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Article

Palladium-Catalyzed Double Cross-Coupling of *E*-vinylic Dibromides with PhZnCl and the Synthesis of Tamoxifen

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Compostos (*E*)-1,2-dibromo vinílicos **11a-f** foram preparados estereosseletivamente via reação de bromação de alcinos empregando-se tribrometo de piridínio em MeOH/CCl_4 a baixa temperatura e utilizados na reação de duplo acoplamento com PhZnCl catalisada por Pd(0), segundo protocolo de Negishi, fornecendo as respectivas olefinas tri e tetrassubstituídas **14a-e**. Tamoxifeno, um agente antiestrogênico de uso clínico na terapia do câncer de mama, foi preparado na forma de uma mistura *Z*:*E* de proporção 2.3:1, em 7 etapas em um rendimento global de 30% a partir do 4-iodofenol (**3**).

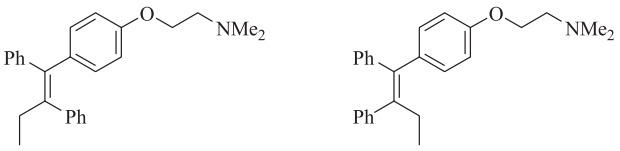
(*E*)-1,2-vinylic dibromides **11a-f** were stereoselectively prepared via bromination of acetylenic compounds with pyridinium tribromide in MeOH/CCl_4 at low temperature and double cross-coupled with PhZnCl under Pd(0) catalysis (Negishi protocol) to afford tri- and tetrasubstituted olefins **14a-e**. Tamoxifen, a selective estrogen receptor modulator clinically prescribed in breast cancer therapy, was prepared in 7 steps and 30% overall yield from 4-iodophenol (**3**) as a 2.3:1 mixture of (*Z*)- and (*E*)-isomers.

Keywords: (*E*)-1,2-vinylic dibromides, double cross-coupling, palladium catalysis, tri- and tetrasubstituted olefins, tamoxifen

Introduction

The stereoselective synthesis of tri- and tetrasubstituted olefins is of great interest in the domain of biologically active compounds where the *E* and *Z* isomers may have completely different biological properties as represented by tamoxifen, a tetrasubstituted stilbene which acts as a selective estrogen receptor modulator (SERM): while (*Z*)-tamoxifen (**1**) displays antiestrogenic activity and is prescribed as the corresponding citrate as an adjuvant for breast cancer therapy, (*E*)-isomer **2** has estrogenic activity and stimulates the proliferation of hormone-responsive breast cancer cells (Figure 1).[1] Methods are available for the separation of (*E*)- and (*Z*)-isomers as well as for isomerization of estrogenic (*E*)-tamoxifen (**2**)[2] to antiestrogenic (Z)-tamoxifen (**1**),[3-5] including large scale operations. Among the routes already described in the literature, the method by Knochel and coworkers[6] is by far the more efficient one: starting from 1-phenyl-1-butyne, (*Z*)-tamoxifen (**1**) is prepared in three steps and 71% yield via Ni(II)-catalyzed *syn* carbozincation, followed by Negishi coupling of the corresponding vinylic iodide with 4-triisopropylsililoxyphenylzinc bromide.

Despite the different approaches already reported for the stereoselective synthesis of tamoxifen (dehydration,[4] McMurry[5] and metal-catalyzed coupling protocols[6-13]), we were attracted by the possibility of preparing (*Z*)-tamoxifen (**1**) from the corresponding (*E*)-1,2-vinylic dibromide via an one-pot tandem coupling with a phenylorganometallic species with retention of configuration.



(*Z*)-Tamoxifen (**1**)
Antiestrogenic activity

(*E*)-Tamoxifen (**2**)
Estrogenic activity

Figure 1. Structures of (*Z*)-tamoxifen (**1**) and (*E*)-tamoxifen (**2**).

1,2-Dihaloalkenes are potentially useful starting materials for the preparation of tri- and tetrasubstituted olefins via transition metal catalyzed cross-coupling with organometallic species.[14] Accordingly, Rossi and coworkers[15] described the utilization of tetrasubstituted (*E*)-

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2,3-dibromopropenoates in the palladium-catalyzed cross-coupling with aryl and alkynylzinc species. The stereoselectivity of these reactions was found to be dependent upon the substituent present at C-3 of the propenoates.

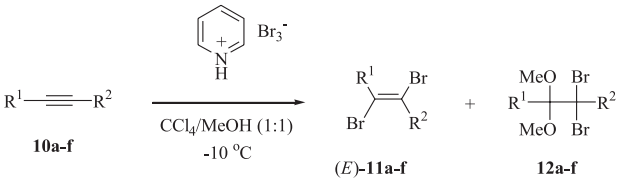
Results and Discussion

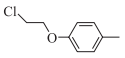
Due to the availability of *E*-1,2-dibromoalkenes from the bromination of the corresponding acetylenes, we were attracted to the possibility of preparing (*Z*)-tamoxifen (**1**) from (*E*)-**9** via the palladium-catalyzed tandem cross-coupling with phenylzinc chloride (Scheme 1). 4-Iodophenol (**3**) was straightforwardly protected as the corresponding chloroethylether **4** before the Sonogashira coupling with trimethylsilylacetylene which afforded acetylene **5** in 99% yield. TMS-deprotection followed by alkylation of the terminal acetylene **6** with ethyl iodide provided disubstituted acetylene **7** (83% yield, 2 steps).

