The synthesis of tethered ligand dimers for PPARγ–RXR protein heterodimers

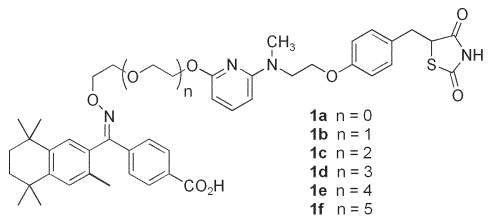
Debra L. Mohler*[a,b] and Gang Shen[a]

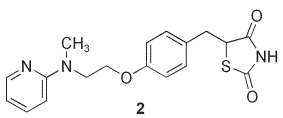
Received (in Pittsburgh, PA, USA) 19 January 2006, Accepted 24th April 2006
First published as an Advance Article on the web 4th May 2006
DOI: 10.1039/b600848h

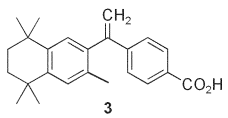
Heterodimeric compounds based on tethering the PPARγ agonist Rosiglitazone to the RXR ligand Targretin have been prepared.

The peroxisome proliferator-activated receptors (PPARs) are transcription factors that play key roles in the body's utilization and storage of dietary fats.[1] When these nuclear hormone receptors are activated by ligand binding, they heterodimerize with retinoic acid X receptors (RXRs)[2] to induce the transcription of genes encoding enzymes involved in fatty acid synthesis, storage, and metabolism (including β- and ω-oxidation, transport, and intracellular binding).[3] Because either PPAR or RXR ligands can initiate this process,[4] the simultaneous administration of agonists for both PPAR and RXR results in greater activity than expected based on a simple summation of the effects of the two individual compounds.[5] In addition, designed molecules combining the 2,4-thiazolidinedione ring of PPARγ ligands with the hydrophobic moiety of RXR agonists have demonstrated a similar synergism in effectiveness in biological assays.[6]

Therefore, we now report the synthesis of heterodimeric compounds **1a**–**f**, which are based on the PPARγ agonist, Rosiglitazone (**2**) and the RXR ligand Targretin (**3**). Rosiglitazone is an agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM, or type II diabetes), and Targretin has also shown anti-NIDDM activity.[7,8] For the tethers, polyethylene glycol chains of various lengths are used, because they are commercially available, stable, and soluble in water. Oligomers containing up to six glycol units provide a total length of approximately 21 Å when fully extended, a length beyond which the effects of increased local concentration are minimized. Because the ligand binding sites of the two enzymes lie at approximately this distance,[9] the compounds with shorter tethers may function as antagonists, by preventing the alignment of the proteins required for heterodimerization. The choice of tether attachment site was dictated by prior structure–activity studies on the glitazones[10,11] and Targretin analogs.[8,12]

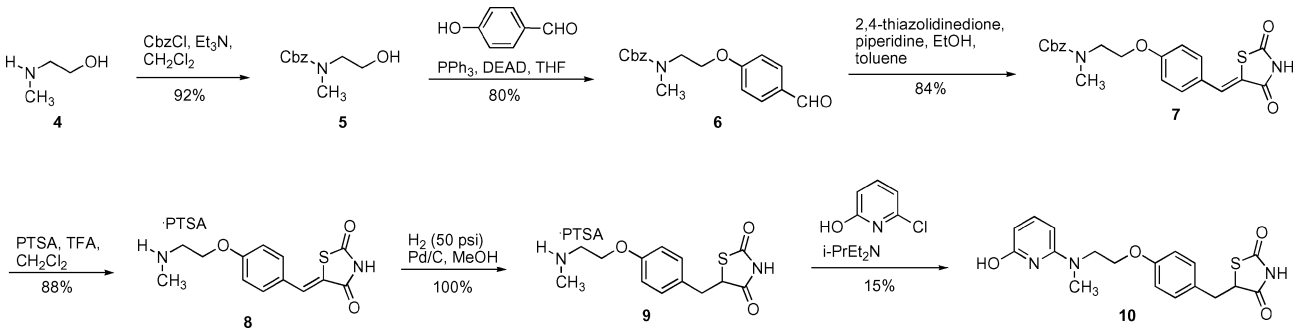



2


3

The synthesis of **1a**–**f** was accomplished *via* a convergent strategy, in which the appropriately-functionalized subunits of Rosiglitazone and Targretin were prepared and then attached to opposite ends of the tether. While the desired Targretin analog had been previously reported, the substituted Rosiglitazone derivative had not; and its preparation (Scheme 1) was based on a recent modification[13] of an earlier route.[11] Thus, the synthesis began with the protection of the amine in commercially available 2-methylaminoethanol (**4**) to give compound **5**[14] in a 92% yield. A Mitsunobu reaction between the alcohol **5** and 4-hydroxybenzaldehyde produced the ether **6**[15] in a yield of 80%, and a Knoevenagel condensation of this aldehyde with 2,4-thiazolidinedione provided the benzylidene 2,4-thiazolidinedione **7**[15] in a yield of 84%. The comparison of the chemical shift of the olefinic proton in **7** to that of a calculated value[16] suggested that (*z*)-isomer of the alkene was formed, as has been reported previously for similar systems.[11]

[a]*Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia, 30322, USA*
[b]*Department of Chemistry, James Madison University, MSC 4501, Harrisonburg, Virginia, 22807, USA. E-mail: mohlerdl@jmu.edu; Fax: 540-568-7938; Tel: 540-568-8803*



Scheme 1 Synthesis of hydroxy-substituted Rosiglitazone derivative **10**.

Unfortunately, a number of subsequent attempts to remove the Cbz group and reduce the olefin in one step were unsuccessful. The alkene could be hydrogenated quantitatively with hydrogen and Pd/C, but the nitrogen was not deprotected under these conditions, even with the use of excess catalyst. Other heterogeneous and homogeneous catalysts also failed, as did hydrogen transfer reactions.[17] Therefore, a variety of other conditions to remove the Cbz group were examined; and the combination of PTSA with trifluoroacetic acid[18] was the most effective, removing the Cbz group in high yield to afford **8**,[15] which was converted to **9**[19] by hydrogenation. The yield of the subsequent nucleophilic substitution reaction to produce **10** was disappointing, due to the thermal decomposition of **9**, which occurred faster than nucleophilic attack on the pyridine functionalized with an electron donating group.

