The total synthesis of a technetium chelate – tamoxifen complex

Russell A. Bell, Kieran C. Dickson, and John F. Valliant

Abstract: A potential agent for imaging breast cancer has been synthesized by derivatization of the anti-estrogen tamoxifen. A multistep synthesis was required to conjugate a technetium chelate to tamoxifen in such a fashion that the biodistribution of the complex should mimic that of the parent compound.

Key words: tamoxifen, radioimaging, technetium, synthesis.

Résumé : En procédant à la préparation d'un dérivé du tamoxifène, un anti-estrogène, on a synthétisé un agent pouvant éventuellement être utilisé dans l'imagerie du cancer du sein. Il a fallu recourir à une synthèse en plusieurs étapes pour conjuguer un chélate du technétium au tamoxifène d'une façon telle que la biodistribution du complexe puisse ressembler à celle du composé parent.

Mots clés : tamoxifène, radioimagerie, technétium, synthèse.

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Introduction

One method of developing a site-specific radioimaging agent is to derivatize a drug or bioactive molecule with a chelate – radio nuclide complex (1). To maintain receptor selectivity the chelate must be attached to the biomolecule at a point distant from the part of the molecule which binds to the receptor. One bioactive compound of particular interest is tamoxifen (Fig. 1), a drug used for the treatment of hormone dependent breast cancer (2). An imaging agent based on tamoxifen could potentially detect tumours in their infancy, which is crucial if chemotherapy is to be effective (3).

Tamoxifen, (*Z*-1(*p*-(2-dimethylaminoethoxy)phenyl)-1,2-diphenylbut-1-ene) exerts its biological effect by binding to estrogen receptors which, for certain types of cancers, are more numerous in cancer cells than normal cells (4). ^{131}I derivatives of *E* and *Z* tamoxifen were used successfully to image tumours in mice (5); however, there was insufficient uptake in human cancer patients to develop a commercial imaging agent. The location of the iodine label and the loss of iodine due to the relatively weak carbon–iodine bond could explain the insufficient tumour uptake in human breast cancer tumours. One method of overcoming these problems is to covalently attach a chelate, the technetium complex of which is known to be stable in vivo, to a site in which substituents do not tend to affect the biodistribution of the parent molecule.

Substitution on ring B of tamoxifen is not feasible because data from binding assays of tamoxifen derivatives suggests that ring B derivatives alter the pharmacological activity of tamoxifen (6). From the aforementioned binding studies of tamoxifen derivatives, ring A appears to be a more attractive location for conjugation to a chelate. *E*-2-methyl-tamoxifen, where the methyl substituent was in the *ortho* position of ring A, had an estrogen receptor binding affinity identical to that of tamoxifen (7). From this, we concluded that the *ortho* position of ring A would be a logical site, through a spacer chain, to attach a chelate.

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Results and discussion

The diamido dithiol (DADT) chelate (**4**, Scheme 1) (8), which is known to bind ^{99m}Tc ($t_{1/2}$ = 6.0, γ = 140 KeV), the most commonly used radionuclide in diagnostic imaging, was synthesized by modifying the approach used by Bell et al. (9). 2,3-Diaminopropionic acid (**1**) was converted to the methyl ester **2** via a Fisher esterification with *p*-toluenesulfonic acid prior to reaction with the *N*-hydroxysuccinimido ester of *S*-triphenylmethylmercaptoacetic acid (1). In preparation for conjugation to the tamoxifen derivative (vide infra) the methyl ester **3** was hydrolysed by reaction with aqueous sodium hydroxide in THF to produce the desired chelate **4**.

Two approaches to the synthesis of DADT-tamoxifen conjugate were used; approach A involved the total synthesis of the tamoxifen derivative before coupling to the chelate, while strategy B entailed coupling of a chloro-tamoxifen species to the chelate prior to the addition of the dimethylamine moiety.

The synthesis, based on the approach of McCague and co-worker (10) (Scheme 2) began by following the literature procedure for the mono substitution of 1,2-dichloroethane by phenolate under phase transfer conditions (11). The chloroether was subsequently subjected to Friedel–Crafts acylation (12) by use of either (±)-2-phenylbutyric acid and trifluoroacetic anhydride (TFAA) or the acid chloride of

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Scheme 1. Synthesis of DADT (**4**).

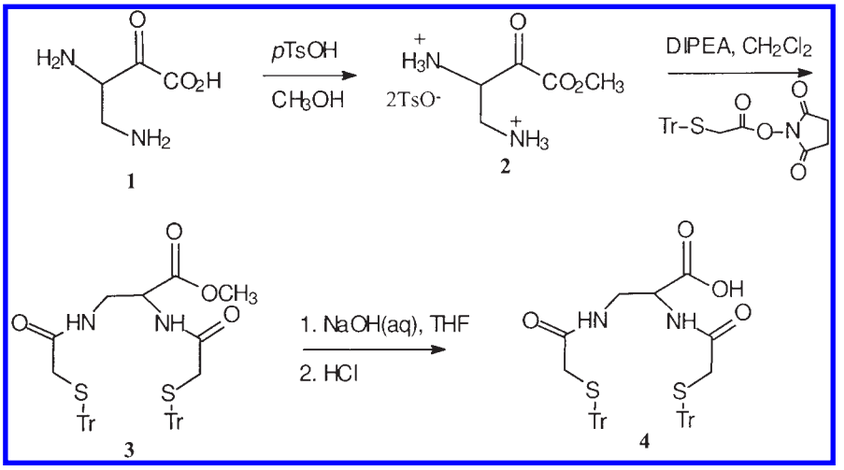
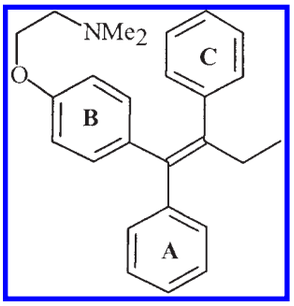


Fig. 1. Tamoxifen.



(±)-2-phenylbutyric acid and aluminum trichloride in carbon disulfide (12) to give **6** in 79 and 57% yields, respectively. Evidence from ^{1}H and ^{13}C NMR confirmed that the acylation product was entirely *para* substituted. The linker arm for the chelate was now added in the form of the *tert*-butyldimethylsilyl ether of 2-bromophenethyl alcohol (13), the nucleophile being generated by metal halogen exchange. The anion reacted with the ketone **6** to generate two diasteriomeric alcohols **9**, which were not normally isolated but converted directly to the alkenes **10** by reaction with thionyl chloride and pyridine at –10°C. These milder elimination conditions were used because the literature procedure employing concentrated HCl in ethanol caused the loss of the silyl protecting group and subsequent elimination of the resultant alcohol. The silyl group of **10** was removed in good yield (96%) by the use of tetrabutylammonium fluoride in THF (13).

The chemical shift of the proton and carbon atoms of each diasteriomer of **10**, at 200 MHz and 50 MHz, respectively, were significantly different and each isomer could be distinguished readily. To assign the signals of each isomer required the use of a two-dimensional nuclear Overhauser effect (2-D NOE) experiment (NOESY). From the ^{1}H spectrum the pair of doublets at 6.812 and 6.50 ppm were assigned to the AB spin system of ring B. The doublet at 6.812 ppm exhibited a NOE correlation to signals in the aromatic region but showed no correlation to the methylene of the ethyl group of tamoxifen; this confirmed that these signals belonged to the *E*-isomer. The COSY spectrum was then used to assign the remaining signals belonging to that isomer, and it was concluded that the major isomer, as Cram's rules (14) predicted, was the *E*-isomer in a ratio of approximately 5:1.

