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(54) Title: PROCESSES FOR PREPARATION OF LUBIPROSTONE

(57) Abstract: Processes for preparing and purifying lubiprostone are disclosed. Intermediates and preparation thereof are also disclosed.

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PROCESSES FOR PREPARATION OF LUBIPROSTONE

Background

Field of the Invention

The present invention provides for an efficient synthetic process for making lubiprostone.

Lubiprostone, 7-[(1*R*,3*R*,6*R*,7*R*)-3-(1,1-difluoropentyl)-3-hydroxy-8-oxo-2-oxabicyclo[4.3.0]non-7-yl]heptanoic acid, is the active pharmaceutical ingredient (API; drug substance) in the drug product Amitiza®, a gastrointestinal agent used for the treatment of Chronic Idiopathic Constipation in adults. It is marketed by Sucampo Pharmaceuticals, Inc. and was approved by the United States Food and Drug Administration (FDA) on January 31, 2006. It is also approved by FDA to treat Irritable Bowel Syndrome with constipation (ISB-C) in adult women aged 18 and over on April 29, 2008. Amitiza® is also being clinically tested for other gastrointestinal disorders. Lubiprostone is a bicyclic 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E1 derivative (a.k.a., a so-called 13,14-dihydro-15-keto-prostaglandin derivative). Prostaglandins possess the prostanoic acid backbone which is a C20 fatty acid (Figure 1).

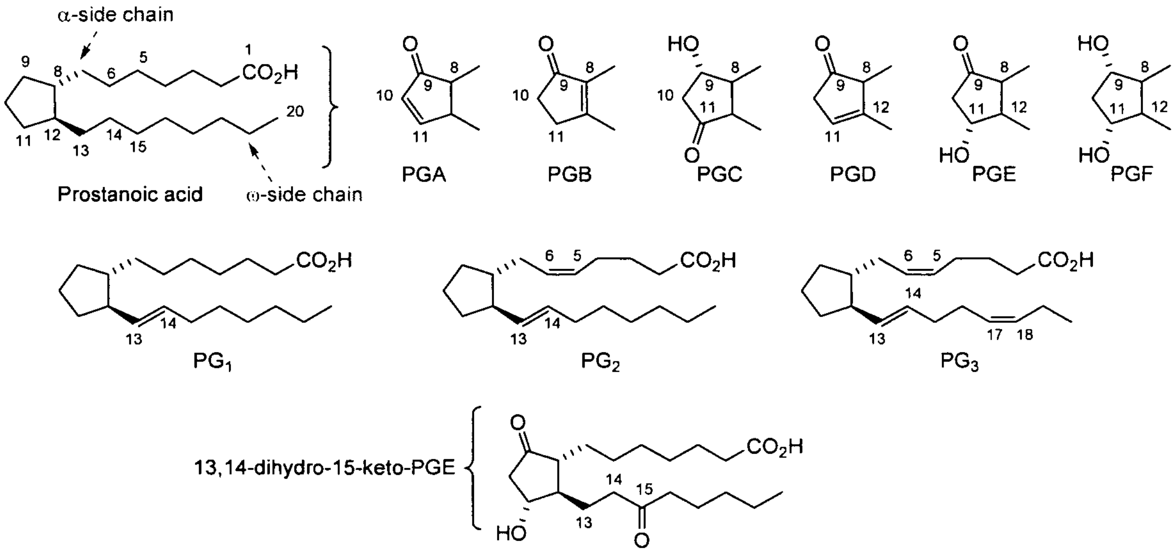
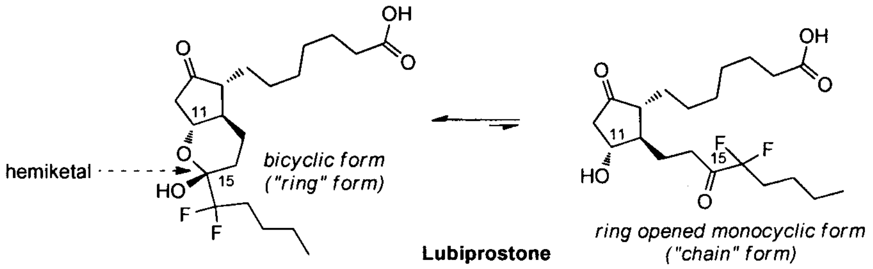


Figure 1 - Prostaglandin nomenclature

The existence of an electron deficient ketone at C15, along with a conveniently positioned hydroxyl group at C11 results in lubiprostone existing predominantly in a bicyclic form that includes a 6-membered hemiketal ring. This form exists in equilibrium with a monocyclic form (**Scheme 1**). Taken together, these two forms are referred to as tautomeric isomers. In sugar chemistry this kind of equilibrium of cyclic and acyclic forms is referred to as ring-chain tautomerisation (R-CT).[1] Whereas in D_2O, the ratio of the bicyclic form to monocyclic form is 6:1, in $CDCl_3$ it is 96:4.[2] Despite this tautomerisation and the predominance of the bicyclic hemiketal form, lubiprostone is still referred to as a 15-keto-prostaglandin E1 derivative. According to US2010056808A1 the two crystalline polymorphs of lubiprostone reported exist as the bicyclic form in the solid state.



Scheme 1 - "Ring-chain tautomer" forms of lubiprostone

Related Art

An early approach with great versatility for the synthesis of prostaglandins and analogues was invented by E. J. Corey[3] in the late 60's and this is probably the strategy most used by industry. To date, besides the presently claimed process, it is the only method that has been disclosed for lubiprostone synthesis. This approach is referred to as the "*Corey method*". The Corey lactone aldehyde (*a.k.a.*, Corey aldehyde),[4] which itself requires many synthetic steps, is central to the Corey

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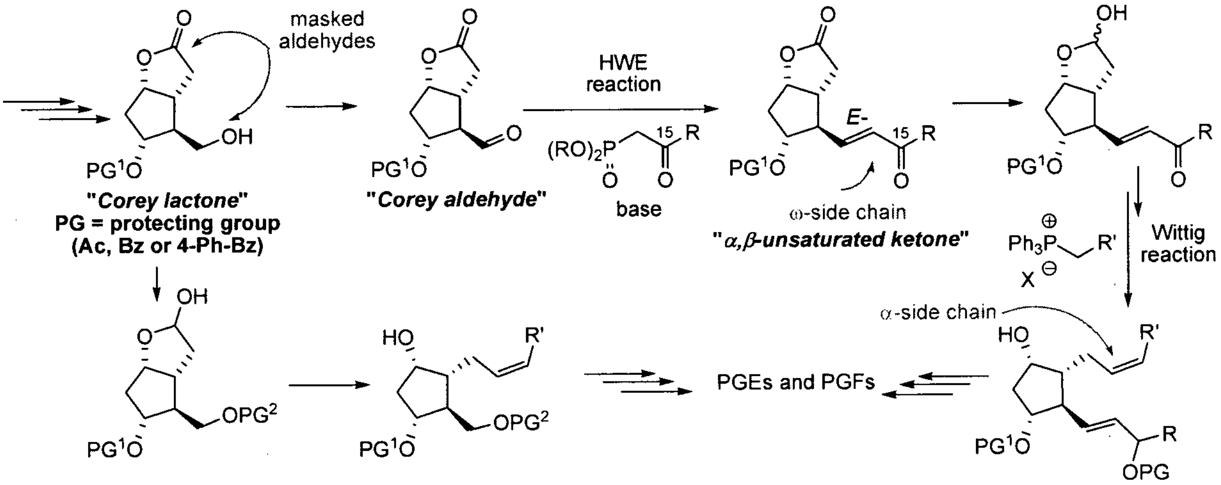
[1] According to http://en.wikipedia.org/wiki/Tautomer , ring-chain tautomerisation "*occurs when the movement of the proton is accompanied by a change from an open structure to a ring, such as the open chain and pyran forms of glucose.*"

[2] US 7,355,064 B2.

[3] *J. Am. Chem. Soc.*, **1969**, *91*, 5675-5676.

[4] *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 455-465.

approach and contains all of the three PGE$_1$ stereochemical centres (such as those required in lubiprostone) already in place, and the ω- and α-side chains are added sequentially by Horner-Wadsworth-Emmons (or HWE reaction) and Wittig reactions (**Scheme 2**). In the Corey approach, the order of addition of the α- and ω-side chains is interchangeable.



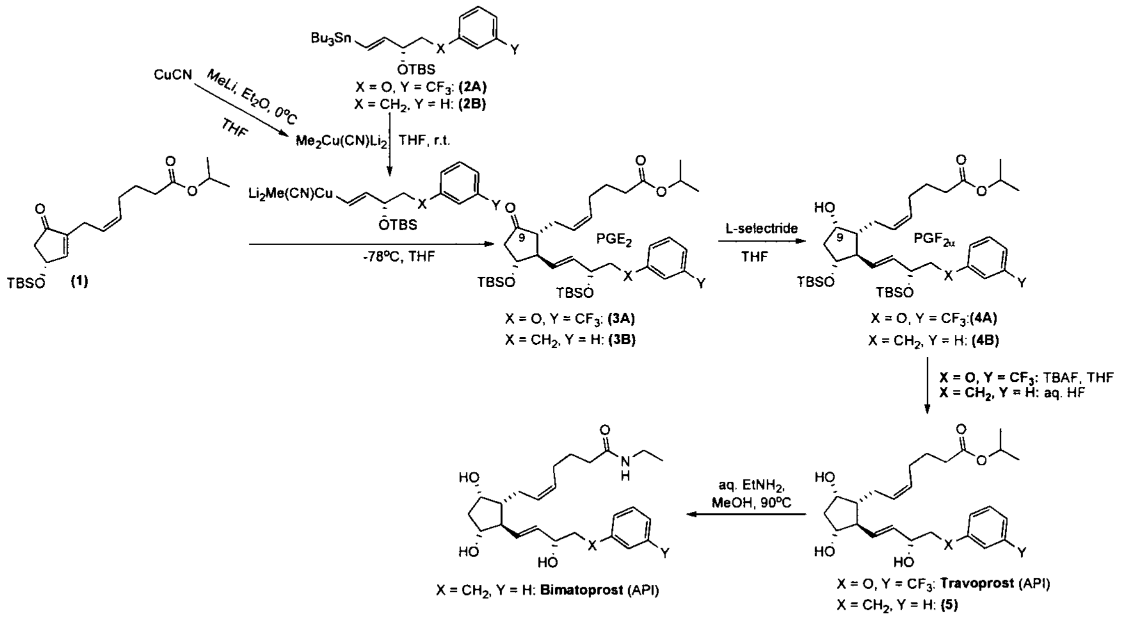
Scheme 2 - The "Corey method" for prostaglandin synthesis

Summary of the invention

Prostaglandin platform technology of the present invention

Our company has previously developed the total syntheses of the prostaglandin analogues travoprost and bimatoprost. These synthetic routes and their processes were published in patent applications US20090259058A1 and WO2009141718A2 in 2009. The final steps in the syntheses of travoprost and bimatoprost are shown in **Scheme 3** and pivot around a key 1,4-conjugate addition reaction (*a.k.a.*, Michael addition) of a higher order cuprate, formed from compound (2A) or (2B), with cyclopentenone (1) (a diverging, common intermediate) to furnish the PGE$_2$s compound (3A) or (3B). Following this the two PGE$_2$s were converted into the PGF$_{2\alpha}$s compound (4A) or (4B) by stereoselective C9 ketone reduction. This was followed by double TBS deprotection (of C11-OTBS and C15-OTBS) to provide travoprost or the isopropyl ester analogue of bimatoprost, compound (5). The isopropyl ester was converted into bimatoprost by ester to amide exchange.