At this juncture, the stereoselective conversion of **7** to the corresponding (*E*)-dibromoalkene **8** was needed. While our preliminary attempts with molecular bromine in either $CHCl_3$ or CCl_4 afforded mixtures of (*E*)- and (*Z*)-1,2-dibromoalkenes as well as the corresponding tribromoderivatives when alkylacetylenes were employed, the use of pyridinium tribromide[16] in a 1:1 mixture of CCl_4-MeOH at –10 °C provided (*E*)-1,2-dibromoalkene **8** in 86% yield without formation of the corresponding 1,1-dibromo-2,2- dimethoxyalkane as previously reported when the reaction was carried out in methanol.[17] The protocol above proved to be equally efficient for the bromination of either alkyl- or aryl-substituted alkynes **10a-f** (Table 1). The (*E*)-configuration of 1,2-dibromo alkenes **11a-e** was assigned based on literature data[18] while the stereochemistry of **11f** was assumed by analogy.

With a stereoselective route to (*E*)-**9** secured, we explored its Pd(0)-catalyzed double cross-coupling with

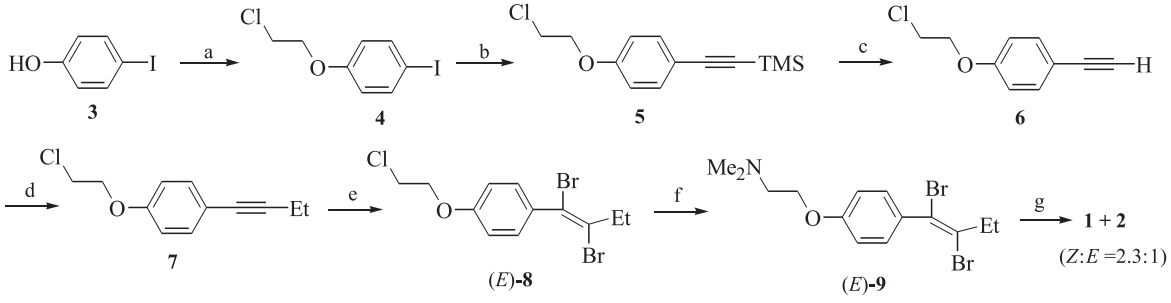
Table 1. Bromination of alkynes **10a-f** with $PyHBr_3$ in CCl_4/MeOH at –10 °C



Entry	R^1	R^2	(*E*)-**11** (%)[a]	**12** (%)[a]
10a	$HOCH_2$-	H	86	-
10b	$HOCH_2$-	Me	78	-
10c	Ph	H	83	**12c** (trace)
10d	Ph	Et	81	**12d** (trace)
10e	Ph	Ph	86	-
10f		H	85	**12f** (10)

[a]Yields after column chromatography on silica gel.

PhZnCl (8 equiv.) generated *in situ* by transmetallation of a 0.5 mol L^{-1} solution of phenyllithium in THF with $ZnCl_2$. The cross-coupling was carried out in refluxing toluene with 10 mol% of $Pd(PPh_3)_4$ and afforded a 2.3:1 mixture of (*Z*)-tamoxifen (**1**) and (*E*)-tamoxifen (**2**) in 52% yield.[19] The diastereoisomeric ratio was determined by capillary GC analysis and the configuration of the major diastereoisomer established by comparison of the NMR data of the synthetic mixture with an authentic sample of (*Z*)-tamoxifen (**1**). The loss of stereochemical integrity during the Pd(0)-catalyzed cross-coupling is reminiscent of the observations by Rossi and coworkers[15] who described similar behavior during the cross-coupling of tetrasubstituted (*E*)-2,3-dibromopropenoates with arylzinc chlorides. However, Rathore and coworkers described that the Pd(0)-catalyzed coupling of aryl Grignard reagents bearing *ortho* methyl groups and (*E*)-1,2-dibromoalkenes efficiently provides (*Z*)-tetrasubstituted alkenes.[20]



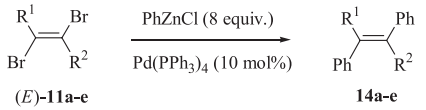
Scheme 1. Reagents and Conditions: a) 1,2-dichloroethane, $Bu_4N(HSO_4)$, NaOH(aq), reflux, 5h, 91%; b)trimethylsilylacetylene, $(PPh_3)_2PdCl_2$ (5 mol%), CuI (4 mol%), Et_3N, rt, 5h, 99%; c) MeOH, 1 N aq. KOH, rt, 2h, 92%; d) n-BuLi, THF, -78ºC, 15 min, then EtI, DMPU, -78ºC to rt, 90%; e)$PyHBr_3$, CCl_4/MeOH (1:1), -10 ºC, 40 min, 86%; f) N,N-dimethylamine, EtOH, 90 ºC, 72h, 91%; g) PhZnCl (8 eq), $Pd(PPh_3)_4$ (10 mol%), toluene, reflux, 24h, 52%.