Fatty acid derivatives were selected as the spacer chain because the length of the spacer can be altered easily as there are numerous fatty acid derivatives which are commercially available. Once the general synthetic route was developed, varying lengths of spacers can be tested until the optimum length associated with high binding efficiency is found. In the present synthesis (Scheme 3), bromododecanoic acid was converted to the azide prior to reaction with thionyl chloride. The acid chloride was then converted to an ester by reaction with alcohol **11**. An unexpected advantage of using the long-chain fatty acid was that small quantities of each isomer of **12** could be separated by radial chromatography. During the development of the synthetic methodology towards **15**, a relatively large quantity of **12** was required, and for practical purposes, the nonenriched 5:1 *E*:*Z* ratio, material was used. Should the results of the biodistribution studies show promise, the isomers of **12** can be separated and pure *E*-**15** and *Z*-**15** synthesized. Because of the ratio of 5:1 for *E*:*Z* isomers, it was possible to assign many of the NMR signals for each isomer in mixtures of compounds **13**–**17**.

In approach A, the azido-chloride species **12** was converted to the dimethylamino species **13** by reaction with dimethylamine in ethanol at an elevated temperature. If extensive reaction times were used (greater than 4 days) a minor byproduct occurred as a result of cleavage of the ester bond by either a dimethylamine or ethoxide nucleophile with the resulting species being the phenethyl alcohol **11**. The azide **13** was reduced by the use of triphenylphosphine (15) because other methods (lithium aluminum hydride and catalytic hydrogenation) would cause reduction of the alkene and (or) ester groups. Reduction appeared to occur quantitatively as indicated by TLC, however, isolation of the resulting amine was difficult, and only a low yield of product was isolated (25%). The amine **14** was immediately coupled to the chelate (**4**) by the use of EDC (16) in good yield, as judged by thin-layer chromatography. Again, however, puri-

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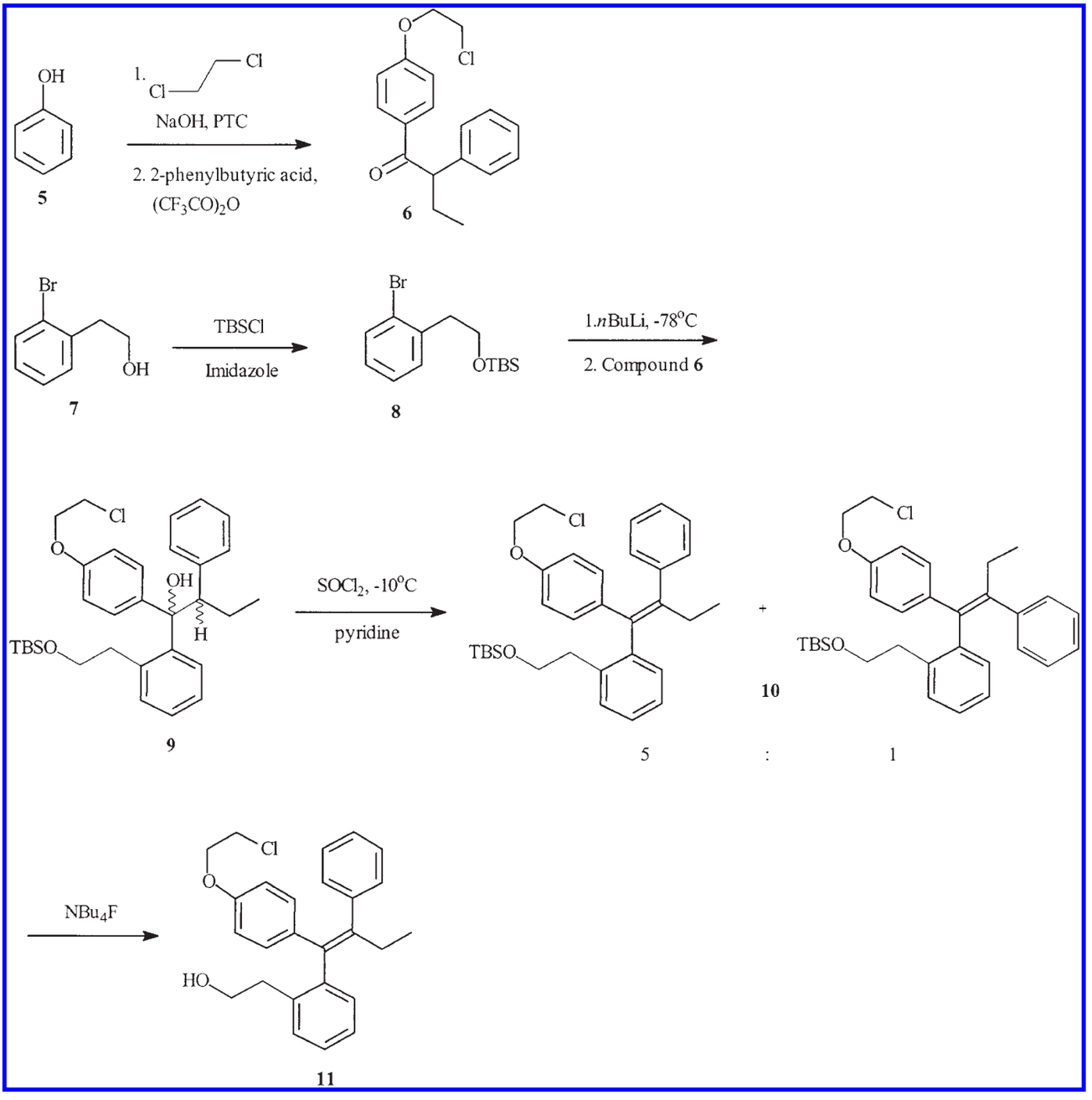
Scheme 2. Synthesis of **11**.



fication of the product proved difficult and resulted in a low yield of the desired product (26%).

In an attempt to improve the yields of synthesis A, strategy B was developed. The azide **12** was reduced by the use of the aforementioned triphenylphosphine approach (Scheme 4). Formation of the phosphonium salt from the alkyl chloride fragment was not a concern because the reduction was carried out at room temperature. The resulting amine **16** was coupled to the chelate in good yield (76%), and replacement of the chloro substituent with dimethylamine also occurred in good yield (60%). There was no evidence for decomposition of the ester or amide bonds so long as the reaction time was kept to a reasonable length (20–24 h).

The addition of dimethylamine to **17** could be observed in the ^{1}H NMR as the two singlets at 2.325 and 2.267 ppm, corresponding to the two isomers, were assigned to the *N*-methyl protons. There was also a significant shift of the methylene protons adjacent to the dimethylamine moiety, upon substitution, the protons shifted upfield by approximately 1 ppm. The ^{13}C NMR contained no ambiguities, the resonances associated with the *N*-methyl protons were ob-