For lubiprostone, which is the subject of the present invention, we have utilised a different synthetic route since the structure of the API is significantly different from that of bimatoprost, and travoprost, however, the key intermediate compound (1) is still similarly utilised in a 1,4-conjugate addition of a cuprate compound. Thus, diverging intermediate (1) which we have a manufacturing process for, can still be used in lubiprostone synthesis.



Scheme 3 - The final steps in the synthesis of travoprost and bimatoprost using our prostaglandin platform technology (US20090259058A1 and WO2009141718A2).

Application of prostaglandin platform technology to the synthesis of lubiprostone:

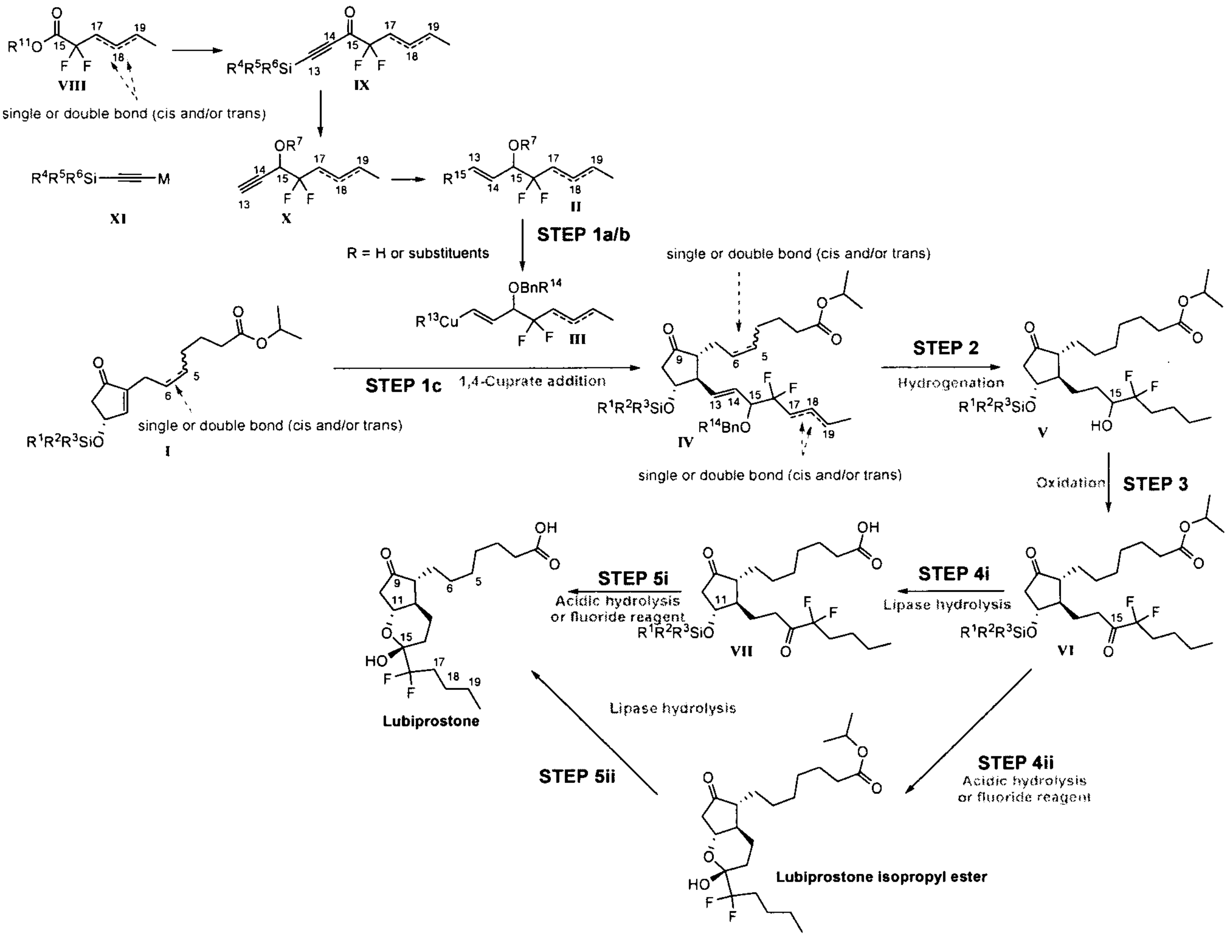
Our preferred synthesis of lubiprostone is shown in **Scheme 4**. We propose that the silyl protecting group can be selected from a range of analogues, but TBS is preferred. The α-side chain may possess a double bond between C5 and C6, and this may be *cis-* or *trans-* or a mixture of *cis-* and *trans-*, or C5 to C6 may be saturated. The C17 to C18 to C19 bonds can all be single C-C bonds, or can contain one double and one single bond. The existence of a double bond between C17 to C18, or C18 to C19 is only an artifact of the synthesis of **II**. The stereochemical configuration of C15 may be (*R*)- or (*S*)- and may be a mixture.

The benzyl protecting group may be unsubstituted (*i.e.*, R^{14} = H) or substituted (*i.e.*, R^{14} = 4-MeO, 2,4-DiMeO *etc.*). R^{13} can be any substituent or combination of substituents that allows cuprate **III** to efficiently transfer its vinyl group to cyclopentenone **I**, but which itself does not react with cyclopentenone **I**. R^{13} is preferably selected from the group of cyano, methyl and thienyl and combinations of these with lithium counter ions. Other organocopper reagents could also be conceivably used. Following the 1,4-conjugate addition (**STEP 1c**) of cuprate **III** and cyclopentenone **I**, all double bonds (C13,C14 and any others if present such as between C5 and C6, C17 and C18, and C18 and C19) of compound **IV** are removed along with the benzyl or substituted benzyl group (**STEP 2**) using a metal catalyst, preferably Pd, in a hydrogen atmosphere. Following this, the C15 alcohol of compound **V** is oxidised to a ketone using any suitable reagent, but preferably one (*e.g.*, Pfitzner-Moffatt type oxidation reagents) that does not contaminate the product with metallic residues. The 15-keto prostaglandin **VI**, which is a doubly protected form of lubiprostone, is converted into lubiprostone, either by isopropyl ester hydrolysis to provide compound **VII** (**STEP 4i**), preferably accomplished by the aid of an enzyme, follow by desilylation to provide the isopropyl ester of lubiprostone (**STEP 5i**) using acid conditions or a fluoride reagent, or by desilylation (**STEP 4ii**) using acid conditions or a fluoride reagent followed by isopropyl ester hydrolysis (**STEP 5ii**), preferably accomplished by the aid of an enzyme.

R^{11} of ester **VIII** can be alkyl, benzyl, aryl, but methyl and ethyl is preferred. R^4, R^5, R^6 may be any of alkyl, aryl, but all methyl is preferred. R^7 is H or BnR^{14}. R^{15} may be $SnR^8R^9R^{10}$, Br, I, $ZrCp_2Me$ but is preferably $SnR^8R^9R^{10}$. R^8, R^9, R^{10} may be any of alkyl, aryl, but all *n*-butyl is preferred. R^{13} is nothing, Li(CN), $Li_2(CN)Me$, $Li_2(CN)$2-thienyl, $Li(CH{=}CHCH(OBnR^{14})CF_2CH_nCH_mCH_oCH_3)$ (*n,m* and *o* is 1 or 2 such that either C17 through to C19 is fully saturated or C17 through to C19 contains one single and one double or triple bond), $Li_2(CN)(CH{=}CHCH(OBnR^{14})CF_2CH_nCH_mCH_oCH_3)$ (*n,m* and *o* is 1 or 2 such that either C17 through to C19 is fully saturated or C17 through to C19 contains one single and one double or triple bond), but is preferably $Li_2(CN)Me$ or $Li_2(CN)$2-thienyl.

Key aspects of this invention that are not before reported include the use of a 1,4-conjugate addition as a key step to form the prostaglandin backbone of lubiprostone in one single step from cyclopentenone **I** and higher order cuprate **III**. Following this, an efficient use of hydrogenation/hydrogenolysis is used to remove all of the double bonds of **IV** that are artefacts of **IV**'s synthesis, as well as simultaneously removing the C15-O protecting group, to provide **V**. Another key aspect in the synthesis is the use of an enzyme to remove the ester protecting group. This is preferable because hydrolysis of the isopropyl ester using acidic or basic aqueous conditions leads to decomposition of the sensitive 15-keto-PGE structure, and would not be orthogonal as the silyl protecting group could also be removed thereby not providing us with synthetic control. The final two steps, which are deprotecting group steps, can be conducted in either order.

Of course other ester analogues (*e.g.*, methyl, ethyl, propyl *etc.*) could be used in the synthesis of lubiprostone following the synthetic route of this invention, however, isopropyl is preferred.