While (*Z*)-tamoxifen (**1**) is formed through a double Negishi coupling, the competitive formation of (*E*)-tamoxifen (**2**) seems to involve *syn*-carbopalladation of alkyne **13** which is observed to be formed from (*E*)-**9** (GC analyses) under the reaction conditions employed (Scheme 2). In fact, although attempts to carry out Pd(0)-catalyzed coupling with alkyne **13** under the reaction conditions employed failed, we were able to observe exclusive formation of (*E*)-tamoxifen (**2**) when **13** was treated with $Pd(PPh_3)_4$/PhBr, followed by addition of PhZnCl (Scheme 2).

We have also examined the formation of tri- and tetrasubstituted olefins **14a-e** from the corresponding (*E*)-**11a-e**. As depicted in Table 2, in all cases good yields of the corresponding tri- and tetrasubstituted olefins **14a-e** were obtained with retention of the double bond configuration being observed when alkyl substituted 1,2-dibromo alkenes (*E*)-**11a,b** were employed.

The low level of diastereoselection reported in the double Negishi coupling of vinylic dibromide (*E*)-**9** with phenylzinc chloride calls for a more efficient catalytic system in order to carry out the coupling reaction. The highest stereoselective methodologies described so far in the literature for the total synthesis of (*Z*)-tamoxifen (**1**) rely on either *syn* carbometallation,[6,12] hidroxymethyl directed *anti* carbometallation[11] or *anti* stannylcupration.[8] However, when

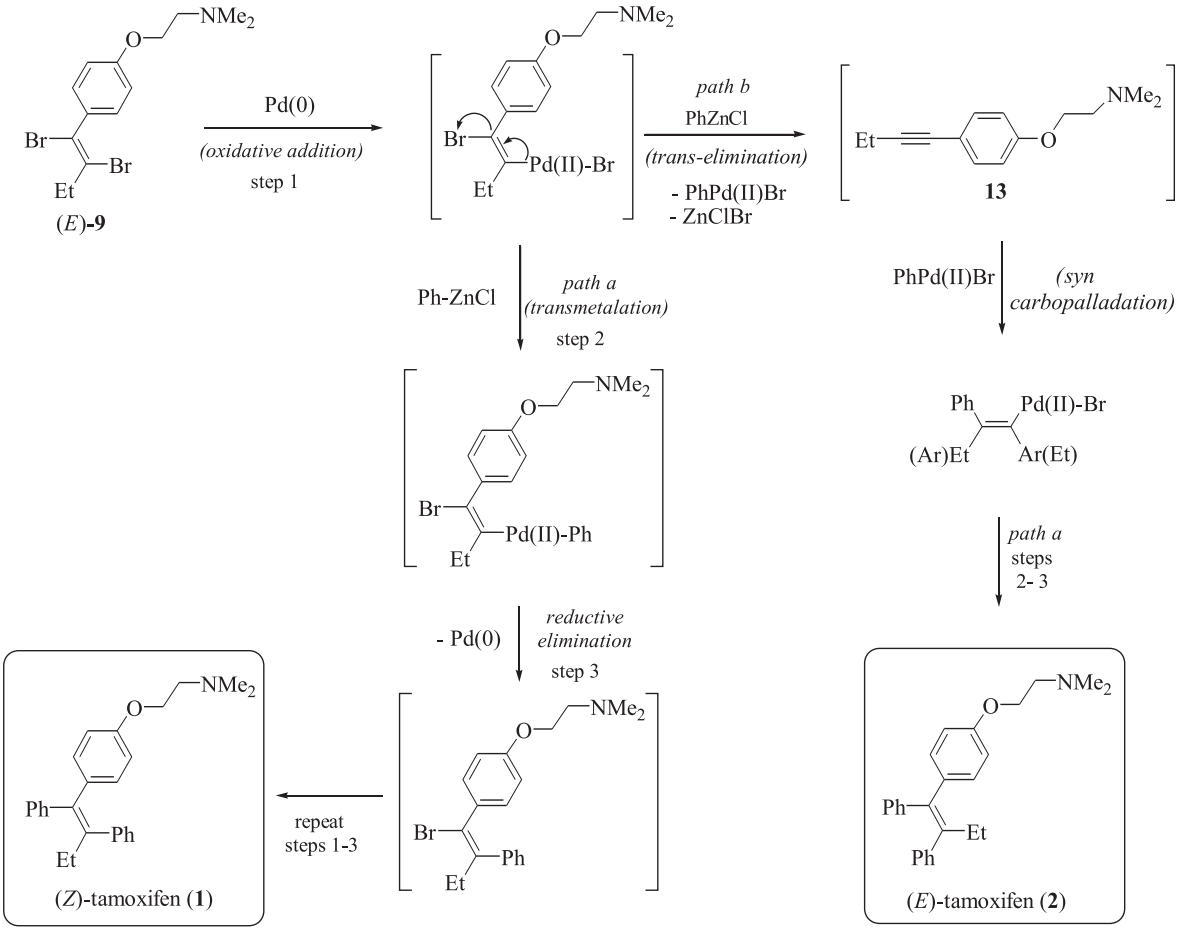
Table 2. Pd(0)-catalyzed double cross-coupling of dibromo alkenes (*E*)-**11a-e** with PhZnCl



