −76 °C, followed after 5 min by a solution of zinc chloride in ether (1.0 M; 2 mL, 2 mmol), and then stirring was maintained at 25 °C for 30 min. In a separate flask containing the vinyl bromide **4a** (183 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in toluene (6 mL) was added the phenylzinc chloride solution. Ether and pentane were removed under reduced pressure, and the remaining solution was heated at 110 °C for 1 h, allowed to cool, and poured into water (30 mL). The product was extracted into ether (2 × 30 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was a 20:1 mixture of *Z* and *E* isomers. Chromatography gave, on elution with 20:1 petroleum ether (bp 60–80 °C)-dichloromethane, **7** as crystals (180 mg, 99%). The pure *Z* isomer obtained by recrystallization from petroleum ether (bp 60–80 °C) had mp 110 °C (lit.[18] mp 107–109 °C).

(*E*)-1-[4-(2-Chloroethoxy)phenyl]-1-[4-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]phenyl]-2-phenyl-1-butene (8). A solution of 1,2-dibromoethane (751 mg, 4.0 mmol) in dry ether (3 mL) was added to a stirred solution of 1-(4-bromophenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene[26] (1.56 g, 4.0 mmol) in dry ether (3 mL) containing magnesium turnings (194 mg, 8.0 mmol). After 1 h at reflux, the brown solution of Grignard reagent was filtered, a solution of zinc chloride in ether (1.0 M; 4 mL, 4.0 mmol) was added, and the mixture was stirred for 30 min. In a separate flask containing the vinyl bromide **4a** (366 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in toluene (12 mL) was added the arylzinc chloride solution. Ether was removed under reduced pressure, and the solution was heated by an oil bath at 110 °C for 1 h. The product formed was a 19:1 mixture of *E* and *Z* isomers. Workup and chromatography as described for the preparation of **7** provided white crystals of **8** (559 mg, 94%) as the pure *E* isomer, mp 117–118 °C (lit.[12] mp 116–118 °C).

(*E*)-1-(4-Bromophenyl)-1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butene (9). To a stirred solution of the vinyl bromide **4a** (183 mg, 0.5 mmol) in dry THF (6 mL) containing $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) was added 4-bromobenzeneboronic acid (201 mg, 1.0 mmol) followed by aqueous sodium carbonate (2 M; 1 mL, 2 mmol), and the mixture was heated by an oil bath at 80 °C. After 1 h, the mixture was cooled and poured into water (30 mL), and the products were extracted with ether (2 × 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The crude product was a 19:1 mixture of *E* and *Z* isomers. Chromatography gave, on elution with 20:1 petroleum ether (bp 60–80 °C)-dichloromethane, **9** as crystals (184 mg, 56% yield). Recrystallization from petroleum ether (bp 60–80 °C) afforded the pure *E* isomer: mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 2.44 (q, J = 7.5 Hz, 2 H, CH_3CH_2), 3.73 (t, J = 5.9 Hz, 2 H, CH_2CH_2Cl), 4.10 (t, J = 5.9 Hz, 2 H, CH_2CH_2Cl), 6.56 (d, J = 8.9 Hz, 2 H, Ar*H* ortho to OR), 6.76 (d, J = 8.9 Hz, 2 H, Ar*H* meta to OR), 7.08–7.21 (m, 7 H), 7.47 (d, J = 8.5 Hz, 2 H, Ar*H* ortho to Br); ^{13}C NMR ($CDCl_3$) δ 13.5 (q, CH_2CH_3), 29.0 (t, CH_2CH_3), 41.8 (t, CH_2CH_2Cl), 67.7 (t, CH_2CH_2Cl), 113.6 (d, Ar*C* ortho to OR), 120.6 (s), 126.2 (d), 127.9 (d), 129.5 (d), 131.15 (d), 131.24 (d), 131.9 (d), 135.6 (s), 136.8 (s), 141.9 (s), 142.1 (s), 142.5 (s) and 156.2 (s, Ar*C*OR); MS m/z 442 (M^+, ^{81}Br), 440 (M^+, ^{79}Br, 100). Anal. Calcd for $C_{24}H_{22}BrClO$: C, 65.25; H, 5.02; Br, 18.09; Cl, 8.02. Found: C, 65.48; H, 5.09; Br, 17.57; Cl, 7.89.