The assembly of the target compounds is shown in Scheme 2. First, the hydroxy groups in the oligoethylene glycols **11a**–**f** were converted into good leaving groups, tosylates, to give **12a**–**f**[20] in high yield. The Targretin derivative was then connected to one end of the tether by nucleophilic substitution with the deprotonated oxime **13**[21] to afford the **14a**–**f**. A second nucleophilic substitution with the alkoxide derived from **10** produced all six of the target compounds as their methyl esters **15a**–**f**. However, a series of attempts to hydrolyze these esters by well documented conditions did not provide the desired acids. While lithium or potassium hydroxide[22] destroyed the molecules, gentler reagents like lithium iodide[23] and potassium carbonate had no effect on the methyl ester **1a**. Fortunately, acceptable deprotection conditions were discovered after screening several less well established methods. With sodium hydride (NaH) in dry, distilled THF, the ester groups were converted to the corresponding acids **1a**–**f**. While the mechanism of this reaction has not been determined, it appears not to involve hydroxide generated from NaH and adventitious water, because NaH in wet THF also led to decomposition, a finding that was in line with our previous observation of the sensitivity of these molecules towards hydroxide.

In summary, a library of tethered Rosiglitazone–Targretin heterodimers has been prepared by a highly convergent route that should be easily adaptable to a larger and more diverse set of compounds as ligands for the PPARγ–RXR protein heterodimer.

Experimental

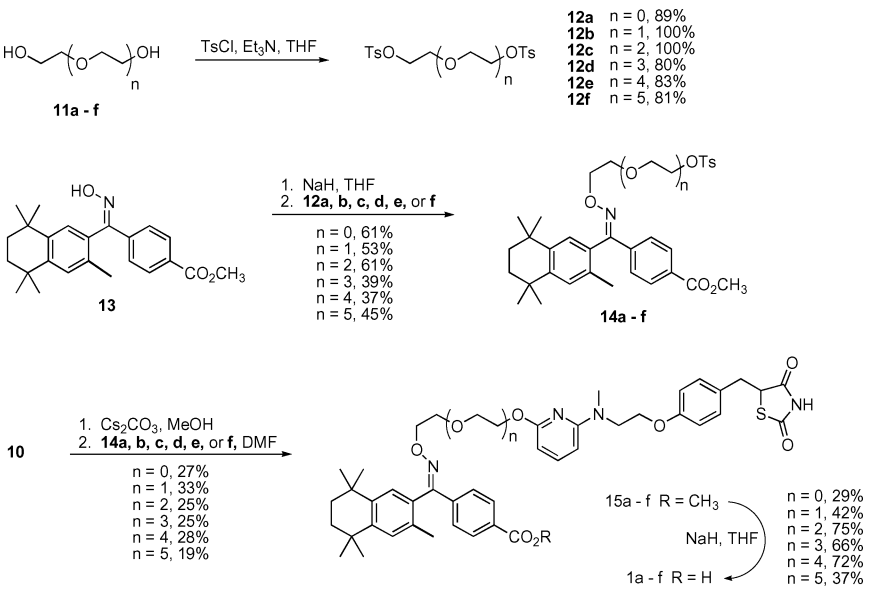
Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. The reactions requiring anhydrous conditions were performed in oven-dried glassware which was cooled under argon or nitrogen. Triethylamine was distilled from CaH_2 and THF was distilled from sodium benzophenone ketyl. Ethanol was distilled from Mg, and acetone was dried over 3 Å molecule sieves. NMR data were collected at room temperature in $CDCl_3$, DMSO-d_6, or CD_3OD referenced to internal nondeuterated solvent.

2-[(*N*-benzyloxycarbonyl)methylamino]ethanol (5)

To a solution of 2-(methylamino)ethanol (4.4 mL, 54.0 mmol) in CH_2Cl_2 (180 mL) were added benzylchloroformate (8.4 mL, 55.9 mmol) and Et_3N (9.6 mL, 68.8 mmol) at 0 °C. The ice bath was removed and the reaction mixture was then stirred under nitrogen for 24 h. The solution was then washed with 10% citric acid (120 mL) and H_2O (2 × 120 mL). The organic phase was dried with $MgSO_4$, concentrated, and purified by chromatography with 40% EtOAc–hexanes to give **5** as a yellow oil (10.4 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.14 (s, 2H), 3.79 (br s, 2H), 3.47 (br s, 2H), 3.00 (s, 3H).

Aldehyde 6

Triphenylphosphine (8.29 g, 31.6 mmol), **5** (5.31 g, 25.4 mmol), 4-hydroxybenzaldehyde (3.77 g, 30.8 mmol), DEAD (5.2 mL, 32.0 mmol), and THF (250 mL) were placed in a 500 mL round-bottom flask, which was then flushed with N_2. After stirring at room temperature for 24 h, the solvent was removed; and Et_2O



Scheme 2 Synthesis of PEG-tethered Rosiglitazone–Targetrin derivatives.

(250 mL) was added to the residue. After filtration, the ethereal filtrate was washed with saturated $NaHCO_3$ (2 × 250 mL) and brine 2 × 250 mL), dried over $MgSO_4$ and filtered. After removal of the ether, the residue was subjected to chromatography on silica with 25% EtOAc–hexanes to give compound **6** as a yellow oil (6.36 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83–7.78 (m, 2H), 7.36–7.30 (m, 5H), 7.00–6.90 (m, 2H), 6.91 (d, J = 6.6, 1H), 5.14 (s, 2H), 4.24–4.12 (m, 2H), 3.73–3.68 (m, 2H), 3.08 (s, 3H).

Substituted 2,4-thiazolidinedione 7

In an oven-dried 250 mL round bottom flask, benzaldehyde **6** (6.02 g, 19.2 mmol) and 2,4-thiazolidinedione (3.99 g, 34.0 mmol) were dissolved in absolute ethanol (70 mL) and anhydrous toluene (70 mL). Under nitrogen, piperidine (0.5 mL, 5.0 mmol) was added, and a Dean–Stark trap filled with toluene was fitted on the flask. The reaction was heated at reflux for 22 h to give a bright yellow solution. The solvent was removed, and the residue was dissolved in EtOAc (100 mL). This solution was washed with brine (2 × 60 mL), dried with $MgSO_4$, concentrated, and purified by chromatography on silica with 25% EtOAc–hexanes to give **7** as a yellow solid (6.64 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.79 (s, 1H), 7.47–7.39 (m, 2H), 7.38–7.33 (m, 5H), 7.01–6.87 (m, 2H), 5.14 (s, 2H), 4.26–4.10 (m, 2H), 3.72–3.65 (m, 2H), 3.07 (s, 3H).

