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Process For The Preparation Of 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid

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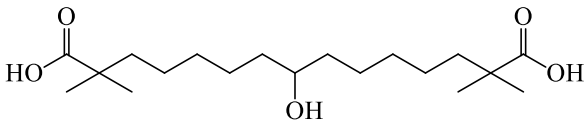
The present invention provides a process for the preparation of 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid represented by the following structural formula-1.



Formula-1

8-Hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid is commonly known as Bempedoic acid. It is approved by United States Food and Drug Administration in February 2020 and sold under the brand names NEXLETOL (Bempedoic acid alone) and NEXLIZET (combination product with Ezetimibe).

NEXLETOL and NEXLIZET contains Bempedoic acid, an adenosine triphosphate-citrate lyase (ACL) inhibitor and are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who requires additional lowering of LDL-C.

US7335799B2 describes Bempedoic acid and process for preparation thereof. This patent exemplified the synthesis of Bempedoic acid in example 6.20.

The process described in US7335799B2 involves longer hours for the completion of the reactions. Further, Bempedoic acid is reported as very viscous oil with low yield and very low HPLC purity (83.8%).

The active pharmaceutical ingredient with said properties such as viscous oily nature and low purity is not suitable for use in the preparation of pharmaceutical product.

In view of these drawbacks, the process reported in the US7335799B2 is neither cost effective nor suitable for manufacturing Bempedoic acid on commercial scale.

Therefore, there is a significant need in the art to develop a cost effective and commercially viable process for the preparation of Bempedoic acid which is suitable for the preparation of finished pharmaceutical product.

The "solvent" used in the present invention can be selected from but not limited to "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and the like; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and the like; "polar-aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcohol solvents" such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and the like; "polar solvents" such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

The first embodiment of the present invention provides a process for the preparation of crystalline 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid of formula-9, comprising;

a) providing a solution of compound of formula-9 in a solvent at a suitable temperature,
b) obtaining crystalline compound of formula-9.

The solvent in step-a) is selected from "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and the like; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and the like; "polar-aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like;

"alcohol solvents" such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and the like; "polar solvents" such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

The temperature in step-a) ranging from about 10^{o}C to reflux temperature of the solvent used.

In one aspect of the present invention, the solution in step-a) can be obtained by mixing compound of formula-9 with a solvent selected from those defined above. The said mixture can be optionally heated to a temperature ranges from about 30^{o}C to reflux temperature of the solvent used.

In another aspect, the solution in step-a) can be obtained directly from the chemical synthesis in which compound of formula-9 has been synthesized.

Obtaining crystalline compound of formula-9 in step-b) can be carried out by removal of the solvent from the solution.

Various techniques that can be used for the removal of the solvent includes but not limited to cooling the clear solution to lower temperatures to precipitate the solid followed by filtration, decantation, combining the solution with an anti-solvent followed by filtering the precipitated solid, distillation optionally under reduced pressure, evaporation, vacuum drying, concentration, centrifugation, filtration or by any other suitable techniques.

An aspect of the present invention provides a process for the preparation of crystalline compound of formula-9, comprising;

a) combining compound of formula-9 with a solvent,
b) heating the mixture to a suitable temperature,
c) cooling the mixture to a suitable temperature,
d) obtaining crystalline compound of formula-9.

Suitable temperature in step-b) ranges from about 25^{o}C to reflux temperature of the solvent used and suitable temperature in step-c) ranges from about 30^{o}C or below.

The second embodiment of the present invention provides a crystalline polymorph of compound of formula-9. The crystalline polymorph of compound of formula-9 of the present invention is characterized by its PXRD (powder X-ray diffraction) pattern having peaks at 6.2, 14.2, 15.6, 18.9, 19.8, 20.4, 24.6 and 26.1 ± 0.2º of 2-theta values.

The crystalline form of compound of formula-9 of the present invention is further characterized by its PXRD pattern as illustrated in figure-1.

The process of the present invention produces compound of formula-9 as a crystalline solid with high purity and the said crystalline compound is useful for the preparation of pure compound of formula-1.

The third embodiment of the present invention provides a process for the purification of 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid compound of formula-1, comprising;

a) treating compound of formula-1 with a base,
b) treating the reaction mixture of step-a) or the obtained base-addition salt with an acid to provide pure compound of formula-1.

The base in step-a) is selected from but not limited to "inorganic bases" selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide and the like; ammonia, “organic bases" like "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, lithium methoxide, lithium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; alkali metal and alkali earth metal salts of acetic acid such as sodium acetate, potassium acetate, magnesium acetate, calcium acetate and the like; organic amines like methyl amine, ethyl amine, n-propyl amine, isopropyl amine, n-butyl amine, iso-butyl amine, tert.butyl amine and the like; dialkyl amines such as dimethylamine, diethyl amine, dipropyl amine, dibutyl amine and the like; dicyclohexyl amine, benzyl amine, ethanolamine, diethanolamine, tromethamine and the like.

The solvent in step-a) & step-b) wherever necessary is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents such as water and the like or mixture of any of the afore mentioned solvents.

The acid in step-b) is selected from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, carbonic acid; and "organic acids" such as formic acid, acetic acid, trifluoroacetic acid, citric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

In an aspect of the third embodiment of the present invention, the base is ammonia, the acid is hydrochloric acid and solvent is water.

The process as described in the third embodiment of the present invention, wherein the reaction mixture comprising compound of formula-1 and base can be directly treated with an acid or when the base utilized in step-a) forms a salt with compound of formula-1, the said salt can be isolated from the reaction mixture as a solid by using conventional techniques and it can be further treated with an acid optionally in presence of a solvent as defined in the present invention to provide pure compound of formula-1.

