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Synthesis on novel Tamoxifen derivatives

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ABSTRACT

The design and synthesis of derivatives of 4-hydroxy-Tamoxifen as potential antagonists of the nuclear receptor LRH-1 are described. Stereoselective McMurry coupling was used to generate the desired internal alkene and a novel method for the synthesis of tetrasubstituted cyclopropane analogues was also developed.

1. Introduction

Liver receptor homolog-1 (LRH-1) is an orphan nuclear receptor (NR) from the superfamily of transcription factors that control a range actions fundamental to human physiology.[1] Of particular interest is the implication of LRH-1 in the control of aromatase expression[2] and its ability to act as a key regulator of ER expression in breast cancer cells.[3] In the light of these considerations, the identification and development of small molecule antagonists of LRH-1 could provide a new approach for potential therapies against breast cancer.

To date, there is only one example of agonists of LRH-1 but no antagonists of this NR have yet been reported.[4] We have recently examined the design and synthesis of novel ring A and D functionalized steroids as potential antagonists but none of these compounds were significantly active in modulating the effects of LRH-1.[5] Using computational methods and the crystal structure of the LRH-1 ligand-binding domain (LBD, PDB ID code 1YOK),[6] we have now designed structures of novel derivatives of Tamoxifen (**2**–**4**), which we believe could be effective as antagonists of LRH-1 (Fig. 1).

Docking studies were initiated with 4-hydroxy-Tamoxifen (**1**)[7] whose structure was modified to generate three virtual antagonists capable of binding to the LRH-1 LBD by hydrophobic interactions. Based on the fact that anti-estrogens, such as 4-hydroxy-Tamoxifen can induce a conformational change in the NR LBD by helix 12 (H12) displacement, we designed compounds capable of generating an inactive conformation of H12 by inducing steric clashes between the amino acid residue Leu532 and an antagonist (Fig. 2). Generating an inactive conformation of LRH-1 could possibly prevent co-activator recruitment and subsequent stimulation of gene expression.[8]

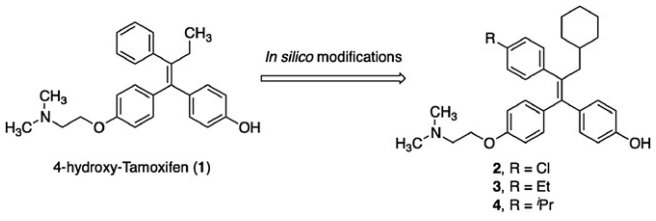

Fig. 1. *In silico* modifications of 4-hydroxy-Tamoxifen (**1**).

2. Results and discussion

The synthesis of these three virtual LRH-1 antagonists was undertaken to test the validity of our computational studies. Many academic groups and pharmaceutical companies have been interested in the synthesis of Tamoxifen and structurally related analogues. While many syntheses have been reported in the literature, few are geometrically selective in the construction of the central alkene unit.[9,10] Synthesis of the hydroxytriphenylethylene motif has been extremely challenging especially in a stereoselective manner. Another challenge in the preparation of compounds

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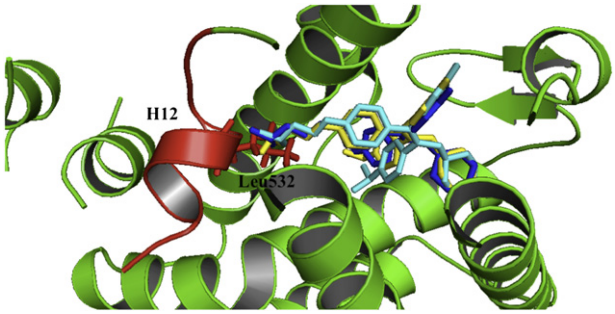
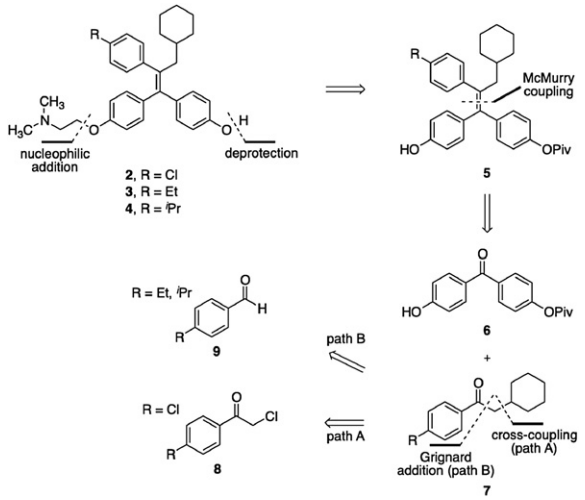


Fig. 2. Molecular modeling of analogues **2** (blue structure), **3** (yellow structure) and **4** (cyan structure) in the LBD of LRH-1 (PDB ID code 1YOK) depict a steric conflict with the key amino acid residue Leu532 on H12 highlighted in red.

bearing this motif was to avoid isomerization of the olefin subsequent to its elaboration.

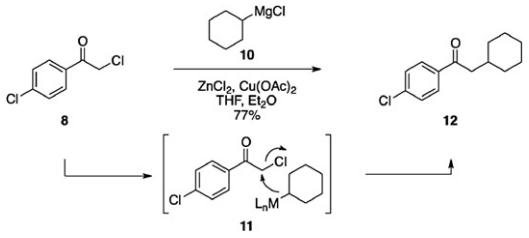
Gauthier's procedure[10b] for the stereoselective synthesis of 4-hydroxy-Tamoxifen (**1**) appeared to be the method of choice to synthesize the computer assisted drug design (CADD) analogues. We believed that the targets **2**–**4** should be available by deprotection of the phenolic pivaloyl groups and subsequent nucleophilic substitution of free phenol **5**. The desired (*E*)-olefin **5** would be stereoselectively synthesized using McMurry intermolecular coupling between ketones **6** and **7**. Finally, depending on the nature of the R-group, ketone **7** could be either obtained by copper-catalyzed cross-coupling from chloroketone **8** (R=Cl) or by Grignard addition to aldehyde **9** (R=Et, ^{i}Pr) followed by subsequent oxidation of the resultant secondary alcohol (Scheme 1).



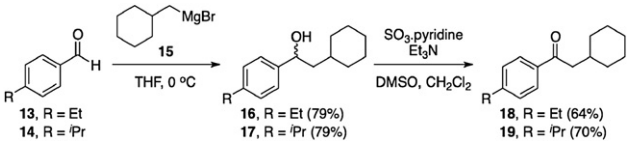
Scheme 1. Retrosynthetic analysis.

Since chloroketone **8** is commercially available, its reactivity toward copper-catalyzed cross-coupling reaction conditions, in presence of an organozinc halide was investigated.[11] Reaction of chloroketone **8** with cyclohexylmagnesium bromide (**10**) in the presence of copper(II) acetate and zinc(II) chloride gave ketone **12** in 77% yield (Scheme 2).