***p*-Toluenesulfonic acid salt 8**

A solution of **7** (6.64 g, 16.1 mmol) and PTSA·H_2O (4.66 g, 24.5 mmol) in CH_2Cl_2 (75 mL) and trifluoroacetic acid (61 mL) was stirred at room temperature for 28 h. The solvent was removed, and the residue was kept under vacuum for 40 h. This solid can be used in next step without further purification. Chromatography on silica with 25% MeOH–$CHCl_3$ provided **8** as a yellow solid (6.34 g, 88%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.71 (d, J = 8.4, 2H), 7.56 (d, J = 8.4, 2H), 7.24 (d, J = 8.4, 2H), 7.15 (dd, J = 6.7, 2.0, 2H), 4.34 (t, J = 5.2, 2H), 3.48 (t, J = 5.2, 2H), 2.80 (s, 3H), 2.37 (s, 3H).

5-(4-(2-methylaminoethoxy)benzyl)-2,4-thiazolidinedione *p*-toluenesulfonic acid salt (9)

Compound **8** (6.34 g, 14.1 mmol) was dissolved in MeOH (160 mL) in a medium pressure reaction flask, to which was added 10% Pd/C (3.48 g, 3.27 mmol). The flask was shaken in a Parr apparatus at room temperature under 50 psi hydrogen pressure for 4 d. the mixture was filtered through celite, and the celite was washed with large amount of MeOH. The filtrate was collected, concentrated, and purified by chromatography with 25% MeOH–$CHCl_3$ to give **9** as a pale yellow solid (6.37 g, 100%), ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 8.0, 2H), 7.24 (d, J = 8.0, 2H), 7.22 (d, J = 8.8, 2H), 6.96 (d, J = 8.8, 2H), 4.71 (dd, J = 9.2, 8.4, 1H), 4.24 (t, J = 5.2, 2H), 3.43 (t, J = 5.2, 2H), 3.36 (dd, J = 14.4, 8.4, 1H), 3.14 (dd, J = 14.4, 9.2, 1H), 2.78 (s, 3H), 2.37 (s, 3H).

Hydroxy-substituted Rosiglitazone 10

In an oven-dried 25 mL round bottom flask, **9** (0.297 g, 0.643 mmol) was mixed with diispropylethylamine (6 mL), followed by the addition of 6-chloro-2-pyridinol (86.3 mg, 0.666 mmol). The mixture was heated at reflux under N_2 for 24 h. The solvent was removed, and the yellow residue was dissolved in $CHCl_3$ (25 mL). The organic phase was washed with H_2O (15 mL), dried over $MgSO_4$, concentrated, and purified by chromatography on silica with 5% MeOH–EtOAc to give **10** as a yellow solid (0.240 g, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 8.0, 1H), 7.09 (d, J = 8.8, 2H), 6.80 (d, J = 8.8, 2H), 5.89 (d, J = 8.0, 1H), 5.48 (d, J = 8.0, 1H), 4.34 (dd, J = 8.8, 4.0, 1H), 4.18–4.09 (m, 2H), 3.85–3.64 (m, 2H), 3.31 (dd, J = 14.0, 4.0, 1H), 3.08 (dd, J = 14.0, 8.8, 1H), 3.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 172.4, 164.3, 157.7, 151.7, 143.7, 130.8, 128.8, 114.8, 103.8, 88.7, 65.9, 53.8, 51.3, 38.5, 37.8. MS (FAB$^+$, 3−NBA/Li) m/z (relative intensity) 397.7 (M+H_2O+Li$^+$, 100%) 380.5 (M+Li$^+$, 9%), 378.6 (M+Li−2H$^+$, 16%).

Oligo(ethylene glycol) ditosylates, general procedure

Tosyl chloride (1.05 equiv.) was dissolved in THF to make a 0.1 M solution. The ethylene glycol oligomer (1.00 equiv.) and triethylamine (1.00 equiv.) were added and the mixture was stirred under N_2 for 24 h. After removal of the solvent, the reside was dissolved in EtOAc and washed with an equal amount of water. After drying the organic solution over $MgSO_4$, the solvent was removed and the residue subjected to chromatography on silica with 25% (**12a**–**b**) 50% (**12c**–**e**) or 70% (**12e**) EtOAc–hexanes.

Ditosylate 12a. White solid (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0, 4H), 7.35 (d, J = 8.0, 4H), 3.53 (s, 4H), 2.44 (s, 6H).

Ditosylate 12b. White solid (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0, 4H), 7.35 (d, J = 8.0, 4H), 4.09 (t, J = 4.8, 4H), 3.61 (t, J = 4.8, 4H), 2.45 (s, 6H)

Ditosylate 12c. Yellow oil (100%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.79 (d, J = 11.2, 4H), 7.34 (d, J = 11.2, 4H), 4.14 (t, J = 6.4, 4H), 3.65 (t, J = 6.4, 4H), 3.53 (s, 4H), 2.44 (s, 6H).

Ditosylate 12d. Yellow oil (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 11.2, 4H), 7.34 (d, J = 11.2, 4H), 4.15 (t, J = 8.0, 4H), 3.68 (t, J = 6.4, 4H), 3.59–3.563 (br s, 8H), 2.44 (s, 6H).

Ditosylate 12e. Yellow oil (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 11.2, 4H), 7.34 (d, J = 11.2, 4H), 4.15 (t, J = 6.4, 4H), 3.68 (t, J = 6.4, 4H), 3.60 (br s, 4H) 3.58 (br s, 8H), 2.44 (s, 6H).

Ditosylate 12f. Yellow oil (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 11.2, 4H), 7.34 (d, J = 11.2, 4H), 4.15 (t, J = 6.4, 4H), 3.68 (t, J = 6.4, 4H), 3.61 (br s, 4H) 3.57 (br s, 12H), 2.44 (s, 6H).

Alkylation of oxime 13. To a solution of oxime **13** (0.04 M in THF) was added 60% NaH in oil (2 equiv. *vs.* **13**) under nitrogen. The mixture was stirred at room temperature for 1 h, and the oligo(ethylene glycol) ditosylate **12** (2 equiv. *vs.* **13**) was then added. A condenser was fitted on the flask, which was heated at reflux for 24 h. The yellow solution was diluted with $CHCl_3$ and washed twice with H_2O. The organic layer was dried over $MgSO_4$, concentrated, and purified by chromatography with 25% (**14a**–**c**) or 50% (**14d**–**f**) EtOAc–hexanes.