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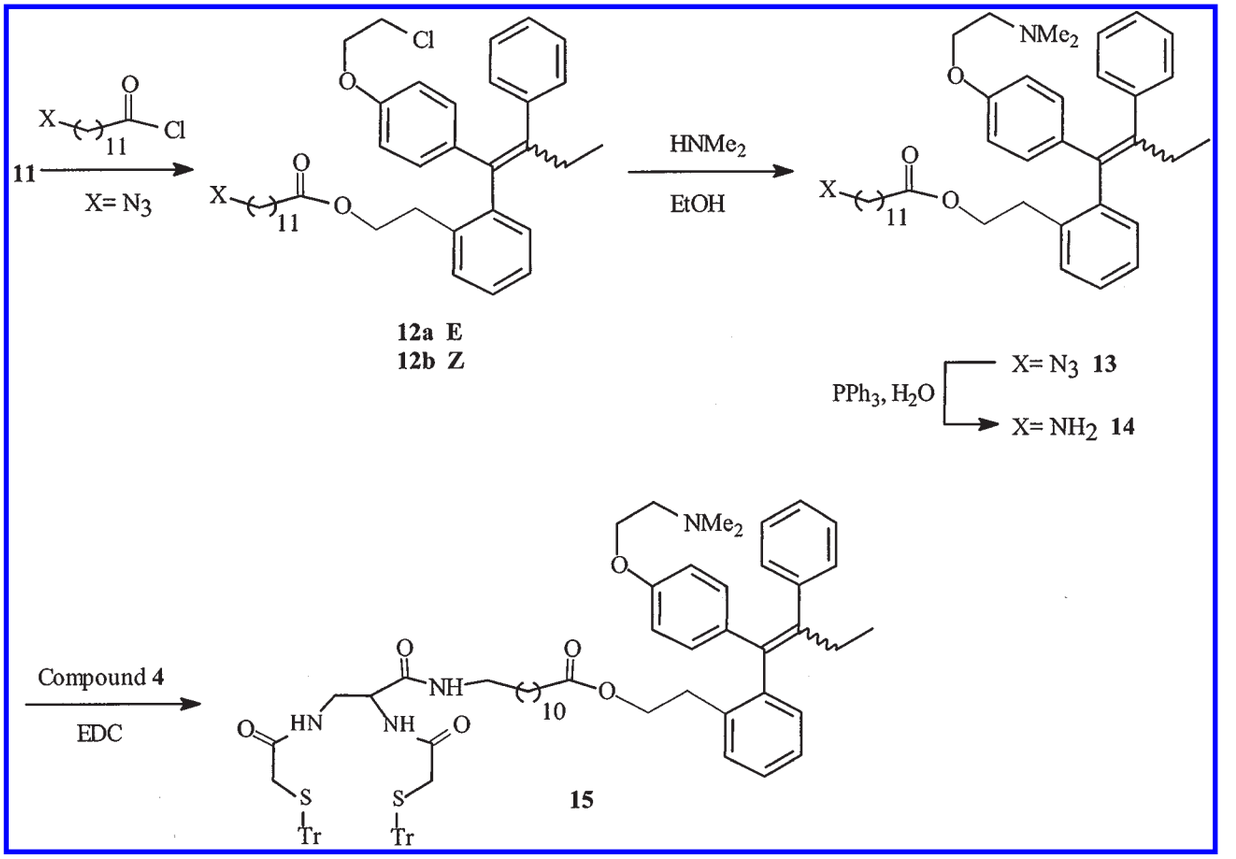
Scheme 3. Synthesis of **15**, approach A.



served at 45.80 ppm. The methylene protons adjacent to the *N*-methyl moiety shifted downfield upon substitution of the chloro group from 41.99 ppm to 58.18 ppm.

Experimental section

Analytical TLC was performed on silica gel 60-F_{254} (Merck) with detection by long wavelength ultraviolet light. Chromatography was performed with a chromatotron (Harrison Research Model 7924T) that used a 4 mm plate (EM Science silica gel 60 PF_{254} that contained gypsum). All commercial reagents were used as supplied. Solvents were distilled, under nitrogen, from calcium hydride. Nitrogen was dried by passing it through calcium sulphate. All reactions were protected from light and carried out under a slow flow of nitrogen. Solvents were evaporated with a rotary evaporator (20 mmHg (1 mmHg = 133.3 Pa)) at moderate temperatures (30–50°C).

Selected NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer. Proton spectra were acquired at 500.130 MHz with a 5 mm broadband inverse probe with triple-axis gradient capability. Spectra were obtained in 8 scans in 32K data points over a 4.006 kHz spectral width (4.096 s acquisition time). The compounds used in this study were dissolved in $CDCl_3$ (Isotec, Inc.) to a concentration of approximately 15.0 mg mL^{-1}. Chemical shifts are reported in ppm relative to TMS. The residual solvent signals at 7.24 and 77.0 ppm were used as internal references for the ^1H and ^{13}C spectra, respectively. Coupling constants are given in Hertz (Hz). All other NMR spectra were recorded on a Bruker AC-200 spectrometer. Proton spectra were acquired at 200.133 MHz with a 5 mm dual frequency probe. Spectra were obtained in 8 scans in 16K data points over a 2.403 KHz spectral width (3.408 s acquisition time). Spectra were acquired at ambient probe temperature. The free induction decay (FID) was processed with exponential multiplication (line broadening: 0.1 Hz) and was zero-filled to 32K before Fourier transformation. Carbon-13 NMR spectra were recorded at 50.323 MHz with the 5 mm QNP probe. The spectra were acquired over a 12.195 kHz spectral width in 16K data points (0.672 s acquisition time).

Synthetic procedures

Methyl 2,3-diaminopropanoate p-*toluenesulfonate salt (**2**)*

To 2.0 g (14.28 mmol) of (±) 2,3-diaminopropionic acid monhydrochloride suspended in methanol (60 mL), *p*-toluenesulfonic acid was added (10.82 g, 56.9 mmol). After the solution was heated at reflux for 24 h it was evaporated to dryness at reduced pressure, and the remaining solid was washed with diethyl ether (200 mL), rendering the methyl ester as colourless crystals. Yield: 6.5 g, 99%; mp 200°C (decomp.); ^1H NMR (CD_3OD) (200 MHz) δ 7.719 (d, J = 8.3, 2H, H-*ortho*), 7.251 (d, 2H, H-*meta*), 5.003 (brd, NH), 4.494 (m, 1H, C*H*), 3.853 (s, 3H, OCH_3), 3.529 (m, 2H, CH_2), 2.354 (s, 3H, PhCH_3); ^{13}C NMR (CD_3OD)

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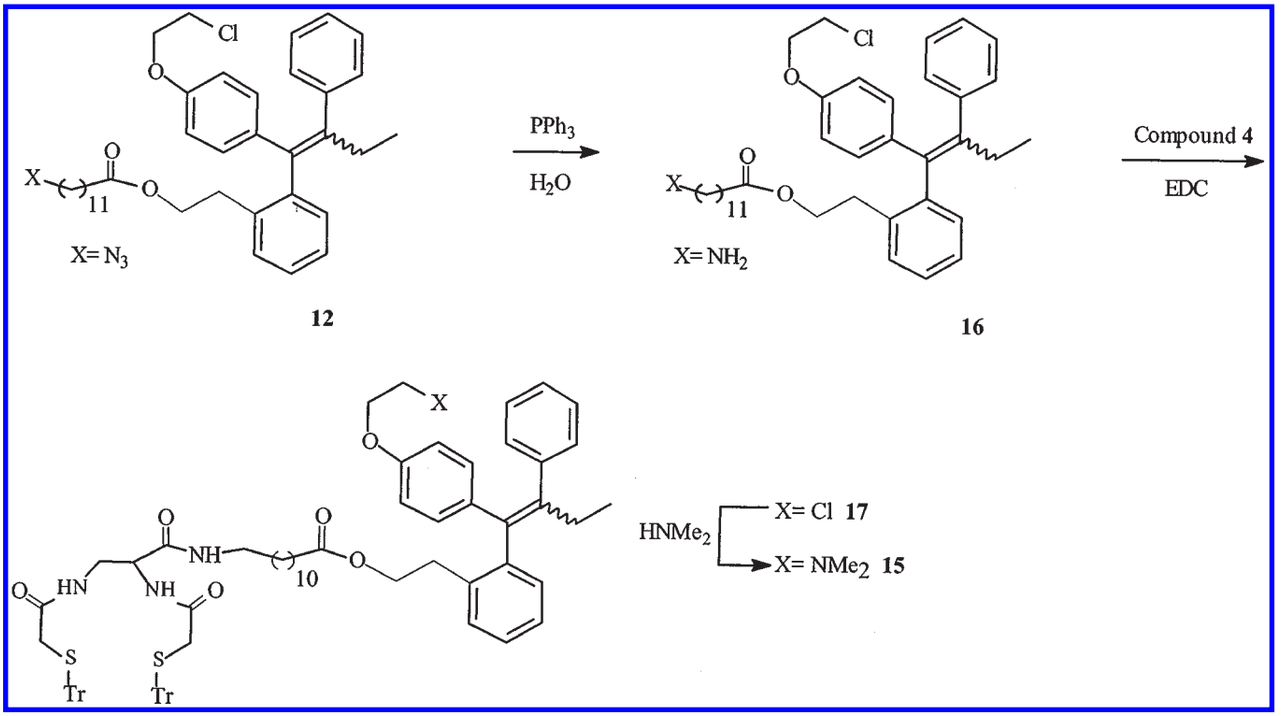
Scheme 4. Synthesis of **15**, approach B.