A two-step procedure was developed for the synthesis of the McMurry coupling precursors **18** and **19**. Aldehydes **13** and **14** were allowed to react with (cyclohexylmethyl)magnesium bromide (**15**) to generate the corresponding racemic secondary alcohols **16** and **17** in good yields. The latter were subsequently oxidized under Parikh–Doering conditions, to give ketones **18** and **19** in 64% and 70% yields, respectively (Scheme 3).[12]

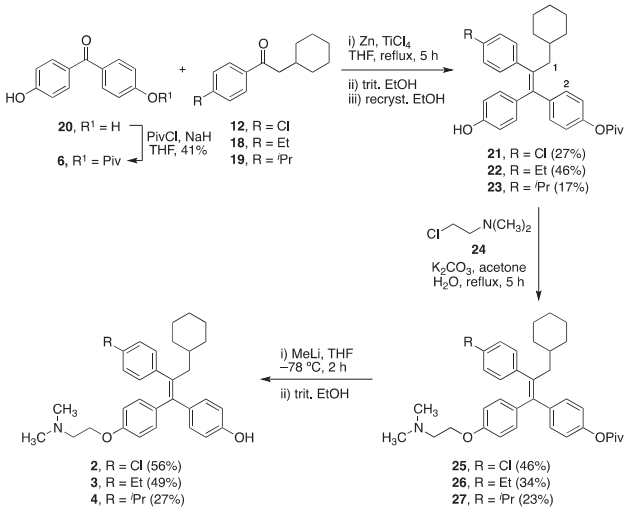


Scheme 2. Cross-coupling to access ketone **12**.



Scheme 3. Syntheses of ketones **18** and **19**.

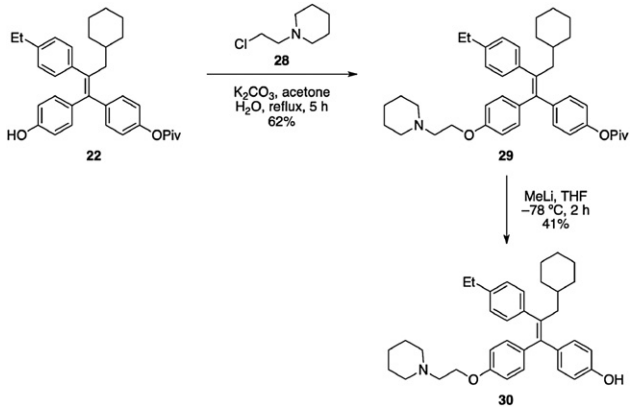
Reaction of ketones **12**, **18** and **19** with the benzophenone **6** under McMurry conditions stereoselectively gave the corresponding (*E*)-alkenes (*E*/*Z* >10:1) (Scheme 4). This geometric selectivity is possibly the result of intramolecular π-stacking between both the phenyl and the more electron-rich phenol ring during the formation of the initial diol titanium complex. Attempted recrystallization of the crude mixtures from a wide range of solvent mixtures was examined. Several triturations and recrystallization from ethanol gave the (*E*)-alkene **21** in moderate yield. Recrystallization of alkenes **22** and **23** was unsuccessful and these intermediates, slightly contaminated with their undesired (*Z*)-isomers, were used in the next step with no further purification. The desired (*E*)-geometry of the product alkenes **21** to **23** was confirmed by nOe experiments in which crucially selective irradiation of the signal due to H-1 showed spatial relationship with H-2. The alkenes **21** to **23** were then carefully alkylated with 2-(dimethylamino)ethyl chloride (**24**) to avoid trans-esterification and the pure (*E*)-alkenes **25** to **27** were formed in moderate yields. Finally, the pivaloyl groups were deprotected using methyllithium at −78 °C and Tamoxifen analogues **2**–**4** were isolated as white solids after repeated trituration with ethanol. The low overall yields obtained for the whole sequence resulted from the need to purify every intermediate to avoid isomerization of the central tetrasubstituted



Scheme 4. Syntheses of 4-hydroxy-Tamoxifen derivatives by McMurry coupling.

alkene. Yields of each of the isolated intermediates **25** to **27** and final products referred to single geometric isomers (>95:5) as shown by their respective ^{1}H NMR spectra and LCMS analysis.

From CADD, the most favorable energetically docking poses were obtained for compounds **2**–**4** displaying a steric clash with H12 via their 2-(dimethylamino)ethyl side chains. With this in mind, it was believed that replacement of the dimethyl amino tail by a bulkier functionality could eventually generate compounds with a better probability of showing antagonistic activities and, therefore, docking studies were carried out with compounds bearing cyclic amine side chains. The best result was obtained for analogue **30** that took the desired antagonistic docking pose with the piperidine ring inducing additional steric hindrance around H12. Alkylation of phenol **22** with *N*-(2-chloroethyl)-piperidine (**28**) gave the Tamoxifen analogue **29** as a single geometric isomer in 62% yield (Scheme 5). Deprotection of the pivaloate ester with methyllithium, trituration of the crude product with ethanol and recrystallization from dichloromethane and methanol gave solely the (*Z*)-isomer **30** in 41% yield.



Scheme 5. Synthesis of piperidine analogue **30**.

The major issue in synthesizing and handling these analogues was their instability even under slightly acidic conditions. For instance, if chloroform-d_1 was used as an NMR solvent, the Tamoxifen analogues underwent facile acid catalyzed *E*/*Z* isomerization to a mixture of isomers. In the solid state, the geometrically pure (*Z*)-analogues proved to be stable for months when stored at low temperature, but we harbored doubts as to their geometric stability when used in solution for biological evaluation. In order to overcome this isomerization problem, we sought to replace the acid-sensitive alkene by a cyclopropane. Further CADD docking studies led to the design of analogues **31** and **32** (Fig. 3). Introduction of a cyclopropane ring did not seem to alter the antagonistic binding pose of these new compounds.

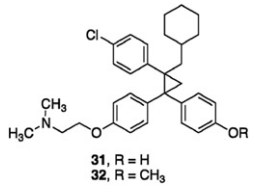
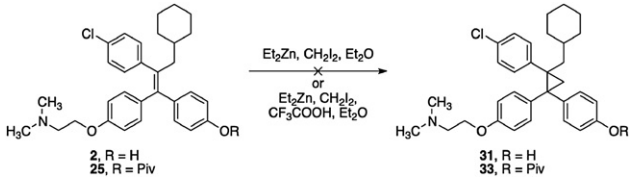


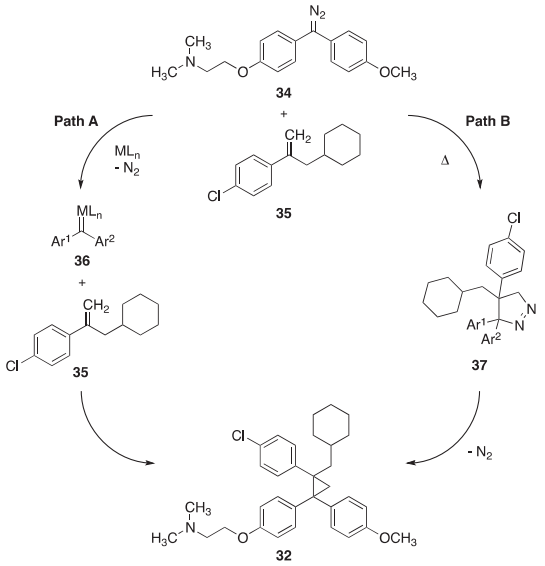
Fig. 3. Cyclopropane analogues **31** and **32**.

Many methods for efficient diastereoselective and enantioselective cyclopropanations have been reported in the literature including the use of chiral auxiliaries, chiral ligands in stoichiometric quantities and chiral catalysts.[13] We initially sought to directly cyclopropanate alkene **2** to generate the corresponding racemic cyclopropane **31**. Unfortunately, reaction of alkenes **2** and **25** under Simmons–Smith cyclopropanation conditions[14] did not provide the desired products even when trifluoroacetic acid was added to generate a more active carbenoid[15] (Scheme 6). The lack of reactivity was presumably the result of steric hindrance with these tetrasubstituted alkenes.