Alkylated oxime 14a. Off-white solid (61%). Mp: 45–48° C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.4$, 2H), 7.79 (d, $J = 8.4$, 2H), 7.49 (d, $J = 8.4$, 2H), 7.29 (d, $J = 8.4$, 2H), 7.19 (s, 1H), 6.94 (s, 1H), 4.37 (br s, 4H), 3.95 (s, 3H), 2.42 (s, 3H), 2.04 (s, 3H), 1.73 (br s, 4H), 1.35 (s, 6H), 1.25 (s, 6H).

Alkylated oxime 14b. Off white solid (53%). Mp: 36–39° C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.4$, 2H), 7.76 (d, $J = 8.4$, 2H), 7.54 (d, $J = 8.4$, 2H), 7.28 (d, $J = 8.4$, 2H), 7.17 (s, 1H), 6.93 (s, 1H), 4.24 (t, $J = 4.8$, 2H), 4.09 (t, $J = 4.8$, 2H), 3.92 (s, 3H), 3.68 (t, $J = 4.8$, 2H), 3.56 (t, $J = 4.8$, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.20 (s, 6H).

Alkylated oxime 14c. Colorless liquid (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J = 8.8$, 2H), 7.78 (d, $J = 8.8$, 2H), 7.53 (d, $J = 8.8$, 2H), 7.31 (d, $J = 8.8$, 2H), 7.15 (s, 1H), 6.93 (s, 1H), 4.31 (t, $J = 4.8$, 2H), 4.11 (t, $J = 4.8$, 2H), 3.91 (s, 3H), 3.73 (t, $J = 4.8$, 2H), 3.63 (t, $J = 4.8$, 2H), 3.50 (br s, 4H), 2.42 (s, 3H), 2.06 (s, 3H), 1.67 (s, 4H), 1.30 (s, 6H), 1.19 (s, 6H).

Alkylated oxime 14d. Colorless liquid (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J = 8.4$, 2H), 7.79 (d, $J = 8.4$, 2H), 7.53 (d, $J = 8.4$, 2H), 7.32 (d, $J = 8.4$, 2H), 7.14 (s, 1H), 6.93 (s, 1H), 4.33 (t, $J = 5.2$, 2H), 4.13 (t, $J = 4.8$, 2H), 3.91 (s, 3H), 3.76 (t, $J = 5.2$, 2H), 3.65 (t, $J = 4.8$, 2H), 3.54 (br s, 8H), 2.43 (s, 3H), 2.06 (s, 3H), 1.68 (s, 4H), 1.30 (s, 6H), 1.19 (s, 6H).

Alkylated oxime 14e. Colorless liquid (37%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, $J = 8.4$, 2H), 7.79 (d, $J = 8.4$, 2H), 7.53 (d, $J = 8.4$, 2H), 7.33 (d, $J = 8.4$, 2H), 7.14 (s, 1H), 6.93 (s, 1H), 4.33 (t, $J = 5.1$, 2H), 4.14 (t, $J = 4.8$, 2H), 3.90 (s, 3H), 3.76 (t, $J = 5.1$, 2H), 3.68 (t, $J = 4.8$, 2H), 3.58–3.52 (m, 12H), 2.43 (s, 3H), 2.06 (s, 3H), 1.67 (s, 4H), 1.30 (s, 6H), 1.19 (s, 6H).

Alkylated oxime 14f. Colorless liquid (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, $J = 8.7$, 2H), 7.79 (d, $J = 8.4$, 2H), 7.53 (d, $J = 8.7$, 2H), 7.33 (d, $J = 8.4$, 2H), 7.14 (s, 1H), 6.93 (s, 1H), 4.34 (t, $J = 5.1$, 2H), 4.15 (t, $J = 4.8$, 2H), 3.91 (s, 3H), 3.77 (t, $J = 5.1$, 2H), 3.67 (t, $J = 4.8$, 2H), 3.60 (br s, 8H), 3.57 (br s, 8H), 2.44 (s, 3H), 2.06 (s, 3H), 1.68 (s, 4H), 1.30 (s, 6H), 1.20 (s, 6H).

Formation of protected heterodimer 15. To a solution of compound **10** (0.07 M in MeOH) was added Cs_2CO_3 (1.25 equiv.) under nitrogen. The mixture was gently heated (at about 40 °C), and was stirred for 3 h. The solvent was removed first *via* rotary evaporation and then under high vacuum. The residue was dissolved in DMF to make a 0.09 M solution and compound **14** (1 equiv., 0.05 M in DMF) was added under nitrogen. The solution was heated at 80–85 °C for 18 h. The resulting suspension was diluted with 3 volumes of $CHCl_3$ and was washed with H_2O. The aqueous layer was separated and was extracted with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated *via* rotary evaporation; and the DMF was removed *via* vacuum transfer. Chromatography of the residue on silica was accomplished with 25% (**15a**–**b**), 50% (**15c**–**e**), or 70% (**15f**) EtOAc–hexanes.

Methyl ester 15a. Yellow oil (27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, $J = 8.4$, 2H), 7.54 (d, $J = 8.4$, 2H), 7.37 (t, $J = 8.0$, 1H), 7.15 (s, 1H), 7.09 (d, $J = 8.8$, 2H), 6.96 (s, 1H), 6.80 (d, $J = 8.8$, 2H), 6.02 (d, $J = 8.0$, 1H), 6.01 (d, $J = 8.0$, 1H), 4.58–4.51 (m, 4H), 4.48 (dd, $J = 9.2$, 4.0, 1H), 4.16–4.11 (m, 2H), 3.95–3.92 (m, 2H), 3.92 (s, 3H), 3.41 (dd, $J = 14.4$, 4.0, 1H), 3.12–3.07 (m, 1H), 3.10 (s, 3H), 2.06 (s, 3H), 1.68 (br s, 4H), 1.31 (s, 6H), 1.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.5, 167.2, 162.6, 158.5, 157.3, 156.7, 145.5, 142.3, 141.0, 140.3, 133.0, 130.6, 130.5, 130.3, 129.7, 128.1, 127.8, 127.3, 126.7, 114.9, 97.3, 97.2, 73.2, 66.6, 63.9, 53.9, 52.5, 49.7, 38.1, 38.0, 37.9, 35.3, 35.2, 34.3, 34.1, 32.1, 19.6.

