An Efficient, Stereospecific Synthesis of the Dimer-Selective Retinoid X Receptor Modulator (2*E*,4*E*,6*Z*)-7-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-(*n*-propyloxy)naphthalen-3-yl]-3-methylocta-2,4,6-trienoic Acid

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Received December 17, 1999

The recent discovery of 9-*cis*-retinoic acid (**1**)[1] as the endogenous ligand for the retinoid X receptor (RXR) subfamily of nuclear receptors has generated considerable interest in the exploration of molecules that bind to this important group of nuclear receptors and modulate their transcriptional activity.[2] These research efforts have resulted in the discovery of novel agents that have the potential to address a broad range of therapeutic indications, including oncologic and metabolic disease targets. The first compound discovered to be a potent and highly selective ligand for the RXRs, Targretin (LGD1069, **2**),[3] has recently been granted FDA approval for treatment of early and advanced-stage refractory cutaneous T-cell lymphoma (CTCL) and is in late-phase clinical trials for a variety of other indications, including breast cancer.[4] Recent preclinical evidence further suggests an important role for modulators of this receptor as insulin sensitizers.[5] Continued investigations in this area led to the discovery of the first reported RXR homodimer antagonist, (2*E*,4*E*,6*Z*)-7-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-(*n*-propyloxy)naphthalen-3-yl]-3-methylocta-2,4,6-trienoic acid (LG100754, **3**).[6] (See Figure 1.) The unique biological activity of this RXR ligand has prompted its use as a molecular tool in studying the physiologic relevance of transcriptional activation or repression resulting from RXR heterodimeric interactions with other nuclear receptors.[7] These studies revealed a previously undiscovered pharmacologic profile, that of a functional agonist of specific RXR heterodimers, including the retinoic acid receptors (RARs) and the peroxisome proliferator-activated receptors (PPARs), which have recently been shown to play a critical role in the regulation of glucose and lipid metabolism.[8]

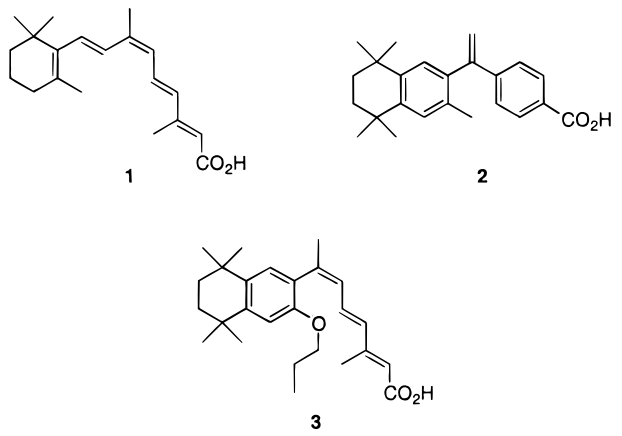

Figure 1. Selected RXR modulators.

The previously reported synthesis of trienoic acid **3**[6] involved a somewhat lengthy route, in which the introduction of the *cis*-olefin-containing skeletal fragment and its subsequent conversion to a suitable Horner−Wadsworth−Emmons precursor required several steps. Furthermore, the key step used to set the *cis*-olefin geometry involved methyl cuprate addition to an aralkynylnitrile,[9] which has proven to be capricious and subject to stereochemical leakage, as well as unsuitable for reproduction on a large scale. As multigram quantities of several molecules of this general structural class were required to further elucidate the novel pharmacology associated with **3** and related analogues, efforts were focused on a more efficient, versatile, and stereocontrolled route to 6-*cis*-7-aryltrienoic acids.

Capitalizing on the inherent stereospecificity in utilizing a coumarin intermediate, the present synthesis allows efficient installation of the requisite *cis*-olefin without loss of stereochemical integrity. Beginning with the previously described tetramethyltetrahydronaphthol

