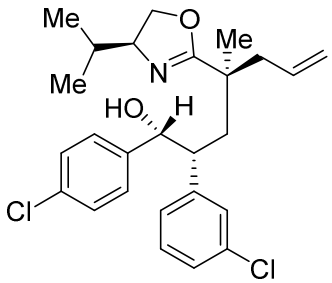
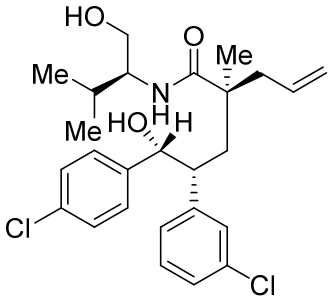
WO 2011/153509 (Example No. 362) and is being investigated in human clinical trials for the treatment of various cancers. The present invention provides improved processes for preparing Compound A as well as intermediate compounds thereof.

SUMMARY ~~OF THE INVENTION~~

[0005a] In one aspect, the present disclosure provides process of preparing compound

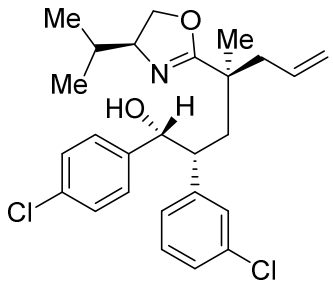


, the process comprising: reacting



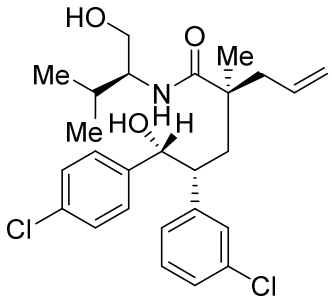
with methoxymethylene-*N*,*N*-dimethyliminium methyl sulfate, wherein the reaction is carried out in the presence of a base.

[0006] In one ~~embodiment~~example, the present ~~invention~~ disclosure provides a process of preparing the following compound **(DHO)**



DHO,

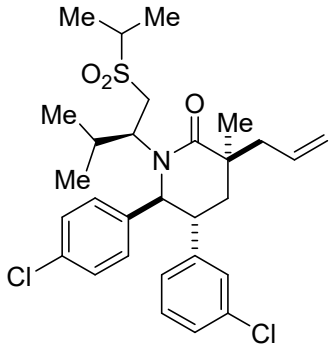
the process comprising: reacting compound **(ABA)**



ABA

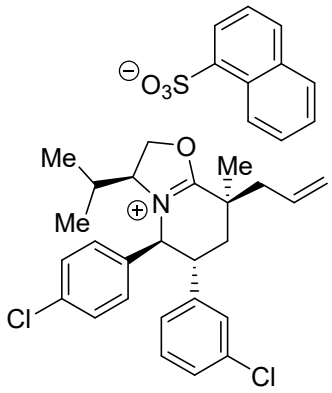
with methoxymethylene-*N*,*N*-dimethyliminium methyl sulfate. In an ~~embodiment~~example, this reaction is carried out in the presence of a base. In a particular ~~embodiment~~example, the base is an alkali metal salt or an alkaline earth metal salt, such as, for example, KOAc, NaOAc, LiOAc, $CaCO_3$ and K_2CO_3. In an ~~embodiment~~example, the reaction is carried out in a solvent. In a particular ~~embodiment~~example, the solvent is benzene, toluene, o-xylene, m-xylene, p-xylene, hexane, tetrahydrofuran, ethyl acetate, HMPA, HMPT, DMSO, ethylene glycol, DME, DMF, diethyl ether, acetonitrile, methanol, ethanol, acetone or mixtures thereof.

[0007] In one ~~embodiment~~example, the present ~~invention~~disclosure provides a process of preparing compound **(SUL)**



SUL,

the process comprising: reacting compound



with an isopropylation agent such as, but not limited to, isopropylsulfinate zinc chloride. In an ~~embodiment~~example, the reaction is carried out in presence of an alkaline earth metal salt. In a particular ~~embodiment~~example, the alkaline earth metal salt is a magnesium salt, such as, but not limited to, $MgBr_2$ or $MgCl_2$. In a particular ~~embodiment~~example, the isopropylation agent is generated *in situ* from isopropyl magnesium chloride. In an ~~embodiment~~example, the reaction is carried out at a temperature between 100 ºC and 200 ºC, such as between 100 ºC and 150 ºC, such as at 120 ºC or between 150 ºC and 200 ºC, such as at 180 ºC.