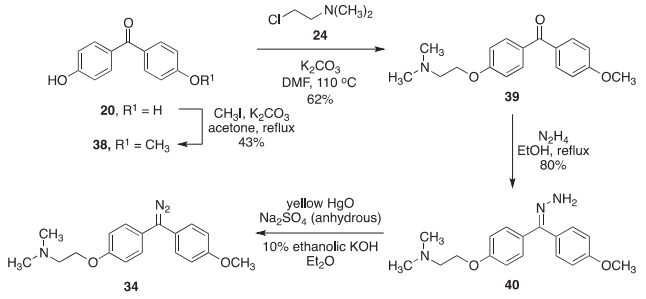
Scheme 6. Direct cyclopropanation of internal olefin.

Cyclopropanation of olefins with diazoalkanes in the presence of transition metal catalysis appeared to be a possible alternative for the synthesis of these analogues. Many metals, such as Cu, Rh and Pd have been reported as excellent catalysts for carbenoid formation followed by cyclopropanation with an alkene.[16] We considered that cyclopropane **32** could be obtained from diazo intermediate **34** and alkene **35** (Scheme 7) either via metal carbenoid **36** formation followed by cyclopropanation (Scheme 7, path A) or, without addition of catalyst, via 1,3-dipolar cycloaddition to form pyrazoline intermediate **37**, which under thermal conditions could react to form the cyclopropane **32** (Scheme 7, path B).



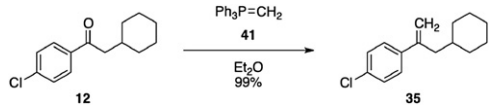
Scheme 7. Metal carbenoid and pyrazoline pathways to cyclopropane **32**.

Monomethylation of 4,4′-dihydroxybenzophenone (**20**) with iodomethane and subsequent condensation under basic conditions with 2-(dimethylamino)ethyl chloride (**24**) gave ketone **39** in 62% yield. This was converted to a mixture of isomeric hydrazones **40** using hydrazine hydrate in ethanol at reflux. Finally, by following Miller's work on the preparation of crystalline diphenyldiazomethane,[17] **40** was oxidized with yellow mercury(II) oxide and ethanolic potassium hydroxide as catalyst. In this reaction, strictly anhydrous conditions were essential to prevent decomposition of the sensitive diazoalkane **34**, which was isolated as a purple solid (Scheme 8).



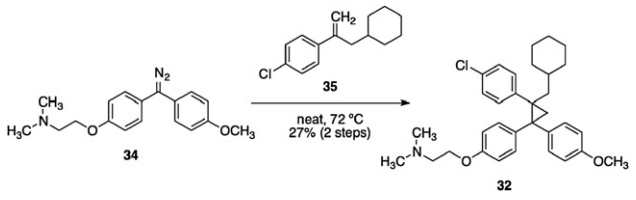
Scheme 8. Synthesis of diazo intermediate **34**.

Alkene **35** was prepared quantitatively by Wittig reaction between ketone **12** and methylenetriphenylphosphorane (**41**) (Scheme 9).[18]



Scheme 9. Wittig reaction to access alkene **35**.

The cyclopropanation reaction between diazoalkane **34** and alkene **35** via metal carbenoid formation was investigated. Unfortunately, reaction of diazoalkane **34** with dirhodium(II) tetraoctanoate, palladium(II) diacetate or copper(II) triflate in presence of alkene **35** did not provide the desired cyclopropane **32**. Heating diazoalkane **34** and alkene **35** in THF at reflux only led to formation of unidentified byproducts. However, when diazoalkane **34** was added to the neat pre-heated alkene **35**, cyclopropane **32** was isolated as a 1:1 mixture of diastereoisomers in 27% yield over two steps (Scheme 10). Variation of the number of alkene equivalents and/or temperature did not improve the yield of the reaction. All of our attempts to selectively deprotect the methoxy group of cyclopropane **32** failed, and the only product that could be isolated was the di-phenol with cleavage of both the methyl and 2-(dimethylamino)ethyl groups.



Scheme 10. Synthesis of cyclopropane analogue **32**.

3. Conclusion

Computational studies led to the design of novel analogues of Taxoxifen **2**–**4** and **30** that were stereoselectively synthesized by McMurry coupling to generate the desired tetrasubstituted alkene. These alkenes proved to be sensitive under acidic conditions and replacement of the alkene by a cyclopropane was successfully achieved via 1,3-dipolar cycloaddition between an alkene and a diazoalkane. The analogues were of insufficient solubility in polar media, which precluded meaningful assay against LRH-1.

4. Experimental section

General remarks: All chemicals were used as received, or purified using standard procedures. Solvents were dried by standard techniques and distilled under nitrogen before use. All experiments were carried out in oven-dried glassware under an atmosphere of N_2 or Ar, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum plates (Silicagel 60 F_{254}). Visualization was by UV light and/or treatment with potassium permanganate ($KMnO_4$) or vanillin stains followed by heating as deemed appropriate. Flash column chromatography was carried out using Merck 9385 Kieselgel 60 (230–400 mesh) under a positive pressure of nitrogen. Melting points (mp) were determined using a hot-stage microscope and are uncorrected. Infrared (IR) spectra were recorded with ATR technique, monitoring from 4000–700 cm^{-1}. NMR spectra were recorded using an internal deuterium lock at ambient probe temperatures (^1H NMR recorded at 400 or 500 MHz and ^{13}C NMR recorded at 100 or 125 MHz). Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to a residual solvent peak.

4.1. Computational details

The crystal structure of LRH-1 LBD (PDB code: 1YOK) and the Schrödinger Suite 2010[19] were used to perform the docking studies. In order to mimic the inactive state of LRH-1, residues on H12 and the adjacent loop between H11 and H12 (residues 522–538) in LRH-1 LBD were removed from the protein structure in the CADD analysis. All analogues were generated using LigPrep 2.3 and were docked into LRH-1 LBD crystal structure using Glide 5.5. A Prime 2.1 MM-GBSA rescoring was performed to predict LRH-1 binding affinities of the potential antagonists.

4.2. Experimental details

*4.2.1. Synthesis of (**12**).* Cyclohexylmagnesium chloride (**10**) (4.00 mL, 7.95 mmol, 1.5 equiv, 2 M in Et_2O) was added to $ZnCl_2$ (1.08 g, 7.95 mmol, 1.5 equiv) in Et_2O (40.0 mL) and the mixture was stirred vigorously at 0 °C for 30 min. The resulting white suspension was added to chloroketone **8** (1.00 g, 5.30 mmol, 1.0 equiv) and $Cu(OAc)_2$ (48.5 mg, 0.265 mmol, 0.05 equiv) in THF (10.6 mL) at room temperature. The mixture was stirred at room temperature for 17 h, diluted with Et_2O and quenched by addition of saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O (×1) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated and chromatographed (97:3 hexanes/Et_2O) to yield ketone **12** (960 mg, 77%) as a white solid: mp=55–60 °C (hexanes); R_f (3% Et_2O/hexanes) 0.35; IR (neat) 1686, 1583, 1398, 1284, 1217, 1088, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=8.8 Hz, 2H), 7.42 (d, J=8.8 Hz, 2H), 2.78 (d, J=6.9 Hz, 2H), 2.00–1.90 (m, 1H), 1.76–1.64 (m, 5H), 1.33–0.96 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 139.3, 135.7, 129.6, 128.8, 46.2, 34.5, 33.4, 26.2, 26.1 ppm; MS (EI) m/z=236 [M (^{35}Cl)]$^{+\bullet}$, 238 [M (^{37}Cl)]$^{+\bullet}$; HRMS (EI) calcd for $C_{14}H_{17}{}^{35}ClO$ [M]$^{+\bullet}$ 236.0968, found: 236.0961.