Scheme 4 – Summary of the preferred method for the synthesis of lubiprostone (the numberings show reflect the numbers of atoms as would be found in lubiprostone)

Accordingly, the present invention encompasses a new synthetic route to lubiprostone (**Scheme 5**), which involves 1,4-conjugate addition of a higher order cuprate compound **Cu-IM7** (prepared *in situ* from **IM7**) to protected cyclopentenone (1) as a key step. We have also provided synthetic routes to **IM7** (**Scheme** 7) and **IM7b** (**Scheme 8**) (and 4-methoxybenzyl derivatives **IM7i** and **IM7bi**), which are the starting materials for the ω-side chain of lubiprostone. Unlike all the prior art syntheses of lubiprostone that we are aware of, we have utilised a silicon-based protecting group for the protection of the alcohol that ultimately becomes C11-O in lubiprostone. All other prior art methods that have been disclosed to our knowledge disclose the use of carbon based protecting groups such as THP. Also, unlike all of the other prior art methods that we are aware of, we prepared lubiprostone using a 1,4-conjugate addition approach, which differs greatly from the Corey method used in all the other prior art methods. This also sets our approach apart from all the other methods.

The synthetic route is discussed in detail below.

*1) –Synthesis of lubiprostone (**Scheme 5**):*

STEP 1: The first step involves the 1,4-conjugate addition of higher order cuprate **Cu-IM7** with key diverging intermediate (1) (**STEP 1c**) to provide the PGE_2 product **(7)**. The higher order cuprate **Cu-IM7** in that step was prepared *in situ* (**STEP 1a**) by the stepwise reaction of **IM7** with MeLi to form the vinyl lithium derivative **Li-IM7** followed by conversion (**STEP 1b**) to the higher order cuprate **Cu-IM7** by reaction with an *in situ* prepared cuprate salt (MeCu(CN)Li) (also see **Scheme 6**) . THF was preferred as the main solvent for this reaction step and the reaction was conducted at low temperatures (preferably below -30°C).

In addition to the benzyl protecting group that is used to protected C15-OH (*i.e.*, C3-OH of **IM7**), *p*-methoxybenzyl (*a.k.a.*, 4-methoxybenzy)as a protecting group is also tested. Thus, **STEP 1** was also tested using the *p*-methoxybenzyl derivative by conducting the 1,4-conjugate addition of higher order cuprate **Cu-IM7i** (prepared from the *p*-methoxybenzyl **IM7** analogue, **IM7i)** with compound (1) to provide product *p*-methoxybenzyl ether **(7i)**.

STEP 2: We conducted a global hydrogenation/hydrogenolysis in an organic solvent using a palladium catalyst supported on carbon in a hydrogen atmosphere which removed all three double bonds (C5-C6, C13-C14 and C17-C18) and the benzyl protecting group (or *p*-methoxybenzyl group when compound **(7i)** was used) simultaneously to provide compound **(8)**. Although EtOAc was the preferred solvent, other solvents including EtOH could be used. An acid catalyst (such as *p*-TsOH) could also be used in the reaction.

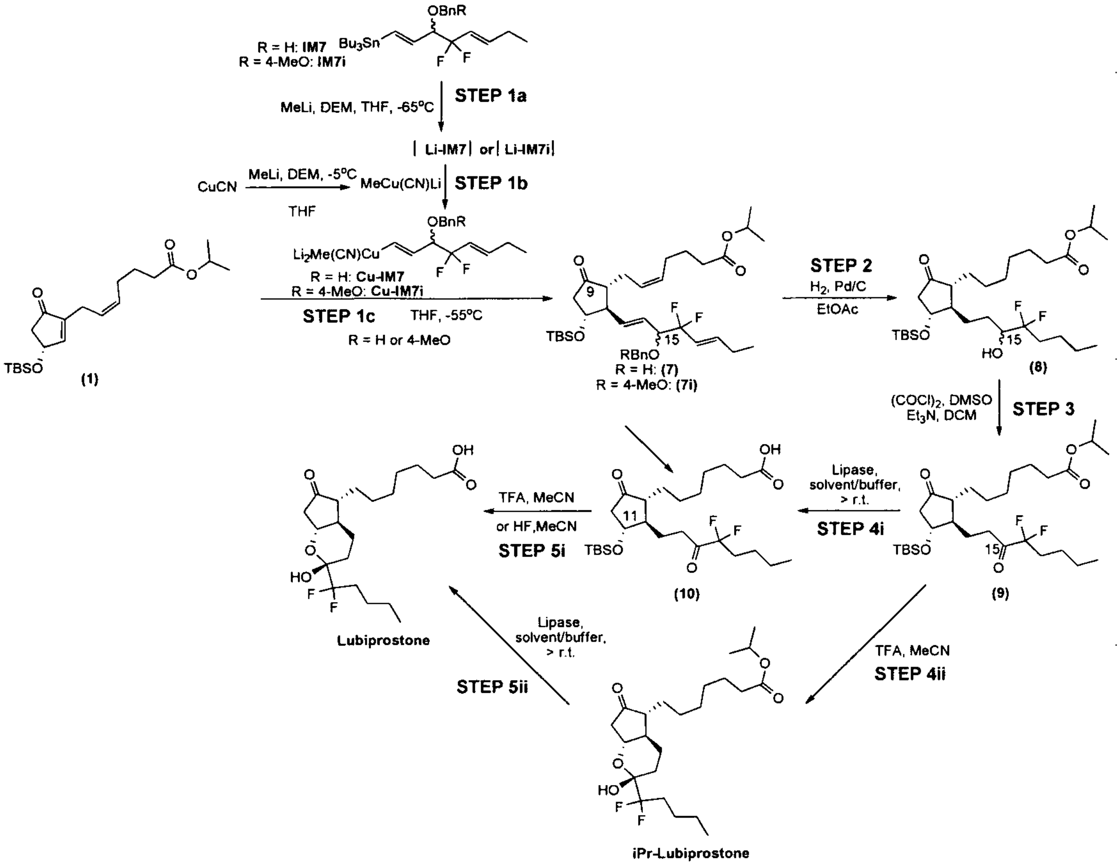
STEP 3: The C15-OH was oxidized to provide the diketone **(9)** using the Swern oxidation method (*i.e.*, $(COCl)_2$ with DMSO). Other oxidants, including pyridine sulfur trioxide complex/DMSO, can also be used.

STEP 4i: A range of enzymes that can catalyse the hydrolysis of esters (including Lipase PS IM, Lipase PS SD, PPL, PS IM) under a range of reaction conditions were found to be able to hydrolyse the isopropyl ester of compound **(9)** to provide its carboxylic acid form **(10)**. A large range of organic solvents could be used including acetone, glycol, glycerol, DMSO. Typically the hydrolysis reaction was conducted at an elevated temperature (*e.g.*, between 30 – 60°C) and appropriate pH range . Commercially available Lipase PS SD was preferred when acetone was used as an organic solvent in conjunction with an aqueous buffer at an elevated temperature.

STEP 5i: Lubiprostone is prepared by TBS deprotection of the C11-OTBS of the compound **(10)** using mineral or organic acids such as H_2SO_4, HCl, TFA or fluoride reagents including TBAF and aq. HF in an organic solvent. H_2SO_4 in MeCN is preferred.

Alternatively the last two steps (*i.e.*, **STEP 4i** and **STEP 5i**) can be conducted in reverse order with TBS deprotection (using an acid or fluoride reagent) in **STEP 4ii** followed by ester hydrolysis (using an ester hydrolysing enzyme in aqueous buffer/organic solvent) in **STEP 5ii**.

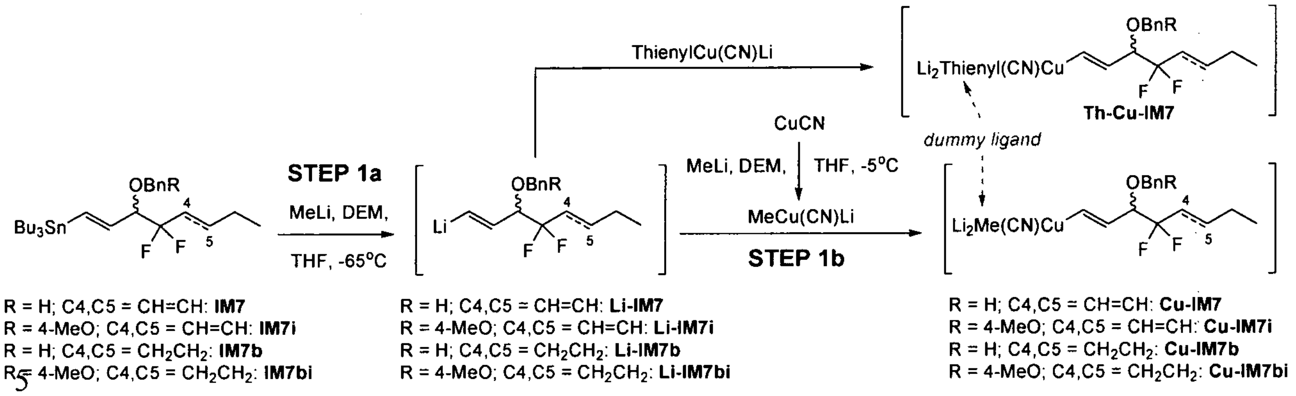
Lubiprostone can be converted into salt derivatives by reaction with bases, including nitrogen containing bases such as guanidine for example. These salts can possess different melting points and solubilities as compared to that of lubiprostone thereby providing access to alternative methods by which lubiprostone can be purified. We provide a simple method to form the guanidine salt of lubiprostone.



Scheme 5 - Synthesis of lubiprostone.