(50 MHz) δ: 167.99 (*C*OOMe), 143.00 (C-*para*), 141.99 (C-*ipso*), 129.91 (C-*meta*), 126.90 (C-*ortho*), 54.55 (*C*H), 51.14 (O*C*H$_3$), 39.51 (*C*H$_2$), 21.32 (Ph-*C*H$_3$).

Methyl 2,3-bis(triphenylmethylthioacetylamino)propanoate (3)

To 3.62 g (8.40 mmol) of 2-(triphenylmethylthio)ethanoic acid-*N*-hydroxysuccinimido ester (1) dissolved in dichloromethane (50 mL), 1.92 g (4.16 mmol) of **2** was added. To the rapidly stirred mixture, diisopropylethylamine (DIPEA) (1.34 mL, 7.69 mmol) was added and the solution heated to reflux for 8 h. The solution was cooled and extracted with 1 M HCl (2 × 10 mL), 1 M NaHCO$_3$ (2 × 10 mL), and distilled water (distilled water) (3 × 15 mL). The solution was evaporated to dryness at reduced pressure, and the solid was washed with distilled water (200 mL), methanol (5 mL), and ether (5 mL). The colourless solid was recrystallized from acetone and subsequently dried in vacuo to give 2.2 g (78%) of **3**. The compound showed mp 68–70°C; TLC: R_f = 0.44 (2% CH$_3$OH–CH$_2$Cl$_2$); ^{1}H NMR (CDCl$_3$) (200 MHz) δ: 7.324–7.075 (m, 17H, H-*aryl*), 6.708 (d, *J* = 6.7, 1H, CHN*H*), 6.094 (m, 1H, CH$_2$N*H*), 4.064 (m, 1H, C*H*), 3.087 (m, 2H, CHC*H*$_2$), 2.934 (s, 2H, C*H*$_2$); ^{13}C NMR (CDCl$_3$) (50 Mhz) δ: 170.06 (*C*OOMe), 168.55, 168.89 (*C*(O)NH), 143.87 (C-*ipso*), 129.50 (C-*ortho*), 128.09 (C-*meta*), 126.98 (C-*para*), 67.71 (Ph$_3$*C*), 52.72 (*C*H and O*C*H$_3$), 41.24 (CH*C*H$_2$), 35.93 (*C*H$_2$), 35.72 (S*C*H$_2$).

2,3-Bis(triphenylmethylthioacetylamino)propanoic acid (4)

To 1.0 g (1.33 mmol) of **3** in a 1:1 mixture of THF and water (80 mL), 100 mg (2.5 mmol) of NaOH was added. After the mixture was heated to reflux for 3 h under an atmosphere of nitrogen, the solution was cooled, acidified to pH 3.9 using 6 M HCl, and concentrated to 30 mL under reduced pressure. The precipitate that formed was collected by filtration, and the colourless solid washed with distilled water (100 mL) and sparingly with ether (5 mL). The filtrate was concentrated and diluted with methanol (15 mL) and refrigerated overnight. The resulting solid was collected by filtration and washed again with distilled water and ether as above, yielding an additional crop of the title compound. Yield 900 mg, (97%); mp 214–215°C; TLC: R_f = 0.22 (10% CH$_3$OH–CH$_2$Cl$_2$); ^{1}H NMR (CD$_3$OD) (200 MHz) δ 7.643 (m, 15H, H-*aryl*), 4.590 (m, 1H, C*H*), 4.063 (m, 2H, C*H*$_2$CH), 3.269 (m, 2H, TrSC*H*$_2$); ^{13}C NMR (CD$_3$OD) (50 MHz) δ 171.21 (C-*C*OOH), 168.90, 168.55 (*C*(O)NH), 143.87 (C-*ipso*), 129.50 (C-*ortho*), 128.09 (C-*meta*), 126.98 (C-*para*), 65.88 (Ph$_3$*C*), 52.05 (*C*H), 43.96 (*C*H$_2$CH), 35.85, 32.33 (TrS*C*H$_2$).

(2-Chloroethoxy)benzene

The procedure described by McCague (10) was used. Phenol (28.2 g, 300 mmol), dimethyldioctadecylammonium bromide (1.8 g, 3.0 mmol), sodium hydroxide (24.0 g, 600 mmol) in distilled water (225 mL), and 1,2-dichloroethane (225 mL) were heated to reflux for 48 h. The organic phase was separated, dried with magnesium sulfate, and concentrated under reduced pressure to produce a translucent yellow oil. This crude product was subsequently purified by vacuum distillation to give the title compound as a colourless oil (35.6 g, 76%). The compound showed bp 100–102°C @ 12 mmHg; ^{1}H NMR (CDCl$_3$) (200 MHz) δ: 7.30 (m, 5H, H-*aryl*), 4.23 (t, 2H, OC*H*$_2$), 3.81 (t, 2H, *J* = 5.9, C*H*$_2$Cl); ^{13}C NMR (CDCl$_3$) (50 MHz) δ 159.8 (C- *ipso*), 131.0 (C-*meta*), 122.5 (C-*para*), 118.3 (C-*ortho*), 67.86 (O*C*H$_2$), 41.86 (*C*H$_2$Cl).

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*1-[4-(2-Chloroethoxy)phenyl]-2-phenyl-1-butanone (**6**)*

The procedure developed by McCague was used (10). 1-Chloro-2-phenoxyethane (21.8 g, 140 mmol), (±)-2-phenylbutyric acid (20.2 g, 120 mmol), and trifluoroacetic anhydride (27.3 g, 130 mmol) were mixed and stirred magnetically at 20°C for 70 h. The reaction mixture was then poured slowly into distilled water (150 mL) to give a pink solid which was collected and recrystallized from ethanol to give colourless crystals (28.8 g, 79%). The compound showed mp 65–70°C; TLC: R_f = 0.79 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 7.98–6.85 (m, 9H, H-*aryl*), 4.39 (t, 1H, *J* = 7.3, PhC*H*), 4.24 (t, 2H, OCH_2), 3.80 (t, 2H, *J* = 5.8, CH_2Cl), 2.02 (m, 2H, CH_2CH$_3$), 0.89 (t, 3H, *J* = 7.4, CH_3); ^{13}C NMR ($CDCl_3$) (50 MHz) δ: 198.07 (*C*(O)), 162.11–107.38 (*C*-aryl), 67.53 (*C*HPhCH$_2$CH$_3$), 55.17 (O*C*H$_2$), 41.39 (*C*H$_2$Cl), 26.48 (*C*H$_2$), 12.15 (*C*H$_3$).