(*E*)-**11a-e** **14a-e**

(*E*)-**11**	R^1	R^2	Conditions[a]	**14** (%)
a	$HOCH_2$-	H	A	78
b	$HOCH_2$-	Me	A	68
c	Ph	H	A	68
d	Ph	Et	A	70
e	Ph	Ph	B	78

[a]A: 10 mol% $Pd(PPh_3)_4$, THF, rt; B: 10 mol% $Pd(PPh_3)_4$, toluene, reflux.



Scheme 2. Competitive pathways for (*Z*)- and (*E*)-tamoxifen (**1** and **2**).

compared with the routes based on dehydration[4] or McMurry coupling,[5] the results described herein display about the same level of diastereoselection. Considering the availability of methods for separation of (*E*)- and (*Z*)-tamoxifen and for the interconversion of (*E*)- to (*Z*)-tamoxifen, our results are an useful asset to those already known as it allows the preparation of tamoxifen as a 2.3:1 mixture of *Z*- and *E*-isomers in 7 steps and 30% overall yield from commercially available 4-iodophenol (**3**).

Experimental

General

All reactions of air- and water-sensitive materials were performed in flame dried glassware under an atmosphere of argon. Triethylamine was distilled from CaH_2, tetrahydrofuran was previously treated with CaH_2 and distilled from sodium, toluene was distilled from sodium. DMPU and bromobenzene were previously treated with CaH_2, distilled from CaH_2 and stored over molecular sieves. 4-iodophenol (**3**), 1,2-dichloroethane,trimethylsilylacetylene,dichloro(triphenylphosphine)palladium(II), ethyl iodide, pyridinium tribromide, tetrakis(triphenylphosphine) palladium(0) and alkynes **10a-e** were commercially available. The compounds were purified by column chromatography on silica gel (70-230 mesh). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini (7.05T), Varian Inova (11.7T) spectrometers. Chemical shifts (δ) are recorded in ppm with the solvent resonance as the internal standard and coupling constants (*J*) recorded in Hz. The infrared spectra were recorded as films in KBr cells on a Nicolet Impact 410 (FTIR). High resolution mass spectroscopy (HRMS) were performed on a VG Autoespec-Micromass-EBE. The melting points were measured on an Electrothermal 9100 apparatus. The gas chromatography analyses (FID detector) were performed using a Hewlett Packard 5890-II equipament. Gas chromatography-mass spectrometry (GC-MS) analyses were performed on a Hewlett Packard 5890/ Hewlett Packard 5970 MSD.

*1-(2-Chloroethoxy)-4-iodobenzene, (**4**)*[8]

To a solution of 4-iodophenol (**3**) (2.09 g, 95.0 mmol) and tetrabutylammonium hydrogensulfate (160 mg, 0.47 mmol) in 1,2-dichloroethane (10 mL, 0.90 mol) was added 3 mol L^{-1} aqueous sodium hydroxide (5.5 mL) and the mixture was refluxed for 1h after which 6 mol L^{-1} aqueous sodium hydroxide (1.0 mL) was added. The resulting solution was refluxed for 24 h and cooled to room temperature. The organic layer was separated, diluted with petroleum ether (30 mL) and extracted with saturated aqueous ammonium chloride (3 x 10 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chormatography (hexane:ethyl acetate, 9:1) affording chloroethylether **4** (3.30 g, 86.4 mmol) in 91% yield as a white solid, mp: 56.8-57.2 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.78 (2H, t, *J* 5.9 Hz), 4.20 (2H, t, *J* 5.9 Hz), 6.68 (2H, d, *J* 8.4 Hz), 7.55 (2H, d, *J* 8,4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 41.6 (CH_2), 68.1 (CH_2), 83.6 (C), 117.8 (CH), 136.4 (CH), 158.1 (C). IR (KBr film) ν_{max}/cm^{-1}: 3082, 2958, 2931, 2870, 1587, 1487, 1454, 1254, 1117, 1036, 829, 814, 669.