*4.2.2. Synthesis of (**16**).* (Cyclohexyl)methylmagnesium bromide (**15**) (44.8 mL, 22.4 mmol, 3 equiv, 0.5 M in THF) was added dropwise with stirring to aldehyde **13** (1.03 mL, 7.45 mmol, 1 equiv) in THF (53 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and quenched with 1 M aqueous HCl. The aqueous phase was extracted with Et_2O (×3) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated and chromatographed (9:1 to 7:3 hexanes/Et_2O) to yield alcohol **16** (1.37 g, 79%) as a colorless oil: R_f (20% Et_2O/hexanes) 0.25; IR (neat) 3295, 1463, 1447, 1343, 1089, 1064, 1045, 992, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=7.8 Hz, 2H), 7.18 (d, J=7.8 Hz, 2H), 4.78–4.74 (m, 1H), 2.65 (q, J=7.3 Hz, 2H), 1.85–1.79 (m, 1H), 1.74–1.63 (m, 6H), 1.55–1.48 (m, 1H), 1.47–1.38 (m, 1H), 1.24 (t, J=7.3 Hz, 3H), 1.26–1.14 (m, 3H), 1.02–0.88 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.6, 127.9, 125.8, 71.9, 46.9, 34.2, 33.9, 32.9, 28.5, 26.6, 26.3, 26.1,

15.6 ppm; MS (CI) m/z=232 $[M]^{+\bullet}$; HRMS (CI) calcd for $C_{16}H_{28}NO$ $[M+NH_4]^{+\cdot}$ 250.2171, found: 250.2173.

*4.2.3. Synthesis of (**17**).* (Cyclohexyl)methylmagnesium bromide (**15**) (50.0 mL, 25.0 mmol, 3 equiv, 0.5 M in THF) was added dropwise with stirring to aldehyde **14** (1.26 mL, 8.33 mmol, 1 equiv) in THF (60 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and quenched with 1 M aqueous HCl. The aqueous phase was extracted with Et_2O (×3) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated and chromatographed (85:15 to 7:3 hexanes/Et_2O) to yield alcohol **17** (1.61 g, 79%) as a colorless oil: R_f (20% Et_2O/hexanes) 0.32; IR (neat) 3293, 1461, 1447, 1415, 1048, 990, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J=8.3 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 4.81–4.78 (m, 1H), 2.99–2.89 (*app*-m, 1H), 1.88–185 (m, 1H), 1.79–1.67 (m, 6H), 1.58–1.45 (m, 2H), 1.29–1.23 (m, 9H), 1.06–0.91 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 142.8, 126.5, 125.8, 71.9, 46.9, 34.2, 34.0, 33.8, 32.9, 26.6, 26.3, 26.1, 24.0 ppm; MS (CI) m/z=246 $[M]^{+\bullet}$; HRMS (CI) calcd for $C_{17}H_{30}NO$ $[M+NH_4]^{+\cdot}$ 264.2327, found: 264.2333.

*4.2.4. Synthesis of (**18**).* DMSO (9.0 mL) and SO_3·pyridine (5.33 g, 15.1 mmol, 3.5 equiv, 45% purity) were added to alcohol **16** (1.00 g, 4.30 mmol, 1.0 equiv) and Et_3N (2.95 mL, 21.1 mmol, 4.9 equiv) in CH_2Cl_2 (35 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and diluted with EtOAc. The resulting solution was washed successively with H_2O (×3), saturated aqueous $NaHCO_3$ (×1) and brine (×1). The organic phase was dried ($MgSO_4$), filtered, concentrated and chromatographed (98:2 to 95:5 hexanes/Et_2O) to yield ketone **18** (635 mg, 64%) as a colorless oil: R_f (5% Et_2O/hexanes) 0.35; IR (neat) 1679, 1606, 1447, 1410, 1223, 1004, 959, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 2.80 (d, J=6.9 Hz, 2H), 2.71 (q, J=7.3 Hz, 2H), 2.02–1.91 (m, 1H), 1.77–1.64 (m, 5H), 1.26 (t, J=7.3 Hz, 3H), 1.28–1.14 (m, 3H), 1.06–0.96 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 149.7, 135.2, 128.4, 128.0, 46.1, 34.7, 33.5, 28.9, 26.3, 26.2, 15.2 ppm; MS (ESI) m/z=231 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{23}O$ $[M+H]^+$ 231.1749, found: 231.1740.

*4.2.5. Synthesis of (**19**).* DMSO (13 mL) and SO_3·pyridine (7.54 g, 21.3 mmol, 3.5 equiv, 45% purity) were added to alcohol **17** (1.50 g, 6.09 mmol, 1.0 equiv) and Et_3N (4.16 mL, 29.8 mmol, 4.9 equiv) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and diluted with EtOAc. The resulting solution was washed successively with H_2O (×3), saturated aqueous $NaHCO_3$ (×1) and brine (×1). The organic phase was dried ($MgSO_4$), filtered, concentrated and chromatographed (98:2 to 95:5 hexanes/Et_2O) to yield ketone **19** (1.03 g, 70%) as a colorless oil: R_f (5% Et_2O/hexanes) 0.38; IR (neat) 1677, 1604, 1405, 1222, 1058, 1000, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=8.3 Hz, 2H), 7.30 (d, J=8.3 Hz, 2H), 3.00–2.91 (*app*-m, 1H), 2.80 (d, J=6.8 Hz, 2H), 2.02–1.92 (m, 1H), 1.77–1.60 (m, 5H), 1.33–1.10 (m, 9H), 1.06–0.96 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 154.3, 135.4, 128.4, 126.6, 46.1, 34.6, 34.2, 33.5, 26.3, 26.2, 23.7 ppm; MS (ESI) m/z=245 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{25}O$ $[M+H]^+$ 245.1905, found: 245.1911.

4.3. General procedure 1: formation of olefin via McMurry coupling

$TiCl_4$ (4 equiv) was added dropwise with stirring to a suspension of zinc (8 equiv) in THF (8.7 mL/mmol) under N_2 and the mixture was stirred at reflux for 2 h. Ketone **6** (1 equiv) and ketone (3 equiv) in dry THF (14 mL/mmol) was added and the reflux was continued for 5 h. The mixture was cooled to room temperature and poured onto 10% aqueous K_2CO_3 and EtOAc. The resulting black suspension was filtered through a short pad of Celite, the layers separated and the aqueous phase extracted with EtOAc (×2). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The resulting solid was purified by trituration and recrystallization.