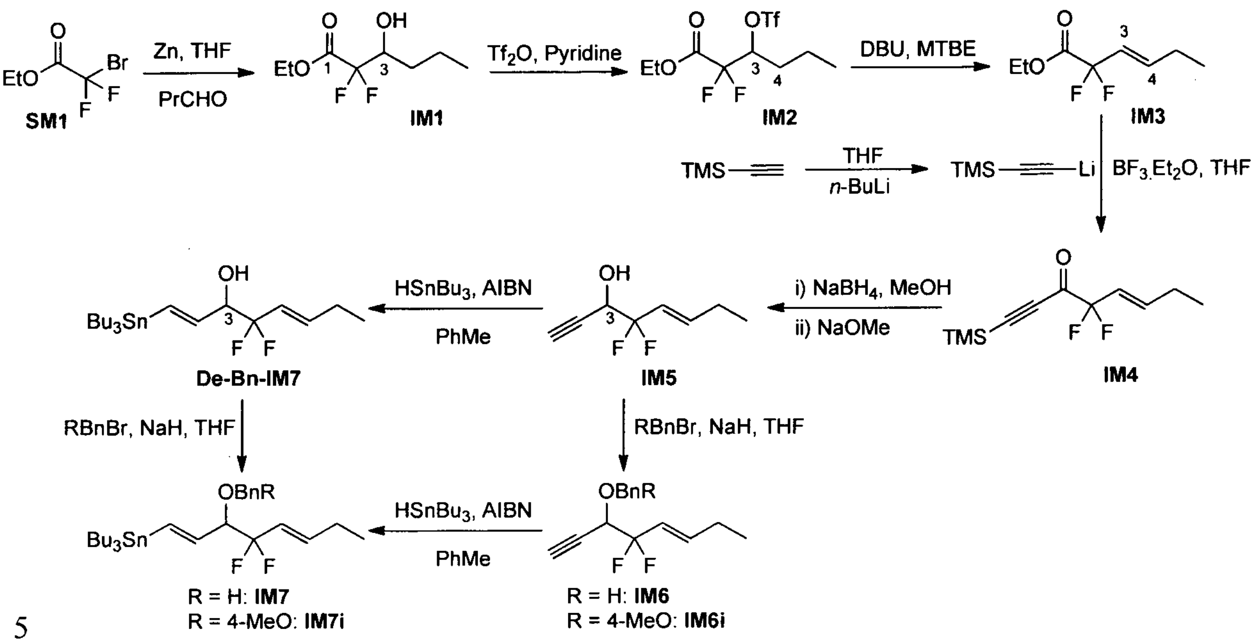
2) Synthesis of the ω-side chain:

Lubiprostone is prepared by the 1,4-conjugate addition of a higher order cuprate (**Cu-IM7**, **Cu-IM7b**, **Cu-IM7i** or **Cu-IM7bi**) with the compound **(1)** to form a PGE_2 compound. The higher order cuprate **Cu-IM7** (or **Cu-IM7b**, **Cu-IM7i** or **Cu-IM7bi**) is prepared from *trans*-vinyl stannane **IM7** (or **IM7i** , **IM7b**, or **IM7bi**) as shown in **Scheme 6**. The methyl dummy ligand can be substituted with a 2-thienyl group by the use of the commercially available lower order cuprate salt 2-thienyl(cyano)copper lithium in **STEP 1b** to provide **Th-Cu-IM7**, in place of methyl(cyano)copper lithium (MeCu(CN)Li).



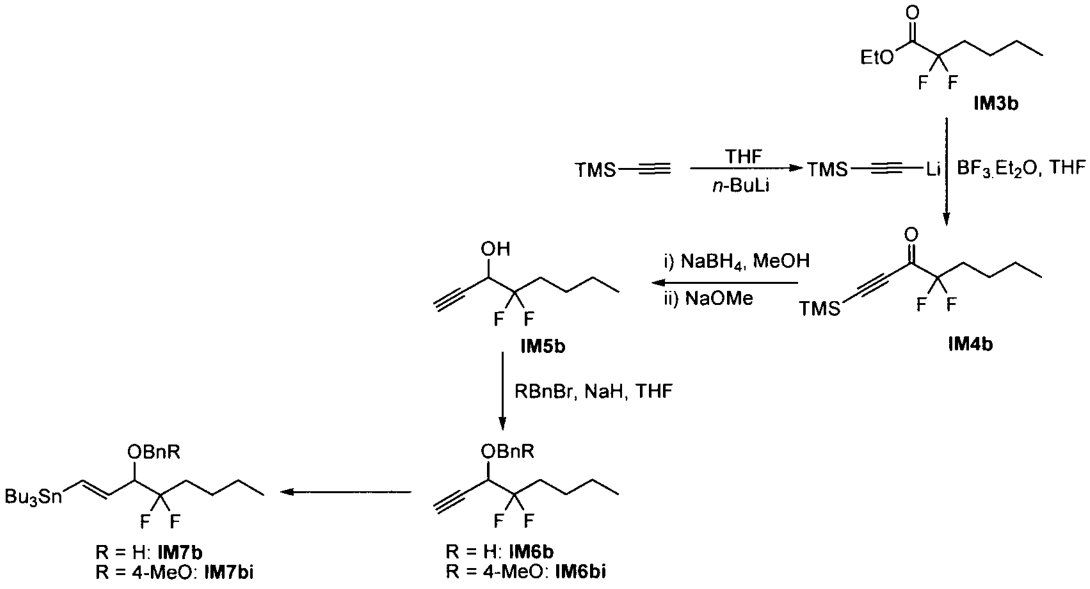
Scheme 6 - Synthesis of requisite higher order cuprate required in 1,4-conjugate addition with the compound (1)

We prepared the requisite *trans*-vinyl stannane **IM7** (or **IM7i**) using the process as shown in **Scheme 7**. Cheap and commercially available **SM1** was converted *in situ* to its organozinc bromide derivative and was reacted with cheap and commercially available butanal to provide alcohol **IM1**. This was preferably conducted in THF and the addition of Lewis acids could be beneficial. Removal of the C3-oxygen was achieved by its conversion to triflate **IM2**, followed by elimination promoted by bases including DBU to furnish **IM3**. The existence of the double bond in **IM3** is of no consequence and lubiprostone can be synthesized from either **IM3** or **IM3b** (see **Scheme 8**). Following its synthesis, **IM3** was converted into the acyl acetylene **IM4** which was reduced and desilylated in one-pot to provide propargyl alcohol **IM5**. Thus, **IM5** was treated with Bu$_3$SnH in the presence of the radical initiator AIBN to provide **De-Bn-IM7**, which was then *O*-protected with benzyl bromide under basic conditions (*e.g.*, NaH or *t*-BuONa, the former was preferred) to furnish **IM7**. Alternatively, C3-OH of **IM5** could be protected and the product **IM6** then stannylated to give **IM7**.



Scheme 7 - Synthesis of IM7 as required for the order cuprate Cu-IM7

As mentioned above, the **IM3** analogue ethyl 2,2-difluorohexanoate (**IM3b**) is commercially available. Using the same synthetic sequence as described in **Scheme 7**, **IM3b** was converted it into **IM7b** (**Scheme 8**)..



Scheme 8 - Synthesis of IM7b as required for the order cuprate Cu-IM7b

EXAMPLES

EXAMPLE 1

*Step 1: Synthesis **IM1*** (ethyl 2, 2-difluoro-3-hydroxyhexanoate)

To a mechanically stirred mixture of zinc (108 g, 1.66 mol), *n*-butanal (100 g, 1.39 mol), $CeCl_3.7H_2O$ (10.14 g, 0.027 mol) and anhydrous THF (1.3 L) at about 25°C was added ethyl 2-bromo-2,2-difluoroacetate (**SM1**, 33.8 g, 0.167 mol) under N_2. The mixture was stirred at about 25°C until the reaction had initiated, then **SM1** (304 g, 1.50 mol) was added dropwise at 35°C without external heating. After the addition completed, the mixture was stirred at 20~35°C until *n*-butanal was less than 2.0%. The reaction mixture was then cooled to about 5°C and sat. aq. NH_4Cl (800 mL) was added slowly at about 5°C, and then adjust pH 3.0 with 6 N HCl. The mixture was stirred for 15 min. and then filtered through a plug of celite; the filter cake was washed once with MTBE (1 L). The combined filtrate was then separated and the aqueous layer was extracted once with MTBE (1 L). The combined organic layers were washed once with sat. aq. $NaHCO_3$ (1 L), once with sat. aq. NH_4Cl (1 L) and then concentrated at <50°C under reduced pressure to give 281 g of crude **IM1** with 80% GC purity. The crude **IM1** was purified by vacuum distillation to provide 160 g **IM1** with 98% GC purity in 58% GC total yield.

^{1}H NMR (300MHz, $CDCl_3$): δ 4.36 (q, J = 7.1 Hz, 2H), 4.10 – 3.98 (m, 1H), 1.68 – 1.58 (m, 2H), 1.57 –1.40 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.1 Hz, 3H)

m/z (GC-MS): 197 ($[MH]^+$, 1), 124 (75), 96 (100), 73 (45), 55 (80)

EXAMPLE 2

*Step 2 Synthesis **IM2*** (ethyl 2,2-difluoro-3-(trifluoromethylsulfonyloxy) hexanoate)

To a mechanically stirred solution of **IM1** (3 g, 0.015 mol) and pyridine (1.42 g, 0.018 mol) in anhydrous DCM (6 mL) at 0-5°C was added a mixture of Tf_2O (4.53 g, 0.016 mol) in anhydrous DCM (3 mL) dropwise at 0-15°C under N_2. The mixture was stirred at 5-15°C until **IM1** was less than 2.0%. Then water (9 mL) was added and the resulted mixture was separated. The aqueous layer was extracted once with DCM (9 mL) and the combined organic layer was washed once with 5% aq. HCl (9 mL), once with sat. aq. $NaHCO_3$ (9 mL) and once with brine (9 mL) and then concentrated at <45°C under reduced pressure to give 4.2 g of crude **IM2** with 96% GC purity

^1H NMR (300MHz, $CDCl_3$): ^1H NMR (300 MHz, $CDCl_3$) δ 5.21 (m, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.00 – 1.74 (m, 2H), 1.70-1.43 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H)

m/z (GC-MS): 329 ($[MH]^+$, 1), 151 (20), 124 (15), 106 (70), 77 (100), 69 (45), 55 (55)