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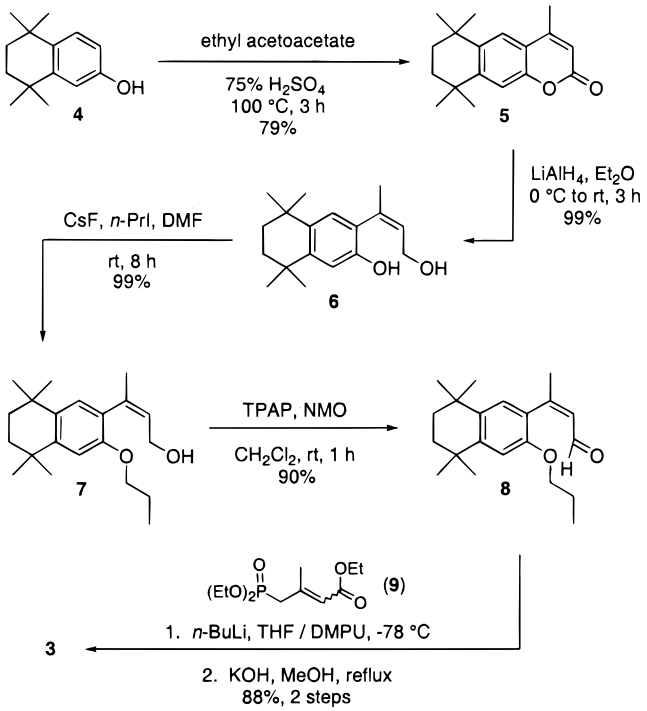
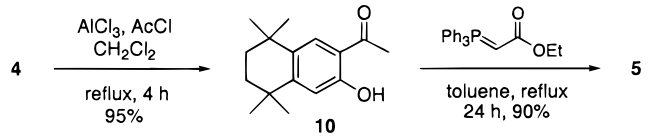
10.1021/jo991936x CCC: $19.00
Published on Web 04/13/2000

Scheme 1



4,[6] a classical von Pechmann cyclization[10] reaction using ethyl acetoacetate in 75% aqueous H_2SO_4 was used to regioselectively generate the 4-methylcoumarin ring system of **5**,[11] setting the olefin geometry present in the target compound. Reductive ring opening of the lactone ring with $LiAlH_4$ cleanly provides diol **6**. Selective alkylation of the phenol oxygen under extremely mild conditions is achieved using excess cesium fluoride[12] and stoichiometric 1-iodopropane in DMF to yield primary allylic alcohol **7**. Oxidation to aldehyde **8** is accomplished with TPAP[13] and NMO in CH_2Cl_2. Horner−Wadsworth−Emmons olefination[14] of **8** with phosphonate **9** installs the remainder of the triene chain, which is subsequently subjected to saponification using KOH in methanol to reveal the free acid target compound **3**. (See Scheme 1.)

Synthesis of certain related analogues in this series of RXR modulators[15] proved incompatible with the strongly acidic conditions employed in the von Pechmann cyclization step, as unwanted alkyl migrations occurred under these conditions. Milder alternative routes to the coumarin intermediates were explored using the present substrate as a model, as it was reasoned that construction of the lactone ring under neutral conditions would circumvent these undesired side reactions. Recently published routes to coumarins involving montmorillonite clays[16] or Pd-catalyzed reaction of unsaturated esters[17] generally required highly electron-rich aryls for efficient C−C bond formation to close the coumarin ring, and therefore, a potentially more generally applicable stabilized ylide approach was investigated.[18] Treatment of hydroxyacetophenone **10**, prepared by acylation/Fries rearrangement[19] of **4**, with excess carbethoxymethylenetriphenylphosphorane in refluxing toluene cleanly produced coumarin **5**, which was identical in every respect to the compound obtained by the von Pechmann cyclization route. Given the ready availability of acetophenones and related precursors with varied alkyl substitution on the aromatic ring, this two-step approach to the key coumarin intermediate is complementary with the von Pechmann cyclization method.



The title trienoic acid **3** was synthesized in six steps in 61% overall yield (seven steps, 66% overall yield via stabilized ylide variation) from tetrahydronaphthol **4** (in ref 6, 9 steps, 18% overall yield). Stereospecific introduction of the 6-*cis*-olefin was accomplished through two complementary cyclization approaches to coumarin intermediate **5**. Additionally, the entire synthetic sequence reported herein (both von Pechmann and stabilized ylide variants) has been carried out on a multigram scale with comparable yields, 100% stereochemical purity and with minimal purification of intermediates required. Utilization of a coumarin intermediate as a means of completely controlling the *cis*-olefin geometry, critical for the desired biological profile, should constitute a general route to this important new class of RXR modulating compounds, allowing further elucidation of novel retinoid pharmacology.

Experimental Section

General procedures and methods for characterization of new compounds have been described previously (see ref 20).