*2-Chloroethyl 4-(trimethylsilylethynyl)phenyl ether, (**5**)*

To a solution of **4** (1.42 g, 5.03 mmol) and trimethylsilylacetylene (0.87 mL, 6.01 mmol) in dry triethylamine (20.0 mL) at room temperature was added dichloro(triphenylphosphine)palladium(II) (187 mg, 0.25 mmol) and copper(I) iodide (53.0 mg, 0.23 mmol) under argon atmosphere. After 2 h the reaction mixture was concentrated under reduced pressure and was purified by column chromatography (hexane:ethyl acetate, 9:1) affording **5** (1.26 g, 5.02 mmol) in 99% yield as a white solid, mp: 44.2-44.4 ºC. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.24 (9H, s), 3.80 (2H, t, *J* 5.8 Hz), 4.21 (2H, t, *J* 5.8 Hz), 6.82 (2H, d, *J* 8.7 Hz), 7.41 (2H, d, *J* 8,7 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 0.2 (CH_3), 42.8 (CH_2), 68.0 (CH_2), 92.8 (C), 104.8 (C), 114.4 (C), 116.0 (CH), 133.4 (CH), 158.1 (C). IR (KBr film) ν_{max}/cm^{-1}: 3043, 2964, 2896, 2158, 1604, 1506, 1250, 1176, 1038, 869, 843, 761. GC-MS (EI) *m/z* 254(12%), 252(37%), 237(100%). HRMS (EI): Found: 252.07044; Calc. For: $C_{18}H_{17}SiOCl$: 252.07072.

*2-Chloroethyl 4-ethynylphenyl ether, (**6**)*

To a solution of **5** (1.26 g, 5.00 mmol) in methanol (10.0 mL) at room temperature was added 1 mol L^{-1} aqueous potassium hydroxide (8 mL). After 2 h diethyl ether (30 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 15 mL) and the combined organic phase was extracted with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane:ethyl acetate, 8:2) affording **6** (840 mg, 4.67 mmol) in 92% yield as a yellow solid, mp: 53.2-53.6 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.02 (1H, s), 3.81 (2H, t, *J* 5.9 Hz), 4.22 (2H, t, *J* 5.9 Hz), 6.85 (2H, d, *J* 8.8 Hz), 7.43 (2H, d, *J* 8,8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 41.7 (CH_2), 68.0 (CH_2), 76.6 (CH),

83.4 (C), 114.5 (C), 114.5 (CH), 133.5 (CH), 158.1 (C). IR (KBr film) ν_{max}/cm^{-1}: 3290, 3043, 2966, 2925, 2872, 2109, 1604, 1504, 1240, 1035, 829. GC-MS (EI) *m/z* 182(32%), 180(95%), 118(100%). HRMS (EI): Found: 180.03876; Calc. for: $C_{10}H_9ClO$: 180.03419.

*4-(But-1-yn-1-yl)phenyl 2-chloroethyl ether, (**7**)*

To a solution of **6** (704 mg, 3.91 mmol) in dry THF (15.0 mL) at –78 ºC was added a 1.52 mol L^{-1} solution of n-butyllithium in hexanes (3.10 mL, 4.71 mmol). The mixture was stirred at –78 ºC for 20 min, under argon atmosphere, followed by slow addition of a solution of ethyl iodide (0.38 mL, 4.69 mmol) in DMPU (1.0 mL). After completed addition, the temperature was raised to rt. After 2 h the reaction mixture was quenched with 1% aqueous HCl and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic phase was extracted with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane:ethyl acetate, 9:1) affording **7** (732 mg, 3.48 mmol) in 90% yield as a white solid, mp: 52.4-52.6 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, *J* 7.3 Hz), 2.40 (2H, q, *J* 7.3 Hz), 3.80 (2H, t, *J* 5.9 Hz), 4.21 (2H, t, *J* 5.9 Hz), 6.82 (2H, d, *J* 8.8 Hz), 7.32 (2H, d, *J* 8,8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.2 (CH_3), 14.1 (CH_2), 41.8 (CH_2), 67.9 (CH_2), 79.3 (C), 90.3 (C), 114.4 (C), 116.9 (CH), 132.8 (CH), 157.3 (C). IR (KBr film) ν_{max}/cm^{-1}: 3058, 2964, 2920, 2872, 1611, 1514, 1460, 1303, 1255, 1113, 1040, 837, 828, 673. GC-MS (EI) *m/z* 210(33%), 208(100%), 131(50%). HRMS (EI): Found: 208.06642; Calc. for: $C_{12}H_{13}ClO$: 208.06549.