EXAMPLE 3

*Step 3 Synthesis **IM3*** *(*ethyl 2,2-difluorohex-3-enoate*)*

To a mechanically stirred flask was added **IM2** (300 g, 0.91 mol) and DBU (165 g, 1.08 mol) in anhydrous MTBE (900 mL), the mixture was heated to reflux with stirring until **IM2** was less than 3.0%. The reaction mixture was then cooled to 0 ~ 10°C followed by adding of 5% aq. HCl (900 mL). The resulted solution was separated and the aqueous layer was extracted once with MTBE (900 mL). The combined organic layer was washed once with sat. aq. $NaHCO_3$ (900 mL), once with brine (900 mL), dried with anhydrous $MgSO_4$ and then concentrated at <45°C under reduced pressure to give 167 g of crude **IM3**. The crude **IM3** was purified by vacuum distillation to give 125 g **IM3** with 85% GC purity in 66% GC yield based on **IM1**

^1H NMR (300MHz, $CDCl_3$): δ 6.33 (dtt, *J* = 11.5, 6.2, 2.6 Hz, 1H), 5.75 – 5.58 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.24 – 2.11 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H)

m/z (GC-MS): 179 ($[MH]^+$, 4), 106(65), 77 (100), 55 (20)

EXAMPLE 4

*Step 4 Synthesis **IM4** (*4,4-difluoro-1-(trimethylsilyl)oct-5-en-1-yn-3-one*)*

To a mechanically stirred solution of **TMS-acetylide** (182 g, 1.85 mol) in anhydrous THF (880 mL) at 0-10°C was added a solution of *n*-BuLi (2.5mol/L, 748 mL, 1.87 mol) dropwise at 0-10°C under N_2. The reaction mixture was stirred at this temperature for 1 h. To a mechanically stirred flask was added **IM3** (220 g, 1.23 mol, 1.0 eq., 92% GC purity) and BF_3/Et_2O (264 g, 1.86 mol) in anhydrous THF (220 mL) under N_2. The solution was cooled to -70 ~ -78°C and then ***TMS-acetylene-lithium solution*** was added at -60 ~ -78°C in 2 h. The reaction solution was stirred at -70 ~ -78°C until **IM3** disappeared. Sat. aq. NH_4Cl (1.1 L) was added slowly into the reaction, the temperature was allowed to warm to 0~10°C. The mixture was then extracted once with EtOAc (550 mL) and then separated; the aqueous layer was extracted once with EtOAc (550 mL). The combined organic layer was washed once with water (660 mL) and once with brine (660 mL) and then concentrated at <55°C under reduced pressure to give 297 g of crude **IM4** with 87% GC purity.

^{1}H NMR (300MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (dtt, J = 11.3, 6.3, 2.5 Hz, 1H), 5.69 – 5.52 (m, 1H), 2.26 – 2.13 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H), 0.28 (s, 9H)

m/z (GC-MS): 231 ($[MH]^+$, 1), 125 (100), 97 (35), 73 (30)

EXAMPLE 5

*Step 5 Synthesis **IM5*** (4, 4-difluorooct-5-en-1-yn-3-ol)

To a solution of **IM4** (321 g, 1.4 mol) in MeOH (1.5 L) at 0 ~ -5°C was added solid $NaBH_4$ (19.6 g, 0.7 mol) slowly. The reaction solution was stirred at this temperature until **IM4** consumed. Then solid NaOMe (37.7 g, 0.7 mol) was added and the reaction solution was stirred at this temperature until **TMS-IM5** consumed. Sat. aq. NH_4Cl (1 L) and H_2O (1 L) was added and then the mixture was adjusted to pH 5~6 with 6 M HCl, the mixture was then extracted three times with MTBE (600 mL each). The combined organic layer was washed once with water (600 mL), once with brine (600 mL) and then concentrated at <45°C under reduced pressure to give 224 g of crude **IM5** with 87% GC purity.

^1H NMR (300MHz, $CDCl_3$): δ 6.32 (dtd, J = 10.8, 6.1, 2.3 Hz, 1H), 5.78 – 5.59 (m, 1H), 4.57 – 4.46 (m, 1H), 2.55 (d, J = 2.2 Hz, 1H), 2.26 – 2.12 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H)

m/z (GC-MS): 159 ($[M-H]^+$, 1), 105 (5), 77 (100), 55 (30)

EXAMPLE 6

Step 6 Synthesis ***De-Bn-IM7*** *(*(1E)-4,4-difluoro-1-(tributylstannyl)octa-1,5-dien-3-ol*)*

To the hot (70°C) solution of **IM5** (110 g, 0.68 mol) in toluene (550 mL) was added Bu_3SnH (219 g, 0.75 mol) and AIBN (12.4 g, 0.075 mol) with stirring, the mixture was stirred at 80~85°C until **IM5** consumed. The reaction mixture was evaporated at <55°C to give 338 g crude **De-Bn-IM7**. The crude **De-Bn-IM7** was purified by column chromatography providing 82.5 g of **De-Bn-IM7** with 91% GC purity and 111.5 g mixture of ***cis***- **De-Bn-IM7** and **De-Bn-IM7**.

^1H NMR (300MHz, $CDCl_3$): δ 6.48 – 6.40 (m, 1H), 6.27 – 6.13 (m, 1H), 6.01 (dd, *J* = 19.3, 5.1 Hz, 1H), 5.55 (dtt, *J* = 15.4, 11.9, 1.7 Hz, 1H), 4.34 – 4.22 (m, 1H), 2.20 – 2.11 (m, 2H), 1.55 – 1.43 (m, 6H), 1.30 (dq, *J* = 14.0, 7.1 Hz, 6H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.90 (dd, *J* = 14.5, 7.3 Hz, 15H)

m/z (ES-API, Neg): 451, 495 ($M+HCOO^-$)

EXAMPLE 7

*Step 7 Synthesis **IM7** (((1E, 5E)-3-(benzyloxy)-4,4-difluoroocta-1,5-dienyl)tributylstannane)*

To a mechanically stirred mixture of NaH (4.0 g, 60%, 0.1 mol) in DMF (170 mL) was added a solution of **De-Bn-IM7** (42 g, 93.1 mmol) in DMF (20 mL) at -10 ~0°C, the reaction mixture was stirred at this temperature for 1 h, a solution of BnBr (16.7 g, 97.7 mmol) in DMF (20 mL) was added dropwise into the reaction mixture at -10~0°C until **De-Bn-IM7** consumed. Water (210 mL) was added and the mixture was extracted twice with MTBE (210 mL each). The combined organic layer was washed once with sat. aq. NH_4Cl (210 mL), once with water (210 mL) and once with brine (210 mL) and then concentrated at <45°C under reduced pressure to give 52.3 g of crude **IM7** with 91.1 % HPLC purity.

^1H NMR (300MHz, $CDCl_3$): δ 7.39 – 7.26 (m, 5H), 6.38 (d, J = 19.2 Hz, 1H), 6.19 – 6.09 (m, 1H), 5.88 (dd, J = 19.2, 6.8 Hz, 1H), 5.60 (dtt, J = 15.4, 11.9, 1.7 Hz, 1H), 4.69 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 3.94 – 3.87 (m, 1H), 2.20 – 2.06 (m, 2H), 1.57 – 1.43 (m, 6H), 1.32 (dt, J = 15.0, 7.4 Hz, 6H), 1.02 (t, J = 7.4 Hz, 3H), 0.91 (q, J = 7.5 Hz, 15H)

m/z (EI): 581 ([$M+K^+$], 100), 565 ([$M+Na^+$], 60)

EXAMPLE 8

Step 8 Synthesis ***IM7i*** (((1E, 5E)-3-(benzyloxy)-4,4-difluoroocta-1,5-dienyl)tributylstannane*)*

To a mechanically stirred mixture of NaH (0.49 g, 60%, 0.012 mol) in DMF (20 mL) was added a solution of **De-Bn-IM7** (5 g, 0.011 mol) in DMF (2.5 mL) at -10 ~0°C, the reaction mixture was stirred at this temperature for 1 h, a solution of 1-(bromomethyl)-4-methoxybenzene (2.34 g, 0.0116 mol) in DMF (2.5 mL) was added dropwise into the reaction mixture at -10~0°C until **De-Bn-IM7** consumed. Water (25 mL) was added and the mixture was extracted twice with MTBE (25 mL each). The combined organic layer was washed once with sat. aq. NH_4Cl (25 mL), once with water (25 mL) and once with brine (25 mL) and then concentrated at <45°C under reduced pressure to give 6.3 g of crude **IM7i**. The crude **IM7*i*** was purified by column chromatography providing 4.2 g of **IM7i** with 92% GC purity in 64% HPLC yield.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.42 – 6.31 (m, 1H), 6.13(d, *J* = 15.8 Hz, 1H), 5.87 (dd, *J* = 19.2, 6.7 Hz, 1H), 5.58 (dd, *J* = 26.5, 13.2 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 3.94 – 3.87 (m, 1H), 2.20 – 2.06 (m, 2H), 1.57 – 1.43 (m, 6H), 1.32 (dt, *J* = 15.0, 7.4 Hz, 6H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.91 (q, *J* = 7.5 Hz, 15H)

m/z (ES API, Pos): 611 ([M+K$^+$], 100), 595 ([M+Na$^+$], 70)

EXAMPLE 9

*Step 9 Synthesis **IM6*** ((E)-((4,4-difluorooct-5-en-1-yn-3-yloxy)methyl)benzene)

To a mechanically stirred mixture of **IM5** (100 g, 76% GC purity, 0.62 mol) and *t*-BuOK (71.4 g, 0.74 mol) in THF (300 mL) was added a solution of BnBr (116 g, 0.68 mol) in THF (200 mL) at 60 ~ 70°C, the reaction mixture was stirred at this temperature for 1 h until **IM5** was less than 5%. The mixture was cooled to 15~30°C, water (1 L) and MTBE (1 L) was added and the mixture was stirred for 15 min., the aqueous layer was extracted once with MTBE (500 mL). The combined organic layer was washed once with sat. aq. NH_4Cl (500 mL) and once with brine (500 mL) and then concentrated at <45°C under reduced pressure to give 155 g of crude **IM6** with 61% HPLC purity. The crude **IM6** was purified by column chromatography providing 86 g of **IM6** with 86% GC purity in 62% GC yield.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.37 – 7.31 (m, 5H), 6.35 – 6.22(m, 1H), 5.78 – 5.61 (m, 1H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.29 (dt, *J* = 8.0, 2.2 Hz, 1H), 2.55 (d, *J* = 8.0, 2.1 Hz, 1H), 2.22 – 2.09 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H)

EXAMPLE 10

Step 10 Synthesis ***IM7***

To the hot (80°C) solution of **IM6** (69 g, 86%, 0.28 mol) in toluene (340 mL,) was added Bu_3SnH (88 g, 0.30 mol) and AIBN (5.1 g, 0.03 mol) under stirring. The mixture was stirred at 80~85°C until **IM6** consumed. The reaction mixture was evaporated at <55°C to give 150 g crude **IM7**. The crude **IM7** was purified by column chromatography providing 75 g of **IM7** with 61.2% GC purity in 65% GC yield.