*2-(2-Bromophenyl)-*O*-(*tert*-butyldimethylsilyl)ethan-2-ol (**8**)*

The procedure developed by Corey and Venkateswarlu (13) was used. 2-Bromophenethyl alcohol (2.0 g, 9.95 mmol) and imidazole (1.02 g, 14.9 mmol) were dissolved in dichloromethane (30 mL) under nitrogen and cooled over ice before *tert*-butyldimethylsilyl chloride (2.25 g, 14.9 mmol) was added. After 8 h the reaction mixture was filtered and the residue washed with dichloromethane (25 mL). The filtrate was extracted with distilled water (3 × 30 mL), concentrated to 1 mL, and passed down a silica column (petroleum ether – dichloromethane). The first band to elute from the column was collected, evaporated to dryness, and dried under high vacuum until the odour of the silicon starting material could no longer be detected (2–3 h). The product, a colourless oil (2.6 g, 83%), showed TLC: R_f = 0.66 (50:50 v/v CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 7.58–6.99 (m, 4H, H-*aryl*), 3.85 (t, 2H, *J* = 8.8, CH_2O), 2.99 (t, 2H, PhCH_2), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.03 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) (50 MHz) δ 138.29 (C-2), 131.7, 132.6 (C-3, C-6), 127.8, 127.1, (C-4, C-5), 124.56 (C-*ipso* i.e., C-1), 62.40 (*C*H$_2$O), 53.27 (Si*C*(CH$_3$)$_3$), 39.59 (PhCH$_2$), 25.89 (SiC(*C*H$_3$)$_3$), 18.22 (Si(*C*H$_3$)$_2$); MS (NH_3 DCI) *m*/*z* (RI%): 334 (100) (M + 2H$^+$ + NH_3), 332 (89) (M + NH_3), 331 (20) (M + NH_3 – H$^+$), 317 (100) (M + 2H$^+$), 315 (90) (M).

*1-[4-(2-Chloroethoxy)phenyl]-1-[2-(*O*-(*tert*-butyldimethylsilyl)ethyl)phenyl]-2-phenyl butan-1-ol (**9**)*

Compound **8** (2.02 g, 6.41 mmol) was dissolved in 5 mL of dry THF in a flame-dried flask under an argon atmosphere and cooled to –78°C. When *n*-butyllithium (4.0 mL, 1.6 M solution in hexanes) was added via syringe the solution became heterogeneous; it was left to stir for an additional 20 min. After the addition of compound **6** (1.09 g, 3.6 mmol in 5 mL dry THF) the solution cleared. The solution was allowed to gradually warm to room temperature and after 12 h the reaction was complete. Distilled water (50 mL) was added slowly and the solution extracted with ether (3 × 50 mL). The organic layers were combined, dried over sodium sulfate, filtered, and evaporated to dryness. The resulting oil was used without further purification or characterization.

*1-[4-(2-Chloroethoxy)phenyl]-1-[2-(*O*-(*tert*-butyldimethylsilyl)ethyl)phenyl]-2-phenyl but-1-ene (**10**)*

Compound **9** was dissolved in freshly distilled pyridine (10 mL) and cooled to –10°C; thionyl chloride (788 µL, 10.8 mmol) was added and the mixture stirred under argon for 3 h. The yellow–orange coloured solution was diluted cautiously with distilled water (20 mL) and extracted with diethyl ether (4 × 40 mL). The organic layers were combined and evaporated to dryness. The product was isolated by radial chromatography (10:1 low boiling petroleum ether/ether). The compound, a yellow oil (1.18 g, 64%), showed TLC: R_f = 0.72 (10:90 v/v ether/petroleum ether); ^{1}H NMR ($CDCl_3$) (200 MHz) δ:7.102 (m, H-aryl), 6.500 (d, 2H, H-*ortho* ring B), 4.189 (t, *J* = 3.9, 2H, *Z*-isomer OCH_2CH$_2$Cl), 4.042 (t, *J* = 3.8, 2H, *E*-isomer OCH_2CH$_2$Cl), 3.910 (m, 1H, SiOCH_2), 3.769 (t, *J* = 3.9, 2H, *Z*-isomer CH_2Cl), 3.672 (t, *J* = 4.0, 2H, *E*-isomer CH_2Cl), 3.449 (m, TBSOCH_2), 2.867 (t, *J* = 3.6, 2H, *E*-isomer CH_2Ph), 2.787 (m, 1H, *E*-isomer CH_2CH$_3$), 2.686 (t, *J* = 4.9, 2H, *E*-isomer CH_2Ph), 2.560 (m, 1H, *Z*-isomer CH_2CH$_3$), 2.276 (m, 2H, *Z*-isomer CH_2CH$_3$), 1.007 (t, *J* = 4.9, CH_3), 0.814 (m, SiC(CH_3)$_3$), 0.02 (s, Si-CH_3); ^{13}C NMR ($CDCl_3$) (50 MHz) δ 156.77, 156.06, 142.77, 142.53, 142.16, 141.89, 141.74, 137.55, 136.95, 135.97, 134.77, 131.71, 131.55, 130.65, 130.42, 130.01, 129.73, 129.46, 128.96, 128.26, 127.97, 127.47, 126.95, 126.20, 126.0, 125.36, 120.05, 117.0, 114.18, 113.505 (C-*aryl*), 67.93 (*Z*-isomer OCH$_2$CH$_2$Cl), 67.70 (*E*-isomer OCH$_2$CH$_2$Cl), 63.43 (*E*-isomer SiO*C*H$_2$), 63.20 (*Z*-isomer SiO*C*H$_2$), 41.76 (*C*H$_2$Cl), 36.72 (*E*-isomer *C*H$_2$Ph), 36.43 (*Z*-isomer *C*H$_2$Ph), 29.51 (*C*H$_2$CH$_3$), 25.93 (SiC(*C*H$_3$)$_3$), 18.31 (Si*C*H$_3$), 13.80 (*Z*-isomer CH$_2$*C*H$_3$), 12.93 (*E*-isomer CH$_2$*C*H$_3$); MS (NH_3 DCI) *m*/*z* (RI%): 538 (100) (M + NH_3), 520 (80) (M), 406 (85) (M – TBS + H).