Methyl ester 15b. Yellow oil (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J = 8.4$, 2H), 7.54 (d, $J = 8.4$, 2H), 7.36 (t, $J = 8.0$, 1H), 7.14 (s, 1H), 7.11 (d, $J = 8.8$, 2H), 6.95 (s, 1H), 6.82 (d, $J = 8.8$, 2H), 6.03 (d, $J = 8.0$, 1H), 6.01 (d, $J = 8.0$, 1H), 4.48 (dd, $J = 9.2$, 4.0, 1H), 4.38–4.32 (m, 4H), 4.14 (t, $J = 5.2$, 2H), 3.94–3.90 (m, 2H), 3.92 (s, 3H), 3.83 (t, $J = 5.2$, 2H), 3.75 (t, $J = 5.2$, 2H), 3.39 (dd, $J = 14.4$, 4.0, 1H), 3.13 (dd, $J = 14.4$, 9.2, 1H), 3.09 (s, 3H), 2.07 (s, 3H), 1.68 (br s, 4H), 1.30 (s, 6H), 1.20 (s, 6H).

Methyl ester 15c. Yellow oil (25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.95 (d, $J = 8.4$, 2H), 7.53 (d, $J = 8.4$, 2H), 7.35 (t, $J = 8.0$, 1H), 7.14 (s, 1H), 7.10 (d, $J = 8.8$, 2H), 6.93 (s, 1H), 6.82 (d, $J = 8.8$, 2H), 6.03 (d, $J = 8.0$, 1H), 6.01 (d, $J = 8.0$, 1H), 4.46 (dd, $J = 8.8$, 4.0, 1H), 4.38–4.31 (m, 4H), 4.16–4.11 (m, 2H), 3.96–3.82 (m, 3H), 3.90 (s, 3H), 3.82–3.574 (m, 4H), 3.63–3.56 (m, 4H), 3.35 (dd, $J = 14.4$, 4.0, 1H), 3.13 (dd, $J = 14.4$, 8.8, 1H), 3.08 (s, 3H)), 2.06 (s, 3H), 1.67 (s, 4H), 1.30 (s, 6H), 1.19. (s, 6H).

Methyl ester 15d. Yellow oil (25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.96 (d, $J = 8.4$, 2H), 7.53 (d, $J = 8.4$, 2H), 7.35 (t, $J = 8.0$, 1H), 7.14 (s, 1H), 7.10 (d, $J = 8.8$, 2H), 6.93 (s, 1H), 6.82 (d, $J = 8.8$, 2H), 6.03 (d, $J = 8.0$, 1H), 6.01 (d, $J = 8.0$, 1H), 4.46 (dd, $J = 8.8$, 4.0, 1H), 4.37 (t, $J = 4.8$, 2H), 4.33 (t, $J = 5.2$, 2H), 4.13 (t, $J = 6.8$, 2H), 3.96–3.88 (m, 2H), 3.90 (s, 3H), 3.80–3.73 (m, 4H), 3.68–3.60 (m, 4H), 3.57 (br s, 4H), 3.33 (dd, $J = 14.0$, 4.0, 1H), 3.14 (dd, $J = 14.0$, 8.8, 1H), 3.08 (s, 3H), 2.06 (s, 3H), 1.67 (br s, 4H), 1.30 (s, 6H), 1.19 (s, 6H).

Methyl ester 15e. Yellow oil (28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 7.96 (d, $J = 8.4$, 2H), 7.53 (d, $J = 8.4$, 2H), 7.35 (t, $J = 8.1$, 1H), 7.14 (s, 1H), 7.10 (d, $J = 8.7$, 2H), 6.93 (s, 1H), 6.82 (d, $J = 8.7$, 2H), 6.03 (d, $J = 8.1$, 1H), 6.00 (d, $J = 8.1$, 1H), 4.45 (dd, $J = 8.7$, 3.9, 1H), 4.39–4.30 (m, 4H), 4.18–4.10 (m, 2H), 3.94–3.86 (m, 2H), 3.90 (s, 3H), 3.81–3.74 (m, 4H), 3.66–3.60 (m, 8H), 3.56 (br s, 4H), 3.34 (dd, $J = 14.1$, 3.9, 1H), 3.15–3.08 (m, 1H), 3.07 (s, 3H), 2.06 (s, 3H), 1.67 (s, 4H), 1.30 (s, 6H), 1.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 174.4, 170.5, 167.1, 162.7, 158.5, 157.3, 156.6, 145.5, 142.4, 140.9, 140.3, 133.0, 130.7 130.6, 130.5, 130.2, 129.8, 128.1, 127.9, 127.3, 126. 6, 115.0, 97.4, 97.2, 74.2, 70.8 (br), 70.1, 69.9, 69.2, 67.3, 66.3, 64.7, 55.0, 53.7, 52.4, 49.7, 37.9, 37.7, 35.4, 35.3, 34.4, 34.2, 32.1 (br), 19.7.

Methyl ester 15f. Yellow oil (19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 7.96 (d, $J = 8.4$, 2H), 7.53 (d, $J = 8.4$, 2H), 7.36 (t, $J = 8.0$, 1H), 7.14 (s, 1H), 7.10 (d, $J = 8.8$, 2H), 6.93 (s, 1H), 6.82 (d, $J = 8.8$, 2H), 6.03 (d, $J = 8.0$, 1H), 6.01 (d, $J = 8.0$, 1H), 4.47 (dd, $J = 9.0$, 4.0, 1H), 4.38–4.31 (m, 4H), 4.17–4.11 (m, 2H), 3.97–3.90 (m, 2H), 3.90 (s, 3H), 3.80–3.74 (m, 4H), 3.70–3.59 (m, 12H), 3.57 (br s, 4H), 3.33 (dd, $J = 14.0$, 4.0,

1H), 3.13 (dd, J = 14.0, 9.0, 1H), 3.07 (s, 3H), 2.06 (s, 3H), 1.67 (s, 4H), 1.30 (s, 6H), 1.19 (s, 6H).

Deprotection of the methyl esters to give the final acids

To a solution of methyl ester **15** (0.04 M in THF), was added 60% NaH in oil (10 equiv.) under nitrogen in one portion. The suspension was stirred at room temperature for 8 h. The reaction mixture was quenched with an equal volume of saturated NH_4Cl, and the aqueous layer was adjusted to pH 2 with 1 N HCl. The mixture was extracted twice with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$, and concentrated. The residue was purified by chromatography with 50% (**1a**–**b**), 60% (**1c**–**d**), or 70% (**1e**–**f**) EtOAc–hexanes.