Step 1a: Synthesis COMPOUND (7)

(Z)-isopropyl7-((1R,2R,3R)-2-((1E,5E)-3-(benzyloxy)-4,4-difluoroocta-1,5-dienyl)-3-(tert-butyldimethyl-silyloxy)-5-oxocyclopentyl)hept-5-enoate)

EXAMPLE 11

To a mixture of CuCN (26.7 g, 0.3 mol) in THF (375 mL) at -10~0°C was added a solution of MeLi in diethoxymethane (91 mL, 3 M, 0.27 mol) dropwise under N_2. The reaction mixture was stirred at this temperature for 0.5 h. To a solution of **IM7** (147 g, 90% HPLC purity, 0.27 mol) in THF (750 mL) at -60 ~ -70°C was added a solution of MeLi in diethoxymethane (91 mL, 3 M, 0.27 mol) dropwise under N_2. The reaction mixture was stirred at this temperature until **IM7** was consumed. The prepared MeCu(CN)Li solution was added dropwise into the reaction at -40 ~ -50°C for another 0.5 h. Solution of compound (1) (82.7 g, 0.22 mol) in THF (375 mL) was then added dropwise into the former reaction solution at -50 ~ -60°C. The reaction mixture was stirred at this temperature until the reaction completed. Sat. aq. NH_4Cl (750 mL) was added at this temperature and the resulted mixture was then warmed to r.t and filtered, the filter cake was washed once with MTBE (750 mL). The filtrate was separated and the aqueous layer was extracted once with MTBE (375 mL). The combined organic layer was washed once with brine (750 mL) and then concentrated at <55°C under reduced pressure to give 228 g of crude compound (7), it was purified by column chromatography providing 107 g of compound (7) with 90% HPLC purity in 70 % yield based on the compound (1).

EXAMPLE 12

To a solution of **IM7** (5 g, 9.2 mmol) in THF (30 mL) at -60 ~ -70°C was added a solution of MeLi in diethoxymethane (3.1 mL, 3 M, 9.3 mmol) dropwise under N_2. The reaction mixture was stirred at this temperature until **IM7** consumed. Lithium 2-thienylcyanocuprate (37 mL, 0.25 M, 9.25 mmol) was added dropwise under N_2. The reaction mixture was stirred at this temperature for 1 h. Solution of compound (1) (2.8 g, 7.4 mmol) in THF (20 mL) was then added dropwise into the former reaction solution at -50 ~ -60°C. The reaction mixture was stirred at this temperature until the reaction completed. Sat. aq. NH_4Cl (15 mL) was added at this temperature and the resulted mixture was then warmed to r.t. and filtered, the filter cake was washed once with EtOAc (25 mL). The filtrate was separated and the aqueous layer was extracted once with EtOAc (25 mL). The combined organic layer was washed once with brine (25 mL) and then concentrated at <55°C under reduced pressure to give 8.2 g of crude compound (7) with 29.5% HPLC purity in 51.8% HPLC yield based on compound (1).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 6.24 – 6.10 (m, 1H), 5.81 – 5.69 (m, 1H), 5.68 – 5.50 (m, 2H), 5.49 – 5.27 (m, 2H), 4.99 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.68 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.52 (dd, *J* = 12.0, 5.9 Hz, 1H), 4.14 – 4.04 (m, 1H), 4.04 –3.92 (m, 1H), 2.74 – 2.66 (m, 1H), 2.65 – 2.51 (m, 2H), 2.49 – 2.28 (m, 2H, H8), 2.28 – 1.96 (m, 5H), 1.75 – 1.58 (m, 2H), 1.30 – 1.23 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 6H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.05 (dd, *J* = 5.9, 3.4 Hz, 6H)

m/z (API-ES, Pos): 655 ([M+Na$^+$], 100)

EXAMPLE 13

Step 1b: Synthesize of compound (7i)

((Z)-isopropyl7-((1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-2-((1E,5E)-4,4-difluoro-3-(4-methoxybenzyloxy)octa-1,5-dienyl)-5-oxocyclopentyl)hept-5-enoate)

To a mixture of CuCN (0.77 g, 8.5 mmol) in THF (10 mL) at -10~0°C was added a solution of MeLi in diethoxymethane (2.6 mL, 3 M, 7.8 mmol) dropwise under N_2. The reaction mixture was stirred at this temperature for 0.5 h. To a solution of **IM7*i*** (4.1 g, 92% HPLC purity, 7.8 mmol) in THF (20 mL) at -60 ~ -70°C was added a solution of MeLi in diethoxymethane (2.6 mL, 3 M, 7.8 mmol) dropwise under N_2. The reaction mixture was stirred at this temperature until **IM7i** consumed. The prepared MeCu(CN)Li solution was added dropwise into the reaction at -40 ~ -50°C for another 0.5 h. Solution of compound (1) (2.37 g, 6.2 mmol) in THF (10 mL) was then added dropwise into the former reaction solution at -50 ~ -60°C. The reaction mixture was stirred at this temperature until the reaction completed. Sat. aq. NH_4Cl (20 mL) was added at this temperature and the resulted mixture was then warmed to r.t. and filtered, the filter cake was washed once with MTBE (20 mL). The filtrate was separated and the aqueous layer was extracted once with MTBE (10 mL). The combined organic layer was washed once with brine (20 mL) and then concentrated at <55°C under reduced pressure to give 6.8 g of crude compound (7i), it was purified by column chromatography providing 2.3 g of compound (7i) with 88.6% HPLC purity in 51 % HPLC yield based on compound (1).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 2H), 6.91 – 6.83 (m, 2H), 6.25 – 6.08 (m, 1H), 5.72 (ddd, *J* = 17.3, 12.8, 4.8 Hz, 1H), 5.65 – 5.50 (m, 2H), 5.49 – 5.28 (m, 2H, H5), 4.99 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.62 (dd, *J* = 11.6, 2.3 Hz, 1H), 4.45 (dt, *J* = 11.6, 5.6 Hz, 1H), 4.17 – 4.02 (m, 1H), 4.02 – 3.89 (m, 1H), 3.81 (s, 3H), 2.74 – 2.50 (m, 2H), 2.49 – 1.96 (m, 9H), 1.73 – 1.59 (m, 2H), 1.28 (dd, *J* = 9.6, 4.4 Hz, 2H), 1.21 (d, *J* = 6.3 Hz, 6H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.05 (dd, *J* = 6.0, 3.3 Hz, 6H).

m/z (API-ES, Pos): 680 ($[M+NH_4]^+$, 100), 664 (M^+, 10)

Step 2: Synthesize of compound (8)

(Isopropyl7-((1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-2-(4,4-difluoro-3-hydroxyoctyl)-5-oxocyclopentyl)heptanoate)

EXAMPLE 14

The former prepared **compound (7)** (57 g, 91% HPLC purity, 0.90 mol), 10% of Pd/C (5.7 g, 53% of H_2O) and EtOAc (570 mL) was heated to 60°C at 0.4 MPa under H_2, the reaction was stirred until **compound (7)** consumed. Then the reaction mixture was filtered through a plug of celite and the filter cake was washed once with EtOAc (285 mL), the filtrate was then concentrated at <55°C under reduced pressure to give 54 g of **compound (8)**. The residue was purified by column chromatography (EtOAc : *n*-heptane = 1 : 10) to isolate 47 g **compound (8)** in 96% crude yield.

EXAMPLE 15

The former prepared **compound (7i)** (2.3 g, 89% HPLC purity, 3.5 mmol), 10% of Pd/C (0.23 g, 40% of H_2O) and EtOAc (23 mL) was heated to 60°C at 0.4 MPa under H_2, the reaction was stirred until **compound (7i)** consumed. The reaction mixture was then filtered through a plug of celite and the filter cake was washed once with EtOAc (12 mL), the filtrate was then concentrated at <55°C under reduced pressure to give 2.0 g of **compound (8)**.

^1H NMR (300MHz, $CDCl_3$): δ 5.07 – 4.91 (m, 1H), 4.14 – 4.00 (m, 1H), 3.78 – 3.58 (m, 1H), 2.65 – 2.54 (m, 1H), 2.33 (dd, *J*=6.3, 30.2 Hz, 1H), 2.25 (t, *J*= 7.5 Hz, 3H), 2.17 (dd, *J*=6.7, 5.3 Hz, 1H), 2.02 – 1.71 (m, 7H), 1.67 – 1.25 (m, 14H), 1.22 (d, *J*=6.3, 6H), 0.93 (t, *J*=7.2 Hz, 3H), 0.89 (d, *J*=1.5 Hz, 9H), 0.07 (dd, *J*=9.3, 2.6 Hz, 6H) m/z (API-ES, Pos): 549 ($M+H^+$, 100)

EXAMPLE 16

Step 3: Synthesize of compound (9)

(Isopropyl7-((1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-2-(4,4-difluoro-3-oxooctyl)-5-oxocyclopentyl)heptanoate)

A solution of oxalyl chloride (1.27 g, 10.0 mmol) in DCM (20 mL) was cooled to -60 ~ -70°C, DMSO (1.56 g, 20.0 mmol) in DCM (5 mL) was added dropwise and the solution was stirred for 30 min. A solution of **compound (8)** (5.0 g, 9.1 mmol) in DCM (10 mL) was added dropwise and the mixture was stirred for 1 h at -60 ~ -70°C. Et_3N (3.04 g, 30.0 mol) was added dropwise into the mixture and the reaction stirred at this temperature until the reaction completed. The mixture warmed to 0°C, water (50 mL) was added to the solution and the mixture was stirred for 5 min. and then separated. The aqueous layer was extracted with DCM (50 mL). The combined organic layer was washed once with sat. NH_4Cl (50 mL), once with water (50 mL) and then concentrated at <50°C under reduced pressure to give 4.57 g **compound (9)** with 87% HPLC purity in 91% HPLC yield.