*1-[4-(2-Chloroethoxy)phenyl]-1-[2-(hydroxyethyl)phenyl]-2-phenyl but-1-ene (**11**)*

The procedure developed by Corey and Venkateswarlu (13) was used. To compound **10** (800 mg, 1.54 mmol) in 10 mL of THF, tetrabutylammonium fluoride (5.07 mL, 1.0 M solution in THF) was added. The reaction was allowed to stir for 24 h before dilution with distilled water (20 mL) and extraction with diethyl ether (4 × 25 mL). The organic layer was concentrated to a volume of 2 mL and the product isolated by radial chromatography (hexanes–dichloromethane). The title compound (600 mg, 96%), an oil, showed TLC: R_f = 0.15 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 7.20 (m, H-*aryl*), 6.520 (d, 2H, H-*ortho* ring B), 4.143 (t, *J* = 5.9, *Z*-isomer, OCH_2CH$_2$Cl), 3.996 (t, *J* = 5.9, 2H, *E*-isomer OCH_2CH$_2$Cl), 3.725 (t, *J* = 5.8, 2H, *Z*-isomer CH_2Cl), 3.629 (t, *J* = 5.9, 2H, *E*-isomer CH_2Cl), 3.425 (m, *E*/*Z*, CH_2OH), 2.711, 2.200 (m, overlap, CH_2Ph, CH_2CH$_3$), 0.954 (t, *J* = 7.5, 3H, *Z*-isomer CH_3), 0.769 (t, *J* = 7.4, 3H, *E*-isomer CH_3); ^{13}C NMR ($CDCl_3$) (50 MHz) δ: 156.10, 156.06, 142.98, 142.69, 142.05, 141.70, 136.65, 136.37, 136.15, 135.86, 134.60, 132.01, 131.50, 130.35, 130.24, 129.65, 128.87, 127.98, 127.52, 127.22, 126.50, 126.26, 126.06, 125.64, 114.24, 113.52 (C-*aryl*), 67.93 (*Z*-isomer OCH_2CH$_2$Cl), 67.67 (*E*-isomer OCH_2CH$_2$Cl), 62.63 (*E*-isomer *C*H$_2$OH), 62.41 (*Z*-isomer *C*H$_2$OH), 41.79 (*C*H$_2$Cl), 36.47 (*E*-isomer PhCH_2), 36.14 (*Z*-isomer PhCH_2),

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29.49 (*E*-isomer CH_2CH_3), 28.04 (*Z*-isomer CH_2CH_3), 13.77 (*Z*-isomer CH_3), 12.92 (*E*-isomer CH_3).

12-Azido-dodecanoic acid

Sodium azide (4.7 g, 72.3 mmol) was added to a solution of 12-bromododecanoic acid (2.0 g, 7.16 mmol) in DMF (45 mL). After heating at 80°C for 12 h, the reaction mixture was cooled to room temperature and poured into distilled water (100 mL). The solution was extracted with ether (2 × 70 mL) and the organic fractions pooled and evaporated in vacuo. The resulting yellow oil was diluted with a 3:1 mixture of water/brine (10 mL) and refrigerated overnight. The resulting colourless precipitate was collected by filtration, washed with cold water (30 mL), and dried in air. The compound (1.56 g, 90%) showed ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.320 (t, *J* = 6.8, 2H, CH_2-N_3), 2.313 (t, *J* = 7.4, 2H, CH_2COOH), 1.570 (m, 4H, CH_2), 1.257 (m, 18H, CH_2); ^{13}C NMR ($CDCl_3$) (50 MHz) δ: 180.04 (*C*OOH), 51.45 (CH_2-N_3), 34.15 (CH_2COOH), 29.40, 29.18, 29.09, 29.02, 28.8, 26.67, 24.68 (CH_2); MS(ES) *m*/*z* (RI%): 241.4 (18) (M), 240.4 (100) (M – H).

*1-[4-(2-Chloroethoxy)phenyl]-1-[2-[(12-azidododecanoyl)oxyethyl)phenyl]-2-phenyl but-1-ene (**12**)*

12-Azido-dodecanoic acid (500 mg, 2.07 mmol) was dissolved in thionyl chloride (8 mL) and heated to reflux under nitrogen for 1 h. Residual thionyl chloride was evaporated in vacuo and the residue dissolved in dry dichloromethane (25 mL), which was subsequently evaporated. The oily residue was redissolved in dry dichloromethane (20 mL) and compound **11** (766 mg, 1.89 mmol) in dry dichloromethane (5 mL) was added. The solution was heated to reflux for 12 h before the slow addition of 10% Na_2CO_3 (20 mL). The solution was extracted with chloroform (2 × 50 mL), and the organic layers were pooled, concentrated to 2 mL, and the product, a yellow oil (766 mg, 64%), isolated by radial chromatography (petroleum ether – ether). Samples of pure *E*-12 and pure *Z*-12 can be isolated by using a new chromatatron plate (activated with petroleum ether), a very gradual gradient of 100% petroleum ether up to 10% ether and collecting small aliquots as the major product band elutes from the chromatatron. The compound showed MS (HRDEI): obs: 629.33695, calcd.: 629.3384. *E*-Isomer: ^{1}H NMR ($CDCl_3$) (500 MHz) δ: 7.280 (m, H-*aryl*), 6.764 (d, *J* = 9.3, 2H, H-*meta*- ring B), 6.512 (d, 2H, H-*ortho*- ring B), 4.117 (m, 1H, OCH_2CH_2Ph), 4.063 (m, 2H, OCH_2CH_2Cl), 3.914 (m, 1H, OCH_2CH_2Ph), 3.694 (t, 2H, *J* = 6.0, CH_2Cl), 3.233 (t, 2H, CH_2N_3), 2.734 (m, 2H, OCH_2CH_2Ph), 2.325 (m, 1H, CH_2CH_3), 2.224 (t, *J* = 6.2, 2H, $CH_2C(O)$), 2.211 (m, 1H, CH_2CH_3), 1.564, 1.344, 1.245 (m, CH_2), 0.810 (t, *J* = 7.4, 3H, CH_3); ^{13}C NMR ($CDCl_3$) (125 MHz) δ 173.61 (*C*OOR), 156.13, 142.68, 142.28, 141.76, 136.50, 135.82, 134.48, 131.53, 130.28, 130.20, 129.70, 128.00, 127.20, 126.44, 126.28, 113.60 (C-*aryl*), 67.78 (OCH_2CH_2Cl), 63.71 (OCH_2CH_2Ph), 51.48 (CH_2N_3), 41.78 (CH_2Cl), 34.32 ($CH_2OC(O)$), 32.48 OCH_2CH_2Ph), 29.42, 29.38, 29.23, 29.10 (CH_2), 28.82 (CH_2CH_3), 26.69, 24.94 (CH_2), 12.90 (CH_3). *Z*-Isomer: ^{1}H NMR ($CDCl_3$) (500 MHz) δ: 7.00 (m, H-*aryl*), 4.166 (t, *J* = 6.0, 2H, OCH_2CH_2Cl), 3.816 (m, OCH_2CH_2Ph), 3.746 (t, *J* = 6.0, 2H, OCH_2CH_2Cl), 3.652 (m, OCH_2CH_2Ph), 3.191 (t, *J* = 7.0, 2H, CH_2N_3), 2.801, 2.620, 2.553 (m, overlap, OCH_2CH_2Ph and CH_2CH_3), 2.192 (t, *J* = 7.6, 2H, $CH_2C(O)$), 1.511, 1.288 (m, CH_2), 0.960 (t, *J* = 7.4, 3H, CH_3); ^{13}C NMR ($CDCl_3$) (125 MHz) δ: 173.60 (*C*OOR), 142.92, 142.01, 137.18, 135.65, 131.95, 130.39, 129.71, 128.95, 127.54, 126.52, 126.12, 125.80, 114.35 (C-*aryl*), 68.05 (OCH_2CH_2Cl), 63.72 (OCH_2CH_2Ph), 51.48 (CH_2N_3), 41.83 (CH_2Cl), 34.33 ($CH_2OC(O)$), 32.05 (OCH_2CH_2Ph), 29.45, 29.25, 29.13, 28.82 (CH_2), 26.70 (CH_2CH_3), 24.95 (CH_2), 13.79 (CH_3).