[0008] In one ~~embodiment~~example, the present ~~invention~~disclosure provides a crystalline form of (1R,2R,4S)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-4-((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4-methylhept-6-en-1-ol (**DHO**) characterized by a reflection X-ray powder diffraction pattern comprising peaks at 7.3° ± 0.2° 2θ, 14.5° ± 0.2° 2θ, 15.8° ± 0.2° 2θ, 15.9° ± 0.2° 2θ, and 23.1° ± 0.2° 2θ. In an ~~embodiment~~example, the reflection X-ray powder diffraction pattern of the **DHO** crystalline further comprises peaks at 8.5° ± 0.2°

2θ, 10.0° ± 0.2° 2θ, 11.0° ± 0.2° 2θ, 13.4° ± 0.2° 2θ, 18.8° ± 0.2° 2θ, and 22.0° ± 0.2° 2θ. In an ~~embodiment~~example, the reflection X-ray powder diffraction pattern of the **DHO** crystalline further comprises one or more peaks at 6.3° ± 0.2° 2θ, 10.5° ± 0.2° 2θ, 11.5° ± 0.2° 2θ, 12.8° ± 0.2° 2θ, 14.8° ± 0.2° 2θ, 15.2° ± 0.2° 2θ, 17.0° ± 0.2° 2θ, 17.5° ± 0.2° 2θ, 17.8° ± 0.2° 2θ, 18.4° ± 0.2° 2θ, 19.0° ± 0.2° 2θ, 19.7° ± 0.2° 2θ, 19.9° ± 0.2° 2θ, 20.7° ± 0.2° 2θ, 21.2° ± 0.2° 2θ, 21.3° ± 0.2° 2θ, 22.4° ± 0.2° 2θ, 23.6° ± 0.2° 2θ, 24.2° ± 0.2° 2θ, 24.9° ± 0.2° 2θ, 25.7° ± 0.2° 2θ, 26.3° ± 0.2° 2θ, 27.0° ± 0.2° 2θ, 28.3° ± 0.2° 2θ, 28.7° ± 0.2° 2θ, 29.3° ± 0.2° 2θ, 29.7° ± 0.2° 2θ, 30.8° ± 0.2° 2θ, 31.4° ± 0.2° 2θ, 31.8° ± 0.2° 2θ, 33.0° ± 0.2° 2θ, 34.2° ± 0.2° 2θ, 35.8° ± 0.2° 2θ, 37.0° ± 0.2° 2θ, and 37.5° ± 0.2° 2θ. In an ~~embodiment~~example, the crystalline form of **DHO** is a crystalline anhydrate. In an ~~embodiment~~example, the reflection x-ray powder diffraction of the crystalline **DHO** is carried out using Cu-Kα radiation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The following figures represent specific embodiments of the invention as described and are not intended to otherwise limit the invention.

[0010] FIG. 1 illustrates the conversion rate of (3*S*,5*R*,6*R*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2*H*-pyran-2-one **(DLAC)** to (*S*)-2-((2*R*,3*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-3-hydroxypropyl)-*N*-((*S*)-1-hydroxy-3-methylbutan-2-yl)-2-methylpent-4-enamide **(ABA)** over time at 60 ºC.

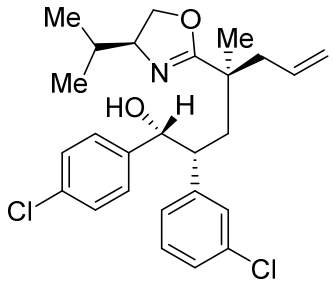
[0011] FIG. 2 illustrates the conversion rate of **DLAC** to **ABA** over time at 115 ºC.

[0012] FIG. 3 illustrates the solubility of (1*R*,2*R*,4*S*)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-4-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4-methylhept-6-en-1-ol (**DHO)** during the crystallization process at 25 °C.

[0013] FIG. 4 illustrates the yield of (3S,5R,6S)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methylpiperidin-2-one **(SUL)** over time using isopropylsulfinate magnesium chloride at 120 °C (14 mol% of water (vs (3S,5S,6R,8S)-8-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-isopropyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-a]pyridin-4-ium naphthalene-1-sulfonate, hemi toluene solvate (**OXOS**)) in the reaction mixture).

What is claimed is:

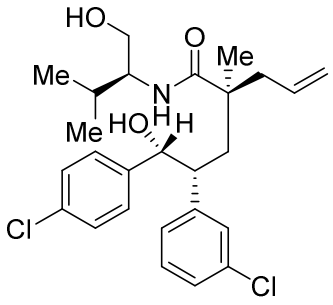
1. A process of preparing compound



,

the process comprising:

reacting



with methoxymethylene-*N*,*N*-dimethyliminium methyl sulfate~~.~~

~~2.~~ ~~The process of claim 1~~, wherein the reaction is carried out in the presence of a base.