5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphth-2-ol (4). This compound was prepared as previously described.[6] Mp: 146−149 °C. ^{1}H NMR: δ 7.17 (d, 1H, J = 8.5 Hz), 6.75 (d, 1H, J = 2.8 Hz), 6.62 (dd, 1H, J = 8.5, 2.8 Hz), 4.49 (s, 1H), 1.66 (s, 4H), 1.25 and 1.24 (2s, 2 × 3H). ^{13}C NMR: δ 153.0, 146.6, 137.3, 127.7, 113.1, 112.7, 35.2, 35.1, 34.4, 33.7, 32.0, 31.8. IR (thin film): 3143 (br, s), 2917 (m), 1455 cm^{-1} (m). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.25; H, 10.07.

1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethylbenzo[5,6-*g*]coumarin (5). To a flame-dried 50-mL round-bottom flask containing 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphth-2-ol (2.03 g, 9.94 mmol) in 4 mL of 75% H_2SO_4 was added ethyl acetoacetate (3.19 mL, 25.0 mmol, 2.52 equiv), and the mixture was heated to 100 °C for 3 h. Upon cooling to room temperature, the mixture was poured over ice, diluted with saturated $NaHCO_3$, and stirred for 30 min. The mixture was then extracted with EtOAc (three times), and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product mixture was purified by flash column chromatography (silica gel; hexanes/EtOAc, 4:1) to remove residual ethyl acetoac-

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etate, providing the desired coumarin as a white solid (R_f 0.62; hexanes/EtOAc, 2:1). Recrystallization from hexanes/EtOAc afforded 2.12 g (79%) of the desired coumarin as white prisms (mp 124−126 °C, lit.[11] mp 119−121 °C). ^{1}H NMR: δ 7.51 (s, 1H), 7.25 (s, 1H), 6.20 (d, 1H, J = 0.8 Hz), 2.43 (d, 3H, J = 0.9 Hz), 1.72 (s, 4H), 1.33 and 1.31 (2s, 2 × 3H). ^{13}C NMR: δ 161.2, 152.2, 151.4, 150.4, 141.5, 122.2, 117.9, 114.3, 107.1, 34.92, 34.84, 34.58, 34.20, 32.22, 31.83, 18.49. IR (thin film): 2923 (m), 1716 (s), 1612 cm^{-1} (m). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.06; H, 8.06.

(2*Z*)-3-(4-Hydroxy-2-buten-2-yl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphth-2-ol (6). To a flame-dried 250-mL round-bottom flask containing 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylbenzo[5,6-*g*]coumarin (2.05 g, 7.60 mmol) in 100 mL of Et_2O at 0 °C was added LAH (288 mg, 7.59 mmol, 1.00 equiv), and the mixture was stirred and allowed to gradually warm to room temperature over 2 h. The mixture was then cooled to 0 °C before the cautious addition of 1 M $NaHSO_4$. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford 2.06 g (99%) of the desired diol as a white solid (mp 144−145 °C). ^{1}H NMR: δ 6.92 (s, 1H), 6.82 (s, 1H), 5.92 (t, 1H, J = 7.4 Hz), 3.96 (d, 2H, J = 7.4 Hz), 2.05 (s, 3H), 1.66 (s, 4H), 1.26 and 1.23 (2s, 2 × 3H). ^{13}C NMR: δ 149.4, 145.8, 137.3, 137.2, 127.4, 126.6, 124.8, 113.3, 60.4, 35.2, 35.1, 34.2, 33.6, 32.0, 31.8, 25.6. IR (thin film): 3147 (br, m), 2919 (m), 1218 cm^{-1} (s). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.71; H, 9.71.

(2*Z*)-3-(4-Hydroxy-2-buten-2-yl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-(*n*-propyloxy)naphthalene (7). To a flame-dried 100-mL round-bottom flask containing 3-(4-hydroxy-2-buten-2-yl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphth-2-ol (1.86 g, 6.71 mmol) in 30 mL of anhydrous DMF at room temperature were added cesium fluoride (3.52 g, 23.1 mmol, 3.45 equiv) and 1-iodopropane (725 μL, 7.41 mmol, 1.10 equiv), and the mixture was stirred for 15 h. The reaction mixture was then diluted with EtOAc, and the resultant organic layer was washed with water (two times), washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford 2.08 g (98%) of the desired propyloxy derivative as a colorless viscous oil. ^{1}H NMR: δ 6.91 (s, 1H), 6.77 (s, 1H), 5.78 (dt, 1H, J = 6.6, 1.4 Hz), 3.88 (m, 4H), 2.04 (s, 3H), 1.75 (m, 2H), 1.28 and 1.23 (2s, 2 × 3H), 1.01 (t, 3H, J = 7.5 Hz). ^{13}C NMR: δ 153.3, 144.9, 138.4, 137.0, 127.7, 126.5, 110.1, 70.3, 60.7, 35.2, 35.1, 34.4, 33.6, 31.9, 31.8, 25.1, 22.8, 10.7. IR (thin film): 3336 (br, s), 2919 (s), 1498 (m), 1455 cm^{-1} (m). Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.60; H, 10.44.