^{1}H NMR (300MHz, $CDCl_3$): δ 5.09 – 4.91 (m, 1H), 4.03 (q, *J*=6.7, 1H), 3.00 – 2.73 (m, 2H), 2.60 (ddd, *J*=18.1, 6.6, 1.1 Hz, 1H), 2.25 (t, *J*=7.5, 2H), 2.20 (d, *J*=7.2 Hz, 1H), 2.14 (d, *J*=7.2 Hz, 1H), 2.10 – 1.25 (m, 21H), 1.22 (d, *J*=6.3 Hz, 6H), 0.92 (t, *J*=6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (d, *J*=8.6, 6H)

m/z (EI): 547 ($M+H^+$, 100), 569 ($M+Na^+$, 45)

EXAMPLE 17

Step 4a: Synthesize ofcompound (10)

(7-((1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-2-(4,4-difluoro-3-oxooctyl)-5-oxocyclo pentyl)heptanoic acid)

To a solution of **compound (9)** (5.0 g, 9.14 mmol) in acetone (15 mL) and pH 7.0 buffer (0.5% NaH_2PO_4 and adjust pH to 7.0 with 1 N NaOH; 35 mL) was added Lipase PS SD (0.5 g) stirred at 50°C until **compound (9)** mostly consumed, the reaction filtrated through a plug of silica gel and wash with MTBE (100 mL), the filtrate washed twice with water (50 mL x 2), then concentrate at <40°C under reduced pressure to give 4.78 g crude compound (10).

^{1}H NMR (300MHz, $CDCl_3$): δ: 4.03 (q, *J*=6.7 Hz, 1H), 3.00 – 2.72 (m, 2H), 2.66 – 2.55 (dd, *J*=12.3 Hz, 7.5 Hz, 1H), 2.34 (t, *J*=7.5, 2H), 2.17 (dd, *J*=18.1Hz, 7.3Hz, 1H), 2.08 – 1.17 (m, 22H), 0.92 (t, *J*=6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (d, *J*=8.6, 6H)

m/z (ES-API, Neg): 503 ($[M-H]^-$, 35), 371(100)

EXAMPLE 18

Step 4b: Synthesize of iPr-Lubiprostone

isopropyl7-((2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxo-octahydrocyclopenta[b]pyran-5-yl)heptanoate

To a solution of **compound (9)** (1.0 g, 1.8 mmol) in MeCN (10 mL), TFA (1.0 g, 8.8 mmol) was added and the mixture was stirred at 15~30°C for 16 h, TLC analysis showed **compound (9)** was less than 20% . Water (10 mL) and MTBE (10 mL) were then added and stirred for 5 min. and then separated. The aqueous layer was extracted once with MTBE (10 mL). The combined organic layer was washed twice with water (10 mL × 2), once with sat. aq. $NaHCO_3$ (10 mL) and then concentrated at <50°C under reduced pressure to give 0.85 g crude **iPr-Lubiprostone**.

EXAMPLE 19

Step 5a: Synthesize of Lubiprostone via compound (10)

(7-((2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxo-octahydrocyclopenta-[b]pyran-5-yl)heptanoic acid)

To a solution of compound (10) (3.6 g, 7.14 mmol) in MeCN (54 mL), H_2SO_4 (2 mol /L, 3.57 mL, 7.14 mmol) was added and the mixture was stirred at 15°C±5 °C until compound (10) consumed. Water (54 mL) was added and extracted twice with MTBE (36 mL x 2). The combined organic layer was washed once with sat. aq. $NaHCO_3$ (36 mL), once with water (36 mL) and dried with anhydrous $MgSO_4$ and then concentrated at <40°C under reduced pressure to give 2.58 g crude product with 65 % HPLC purity, it was purified by column chromatography to provide 1.3 g Lubiprostone with 80% HPLC purity. Lubiprostone (0.5 g, 80% HPLC purity) was dissolved in MTBE (0.5 mL) at 20~30°C and *n*-heptane (2 mL) was then cooled to 0~10°C with vigorously stirring for 2 h. The solid lubiprostone was filtrated and washed with *n*-heptane (2 mL), dried at 40°C under vacuum to give 0.32 g solid lubiprostone.

^{1}H NMR (300MHz, $CDCl_3$): δ 4.19 (ddd, J = 11.4, 10.0, 7.2 Hz, 1H), 2.58 (dd, J = 17.6, 7.2 Hz, 1H), 2.35 (t, J = 7.4 Hz, 2H), 2.26 (dd, J = 17.7, 11.6 Hz, 1H), 2.10 – 1.75 (m, 7H), 1.72 – 1.45 (m, 7H), 1.45 – 1.22 (m, 8H,), 0.94 (t, J = 7.3 Hz, 3H)

m/z (ES-API, Neg): 389 ($[M-H]^-$, 100)

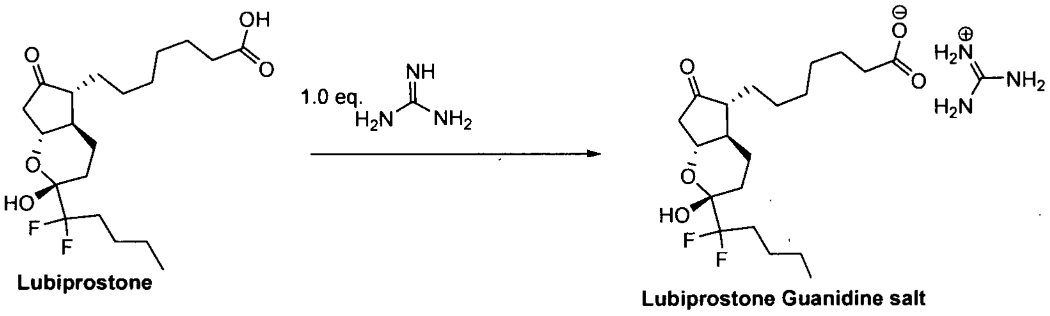
EXAMPLE 20

Step 5b: Synthesize of Lubiprostone via the isopropyl ester of lubiprostone

To a solution of the isopropyl ester of lubiprostone (0.3 g), Lipase PS SD (0.3 g) in acetone (1.5 mL) and pH 8.0 Buffer (2 mL) was stirred at 50~60°C for 22 h. The reaction solution was concentrated at <50°C under reduced pressure to give 0.4 g crude product, water (6 mL) and MTBE (6 mL) was added into the residual and stirred for 5 mins, separate and the aqueous layer extracted with MTBE (6 mL) . The combined organic layer was washed once with water (6 mL) and once with brine (6 mL) and then concentrated at <50°C under reduced pressure to give 0.3 g crude product.

EXAMPLE 21

Step 6: Synthesis Lubiprostone salt.



To a solution of guanidine hydrochloride (10 g, 0.105 mol) in MeOH (100 mL) was added a solution of MeONa (4.0 g, 0.105 mol) in MeOH (50 mL) at about 25. The solution was stirred at this temperature for 1 h and a white solid precipitated. The resulting slurry was filtered to remove the precipitated NaCl providing a solution of guanidine in MeOH. To a solution of lubiprostone (0.2 g, 0.513 mmol) in MeOH (2 mL) was added the solution of guanidine in MeOH (0.73 mL, 0.511 mmol) at about 25°C. The mixture was stirred at this temperature for 1 h and then the solvent was evaporated. MTBE (2 mL) was added to the residue at <30°C and was evaporated under vacuum. This was repeated two more times and then THF (2 mL) was added causing a white solid to form. After stirring at about 25°C the solid was isolated by filtration to give the guanidine salt of lubiprostone as a white solid. ^{1}H NMR analysis of the white solid showed that the methylene signal alpha to the carboxylate group had shifted as compared to free lubiprostone.

^{1}H NMR (300MHz, CD_3OD): δ = 4.22 – 4.10 (m, 1H), 2.48 (dd, J=17.4, 7.2 Hz, 1H), 2.19 (dd, J=17.4, 11.7 Hz, 1H), 2.16 (t, J=7.5 Hz, 2H), 2.10 – 1.26 (m, 22H), 0.93 (t, J = 7.2 Hz, 3H).

We claim

1. A process for the synthesis of lubiprostone comprising:

a) coupling of cyclopentenone **I** with an organocopper compound **III** to provide a compound of formula **IV**,
b) reacting the compound of formula **IV** with hydrogen in the presence of a catalyst to provide a compound of formula **V**,
c) oxidising the compound of formula **V** to provide a compound of formula **VI**, and
d) converting the compound of formula **VI** to lubiprostone.

2. The process of claim 1, wherein step d) comprises the hydrolysis of the isopropyl ester by aid of an enzyme.

3. The process of claim 1, wherein step d) comprises a step of converting compound of formula **VI** to a compound of formula **VII.**

4. A process for the synthesis of a compound of formula **III**, comprising
a) reacting the compound of formula **VIII** with a silyl protected metal acetylene compound of formula **XI**, wherein M is a metal ion, to provide a compound of formula **IX**,
b) treating the compound of formula **IX** with a reducing agent and a desilylating agent to provide a compound of formula **X**,
c) converting the compound of formula **X** to a compound of formula **II**, and
d) converting the compound of formula **II** to **III**.

5. The process of claim 4 wherein M of the compound of formula **XI** is Li.

6. The process of claim 4 wherein the reaction of compound of formula **VIII** with a silyl protected metal acetylene compound of formula **XI** is conducted in the presence of a Lewis acid compound.