*1-[4-(2-Dimethylaminoethoxy)phenyl]-1-{2-[(12-azidododecanoyl)oxyethyl]phenyl}-2-phenyl but-1-ene (**13**)*

The procedure developed by McCague (10) was used. In a round-bottom flask fitted with a dry ice condenser, compound **12** (150 mg, 0.235 mmol) was dissolved in dimethylamine (20 mL, 5.6 M solution in ethanol) and the mixture was heated to reflux for 2 days. The solution was evaporated to dryness, the residue dissolved in DCM (2 mL), and the title compound isolated by centrifugal chromatography ($CHCl_3$–MeOH). The title compound, a yellow oil (76 mg, 50%), showed ^{1}H NMR ($CDCl_3$) (500 MHz) δ: 7.298 (m, H-*aryl*), 6.934 (d, *J* = 8.9, 2H, *H-meta* ring A), 6.512 (d, 2H, H-*ortho*, ring A), 4.110 (m, OCH_2CH_2Ph), 3.916 (overlap, t, *J* = 6.0, $OCH_2CH_2NMe_2$, and m, OCH_2CH_2Ph), 3.242 (t, *J* = 6.8, 2H, CH_2N_3), 2.713 (m, OCH_2CH_2Ph), 2.644 (t, *J* = 5.7, 2H, CH_2NMe_2), 2.210 (m, overlap, CH_2CH_3, CH_2COOR, NCH_3), 1.331 (m, $(CH_2)_n$), 0.813 (t, *J* = 7.2, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) (125 MHz) δ: 173.59 (*C*OOR), 156.69, 142.72, 141.88, 141.74, 136.57, 135.76, 133.68, 131.33, 130.21, 130.11, 129.65, 128.89, 127.90, 127.46, 127.07, 126.34, 126.14, 114.05 (C-*aryl*), 65.52 ($OCH_2CH_2NMe_2$), 63.67 (OCH_2CH_2Ph), 58.13 (CH_2N), 51.38 (CH_2N_3), 45.73 (NCH_3), 34.25 (CH_2COOR), 32.42 (OCH_2CH_2Ph), 29.37, 29.18, 29.05 ($(CH_2)_n$), 28.75 (CH_2CH_3), 26.63, 24.88 ($(CH_2)_n$), 12.90 (CH_2CH_3); MS (HRDEI): obs: 638.4190, calcd.: 638.4196.

*1-[4-(2-Dimethylaminoethoxy)phenyl]-1-{2-[(12-aminododecanoyl)oxyethyl]phenyl]-2-phenyl but-1-ene (**14**)*

To compound **13** (69 mg, 0.108 mmol) in THF (1 mL), triphenylphosphine (29 mg, 0.110 mmol) followed by distilled water (3.0 μL) were added. The reaction was allowed to stir for 24 h whereupon an additional aliquot of triphenylphosphine (29 mg, 0.110 mmol) and water (3.0 μL) were added. After an additional 24 h the solution was evaporated to dryness, diluted with chloroform (1 mL), and the title compound isolated by centrifugal chromatography (16 mg, 25%). The compound showed ^{1}H NMR ($CDCl_3$) (500 MHz) δ 7.230 (m, H-*aryl*), 6.691 (d, *J* = 8.8, 2H, *H-meta* ring A), 6.488 (d, 2H, H-*ortho*, ring A), 4.036 (m, OCH_2CH_2Ph), 3.832 (overlap, t, *J* = 5.8, $OCH_2CH_2NMe_2$, and m, OCH_2CH_2Ph), 2.637 (m, overlap, CH_2NH_2, OCH_2CH_2Ph, CH_2NMe_2), 2.197 (m, CH_2CH_3, CH_2COOR, NCH_3), 1.492, 1.353, 1.182 (m, $(CH_2)_n$), 0.743 (t, *J* = 7.2, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) (125 MHz) δ: 173.64 (*C*OOR), 156.73, 142.72, 141.87, 141.76, 136.58 135.77, 133.66, 131.33, 130.22, 130.22, 130.11, 129.66, 128.25, 127.91, 127.07, 126.34, 126.14, 113.34 (C-*aryl*), 65.60 ($OCH_2CH_2NMe_2$), 63.68 (OCH_2CH_2Ph), 58.18 (CH_2N), 45.78 (NCH_3), 42.08 (H_2NCH_2), 34.27 (CH_2COOR), 33.69 ($(CH_2)_n$), 32.42

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(OCH_2CH_2Ph) 29.44, 29.21(($CH_2)_n$), 29.06 (CH_2CH_3), 26.82, 24.89 (($CH_2)_n$), 12.91 (CH_2CH_3); MS (NH_3 DCI) *m*/*z* (RI%): 613 (100) (M + 1), 541 (14) (M – $CH_2CH_2NMe_2$).

*1-[4-(2-Dimethylaminoethoxy)phenyl]-1-{2-[(12-((2,3-bistriphenylmethylthioacetylamino)propanamido)dodecanoyloxy)ethyl]phenyl}-2-phenyl but-1-ene (**15**)*

Compound **14** (16 mg, 0.026 mmol) was dissolved in DCM (10 mL) and triethylamine was added (1 mL), followed by compound **4** (20 mg, 0.027 mmol). To this well stirred solution, EDC (19 mg, 0.099 mmol) was added slowly. The reaction mixture was stirred for 48 h before dilution with DCM (10 mL) and extraction with brine (3 × 10 mL). The organic phase was concentrated to 1 mL and an impure fraction of the title compound isolated by radial chromatography ($CHCl_3$–MeOH). This fraction was concentrated to 0.5 mL, and a pure sample of the title compound isolated by preparative TLC (silica). The title compound was a yellow oil (9 mg, 26%).

*1-[4-(2-Chloroethoxy)phenyl]-1-{2-[(12-aminododecanoyl)oxyethyl]phenyl}-2-phenyl but-1-ene (**16**)*

Triphenylphosphine (326 mg, 1.24 mmol) was added to a solution of compound **12** (710 mg, 1.13 mmol) in THF (2 mL) and water (50 μL). The solution was stirred (protected from light) for 12 h before concentration of the solvent under reduced pressure. The oily residue was dissolved in chloroform (2 mL), and the product, a yellowish oil (450 mg, 66%), was isolated by radial chromatography ($CHCl_3$–MeOH) and used immediately after isolation.

*1-[4-(2-Chloroethoxy)phenyl]-1-[2-((12-((2,3-bistriphenylmethylthioacetylamino)propanamide)dodecanoyl)oxyethyl)phenyl]-2-phenyl but-1-ene (**17**)*