*2-Chloroethyl 4-[(1E)-1,2-dibromobut-1-en-1-yl]phenyl ether, ((E)-**8**)*

To a solution of alkyne **7** (318 mg, 1.53 mmol) in CCl_4 (7.5 mL) at –10 ºC was added pyridinium tribromide (575 mg, 1.80 mmol) followed by slow addition of MeOH (5.0 mL). The reaction mixture was kept at –10 ºC for 45 min and quenched with 10% aqueous sodium thiosulfate. The organic layer was separated, extracted with brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude mixture was chromatographed on silica gel (hexane:ethyl acetate, 9:1) affording (*E*)-**8** (502 mg, 1.37 mmol) in 86% yield as a yellow solid, mp: 65.6-66.0 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$,) δ 1.22 (3H, t, *J* 7.3 Hz), 2.84 (2H, q, *J* 7.3 Hz), 3.82 (2H, t, *J* 5.9 Hz), 4.24 (2H, t, *J* 5.9 Hz), 6.86 (2H, d, *J* 8.8 Hz), 7.31 (2H, d, *J* 8,8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.1 (CH_3), 35.2 (CH_2), 41.8 (CH_2), 67.9 (CH_2), 114.2 (C), 115.5 (C), 124.7 (C), 130.8 (CH), 134.0 (CH), 158.1 (C). IR (KBr film) ν_{max}/cm^{-1}: 3047, 2979, 2935, 2876, 1604, 1508, 1454, 1246, 1176, 1038, 833, 791. GC-MS (EI) *m/z* 372(8%), 370(1%), 368(61%), 366(25%), 291(23%), 289(100%), 287(76), 208(85%), 145(56%), 115(31%). HRMS (EI): Found 367.90028; Calc. for $C_{12}H_{13}Br_2ClO$: 367.90003.

*General procedure for the bromination of alkynes **10a-f** with $PyHBr_3$ (Table 1)*

To a solution of alkyne **10a-f** (1.00 mmol) in CCl_4 (5.0 mL) at –10 ºC pyridinium tribromide (1.20 mmol) was added, followed by MeOH (5.0 mL). The reaction mixture was kept at –10 ºC for 30-60 min and quenched with 10% aqueous sodium thiosulfate. After extraction with CH_2Cl_2, the combined organic phase was extracted with brine and dried over anhydrous $MgSO_4$. The crude mixture was chromatographed on silica gel to afford dibromo alkenes **11a-f**.

*(E)-2,3-Dibromoprop-2-en-1-ol, ((E)-**11a**).*[18] Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.15 (1H, t, *J* 6.7 Hz), 4.47 (2H, d, *J* 6.6 Hz), 6.57 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 63.9 (CH_2), 104.1 (CH), 125.2 (C). IR (KBr film) ν_{max}/cm^{-1}: 3348, 3082, 2924, 2866, 1608, 1446, 1227, 1053, 960, 795, 706.

*(E)-2,3-Dibromobut-2-en-1-ol, ((E)-**11b**).*[18] White solid, mp: 38.3-38.7 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.34 (1H, t, *J* 6.7 Hz), 2.43 (3H, s), 4.48 (2H, d, *J* 6.6 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$,) δ 28.8 (CH_3), 67.4 (CH_2), 117.8 (C), 120.7 (C). IR (KBr film) ν_{max}/cm^{-1}: 3356, 2924, 2870, 1639, 1426, 1084, 1022.

*[(E)-1,2-Dibromovinyl]benzene, ((E)-**11c**).*[18] White solid, mp: 72.2-73.2 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.76 (1H, s), 7.26-7.39 (3H, m), 7.48-7.52 (2H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 103.3 (CH), 121.2 (C), 128.2 (C), 129.0 (CH), 129.3 (CH), 136.9 (C). IR (KBr film) ν_{max}/cm^{-1}: 3082, 2930, 2847, 1592, 1489, 1450, 1167, 874.

*[(E)-1,2-Dibromobut-1-en-1-yl]benzene, ((E)-**11d**).*[18] Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, t, *J* 7.3 Hz), 2.86 (2H, q, *J* 7.3 Hz), 7.32-7.36 (5H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.1 (CH_3), 35.1 (CH_2), 115.5 (C), 124.8 (C), 128.2 (C), 128.5 (CH), 129.1(CH), 140.8 (C). IR (KBr film) ν_{max}/cm^{-1}: 3059, 2974, 2931, 2873, 1489, 1450, 1215, 1111, 868, 795, 756.

*[(E)-1,2-Dibromobut-1-en-1-yl]benzene, ((E)-**11e**).*[18] White solid, mp: 209.5 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.40 (3H, m), 7.43-7.48 (2H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 118.1 (C), 128.4 (CH), 128.9 (CH), 129.1 (CH), 140,7 (C).

2-Chloroethyl 4-[(E)-1,2-dibromovinyl]phenyl ether,

*((E)-**11f**).* Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.82 (2H, t, *J* 5.9 Hz), 4.26 (2H, t, *J* 5.9 Hz), 6.74 (1H, s), 6.91 (2H, d, *J* 8.8 Hz), 7.48 (2H, d, *J* 8.8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 41.7 (CH_2), 67.9 (CH_2), 102.2 (CH), 114.2 (C), 121.1 (C), 129.4 (CH), 130.9 (CH), 158.7 (C). IR (KBr film) ν_{max}/cm^{-1}: 3080, 2960, 2923, 2867, 1603, 1502, 1246, 1036, 831, 688. GC-MS (EI) *m/z* 344(5%), 342(28%), 340(44%), 338(17%), 263(25%), 261(100%), 259(84%), 180(69%), 118(94%). HRMS (EI): found 339.86859, calc for $C_{10}H_9Br_2ClO$: 339.86872.