*4.3.1. Synthesis of (**21**).* Ketones **6** (1.05 g, 3.50 mmol, 1 equiv) and **12** (2.50 g, 10.6 mmol, 3 equiv) were subjected to general procedure 1. The crude product was purified by trituration (EtOH, 20 mL) and recrystallization (EtOH) providing olefin **21** (480 mg, 27%) as a light yellow solid: IR (neat) 3403, 1723, 1611, 1512, 1267, 1196, 1163, 1015, 903, 827 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.23 (s, 1H), 7.25–7.20 (m, 4H), 7.12–7.09 (m, 4H), 6.65 (d, J=8.8 Hz, 2H), 6.44 (d, J=8.8 Hz, 2H), 2.25 (d, J=6.9 Hz, 2H), 1.59–1.49 (m, 5H), 1.30 (s, 9H), 1.08–0.94 (m, 4H), 0.78–0.69 (m, 2H) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 176.2, 155.3, 149.1, 140.9, 140.5, 139.4, 137.0, 132.9, 131.0, 130.9, 130.4, 129.9, 127.7, 121.3, 114.4, 41.8, 38.4, 35.5, 32.7, 26.7, 25.8, 25.7 ppm.

*4.3.2. Synthesis of (**22**).* Ketones **6** (320 mg, 1.07 mmol, 1 equiv) and **18** (740 mg, 3.21 mmol, 3 equiv) were subjected to general procedure 1. The crude solid was triturated with EtOH (6.0 mL) and collected by filtration. Recrystallization was unsuccessful and olefin **22** (245 mg, 46%) (slightly contaminated with (*Z*)-isomer) was isolated as a white solid. This material was used without further purification: IR (neat) 3456, 1726, 1615, 1513, 1265, 1213, 1135, 833 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.19 (s, 1H), 7.22 (d, J=8.3 Hz, 2H), 7.10 (d, J=8.3 Hz, 2H), 7.03 (*app*-s, 4H), 6.66 (d, J=8.3 Hz, 2H), 6.42 (d, J=8.3 Hz, 2H), 2.56 (q, J=7.3 Hz, 2H), 2.25 (d, J=6.8 Hz, 2H), 1.62–1.50 (m, 5H), 1.31 (s, 9H), 1.15 (t, J=7.3 Hz, 3H), 1.13–1.12 (m, 1H), 0.97–0.94 (m, 3H), 0.77–0.69 (m, 2H) ppm.

*4.3.3. Synthesis of (**23**).* Ketones **6** (407 mg, 1.36 mmol, 1 equiv) and **19** (1.00 g, 4.09 mmol, 3 equiv) were subjected to general procedure 1. The crude solid was triturated with EtOH (4.0 mL) and collected by filtration. Recrystallization was unsuccessful and olefin **23** (115 mg, 17%) (contaminated with (*Z*)-isomer) was isolated as a white solid. This material was used without further purification: IR (neat) 3453, 1726, 1614, 1512, 1268, 1212, 1196, 1136, 836 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.17 (s, 1H), 7.20 (d, J=8.3 Hz, 2H), 7.10–7.00 (m, 6H), 6.64 (d, J=8.3 Hz, 2H), 6.40 (d, J=8.3 Hz, 2H), 2.84–2.77 (*app*-m, 1H), 2.23 (d, J=6.8 Hz, 2H), 1.61–1.49 (m, 5H), 1.30 (s, 9H), 1.16 (d, J=6.8 Hz, 6H), 1.09–1.03 (m, 1H), 0.96–0.92 (m, 3H), 0.76–0.70 (m, 2H) ppm.

4.4. General procedure 2: introduction of the 2-(dimethylamino)ethyl side chain

K_2CO_3 (3.3 equiv) was added to phenol (1.0 equiv) and hydrochloride salt of 2-(dimethylamino)ethyl chloride (**24**) (2.0 equiv) in acetone (13 mL/mmol) and H_2O (0.80 mL/mmol). The mixture was heated to reflux in the dark for 5 h. The solution was cooled to room temperature, dried ($MgSO_4$), filtered, concentrated and chromatographed to yield the corresponding amine.

*4.4.1. Synthesis of (**25**).* Phenol **21** (350 mg, 0.689 mmol, 1 equiv) was subjected to general procedure 2. The crude product was chromatographed (98:2 to 95:5 CH_2Cl_2/MeOH) to yield amine **25** (185 mg, 46%) as a colorless oil: R_f (5% MeOH/CH_2Cl_2) 0.35; IR (neat) 1744, 1608, 1506, 1241, 1199, 1116, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 2H, J=8.3 Hz), 7.13 (d, 2H, J=8.3 Hz), 7.05 (d, 2H, J=8.3 Hz), 7.02 (d, 2H, J=8.3 Hz), 6.74 (d, J=8.8 Hz, 2H), 6.57 (d, J=8.8 Hz, 2H), 3.94 (t, J=5.9 Hz, 2H), 2.67 (t, J=5.9 Hz, 2H), 2.30 (*app*-s, 8H), 1.60–1.54 (m, 5H), 1.36 (s, 9H), 1.18–1.11 (m, 1H), 1.04–1.00 (m, 3H), 0.84–0.76 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 156.8, 149.6, 141.0, 140.7, 139.4, 138.1, 135.1, 131.5, 130.8, 130.5, 128.0, 121.0, 113.5, 65.6, 58.2, 45.8, 42.5, 39.1, 36.1, 33.2 (two carbons), 27.1, 26.3 ppm (one quaternary carbon obscured);

MS (ESI) m/z=574 [M (^{35}Cl)+H]$^+$, 576 [M (^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{36}H_{45}{}^{35}ClNO_3$ [M+H]$^+$ 574.3088, found: 574.3083.

*4.4.2. Synthesis of (**26**).* Phenol **22** (200 mg, 0.403 mmol, 1 equiv) was subjected to general procedure 2. The crude product was chromatographed (98:2 to 95:5 CH_2Cl_2/MeOH) to yield amine **26** (83.5 mg, 34%) as a colorless oil: R_f (5% MeOH/CH_2Cl_2) 0.39; IR ($CHCl_3$) 1753, 1608, 1608, 1507, 1279, 1242, 1198, 1115, 1031, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=8.8 Hz, 2H), 7.04 (d, J=8.8 Hz, 2H), 6.98 (*app*-s, 4H, CH=C), 6.74 (d, J=8.8 Hz, 2H), 6.53 (d, J=8.8 Hz, 2H), 3.96 (t, J=5.9 Hz, 2H), 2.70 (t, J=5.9 Hz, 2H), 2.58 (q, J=7.4 Hz, 2H), 2.33 (s, 6H), 2.29 (d, J=7.4 Hz, 2H), 1.63–1.54 (m, 5H), 1.36 (s, 9H), 1.20 (t, J=7.3 Hz, 3H), 1.19–1.17 (m, 1H), 1.07–0.98 (m, 3H), 0.84–0.78 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 156.4, 149.4, 141.7, 141.3, 139.5, 139.4, 138.2, 135.8, 131.6, 130.7, 129.3, 127.2, 121.0, 113.3, 65.4, 58.1, 45.7, 42.8, 39.1, 36.0, 33.4, 28.4, 27.2, 26.4, 26.3, 15.3 ppm; MS (ESI) m/z=568 [M+H]$^+$; HRMS (ESI) calcd for $C_{38}H_{50}NO_3$ [M+H]$^+$ 568.3791, found: 568.3771.