Heterodimeric ligand 1a. Yellow oil (29%). IR (neat): 3563, 3113, 2959, 1750, 1696, 1596, 1542, 1501, 1300, 1253, 1112, 1065, 1031, 944, 796, 783, 722 cm^{-1}. ^1H NMR (400 MHz $CDCl_3$) δ 8.01 (d, J = 8.4, 2H), 7.55 (d, J = 8.4, 2H), 7.36 (t, J = 8.0, 1H), 7.14 (s, 1H), 7.06 (d, J = 8.4, 2H), 6.95 (s, 1H), 6.76 (d, J = 8.4, 2H), 6.00 (d, J = 8.0, 2H), 4.56 (t, J = 5.0, 2H), 4.50 (t, J = 5.0, 2H), 4.47 (dd, J = 9.2, 4.0, 1H), 4.13–4.06 (m, 2H), 3.97–3.86 (m, 2H), 3.39 (dd, J = 14.0, 4.0, 1H), 3.11–3.03 (m, 1H), 3.08 (s, 3H), 2.05 (s, 3H), 1.670 (br s, 4H), 1.30 (s, 6H), 1.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 170.8, 170.4, 162.6, 158.5, 157.3, 156.6, 145.5, 142.4, 141.7, 140.3, 132.9, 130.6, 130.3, 130.2, 128.1, 127.7, 127.3, 126.7, 114.9, 97.3, 97.1, 73.2, 66.6, 63.7, 53.9, 49.6, 37.9 (br), 35.3 (br), 34.4, 34.1, 32.1 (br), 19.6. MS (FAB^-, glycerol) m/z (relative intensity): 763.4 ($M-H^-$, 18%), 720.4 (6%), 408.4 (55%), 348.2 (21%), 222.9 (100%). HRMS (FAB^-, glycerol) calcd. for $C_{43}H_{47}O_7N_4S_1$ ($[M-H]^-$): 763.3165. Found: 763.3192.

Heterodimeric ligand 1b. Yellow oil (42%). IR (neat): 3543, 3194, 2972, 1743, 1690, 1643, 1542, 1508, 1421, 1260, 1119, 1065, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4, 2H), 7.57 (d, J = 8.8, 2H), 7.36 (t, J = 8.0, 1H), 7.15 (s, 1H), 7.10 (d, J = 8.4, 2H), 6.96 (s, 1H), 6.81 (d, J = 8.4, 2H), 6.03 (d, J = 8.0, 1H), 6.01 (d, J = 8.0, 1H), 4.47 (dd, J = 9.2, 4.0, 1H), 4.38 (t, J = 5.2, 2H), 4.35 (t, J = 5.2, 2H), 4.16–4.10 (m, 2H), 3.94–3.90 (m, 2H), 3.84 (t, J = 5.2, 2H), 3.77 (t, J = 5.2, 2H), 3.40 (dd, J = 14.4, 4.0, 1H), 3.12–3.06 (m,1H), 3.08 (s, 3H)), 2.07 (s, 3H), 1.68 (br s, 4H), 1.31 (s, 6H), 1.20 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 170.8 170.7, 162.6, 158.5, 157.3, 156.5, 145.5, 142.4, 141.6, 140.2, 132.9, 130.6, 130.3, 129.6, 128.1, 127.8, 127.3, 126.5, 115.0, 97.4, 97.2, 74.2, 70.0, 69.9, 66.4, 64.7, 53.8, 49.6, 37.9, 37.8, 35.3, 35.2, 34.3, 34.1, 32.1 (br), 19.6. MS (FAB^-, 3-NBA/Li) m/z (relative intensity): 815.9 (MLi^+, 8%), 809.9 (MH^+, 3%), 459.4 (25%), 401.4 (41%), 397.56 (75%), 327.3 (100%). HRMS (FAB^+, 3-NBA/Li): calcd. for $C_{45}H_{53}O_8N_4S_1(MH^+)$: 809.3584. Found: 809.3613.

Heterodimeric ligand 1c. Yellow oil (75%). IR (neat): 3543, 3070, 1757, 1703, 1596, 1569, 1542, 1508, 1407, 1253, 1125, 1072, 1025, 836, 790, 769, 722 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, J = 8.8, 2H), 7.44 (d, J = 8.8, 2H), 7.36 (t, J = 8.0, 1H), 7.19 (s, 1H), 7.11 (d, J = 8.8, 2H), 6.92 (s, 1H), 6.82 (d, J = 8.8, 2H), 6.08 (d, J = 8.0, 1H), 5.96 (d, J = 8.0, 1H), 4.62 (dd, J = 9.2, 4.0, 1H), 4.31 (t, J = 4.8, 2H), 4.28 (t, J = 4.8, 2H), 4.15 (t, J = 6.0, 2H), 3.92 (t, J = 6.0, 2H), 3.74 (t, J = 5.2, 2H), 3.65 (m, 2H), 3.60–3.52 (m, 4H), 3.37–3.35 (m, 1H), 3.070 (s, 3H), 3.06–3.00 (m, 1H), 2.18 (s, 3H), 1.68 (br s, 4H), 1.28 (s, 6H), 1.18 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 176.7, 171.4, 162.6, 158.4, 157.3, 156.8, 145.1, 142.1, 141.8, 140.3, 132.8, 130.2 (br), 127.9, 126.8 (br), 126.4 (br), 114.9, 97.4, 97.1, 74.2, 70.8 (br), 69.8 (br), 66.2, 64.4, 60.6, 54.4, 49.8, 38.0 (br), 35.4 (br), 34.3, 34.0, 32.1 (br), 19.6. MS (FAB^-, glycerol) m/z (relative intensity): 852.1 (M^-, 61%), 851.1 ($[M-H]^-$ 90%), 496.2 (93%), 348.1 (100%). HRMS (FAB^-, glycerol): calcd for $C_{47}H_{55}O_9N_4S_1$ ($[M-H]^-$): 851.3690. Found: 851.3726.