(*E*)-1-Bromo-1,2-diphenyl-1-butene (11). The method followed was that used to prepare **4a** but with 1,2-diphenyl-1-butanone[27] (**10**; 2.24 g, 10 mmol) and with the exception that after addition of the *N*-phenyltrifluoromethanesulfonimide, the mixture was heated by an oil bath at 70 °C for 12 h. After workup chromatography was with elution by petroleum ether (bp 60–80 °C) and gave (i) the *E* isomer **11** as white crystals (1.04 g, 36%) [mp 62.5–63 °C (from methanol at −20 °C); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 2.81 (q, J = 7.5 Hz, 2 H, CH_3CH_2), 6.98–7.15 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 11.6 (q, CH_3CH_2), 33.1 (t, CH_3CH_2), 120.5 (s), 126.6 (d), 127.3 (d), 127.5 (d), 127.8 (d), 129.0 (d), 130.1 (d), 140.4 (s), 140.9 (s) and 144.3 (s); MS m/z 288 (M^+, ^{81}Br), 286 (M^+, ^{79}Br, 100). Anal. Calcd for $C_{16}H_{15}Br$: C, 66.91; H, 5.26; Br, 27.82. Found C, 66.95; H, 5.34; Br, 27.55] and (ii) the minor *Z* isomer as crystals (0.15 g, 5%), mp 100–102 °C (lit.[10] mp 101–102 °C).

If the reaction mixture was not heated but immediately worked up, enol triflates could be observed by ^{1}H NMR. In a 1:2 ratio these were *E* isomer [δ_H ($CDCl_3$) inter alia 1.00 (t, J = 7.5 Hz, 3 H, CH_3CH_2) 2.75 (q, J = 7.5 Hz, 2 H, CH_3CH_2)] and *Z* isomer [δ_H ($CDCl_3$) inter alia 0.89 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 2.43 (q, J = 7.5 Hz, 2 H, CH_3CH_2)]. These products were unstable with respect to hydrolysis, reforming the ketone if chromatography was attempted.

(*E*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-1-butene (12). A solution of [4-(2-chloroethoxy)phenyl]zinc chloride was prepared by adding a solution of *n*-butyllithium in hexanes (2.0 M, 0.4 mL, 0.8 mmol) to a stirred solution of 4-bromophenyl 2-chloroethyl ether (188 mg, 0.80 mmol) in dry THF (1 mL) at −76 °C, followed after 5 min by a solution of zinc chloride in ether (1.0 M; 0.8 mL, 0.8 mmol) and then stirring at 25 °C for 15 min.

Treatment of a solution of the vinyl bromide (57 mg, 0.2 mmol) in toluene (2 mL) containing $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) with the arylzinc chloride solution and reaction, workup and chromatography as described in the preparation of **7**, gave **12** as crystals (68 mg, 94%) which after recrystallization from petroleum ether (bp 60–80 °C) was pure *E* isomer, mp 85–86 °C (lit.[18] mp 84–86 °C). Analysis of the crude product prior to chromatography by ^{1}H NMR showed an *E*:*Z* ratio of 100:1 (de = 98%).

Acknowledgment. This investigation was supported by a Grant to the Institute of Cancer Research from the Cancer Research Campaign and Medical Research Council. We thank Mr. M. H. Baker for the mass spectra and Dr. M. Jarman for encouraging this study.

Registry No. 1, 10540-29-1; 3, 103628-22-4; (*E*)-**4a**, 129920-99-6; (*Z*)-**4a**, 129921-00-2; (*E*)-**6**, 129921-01-3; (*Z*)-**6**, 129921-02-4; (*Z*)-**7**, 97818-83-2; (*E*)-**7**, 97818-84-3; (*E*)-**9**, 129921-03-5; (*E*)-**9** (Ar = BrC_6H_4), 129942-68-3; **10**, 16282-16-9; (*E*)-**11**, 113619-13-9; (*Z*)-**11**, 96212-86-1; (*E*)-**12**, 97818-84-3; PhZnCl, 28557-00-8; *p*-$BrC_6H_4(OC_7H_7)$, 97631-87-3; *p*-$BrC_6H_4B(OH)_2$, 5467-74-3; *p*-$Cl(CH_2)_2OC_6H_4ZnCl$, 129942-64-9; $PhSnBu_3$, 960-16-7; *p*-$(C_7H_7O)C_6H_4ZnCl$, 129942-65-0; *p*-$(C_7H_7O)C_6H_4MgCl$, 129942-66-1; BrC_6H_4ZnCl, 129942-67-2.

(26) Jarman, M.; McCague, R. *J. Chem. Res. Synop.* **1985**, 114; *J. Chem. Res. Miniprint* **1985**, 1301.

(27) Robertson, D. W.; Katzenellenbogen, J. A.; Long, D. J.; Rorke, E. A.; Katzenellenbogen, B. S. *J. Steroid Biochem.* **1982**, *16*, 1.