7. The process of claim 6 wherein the Lewis acid compound is BF_3.

8. The process of claim 4 wherein the reducing agent in step b) is a hydride reducing agent.

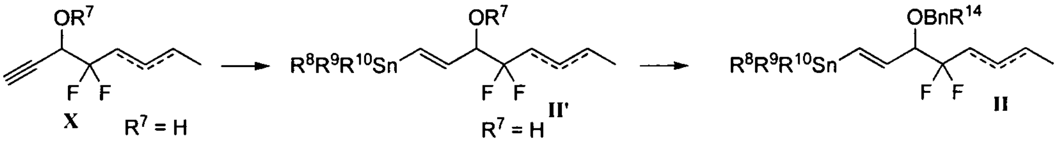
9. The process of claim 8 wherein the hydride reducing agent is a metal hydride, wherein the metal is selected from the group consisting of aluminium, boron, and ruthenium.

10. The process of claim 4 wherein the desilylating agent in step b) is an alkoxide or fluoride reagent.

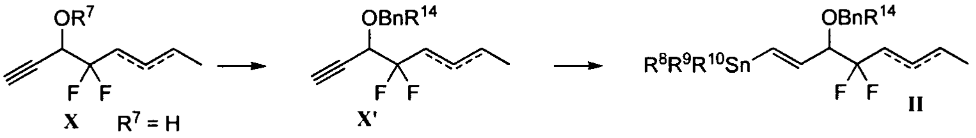
11. The process of claim 10 wherein the alkoxide reagent is NaOMe.

12. The process of claim 4 wherein step b) is conducted in one reaction vessel without isolation of an intermediate.

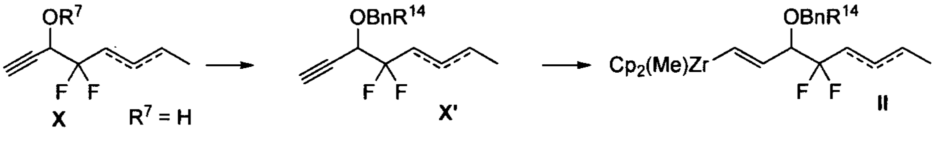
13. The process of claim 4 wherein step c) of converting the compound of formula **X** to a compound of formula **II** comprises first attaching $SnR^8R^9R^{10}$ by reaction of **X** with a trisubstituted tin hydride in the presence of an initiation agent to produce a compound of formula **II'**, and converting R^7 from H to $R^{14}Bn$ by reaction of the compound of formula **II**' with a base and a benzylation agent to produce the compound of formula **II** .



14. The process of claim 4 wherein step c) of converting the compound of formula **X** to a compound of formula **II** comprises first converting R^7 from H to $R^{14}Bn$ by reaction of the compound of formula **X** where R^7 is H with a base and a benzylation agent to produce a compound of formula **X'** and then installing $SnR^8R^9R^{10}$ by reaction of the compound of formula **X'** with a trisubstituted tin hydride in the presence of a an initiation agent to produce the compound of formula **II.**

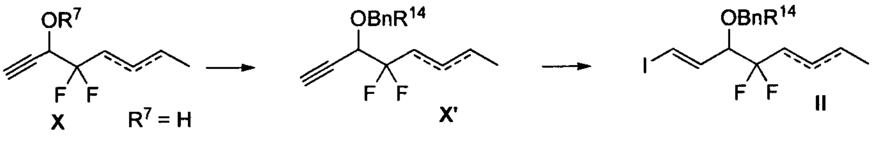


15. The process of claim 4 wherein step c) of converting the compound of formula **X** to a compound of formula **II** comprises first converting R^7 from H to $R^{14}Bn$ by reaction of compound of formula **X** where R^7 is H with a base and a benzylation agent to produce a compound of formula **X'**, and then installing $ZrCp_2Me$ by reaction of the compound of formula **X'** with $Cp_2Zr(H)Cl$ followed by MeLi to produce the compound of formula **II.**

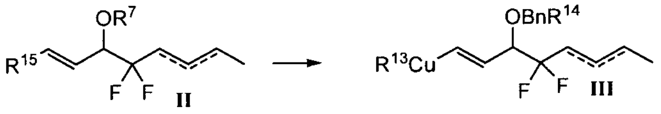


16. The process of claim 4 wherein step c) of converting the compound of formula

X to a compound of formula **II** comprises first converting R^7 from H to R^{14}Bn by reaction of the compound of formula **X** where R^7 is H with a base and a benzylation agent to produce a compound of **X'** and then installing I by reaction of the compound of **X'** with Cp_2ZrCl_2, *t*-BuMgCl followed by I_2 to produce the compound of formula **II**.

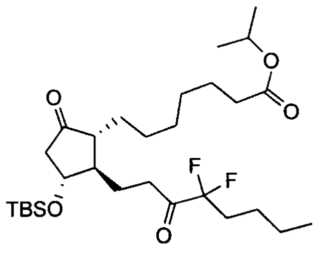


17. The process of claim 4 wherein step d) of converting the compound of formula **II** to **III** comprises reacting the compound of formula **II** wherein R^{15} is $SnR^8R^9R^{10}$ or I and R^7 is BnR^{14} with an organo metallic compound followed by MeCu(CN)Li or 2-thienylCu(CN)Li.



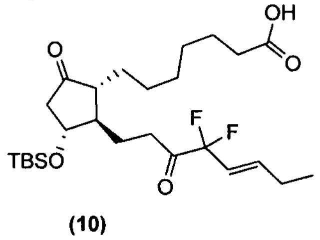
18. The process of claim 17 wherein the organo metallic compound is *t*-BuLi, *s*-BuLi or *n*-BuLi.

19. A compound of formula **(9)** (isopropyl 7-((1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-2-(4,4-difluoro-3-oxooctyl)-5-oxocyclopentyl)heptanoate).



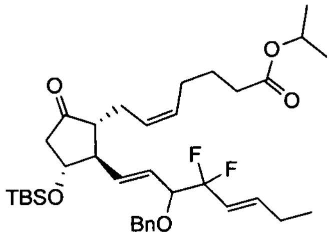
(9)

20. A compound of formula (10) (7-((1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-2-(4,4-difluoro-3-oxooctyl)-5-oxocyclopentyl)heptanoic acid).



(10)

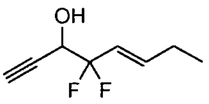
21. A compound of formula **(7)** ((Z)-isopropyl 7-((1R,2R,3R)-2-((1E,5E)-3-(benzyloxy)-4,4-difluoroocta-1,5-dienyl)-3-(tert-butyldimethylsilyloxy)-5-oxocyclopentyl)hept-5-enoate)



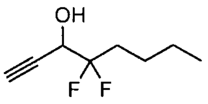
(7)

22. A compound of formula **X** wherein R^7 is H, and the double bond is located between C5 and C6; between C6 and C7, or is not present; and is selected from the group consisting of:

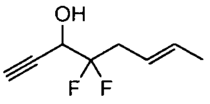
IM5 ((E)-4,4-difluorooct-5-en-1-yn-3-ol); a compound of formula **IM5b** (*i.e.,* **X**; R^7=H; 4,4-difluorooct-1-yn-3-ol); a compound of formula **IM5c** (*i.e.,* **X**; R^7=H, C6-C7 double bond; (E)-4,4-difluorooct-6-en-1-yn-3-ol).



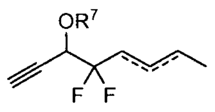
IM5



IM5b



IM5c



X

23. A process for purifying lubiprostone, comprising the step of forming the salt of lubiprostone.

24. The process of claim 23, wherein the salt is the guanidine salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/001614

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D311/-; C07D307/-; C07C31/-; C07C69/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI; EPODOC; CNKI; CNPAT; Registry; CAplus; CASreact: lubiprostone, Ru 0211, Spi 0211, cyclopentanone, organocopper, +copper+, +cuprous, protecting group?, salt, guanidine (in both English and Chinese words)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO2010083597A1(APOTEX PHARMACHEM INC.) 29 July 2010(29.07.2010) see scheme 2 on page 6 and example 26 on pages 54-55 in the description	23-24 1-22
X A	WO2006093348A2(SUCAMPO AG) 08 Sep. 2006(08.09.2006) see synthesis example 2 on pages 52-53 in the description	19 1-18, 20-24
X A	WO2006080549A2(SUCAMPO AG) 03 Aug. 2006(03.08.2006) see synthesis example 1 on pages 48-50 in the description	20-21 1-19, 22-24
X A	WO9501179A1(BRIGHAM & WOMEN'S HOSPITAL), 12 Jan. 1995(12.01.1995) see compound k on page 47 in the description	22 1-21, 23-24

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 03 July 2011(03.07.2011)	Date of mailing of the international search report **21 Jul. 2011 (21.07.2011)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer JIANG, Shichao Telephone No. (86-10)82245589

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/001614

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2010083597A1	29.07.2010	NONE	
WO2006093348A2	08.09.2006	AU2006219152B2	24.02.2011
		AU2006219152A1	08.09.2006
		BR200609393A2	30.03.2010
		TW200714283A	16.04.2007
		NZ561414A	29.10.2010
		EP1853271A2	14.11.2007
		NO20074999A	03.12.2007
		CN101132797A	27.02.2008
		MX2007010746A	01.09.2007
		EP1853271B1	01.12.2010
		EP2329825A1	08.06.2011
		US2006247317A1	02.11.2006
		KR20070108934A	13.11.2007
		JP2008531468T	14.08.2008
		DE602006018583D1	13.01.2011
		EP2308495A1	13.04.2011
WO2006080549A2	03.08.2006	AU2006209072B2	24.02.2011
		MX2007009094A	28.02.2009
		EP1841433A2	10.10.2007
		JP2008528440T	31.07.2008
		KR20070107065A	06.11.2007
		CN101146541A	19.03.2008
		TW200642690A	16.12.2006
		NO20074332A	17.10.2007
		IN200703745P4	23.11.2007
		NZ556710A	27.08.2010
		AU2006209072A1	03.08.2006
		BR200607084A2	04.08.2009
		US2006194880A1	31.08.2006

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/001614

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO9501179A1	12.01.1995	AU7215294A	24.01.1995
		US6100296A	08.08.2000

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/001614

A. CLASSIFICATION OF SUBJECT MATTER

C07D311/94 (2006.01) i
C07D307/935 (2006.01) i
C07C31/38 (2006.01) i
C07C69/738 (2006.01) i