*4.4.3. Synthesis of (**27**).* Phenol **23** (110 mg, 0.216 mmol, 1 equiv) was subjected to general procedure 2. The crude product was chromatographed (98:2 to 95:5 CH_2Cl_2/MeOH) to yield amine **27** (28.4 mg, 23%) as a colorless oil: R_f (5% MeOH/CH_2Cl_2) 0.41; IR ($CHCl_3$) 1754, 1608, 1508, 1483, 1280, 1242, 1198, 1164, 1117, 1032, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=8.3 Hz, 2H), 7.04 (d, J=8.3 Hz, 2H), 6.99 (*app*-s, 4H), 6.73 (d, J=8.3 Hz, 2H), 6.52 (d, J=8.3 Hz, 2H), 3.93 (t, J=5.9 Hz, 2H), 2.86–2.79 (*app*-m, 1H), 2.66 (t, J=5.9 Hz, 2H), 2.30 (*app*-s, 8H), 1.64–1.54 (m, 5H), 1.36 (s, 9H), 1.30–1.26 (m, 1H), 1.21 (d, J=6.8 Hz, 6H), 1.06–1.00 (m, 3H), 0.84–0.78 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 156.5, 149.4, 146.4, 141.3, 139.7, 139.5, 138.2, 135.7, 131.6, 130.7, 129.3, 125.7, 120.9, 113.3, 65.6, 58.2, 45.8, 42.8, 39.1, 36.0, 33.6, 33.4, 27.1, 26.4, 26.3, 23.9 ppm; MS (ESI) m/z=582 [M+H]$^+$; HRMS (ESI) calcd for $C_{39}H_{52}NO_3$ [M+H]$^+$ 582.3947, found: 582.3958.

4.5. General procedure 3: pivaloyl protecting group deprotection

MeLi (3 equiv, 1.6 M in Et_2O) was added to the pivaloyl ester (1 equiv) in THF (21 mL/mmol) at −78 °C. The mixture was stirred at this temperature for 2 h and quenched with saturated aqueous NH_4Cl (10 mL/mmol). The mixture was allowed to warm to room temperature and then extracted with EtOAc (×4). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude solid was triturated to yield the corresponding phenol.

*4.5.1. Synthesis of (**2**).* Ester **25** (110 mg, 0.191 mmol, 1 equiv) was subjected to general procedure 3. The crude solid was triturated with EtOH (1.2 mL) and collected by filtration to yield phenol **2** (52.5 mg, 56%) as a white solid: mp=161–162 °C (EtOH); IR (neat) 1611, 1507, 1447, 1278, 1238, 1168, 1092, 1014, 839, 833, 781 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.13 (d, J=8.3 Hz, 2H), 7.07 (d, J=8.3 Hz, 2H), 7.02 (d, J=8.8 Hz, 2H), 6.79–6.75 (m, 4H), 6.61 (d, J=8.8 Hz, 2H), 3.97 (t, J=5.4 Hz, 2H), 2.69 (t, J=5.4 Hz, 2H), 2.36 (d, J=7.3 Hz, 2H), 2.29 (s, 6H), 1.65–1.56 (m, 5H), 1.19–1.14 (m, 1H), 1.08–0.98 (m, 3H), 0.88–0.79 (m, 2H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 158.3, 157.3, 143.2, 142.0, 138.7, 137.4, 136.0, 132.8, 132.6, 132.5, 131.7, 128.9, 115.9, 114.6, 66.5, 59.2, 45.9, 43.6, 37.7, 34.7, 27.6, 27.5 ppm; MS (ESI) m/z=490 [M (^{35}Cl)+H]$^+$, 492 [M (^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{31}H_{37}{}^{35}ClNO_2$ [M+H]$^+$ 490.2513, found: 490.2526.

*4.5.2. Synthesis of (**3**).* Ester **26** (65 mg, 0.12 mmol, 1 equiv) was subjected to general procedure 3. The crude solid was triturated with EtOH (1.2 mL) and collected by filtration to yield phenol **3** (27 mg, 49%) as a white solid: mp=157–159 °C (EtOH); IR (neat) 1606, 1508, 1449, 1275, 1243, 1166, 1096, 1068, 1049, 967, 835, 829 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.01 (d, J=8.8 Hz, 2H), 6.98 (*app*-s, 4H), 6.78–6.75 (m, 4H), 6.56 (d, J=8.8 Hz, 2H), 3.95 (t, J=5.4 Hz, 2H), 2.68 (t, J=5.4 Hz, 2H), 2.56 (q, J=7.3 Hz, 2H), 2.33 (d, J=7.3 Hz, 2H), 2.29 (s, 6H), 1.65–1.55 (m, 5H), 1.19 (t, J=7.3 Hz, 3H), 1.19–1.17 (m, 1H), 1.07–1.01 (m, 3H), 0.86–0.78 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 157.9, 157.1, 143.0, 141.6, 140.7, 139.9, 137.9, 136.5, 132.8, 131.8, 130.8, 128.3, 115.8, 114.4, 66.4, 59.2, 45.9, 43.8, 37.6, 34.7, 29.5, 27.7, 27.6, 16.0 ppm; MS (ESI) m/z=484 [M+H]$^+$; HRMS (ESI) calcd for $C_{33}H_{42}NO_2$ [M+H]$^+$ 484.3216, found: 484.3200.

*4.5.3. Synthesis of (**4**).* Ester **27** (100 mg, 0.172 mmol, 1 equiv) was subjected to general procedure 3. The crude solid was triturated with EtOH (1.8 mL) and collected by filtration. The latter was then recrystallized from EtOH to yield phenol **4** (23.5 mg, 27%) as a white solid: mp=168–170 °C (EtOH); IR (neat) 1606, 1508, 1449, 1275, 1243, 1166, 1096, 1068, 1049, 969, 835, 829 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.03–7.00 (m, 6H), 6.77–6.75 (m, 4H), 6.56 (d, J=8.8 Hz, 2H), 3.95 (t, J=5.4 Hz, 2H), 2.83–2.78 (*app*-m, 1H), 2.68 (t, J=5.4 Hz, 2H), 2.33 (d, J=6.8 Hz, 2H), 2.29 (s, 6H), 1.66–1.55 (m, 5H), 1.20 (d, J=6.8 Hz, 6H), 1.19–1.18 (m, 1H), 1.08–0.99 (m, 3H), 0.86–0.80 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 157.9, 157.0, 147.7, 141.7, 140.8, 139.9, 137.9, 136.6, 132.8, 131.9, 130.8, 126.8, 115.8, 114.4, 66.4, 59.2, 45.9, 43.8, 37.6, 35.0, 34.7, 27.7, 27.6, 24.5 ppm; MS (ESI) m/z=498 [M+H]$^+$; HRMS (ESI) calcd for $C_{34}H_{44}NO_2$ [M+H]$^+$ 498.3372, found: 498.3379.