To a dichloromethane solution (10 mL) of compound **16** (180 mg, 0.298 mmol) and compound **4** (264 mg, 0.36 mmol), EDC (70 mg, 0.36 mmol) and triethylamine (1 mL) were added. The mixture was allowed to stir for 48 h whereupon the solvent was evaporated at reduced pressure, the oily residue dissolved in chloroform (2 mL), and the product isolated by radial chromatography (hexanes–chloroform). The compound, a yellow oil (300 mg, 76%), showed ^{1}H NMR ($CDCl_3$) (500 MHz) δ: 7.250 (m, H-*aryl*), 6.755 (d, *J* = 8.9, 2H, H-*meta* ring A), 6.491 (d, 2H, H-*ortho*, ring A), 4.150 (t, *J* = 5.8, 2H, *Z*- OCH_2CH_2Cl), 4.118 (m, overlap, OCH_2CH_2Ph), 4.028 (t, *J* = 3.9, 2H, *E*-OCH_2CH_2Cl), 3.771 (m, overlap, $CHCH_2$ and OCH_2CH_2Ph), 3.761 (t, *J* = 4.2, *Z*-OCH_2CH_2Cl), 3.665 (t, *J* = 5.8, 2H, *E*- OCH_2CH_2Cl), 3.181 (m, 2H, $CHCH_2$), 2.971 (s, 4H, CH_2S), 2.718 (m, overlap, *E*/*Z* OCH_2CH_2Ph), 2.246 (m, overlap, *E*/*Z* CH_2CH_3), 2.179 (t, *J* = 5.6, 2H, CH_2COOR), 1.534, 1.385, 1.200 (m, $(CH_2)_n$), 0.988 (t, *J* = 7.5, 3H, *Z*-CH_2CH_3), 0.793 (t, *J* = 7.3, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) (125 MHz) δ 173.54 (ester *C*(O)), 169.71, 169.08, 168.88 (amide C(O)), 156.00, 143.81, 142.78, 142.56, 142.15, 141.63, 136.39, 135.69, 134.32, 131.43, 130.21, 130.08, 129.60, 129.42, 129.35, 128.85, 128.02, 127.45, 127.12, 126.90, 126.36, 126.19, 125.71, 114.22, 113.46 (C-*aryl*), 83.14 (CPh_3), 67.65 (*Z*-OCH_2CH_2Cl), 67.62 (*E*-OCH_2CH_2Cl), 63.61 (OCH_2CH_2Ph), 51.11 ($CHCH_2$), 41.99 (*Z*-CH_2Cl), 41.76 (*E*-CH_2Cl), 39.55 ($CHCH_2$), 36.04, 35.74 (SCH_2), 34.22 (CH_2COOR), 32.38 (OCH_2CH_2Ph), 30.81, 29.42, 29.18, 26.79 (($CH_2)_n$), 29.03 (CH_2CH_3), 26.79, 24.86 (($CH_2)_n$), 13.05 (*Z*-CH_2CH_3); 12.85 (*E*-CH_2CH_3).

*1-[4-(2-Dimethylaminoethoxy)phenyl]-1-{2-[(12-((2,3-bistriphenylmethylthioacetylamino)propanamide)dodecanoyl)oxyethyl]phenyl}-2-phenyl but-1-ene (**15**)*

A sample of 300 mg (0.227 mmol) of **17** was dissolved in a 5.6 M solution of dimethylamine in ethanol (5 mL) in a round-bottom flask that was fitted with a dry-ice condenser. The solution was heated to reflux for 24 h when, after cooling, the solvent was evaporated in vacuo. The product, a dark oily semi-solid (181 mg, 60%), was isolated by radial chromatography (chloroform–methanol). The compound showed TLC: R_f = 0.36 (10% CH_3OH–CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (500 MHz) δ: 7.250 (m, H-*aryl*), 6.735 (d, *J* = 8.9, H, *H-meta* ring A), 6.505 (d, 2H, H-*ortho*, ring A), 4.122 (m, overlap, OCH_2CH_2Ph,$CHCH_2$), 4.055 (m, *Z*-OCH_2CH_2N), 3.926 (m, overlap, OCH_2CH_2Ph), 3.896 (t, *J* = 5.9, *E*-OCH_2CH_2N), 3.194 (m, $CHCH_2$), 2.985 (s, 4H, CH_2S), 2.718 (m, overlap, *Z*-OCH_2CH_2N and OCH_2CH_2Ph), 2.625 (t, *J* = 5.8, 2H, *E*-OCH_2CH_2N), 2.325 (s, *Z*-NCH_3), 2.267 (*E*-NCH_3), 2.211 (m, overlap, *E*/*Z* CH_2CH_3, CH_2COOR), 1.540, 1.407, 1.213 (m, $(CH_2)_n$), 0.994 (t, *J* = 7.4, 3H, *Z* = CH_2CH_3), 0.797 (t, *J* = 7.5, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) (125 MHz) δ 173.63 (ester *C*(O)), 169.86, 169.21, 168.96 (amide *C*(O)), 156.73, 143.87, 142.75, 141.92, 136.60, 135.82, 133.72, 131.37, 130.26, 129.69, 129.50, 129.42, 128.94, 128.11, 126.98, 126.38, 126.19, 114.10, 113.39, (C-*aryl*), 67.73 (CPh_3), 65.57 (OCH_2CH_2N), 63.70 (OCH_2CH_2Ph), 58.18 (CH_2N), 54.55 ($NHCH_2$), 45.80 (NCH_3), 42.07 ($CHCH_2$), 39.64 ($CHCH_2$), 36.10, 35.79 (SCH_2), 34.31 (CH_2COOR), 32.45 (OCH_2CH_2Ph), 29.48, 29.26 (($CH_2)_n$), 29.03 (CH_2CH_3), 26.86, 24.94 (($CH_2)_n$), 13.05 (*Z*-CH_2CH_3); 12.95 (*E*-CH_2CH_3). C, H analysis: calcd. for $C_{85}H_{94}N_4S_2O_6 \cdot 2.5H_2O$: C 74.06, H 7.42%; obs.: C 74.18, H 7.20%.

Conclusions

Using approach B, a 5:1 *E*:*Z* sample of compound 15 was synthesized in 18 steps in reasonable yield. It is was also discovered that the *E* and *Z* isomers of compound 12 could be separated by radial chromatography. This work is an example of a total synthesis of a biomolecule–chelate complex for the purpose of developing a site-specific radioimaging agent. Testing of compound 15 in tumour models remains work in progress.

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References

1. R.K. Hom and J.A. Katzenellenbogen. Nucl. Med. Biol. **24**, 485 (1997); W.A. Volkert and S. Jurisson. Top. Curr. Chem. **176**, 124 (1996); R.A. Bell, D.W. Hughes, C.J.L. Lock, and J.F. Valliant. Can J. Chem. **74**, 1503 (1996).

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2. B.J.A. Furr and V.C. Jordan. Pharmacol. Ther. **25**, 127 (1984).
3. C.L. Carter, G.Allen, and D.E. Henderson. Cancer, **63**,181 (1989).
4. P. Feherty, G. Farrer-Brown, and A.E. Kellie. Br. J. Cancer, **25**, 697 (1971).
5. L.A. Strickland, Y.Z. Ponce, D.H. Hunter, P.L. Zabel, G.M. Powe, A.A. Driedger, and M.J. Chamberlain. Drug Des. Delivery, **6**, 195 (1990).
6. V.C. Jordan. Pharm. Rev. **36**(4) (1984).
7. R. McCague, M. Jarman, On-Tai Leung, A.B. Foster, G. Leclercq, and S. Stoessel. J. Steroid Biochem. **31**, 4B (1988); **31**, 545 (1988).
8. A. Davison, A.G. Jones, C. Orvig, and M. Sohn. Inorg. Chem. **20**, 1629 (1981).
9. R.A. Bell, A. Capretta, and R.B. Maharajh. Carbohydr. Res. **267**, 49 (1995).
10. G.A. Potter and R. McCague. J. Org. Chem. **55**, 6184 (1990); R. McCague. J. Chem. Res. Synop. **58**, 771 (1986); J. Chem. Soc. Perkin Trans 1, 1011 (1987)
11. R. McCague. J. Chem. Res. 771 (1980).
12. F.R. Jensen and G. Goldman. Friedel-Crafts and related reactions. Vol. 2. *Edited by* G. Olah. Wiley Interscience, New York. 1964. Chap. 36.
13. E.J. Corey and A. Venkateswarlu. J. Am. Chem. Soc. **94**, 6190 (1972).
14. D.J. Cram and F.A. Abd Elhafez. J. Am. Chem. Soc. **74**, 5828 (1952).
15. H. Staudinger and J. Meyer. Helv. Chim. Acta, **2**, 635 (1919); M. Vaultier, N. Knouzi, and R. Carrie. Tetrahedron Lett. **24**, 763 (1983).
16. J.C. Sheehan and S.L. Ledis. J. Am. Chem. Soc. **95**, 875 (1973).

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