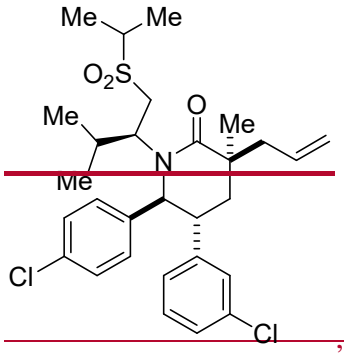
~~3.~~2.The process of claim ~~2~~1, wherein the base is KOAc, NaOAc, LiOAc, or K_2CO_3.

~~4.~~3.The process of claim ~~2~~1, wherein the base is NaOAc.

~~5.~~4.The process of any one of claims 1-~~3~~2, wherein the reaction is carried out in a solvent.

~~6.~~5.The process of claim ~~5~~4, wherein the solvent is toluene.

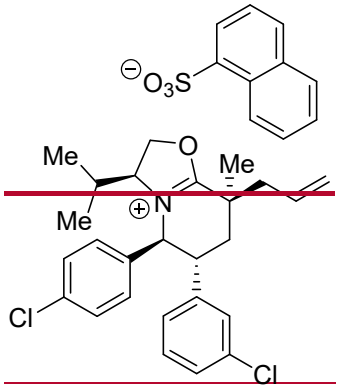
~~7. A process of preparing compound~~



~~,~~

~~the process comprising:~~

~~reacting~~



~~with isopropylsulfinate zinc chloride.~~

~~8. The process of claim 7, wherein the reaction is carried out in presence of a magnesium salt.~~

~~9. The process of claim 8, where the magnesium salt is $MgCl_2$.~~

~~10. The process of claim 7, wherein the isopropylsulfinate zinc chloride is generated *in situ* from isopropyl magnesium chloride.~~

~~11. The process of claim 7, wherein the reaction is carried out at a range of 100 °C to 150 °C.~~

12. The process of claim 7, wherein the reaction is carried out at a range of 150 ºC to 200 ºC.

13. A crystalline form of (1*R*,2*R*,4*S*)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-4-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4-methylhept-6-en-1-ol (**DHO**) characterized by a reflection X-ray powder diffraction pattern comprising peaks at 7.3° ± 0.2° 2θ, 14.5° ± 0.2° 2θ, 15.8° ± 0.2° 2θ, 15.9° ± 0.2° 2θ, and 23.1° ± 0.2° 2θ.

14. The crystalline form of claim 13, wherein the reflection X-ray powder diffraction pattern further comprises peaks at 8.5° ± 0.2° 2θ, 10.0° ± 0.2° 2θ, 11.0° ± 0.2° 2θ, 13.4° ± 0.2° 2θ, 18.8° ± 0.2° 2θ, and 22.0° ± 0.2° 2θ.

15. The crystalline form of claim 14, wherein the reflection X-ray powder diffraction pattern further comprises one or more peaks at 6.3° ± 0.2° 2θ, 10.5° ± 0.2° 2θ, 11.5° ± 0.2° 2θ, 12.8° ± 0.2° 2θ, 14.8° ± 0.2° 2θ, 15.2° ± 0.2° 2θ, 17.0° ± 0.2° 2θ, 17.5° ± 0.2° 2θ, 17.8° ± 0.2° 2θ, 18.4° ± 0.2° 2θ, 19.0° ± 0.2° 2θ, 19.7° ± 0.2° 2θ, 19.9° ± 0.2° 2θ, 20.7° ± 0.2° 2θ, 21.2° ± 0.2° 2θ, 21.3° ± 0.2° 2θ, 22.4° ± 0.2° 2θ, 23.6° ± 0.2° 2θ, 24.2° ± 0.2° 2θ, 24.9° ± 0.2° 2θ, 25.7° ± 0.2° 2θ, 26.3° ± 0.2° 2θ, 27.0° ± 0.2° 2θ, 28.3° ± 0.2° 2θ, 28.7° ± 0.2° 2θ, 29.3° ± 0.2° 2θ, 29.7° ± 0.2° 2θ, 30.8° ± 0.2° 2θ, 31.4° ± 0.2° 2θ, 31.8° ± 0.2° 2θ, 33.0° ± 0.2° 2θ, 34.2° ± 0.2° 2θ, 35.8° ± 0.2° 2θ, 37.0° ± 0.2° 2θ, and 37.5° ± 0.2° 2θ.

16. The crystalline form of claim 13, wherein the crystalline form is a crystalline anhydrate.

17. The crystalline form of any one of claims 13-16, wherein the peaks are present when the reflection x-ray powder diffraction is carried out using Cu-Kα radiation.