*4.5.4. Synthesis of (**29**).* K_2CO_3 (147 mg, 1.06 mmol, 3.3 equiv) was added to phenol **22** (160 mg, 0.321 mmol, 1.0 equiv) and hydrochloride salt of *N*-(2-chloroethyl)-piperidine (**28**) (119 mg, 0.643 mmol, 2.0 equiv) in acetone (4.1 mL) and H_2O (0.30 mL). The mixture was heated to reflux in the dark for 5 h. The solution was cooled to room temperature, dried ($MgSO_4$), filtered, concentrated and chromatographed (98:2 to 95:5 CH_2Cl_2/MeOH) to yield amine **29** (120 mg, 62%) as a colorless oil: R_f (5% MeOH/CH_2Cl_2) 0.40; IR ($CHCl_3$) 1753, 1507, 1279, 1242, 1198, 1164, 1115, 1031, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=8.3 Hz, 2H), 7.04 (d, J=8.3 Hz, 2H), 6.98 (*app*-s, 4H), 6.74 (d, J=8.8 Hz, 2H), 6.52 (d, J=8.8 Hz, 2H), 4.00 (t, J=5.9 Hz, 2H), 2.74 (t, J=5.9 Hz, 2H), 2.58 (q, J=7.3 Hz, 2H), 2.52 (*app*-br s, 4H), 2.29 (d, J=7.3 Hz, 2H), 1.63–1.54 (m, 9H), 1.46–1.42 (m, 2H), 1.36 (s, 9H), 1.20 (t, J=7.3 Hz, 3H), 1.19–1.17 (m, 1H), 1.05–1.00 (m, 3H), 0.81–0.78 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 156.4, 149.4, 141.7, 141.3, 139.5, 139.4, 138.2, 135.8, 131.6, 130.7, 129.3, 127.2, 121.0, 113.4, 65.3, 57.7, 54.9, 42.8, 39.1, 36.0, 33.4, 28.4, 27.2, 26.4, 25.5, 26.3, 23.9, 15.3 ppm; MS (ESI) m/z=608 [M+H]$^+$; HRMS (ESI) calcd for $C_{41}H_{54}NO_3$ [M+H]$^+$ 608.4104, found: 608.4095.

*4.5.5. Synthesis of (**30**).* Ester **29** (100 mg, 0.172 mmol, 1 equiv) was subjected to general procedure 3. The crude solid was triturated with EtOH (1.5 mL) and collected by filtration. The latter was then recrystallized from CH_2Cl_2/MeOH (95:5) to yield phenol **30** (35.0 mg, 41%) as a white solid: mp=188–189 °C (CH_2Cl_2/MeOH); IR (neat) 1607, 1509, 1448, 1240, 1171, 1038, 834 cm^{-1}; ^{1}H NMR (400 MHz, mixture CD_2Cl_2/CD_3OD) δ 7.04 (d, J=8.8 Hz, 2H), 6.99 (*app*-s, 4H), 6.80–6.76 (m, 4H), 6.54 (d, J=8.8 Hz, 2H), 3.96 (t, J=5.4 Hz, 2H), 2.67 (t, J=5.4 Hz, 2H), 2.56 (q, J=7.8 Hz, 2H), 2.47 (*app*-br s, 4H), 2.30 (d, J=6.8 Hz, 2H), 1.63–1.53 (m, 9H), 1.46–1.41 (m, 2H), 1.18 (t, J=7.8 Hz, 3H), 1.17–1.15 (m, 1H), 1.05–1.00 (m, 3H), 0.83–0.78 (m, 2H) ppm; ^{13}C NMR (100 MHz, mixture CD_2Cl_2/CD_3OD) δ 157.1, 156.1, 142.4, 140.9, 139.8, 139.5, 137.4, 136.1, 132.2, 131.3, 130.2, 127.7, 115.4, 113.9, 65.7, 58.4, 55.4, 43.4, 36.8, 34.1, 29.0, 27.1, 27.0, 26.0, 24.5, 15.6 ppm; MS (ESI) m/z=524 [M+H]$^+$; HRMS (ESI) calcd for $C_{36}H_{46}NO_2$ [M+H]$^+$ 524.3529, found: 524.3552.

*4.5.6. Synthesis of (**39**).* K_2CO_3 (6.51 g, 47.1 mmol, 5 equiv) was added to phenol **38** (2.15 g, 9.42 mmol, 1 equiv) and hydrochloride

salt of 2-(dimethylamino)ethyl chloride (**24**) (4.07 g, 28.3 mmol, 3 equiv) in DMF (19 mL). The mixture was heated at 110 °C for 5 h, cooled to room temperature, diluted with EtOAc and quenched by addition of H_2O. The aqueous layer was extracted with EtOAc (×4) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated and chromatographed (99:1 to 9:1 CH_2Cl_2/MeOH) to yield amine **39** (1.74 g, 62%) as an amorphous light brown solid: R_f (5% MeOH/CH_2Cl_2) 0.25; IR (neat) 1640, 1603, 1505, 1418, 1252, 1152, 1031, 853, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.76 (m, 4H), 6.98–6.94 (m, 4H), 4.15 (t, J=5.9 Hz, 2H), 3.88 (s, 3H), 2.77 (t, J=5.9 Hz, 2H), 2.36 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 162.8, 162.1, 132.2 (two carbons), 130.9, 130.8, 114.0, 113.5, 66.2, 58.1, 55.5, 45.9 ppm; MS (ESI) m/z=300 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{22}NO_3$ $[M+H]^+$ 300.1600, found: 300.1602.

*4.5.7. Synthesis of (**40**).* Hydrazine monohydrate (5.20 mL, 107 mmol, 20 equiv) was added to ketone **39** (1.60 g, 5.34 mmol, 1.0 equiv) in absolute EtOH (22 mL). The mixture was heated to reflux for 24 h and cooled to room temperature. Filtration of the crude mixture gave pure hydrazone **40** (1.34 g, 80%) as a 1:1.4 mixture of geometric isomers: IR (neat) 3325, 3152, 1605, 1507, 1457, 1243, 1165, 1035, 953, 839 cm^{-1}; *Mixture of major isomer* (*A*)+ *minor isomer* (*B*): ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 4H, A+B), 7.23–7.19 (m, 4H, A+B), 7.04–7.02 (m, 4H, A+B), 6.84–6.80 (m, 4H, A+B), 5.32 (br s, 4H, A+B), 4.11 (t, J=5.9 Hz, 2H, B), 4.05 (t, J=5.9 Hz, 2H, A), 3.86 (s, 3H, A), 3.79 (s, 3H, B), 2.76 (t, J=5.9 Hz, 2H, B), 2.71 (t, J=5.9 Hz, 2H, A), 2.36 (s, 6H, B), 2.32 (s, 6H, A) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.7, 159.1, 159.0, 149.3, 131.7, 130.2 (A+B), 127.8 (A+B), 125.1, 125.0, 115.3, 114.7 (A+B), 114.1 (A+B), 113.5, 66.1 (B), 66.0 (A), 58.3 (A+B), 55.3 (A+B), 45.9 (A+B) ppm; MS (ESI) m/z=314 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{24}N_3O_2$ $[M+H]^+$ 314.1869, found: 314.1883.

*4.5.8. Synthesis of (**34**).* Anhydrous Na_2SO_4 (73.4 mg, 0.510 mmol, 1.6 equiv), two drops of 10% ethanolic KOH and yellow mercuric(II) oxide (166 mg, 0.763 mmol, 2.4 equiv) were successively added to a suspension of hydrazone **40** (100 mg, 0.318 mmol, 1.0 equiv) in dry Et_2O (1.0 mL). The mixture was stirred at room temperature in the dark for 1 h. The solid was filtered off, washed with dry Et_2O and dried under a N_2 flow to give diazoalkane **34** as a purple solid. The compound was used without further purification: IR (neat) 2030, 1608, 1510, 1245, 1179, 1033, 830 cm^{-1}.