*2-{4-[(1E)-1,2-Dibromobut-1-en-1-yl]phenoxy}-N,N-dimethylethanamine, ((E)-**9**)*

A solution of vinylic dibromide (*E*)-**8** (63 mg, 0.17 mmol) in ethanolic *N,N*-dimethylamine (30% v/v, 2.0 mL) was refluxed for 72 h. The resulting reaction mixture was cooled to room temperature, quenched with 1 mol L^{-1} aqueous sodium hydroxide (5.0 mL) and diethyl ether (5.0 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic phase was extracted with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude mixture was chromatographed on silica gel (hexane:ethyl acetate, 7:3) affording (*E*)-**9** (58 mg, 0.15 mmol) in 91% yield as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, *J* 7.3 Hz), 2.34 (6H, s), 2.74 (2H, t, *J* 5.9 Hz), 2.84 (2H, q, *J* 7.3 Hz), 4.08 (2H, t, *J* 5.9 Hz), 6.88 (2H, d, *J* 8.4 Hz), 7.27 (2H, d, *J* 8,4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.2 (CH_3), 35.3 (CH_2), 45.9 (2 x CH_3), 58.2 (CH_2), 66.0 (CH_2), 114.4 (C), 115.7 (C), 124.3 (C), 130.5 (CH), 133.1 (CH), 158.6 (C). IR (KBr film) ν_{max}/cm^{-1}: 2970, 2935, 2819, 2769, 1604, 1508, 1246, 1173, 1034, 833, 767. GC-MS (EI) *m/z* 379(1%), 377(2%), 375(1%), 58(100). HRMS (EI): Found 376.98162; Calc. for $C_{14}H_{19}Br_2NO$: 376.98135.

*Palladium-catalysed double cross-coupling of (E)-**9** with PhZnCl: Synthesis of (Z)-tamoxifen, (**1**) and (E)-tamoxifen, (**2**)*

To a solution of bromobenzene (84 μL, 0.80 mmol) in dry THF (1.0 mL) at –78 ºC was added a 1.73 mol L^{-1} solution of n-buthyllythium in hexanes (74 μL, 0.82 mmol). After 15 min, a solution of $ZnCl_2$ (122 mg, 0.90 mmol) in dry THF (2.0 mL) was added and the resulting mixture was allowed to warm to room temperature. After 30 min, a solution of (*E*)-**9** (38 mg, 0.10 mmol) in dry THF (2 mL) containing a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.010 mmol) was added. To the resulting mixture was added toluene (10.0 mL) and the solution was refluxed for 24 h and cooled to room temperature. The resultant reaction mixture was quenched with saturated aqueous ammonium chloride (5.0 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude mixture was chromatographed on silica gel ($CHCl_3$:MeOH, 9:1) affording a 2.3:1 mixture of (*Z)*-tamoxifen (**1**) and (*E)*-tamoxifen (**2**) in 52% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91 (*Z* isomer. 3H, t, *J* 7.3 Hz), 0.94 (*E* isomer. 3H, t, *J* 7.3 Hz), 2.28 (*Z* isomer. 6H, s), 2.34 (*E* isomer. 6H, s), 2.42-2.52 (*Z* and *E* isomers. 4H, m), 2.63 (*Z* isomer. 2H, t, *J* 5.9 Hz), 2.74 (*E* isomer. 2H, t, *J* 5.9 Hz), 3.94 (*Z* isomer. 2H, t, *J* 5.9 Hz), 4.07 (*E* isomer. 2H, t, *J* 5.9 Hz), 6.68 (*Z* isomer. 2H, d, *J* 9.7 Hz), 6.76 (*E* isomer. 2H, d, *J* 9.3 Hz), 6.86-7.36 (*Z* and *E* isomers. 10H, m). IR (KBr film) ν_{max}/cm^{-1}: 3081, 3056, 2974, 2826, 2770, 1611, 1509, 1238, 1044. GC-MS (EI) *m/z:* Z isomer, 371(4%), 72 (24%), 58(100%); *E* isomer, 371(3%), 72 (24%), 58(100%). (the diastereoisomeric ratio was determined by capillary GC analysis and the configuration of the major diastereoisomer established by comparison of the NMR data of the synthetic mixture with an authentic sample of (*Z*)-tamoxifen (**1**).