Heterodimeric ligand 1d. Yellow oil (66%). IR (neat): 3543, 2959, 1750, 1703, 1596, 1575, 1549, 1501, 1414, 1260, 1112, 1058, 1031, 957, 836, 796, 722 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 7.94 (d, J = 8.8, 2H), 7.50 (d, J = 8.8, 2H), 7.36 (t, J = 8.0, 1H), 7.22 (s, 1H), 7.13 (d, J = 8.4, 2H), 6.94 (s, 1H), 6.83 (d, J = 8.4, 2H), 6.08 (d, J = 8.0, 1H), 5.96 (d, J = 8.0, 1H), 4.66 (dd, J = 8.8, 4.0, 1H), 4.33 (t, J = 4.8, 2H), 4.29 (t, J = 4.8, 2H), 4.16 (t, J = 5.6, 2H), 3.92 (t, J = 5.6, 2H), 3.75 (t, J = 4.8, 2H), 3.74 (t, J = 4.8, 2H), 3.612–3.55 (m, 4H), 3.53 (br s, 4H), 3.39–3.32 (m, 1H), 3.09–3.05 (m, 1H), 3.07 (s, 3H), 2.06 (s, 3H), 1.70 (br s, 4H), 1.30 (s, 6H), 1.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 176.7, 168.4, 162.6, 158.2, 157.4, 157.2, 145.0 (br), 142.1, 140.2, 132.7, 130.7, 130.2 (br), 127.8, 126.6 (br), 114.8, 97.3, 97.1, 74.1 (br), 70.8 (br), 69.9 (br), 66.4, 49.7, 38.0 (br), 35.5, 35.3, 34.3, 34.0, 32.1 (br), 19.6. MS (FAB^-, glycerol) m/z (relative intensity): 896.4 (M^-, 16%), 895.4 ($[M-H]^-$, 24%), 540.3 (100%). HRMS (FAB^-, glycerol) calcd for $C_{49}H_{59}O_{10}N_4S_1$ ($[M-H]^-$): 895.3952. Found: 895.3934.

Heterodimeric ligand 1e. Yellow oil (72%). IR (neat): 3543, 3093, 2939, 1750, 1696, 1602, 1542, 1501, 1407, 1360, 1260, 1105, 1025, 944, 796, 722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.8, 2H), 7.57 (d, J = 8.8, 2H), 7.36 (t, J = 8.0, 1H), 7.16 (s, 1H), 7.11 (d, J = 8.8, 2H), 6.95 (s, 1H), 6.83 (d, J = 8.8, 2H), 6.04 (d, J = 8.0, 1H), 6.01 (d, J = 8.0, 1H), 4.50 (dd, J = 8.4, 4.0, 1H), 4.38 (t, J = 4.8, 2H), 4.35 (t, J = 4.8, 2H), 4.16–4.11 (m, 2H), 3.98–3.88 (m, 2H), 3.81–3.70 (m, 4H), 3.68–3.63 (m, 4H), 3.61 (br s, 4H), 3.58 (br s, 4H), 3.32 (dd, J = 14.0, 4.0, 1H), 3.18 (dd, J = 14.0, 8.4, 1H), 3.08 (s, 3H), 2.07 (s, 3H), 1.69 (br s, 4H), 1.31 (s, 6H), 1.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 178.2, 174.7, 162.6, 158.4, 157.4, 157.2, 156.6, 147.4, 145.3, 142.2, 140.2 (br), 132.8, 130.6, 130.5, 130.1 (br), 127.9 (br), 127.0, 126.4, 115.0, 97.3, 97.2, 74.1 (br), 70.7 (br), 70.0, 69.8, 66.3, 64.7, 49.6, 37.9, 37.6, 35.4, 35.3, 34.3, 34.1, 32.1 (br), 19.6. MS (FAB^-, glyerol) m/z (relative intensity): 940.6 (M^-, 64%), 939. ($[M-H]^-$, 100%). HRMS (FAB^-, glycerol) calcd for $C_{51}H_{63}O_{11}N_4S_1$ ($[M-H]^-$): 939.4214. Found: 939.4205.

Heterodimeric ligand 1f. Yellow oil (37%). IR (neat): 3543, 3100, 2946, 1750, 1703, 1602, 1542, 1495, 1407, 1260, 1105, 1025, 951, 796, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.8, 2H), 7.55 (d, J = 8.8, 2H), 7.35 (t, J = 8.0, 1H), 7.15 (s, 1H), 7.10 (d, J = 8.8, 2H), 6.94 (s, 1H), 6.82 (d, J = 8.8, 2H), 6.03 (d, J = 8.0, 1H), 6.00 (d, J = 8.0, 1H), 4.48 (dd, J = 8.8, 4.0, 1H), 4.37 (t, J = 4.8, 2H), 4.34 (t, J = 5.6, 2H), 4.16–4.10 (m, 2H), 3.97–3.87 (m, 2H), 3.80–3.75 (m, 4H), 3.68–3.61 (m, 8H), 3.61 (br s, 4H), 3.57 (br s, 4H), 3.33 (dd, J = 14.4, 4.0, 1H), 3.14 (dd, J = 14.4, 8.8, 1H), 3.07 (s, 3H), 2.06 (s, 3H), 1.68 (br s, 4H), 1.30 (s, 6H), 1.20 (s, 6H). ^{13}C NMR (100 MHz, CD_3OD): δ 177.5, 173.3, 172.1, 163.9, 159.8, 158.8, 158.1, 146.6, 143.5, 141.4, 141.0, 134.2, 132.4, 131.7, 130.9, 130.8, 130.7, 130.0, 129.1, 127.9, 127.3, 115.8, 98.4, 97.8, 87.8, 75.3, 71.7 (br), 71.1, 70.9, 70.6, 67.3, 65.7, 55.4, 50.5, 38.2, 37.9, 36.5, 36.3, 36.2, 36.1, 35.2, 35.0, 32.5 (br), 32.2, 32.1, 19.8. MS (FAB^-, glyerol) m/z (relative intensity):

983.8 (M^-, 11%), 349.3 (100%). HRMS (FAB^-, glycerol) calcd for $C_{53}H_{67}O_{12}N_4S_1$ ($[M–H]^-$): 983.4476. Found: 983.4446

Acknowledgements

We gratefully ackowledge funding from the Emory/Georgia Tech Biomedical Technology Center and useful discussions with Dr Tony Shuker (Metastatix, Inc.) and Chris Rito (Eli Lilly and Co.).

References

1 T. M. Willson, P. J. Brown, D. D. Sternbach and B. R. Henke, *J. Med. Chem.*, 2000, **43**, 527–550.

2 H. Keller, C. Dreyer, J. Medin, A. Mahfoudi, K. Ozato and W. Wahli, *Proc. Natl. Acad. Sci. U. S. A.*, 1993, **90**, 2160–2164.