(2*Z*)-3-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-(*n*-propyloxy)naphthalen-3-yl]but-2-en-1-al (8). To an oven-dried 100-mL round-bottom flask containing (2*Z*)-3-(4-hydroxy-2-buten-2-yl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-(*n*-propyloxy)naphthalene (1.02 g, 3.22 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 570 mg, 4.89 mmol, 1.52 equiv) in 20 mL of CH_2Cl_2 at 0 °C was slowly added tetra-*n*-propylammonium perruthenate (TPAP, 53 mg, 5 mol %), and the mixture was allowed to warm to room temperature. After 1 h at room temperature, the reaction mixture was filtered through a pad of silica gel, being washed with CH_2Cl_2. The solvent was then removed under reduced pressure to afford 1.00 g (99%) of the desired aldehyde as a colorless, low-melting solid. The aldehyde thus obtained was more than 98% pure, as judged by the ^{1}H NMR spectrum, and was used directly in the next step without further purification. ^{1}H NMR: δ 9.36 (d, 1H, J = 8.1 Hz), 6.99 (s, 1H), 6.79 (s, 1H), 6.09 (dd, 1H, J = 8.4, 1.1 Hz), 3.90 (t, 2H, J = 6.4 Hz), 2.29 (d, 3H, J = 1.1 Hz), 1.76 (m, 2H), 1.68 (d, 4H, J = 1.6 Hz), 1.30 and 1.23 (2s, 2 × 3H), 1.00 (t, 3H, J = 7.5 Hz). ^{13}C NMR: δ 194.0, 161.7, 153.3, 146.9, 136.6, 129.7, 128.6, 125.3, 109.5, 69.7, 35.1, 35.0, 34.6, 33.6, 31.9, 31.8, 25.9, 22.6, 10.7. IR (thin film): 2922 (br, m), 1674 (s), 1202 (s), 1147 cm^{-1} (s).

(2*E*,4*E*,6*Z*)-7-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-(*n*-propyloxy)naphthalen-3-yl]-3-methylocta-2,4,6-trienoic Acid (3). This compound was prepared from enal **8** as previously described.[6] The ^{1}H NMR spectral data, TLC elution properties, and melting point of the product thus obtained matched those that were previously reported.

3-Acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphth-2-ol (10). This compound was prepared as previously described.[6] Mp: 101−103 °C. ^{1}H NMR: δ 11.65 (folded-over s, 1H), 7.65 (s, 1H), 6.90 (s, 1H), 2.61 (s, 3H), 1.68 (s, 4H), 1.29 and 1.27 (2s, 2 × 3H). ^{13}C NMR: δ 203.9, 159.5, 136.2, 128.7, 118.3, 115.4, 107.1, 35.1, 34.9, 34.6, 33.7, 32.2, 31.6, 26.4. IR (thin film): 2923 (m), 1654 (s), 1459 cm^{-1} (m). Anal. Calcd for $C_{16}H_{22}O$: C, 78.01; H, 9.00. Found: C, 78.28; H, 9.09.

Stabilized Ylide Procedure for Preparation of 1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethylbenzo[5,6-*g*]coumarin (5). To a flame-dried 50-mL round-bottom flask containing 3-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphth-2-ol (1.579 g, 6.41 mmol) in 10 mL of toluene was added carbethoxymethylenetriphenylphosphorane (3.35 g, 9.62 mmol, 1.50 equiv), and the mixture was heated to reflux for 24 h. Upon cooling to room temperature, the solvent was removed under diminished pressure, and the remaining solid was purified by trituration with cold hexanes to afford 1.54 g (90%) of the desired coumarin as a white solid. The ^{1}H NMR spectral data, TLC elution properties, and melting point of the product thus obtained matched those of the product obtained by the previously described von Pechmann cyclization procedure.

Acknowledgment. The author thanks Dr. Robert Ardecky for helpful discussions, Dr. Marcus Boehm for providing an authentic sample of **3**, and Dr. Marcello DiMare for providing phosphonate **9**.

JO991936X