*4.5.9. Synthesis of (**35**).* Potassium *tert*-butoxide (850 mg, 7.60 mmol, 2 equiv) was added to triphenylmethylphosphonium bromide (2.72 g, 7.60 mmol, 2 equiv) in dry Et_2O (9.0 mL) at room temperature. The mixture was vigorously stirred for 30 min and ketone **12** (900 mg, 3.80 mmol, 1 equiv) in dry Et_2O (9.0 mL) was added dropwise. The yellow suspension was stirred at room temperature for 4 h, filtered through Celite and the solid washed with Et_2O. The solvent was concentrated in vacuo and the residue was chromatographed (hexanes) to yield alkene **35** (880 mg, 99%) as a colorless oil: R_f (hexanes) 0.75; IR (neat) 1490, 1448, 1090, 1014, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 4H), 5.25 (s, 1H), 5.02 (s, 1H), 2.36 (d, J=6.9 Hz, 2H), 1.68–1.60 (m, 5H), 1.33–1.25 (m, 1H), 1.15–1.10 (m, 3H), 0.93–0.86 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 139.9, 132.9, 128.4, 127.6, 114.0, 43.6, 35.8, 33.2, 26.5, 26.2 ppm; MS (EI) m/z=234 $[M(^{35}Cl)]^{+\bullet}$, 236 $[M(^{37}Cl)]^{+\bullet}$; HRMS (EI) calcd for $C_{15}H_{19}{}^{35}Cl$ $[M]^{+\bullet}$ 234.1175, found: 234.1177.

*4.5.10. Synthesis of (**32**).* Alkene **35** (375 mg, 1.60 mmol, 5 equiv) was heated at 72 °C for 15 min and crude diazoalkane **34** (0.320 mmol, 1 equiv) was added in one portion. The neat mixture was stirred at 72 °C for 3.5 h, until the purple color had completely disappeared. The mixture was cooled to room temperature and chromatographed (96:4 CH_2Cl_2/MeOH) to yield cyclopropane **32** (45.4 mg, 27% over two steps) (1:1 mixture of diastereoisomers) as a light yellow oil: R_f (4% MeOH/CH_2Cl_2) 0.25; IR (neat) 1608, 1510, 1493, 1450, 1244, 1174, 1034, 839 cm^{-1}; 1:1 *mixture of isomer* (*A*)+ *isomer* (*B*): ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.34 (m, 4H, A+B), 7.10–7.08 (m, 8H, A+B), 6.93–6.89 (m, 4H, A+B), 6.87–6.83 (m, 4H, A+B), 6.51–6.47 (m, 4H, A+B), 4.06 (t, J=5.9 Hz, 2H, A), 3.89 (t, J=5.9 Hz, 2H, B), 3.78 (s, 3H), 3.62 (s, 3H), 2.75 (t, J=5.9 Hz, 2H, A), 2.64 (t, J=5.9 Hz, 2H, B), 2.36 (s, 6H), 2.29 (s, 6H), 2.19–2.16 (m, 4H), 1.91–1.88 (m, 2H), 1.57–1.49 (m, 8H), 1.20–1.17 (m, 2H), 1.09–0.97 (m, 8H), 0.90–0.85 (m, 4H), 0.83–0.79 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.0, 156.1, 140.3, 136.2, 136.0, 135.6, 135.4, 130.9 and 130.8 (A+B), 130.4 (A+B), 130.3 and 130.2 (A+B), 127.8 (A+B), 114.3 (A+B), 113.7 (A+B), 113.0, 65.7 (A), 65.4 (B), 58.2 (A), 58.1 (B), 55.2, 54.9, 46.0, 45.7, 45.6, 39.3, 36.3, 35.4, 34.5, 32.4, 26.5, 26.2, 26.0, 24.3 ppm; MS (ESI) m/z=518 $[M(^{35}Cl)+H]^+$, 520 $[M(^{37}Cl)+H]^+$; HRMS (ESI) calcd for $C_{33}H_{41}{}^{35}ClNO_2$ $[M+H]^+$ 518.2826, found: 518.2838.

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Supplementary data

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References and notes

1. Fayard, E.; Auwerx, J.; Schoonjans, K. *Trends Cell Biol.* **2004**, *14*, 250–260.
2. Clyne, C. D.; Speed, C. J.; Zhou, J.; Simpson, E. R. *J. Biol. Chem.* **2002**, *277*, 20591–20597.
3. Thiruchelvam, P. T. R.; Lai, C.-F.; Hua, H.; Thomas, R. S.; Hurtado, A.; Hudson, W.; Bayly, A. R.; Kyle, F. J.; Periyasamy, M.; Photiou, A.; Spivey, A. C.; Ortlund, E. A.; Whitby, R. J.; Carroll, J. S.; Coombes, C. R.; Buluwela, L.; Ali, S. *Breast Cancer Res. Treat.* **2011**, *127*, 385–396.
4. (a) Whitby, R. J.; Dixon, S.; Maloney, P. R.; Delerive, P.; Goodwin, B. J.; Parks, D. J.; Willson, T. M. *J. Med. Chem.* **2006**, *49*, 6652–6655; (b) Whitby, R. J.; Stec, J.; Blind, R. D.; Dixon, S.; Leesnitzer, L. M.; Orband-Miller, L. A.; Williams, S. P.; Willson, T. M.; Xu, R.; Zuercher, W. J.; Cai, F.; Ingraham, H. A. *J. Med. Chem.* **2011**, *54*, 2266–2281.
5. Rey, J.; O'Riordan, T. J. C.; Hu, H.; Snyder, J. P.; White, A. J. P.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2012**, *20*, 3781–3794.
6. Krylova, I. N.; Sablin, E. P.; Moore, J.; Xu, R. X.; Waitt, G. M.; MacKay, J. A.; Juzumiene, D.; Bynum, J. M.; Madauss, K.; Montana, V.; Lebedeva, L.; Suzawa, M.; Williams, J. D.; Williams, S. P.; Guy, R. K.; Thornton, J. W.; Fletterick, R. J.; Willson, T. M.; Ingraham, H. A. *Cell* **2005**, *120*, 343–355.
7. Jordan, V. C.; Dowse, L. J. *J. Endocrinol.* **1976**, *68*, 297–303.
8. Brzozowski, A. M.; Pike, A. C. W.; Dauter, Z.; Hubbard, R. E.; Bonn, T.; Engström, O.; Öhman, L.; Greene, G. L.; Gustafsson, J.-A.; Carlquist, M. *Nature* **1997**, *389*, 753–758.
9. Selection of non-stereoselective syntheses: (a) Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1982**, *47*, 2387–2393; (b) Olier-Reuchet, C.; Aitken, D. J.; Bucourt, R.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 8221–8224 Yu, D. D.; Forman, B. M. *J. Org. Chem.* **2003**, *68*, 9489–9491.
10. Selection of stereoselective syntheses: (a) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608–4611; (b) Gauthier, S.; Mailhot, J.; Labrie, F. *J. Org. Chem.* **1996**, *61*, 3890–3893; (c) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506–12507.
11. Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240–10241.
12. Parikh, J. R.; Doering, W.; von, E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
13. Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
14. Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324.
15. Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. *J. Org. Chem.* **2004**, *69*, 327–334.
16. Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–935.
17. Miller, J. B. *J. Org. Chem.* **1959**, *24*, 560–561.
18. Justik, M. W.; Koser, G. F. *Tetrahedron Lett.* **2004**, *45*, 6159–6163.
19. Schrödinger, Inc., 120 West 45th Street, 29th Floor, New York, NY 10036-4041; http://www.schrodinger.com/products/14/12/ (accessed Aug 2011).