3 K. Schoonjans, G. Martin, B. Staels and J. Auwerx, *Curr. Opin. Lipidol.*, 1997, **8**, 159–166.

4 S. A. Kliewer, K. Umesono, D. J. Noonan, R. A. Heyman and R. M. Evans, *Nature*, 1992, **358**, 771–774; S. P. Anderson, C. Dunn, A. Laughter, L. Yoon, C. Swanson, T. M. Stulnig, K. R. Steffensen, R. A. S. Chandraratna, J.-Å. Gustafsson and J. C. Corton, *Mol. Pharmacol.*, 2004, **66**, 1440–1452.

5 L.-N. Wei, *Annu. Rev. Pharmacol. Toxicol.*, 2003, **43**, 47–72; Q. Zhao, S. A. Chasse, S. Devarakonda, M. L. Sierk, B. Ahvazi and F. Rastinejad, *J. Mol. Biol.*, 2000, **296**, 509–520; E. Elstner, C. Muller, K. Koshizuka, E. A. Williamson, D. Park, H. Asou, P. Shintaku, J. W. Said, D. Heber and H. P. Koeffler, *Proc. Natl. Acad. Sci. U. S. A.*, 1998, **95**, 8806–8811; J. M. Lenhard, M. E. Lancaster, M. A. Paulik, J. E. Weiel, J. G. Binz, S. S. Sundseth, B. A. Gaskill, R. M. Lightfoot and H. R. Brown, *Diabetologia*, 1999, **42**, 545–554; R. Mukherjee, J. Strasser, L. Jow, P. Hoener, J. R. Paterniti and R. A. Heyman, *Arterioscler., Thromb., Vasc. Biol.*, 1998, **18**, 272–276; R. Mukherjee, P. J. A. Davies, D. L. Crombie, E. D. Bischoff, R. M. Cesario, L. Jow, L. G. Hamann, M. F. Boehm, C. E. Mondon, A. M. Nadzan, J. R. Paterniti and R. A. Heyman, *Nature*, 1997, **386**, 407–410.

6 A. Rowe, *Int. J. Biochem. Cell Biol.*, 1997, **29**, 275–278.

7 S. S. C. Koch, L. J. Dardashti, R. M. Cesario, G. E. Croston, M. F. Boehm, R. A. Heyman and A. M. Nadzan, *J. Med. Chem.*, 1999, **42**, 742–750.

8 M. F. Boehm, L. Zhang, B. A. Badea, S. K. White, D. E. Mais, E. Berger, C. M. Suto, M. E. Goldman and R. A. Heyman, *J. Med. Chem.*, 1994, **37**, 2930–2941.

9 R. T. J. Gampe, V. G. Montana, M. H. Lambert, A. B. Miller, R. K. Bledsoe, M. V. Milburn, S. A. Kliewer, T. M. Willson and H. E. Xu, *Mol. Cell.*, 2000, **5**, 545–555.

10 T. M. Willson, J. E. Cobb, D. J. Cowan, R. W. Wiethe, I. D. Correa, S. R. Prakash, K. D. Beck, L. B. Moore, S. A. Kliewer and J. M. Lehmann, *J. Med. Chem.*, 1996, **39**, 665–668; S. P. Tanis, T. T. Parker, J. R. Colca, R. M. Fisher and R. F. Kletzein, *J. Med. Chem.*, 1996, **39**, 5053–5063; K. A. Reddy, B. B. Lohray, V. Bhushan, A. C. Bajji, K. V. Reddy, P. R. Reddy, T. H. Krishna, I. N. Rao, H. K. Jajoo, N. V. S. M. Rao, R. Chakrabarti, T. Dileepkumar and R. Rajagopalan, *J. Med. Chem.*, 1999, **42**, 1927–1940.

11 B. C. C. Cantello, M. A. Cawthorne, G. P. Cottam, P. T. Duff, D. Haigh, R. M. Hindley, C. A. Lister, S. A. Smith and P. L. Thurlby, *J. Med. Chem.*, 1994, **37**, 3977–3985.

12 M. F. Boehm, L. Zhang, L. Zhi, M. R. McClurg, E. Berger, M. Wagoner, D. E. Mais, C. M. Suto, P. J. A. Davies, R. A. Heyman and A. M. Nadzan, *J. Med. Chem.*, 1995, **38**, 3146–3155.

13 K. M. Brummond and J. Lu, *J. Org. Chem.*, 1999, **64**, 1723–1726.

14 E. Baer and S. K. Pavanaram, *J. Biol. Chem.*, 1961, **236**, 1269–1272.

15 D. Haigh and D. Bell, *Int. Pat.* 9207838, 1992; D. Haigh and D. Bell, *Chem. Abs.*, 1992, **117**, 111595.

16 R. M. Silverstein and F. X. Webster, *Spectrometric Identification of Organic Compounds*, 6th edn, John Wiley & Sons, New York, 1997.

17 G. Chelucci, M. Falorni and G. Giacomelli, *Synthesis*, 1990, 1121–1122; A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki and J. Meienhofer, *J. Org. Chem.*, 1978, **43**, 4194–4196.

18 Y. Kiso, H. Isawa, K. Kitagawa and T. Akita, *Chem. Pharm. Bull.*, 1978, **26**, 2562–2564; K. S Kim, *Heterocycles*, 1990, **31**, 87–94.

19 N. C. O. Tomkinson, A. M. Sefler, K. D. Plunket, S. G. Blanchard, D. J. Parks and T. M. Willson, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2491–2496.

20 E. M. D. Keegstra, J. W. Zwikker, M. R. Roest and L. W. Jenneskens, *J. Org. Chem.*, 1992, **57**, 6678–6680; A. W. Snow and E. E. Foos, *Synthesis*, 2003, 509–512; P. Grosshans, A. Jouaiti, M. W. Hosseini, A. De Cian and N. Kyritsakas-Gruber, *Tetrahedron Lett.*, 2003, **44**, 1457–1460.

21 The acid corresponding to this ester is also an RXR agonist.

22 E. J. Corey, I. Szekely and C. S. Shiner, *Tetrahedron Lett.*, 1977, **18**, 3529–3532; M. Honda, K. Hirata, H. Sueoka, T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.*, 1981, **22**, 2679–2682.

23 P. Magnus and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1984, **6**, 389–390.