*Obtention of an authentic sample of (Z)-tamoxifen [N,N-dimethyl-2[4-(1,2-diphenyl-but-1-en-1-yl)phenoxy]-1-ethylamine], (**1**)[4]*

Two capsules of Nolvadex® (each containing 10 mg of (*Z*)-tamoxifen) was dissolved in water (10 mL) and 10% aqueous ammonium hydroxide was added until pH 9. The aqueous phase was extracted with Et_2O (5 x 5mL) and the combined organic phase was extracted with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The solid was recristallized from MeOH/H_2O 5% affording (*Z*)-tamoxifen (**1**) (8 mg) as a white solid, mp: 95.8-96.3 ºC. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* 7.3 Hz), 2.29 (6H, s), 2.45 (2H, q, *J* 7.3 Hz), 2.65 (2H, t, *J* 5.8 Hz), 3.93 (2H, t, *J* 5.8 Hz), 6.68 (2H, d, *J* 9.5 Hz), 6.78 (2H, d, *J* 9.5 Hz), 7.08-7.28 (10H, m).^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.6 (CH_3), 29.0 (CH_2), 45.8 (CH_3), 58.2 (CH_2), 65.5 (CH_2), 113.4 (C), 126.0 (C), 126.5 (CH), 127.8 (CH), 128.1 (C), 129.7 (C), 131.8 (CH), 135.6 (CH), 138.2 (CH), 141.3 (CH), 142.4 (CH), 143.8 (C), 156.7 (C). IR (KBr film) ν_{max}/cm^{-1}: 3055, 2979, 2925, 2813, 2769, 1606, 1509, 1240, 1035, 707. GC-MS (EI) *m/z* 371(5%), 58(100%).

*General procedure for the palladium-catalysed double cross-coupling of (E)-vinylic dibromides **11a-e** with PhZnCl (Table 2)*

To a solution of bromobenzene (8.0 equiv.) in dry THF

at –78 ºC was added butyllithium (8.2 equiv.). After 15 min., a solution of $ZnCl_2$ (9.0 equiv.) in dry THF was added then the temperature was allowed to room temperature. After 30 min, a solution of vinylic dibromide **11a-e** (1.0 equiv.) and tetrakis(triphenylphosphine)palladium(0) (0.1 equiv.) in dry THF was added and the conditions described in Table 2 were followed. The reaction was periodically monitored by GC analysis of samples previously hydrolysed with an aqueous NH_4Cl solution and extracted with Et_2O. After completion of the reaction, the mixture was treated at room temperature with an aqueous NH_4Cl solution and extracted with Et_2O. The organic was extracted with brine and dried over anhydrous $MgSO_4$. The crude mixture was chromatographed on silica gel to afford **14a-e**.

*(2Z)-2,3-diphenylprop-2-en-1-ol, (**14a**).*[21] Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.72 (1H, s), 4.45 (2H, s), 7.00-7.29 (11H, m). IR (KBr film) ν_{max}/cm^{-1}: 3361, 3053, 3020, 2922, 2852, 1599, 1489, 1024.

*(Z)-2,3-diphenylbut-2-en-1-ol, (**14b**).* [11] Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.38 (1H, s), 2.13 (3H, s), 4.53 (2H, s), 6.88-7.22 (10H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.0, 63.8, 126.1, 126.3, 127.7, 127.9, 128.8, 129.7, 136.5, 137.2, 140.7, 143.6. IR (KBr film) ν_{max}/cm^{-1}: 3345, 3057, 3023, 2920, 2862, 1601, 1489, 1020, 991. GC-MS (EI) *m/z* 224(8%), 206(14%), 115(47%), 105(100%), 91(77%), 77(25%).

*1,1',1''-ethene-1,1,2-triyltribenzene, (**14c**).*[6] White solid, mp: 71.2-72.5 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.96-7.32 (16H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 126.7, 127.4, 127.5, 128.0, 128.2, 128.2, 128.6, 129.5, 130.4, 137.4, 140.4, 142.6, 143.4. IR (KBr film) ν_{max}/cm^{-1}: 3078, 3057, 3022, 2824, 1592, 1493, 1444, 1076, 1030.

*1,1',1''-but-1-ene-1,1,2-triyltribenzene, (**14d**).* [6] White solid, mp: 78.9-79.5 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* 7.6 Hz), 2.48 (2H, q, *J* 7.5 Hz), 6.85-7.36 (15H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.6, 29.0, 125.6, 126.0, 126.5, 127.2, 127.7, 128.0, 129.3, 129.6, 130.6, 138.7, 142.1, 142.8, 143.4. IR (KBr film) ν_{max}/cm^{-1}: 3078, 3055, 3020, 2966, 2927, 2870, 1597, 1493, 1442, 1072, 1030, 775, 698.

*1,1',1'',1'''-ethene-1,1,2,2-tetrayltetrabenzene, (**14e**).*[22] White solid, mp: 224.1-225.3 ºC. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.02-7.48 (20H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 127.4, 130.4, 137.4, 143.4. IR (KBr film) ν_{max}/cm^{-1}: 3086, 3047, 2842, 1591, 1490, 1441, 1030.

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