A preferred aspect of the third embodiment of the present invention provides a process for the purification of compound of formula-1, comprising;

a) providing a mixture of compound of formula-1 and ammonia in a solvent,
b) treating the mixture with an acid to provide pure compound of formula-1.

Wherein the acid and the solvent are same as defined in the third embodiment of the present invention.

The compound of formula-9 and compound of formula-1 which are utilized in the present invention can be synthesized by a process comprising;

a) reacting compound of formula-2 with compound of formula-3 in presence of a base in a solvent to provide compound of formula-4,

b) treating compound of formula-4 with alkali metal iodide in presence of a solvent to provide compound of formula-5,

c) reacting compound of formula-5 with tosylmethyl isocyanide compound of formula-6 in presence of a base and solvent optionally in presence of a phase transfer catalyst to provide compound of formula-7,

d) treating compound of formula-7 with an acid optionally in presence of a solvent to provide compound of formula-8,

e) hydrolyzing the compound of formula-8 in presence of an acid or a base optionally in presence of a solvent to provide compound of formula-9,

f) reducing the compound of formula-9 with a reducing agent in a solvent to provide compound of formula-1,

g) purifying the compound of formul-1 from a solvent or mixture of solvents.

The base in step-a) & step-c) can be selected from but not limited to "inorganic bases" selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal amides" such as sodium amide, potassium amide, lithium amide and the like; “organic bases" like "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, lithium methoxide, lithium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; alkali metal and alkali earth metal salts of acetic acid such as sodium acetate, potassium acetate, magnesium acetate, calcium acetate and the like; "organolithium bases" such as methyl lithium, n-butyl lithium, lithium diisopropylamide (LDA) and the like; "organosilicon bases" such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) and the like or mixtures thereof. Alkali metal iodide in step-b) can be selected from NaI, KI, LiI and CsI. The phase transfer catalyst in step-c) can be selected from tetra alkyl ammonium halides/hydroxides.

The acid in step-d) & step-e) can be independently selected from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; and "organic acids" such as formic acid, acetic acid, trifluoroacetic acid, citric acid and the like.

The base in step-e) can be selected from but not limited to "inorganic bases" selected from “alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, lithium methoxide, lithium ethoxide and the like.

The reducing agent in step-f) can be selected from sodium borohydride, sodium aluminium hydride, lithium borohydride, lithium aluminium hydride, sodium cyano borohydride, sodium triacetoxy borohydride, vitride (Red-Al), diisobutyl aluminium hydride (DIBAL) and the like.

The solvent in step-a) to step-g) is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents such as water and the like or mixtures thereof.

The ethyl isobutyrate compound of formula-2a, 1-bromo-5-chloropentane compound of formula-3a and tosylmethyl isocyanide compound of formula-6 which are utilized in the present invention can be prepared by any of the processes known in the art or they can be procured from any of the commercial sources available.

The fourth embodiment of the present invention provides a process for the preparation of compound of formula-5, comprising treating compound of formula-4 with an alkali metal iodide in presence of a solvent system comprising hydrocarbon solvent, wherein the hydrocarbon solvent is selected from n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like or mixtures thereof.

In a first aspect of the fourth embodiment of the present invention, the solvent system comprises hydrocarbon solvent optionally in mixture with a second solvent selected from "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate; "polar-aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP); "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutyl ketone; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile; "alcohol solvents" such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol; water, formic acid, acetic acid or mixture of any of the afore mentioned solvents.

The process of the present invention provides highly pure compound of formula-1 having purity greater than 99%, preferably greater than 99.5%, more preferably greater than or equal to 99.7% as measured by HPLC.

Compound of formula-1 was analyzed by HPLC under the following conditions; Apparatus: A liquid chromatographic system equipped with variable wavelength UV detector; Column: Reliant C18, 250 mm X 4.6 mm, 5 µm or equivalent; Column temperature: 45°C; Wavelength: 225 nm; Injection volume: 40 µL; Elution: Gradient; Diluent: Acetonitrile: 0.01M Na_2HPO_4, pH 9.0 (70:30 v/v); Buffer preparation: Transfer 1.0 mL of Orthophosphoric acid (85%) into 1000 mL of milli-Q-water, adjust its pH to 2.0 ± 0.02 with diluted Ortho phosphoric acid (or) with dil. Potassium hydroxide. Mobile phase-A: Buffer (100%); Mobile phase-B: Transfer 900 mL of Acetonitrile and 100 mL of Water into a 1000 mL Mobile phase bottle, mix well and sonicate to degas it.

The crystalline form of compound of formula-1 of the present invention is useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used where at least a portion of compound of formula-1 is present in the composition in particular polymorphic form mentioned.

An aspect of the present invention provides the use of crystalline form of compound of formula-1 of the present invention for the preparation of various pharmaceutical formulations.

The other aspect of the present invention provides a pharmaceutical composition comprising crystalline form of compound of formula-1 of the present invention and at least one pharmaceutically acceptable excipient.

Another aspect of the present invention provides a method of treating or preventing a disease in a patient comprising administering to the said patient a finished dosage form comprising crystalline form of compound of formula-1 of the present invention.

The crystalline compound of formula-1 produced by the process of the present invention may have particle size distribution of D_{90} less than about 400 µm, preferably less than about 300 µm, more preferably less than about 200 µm.

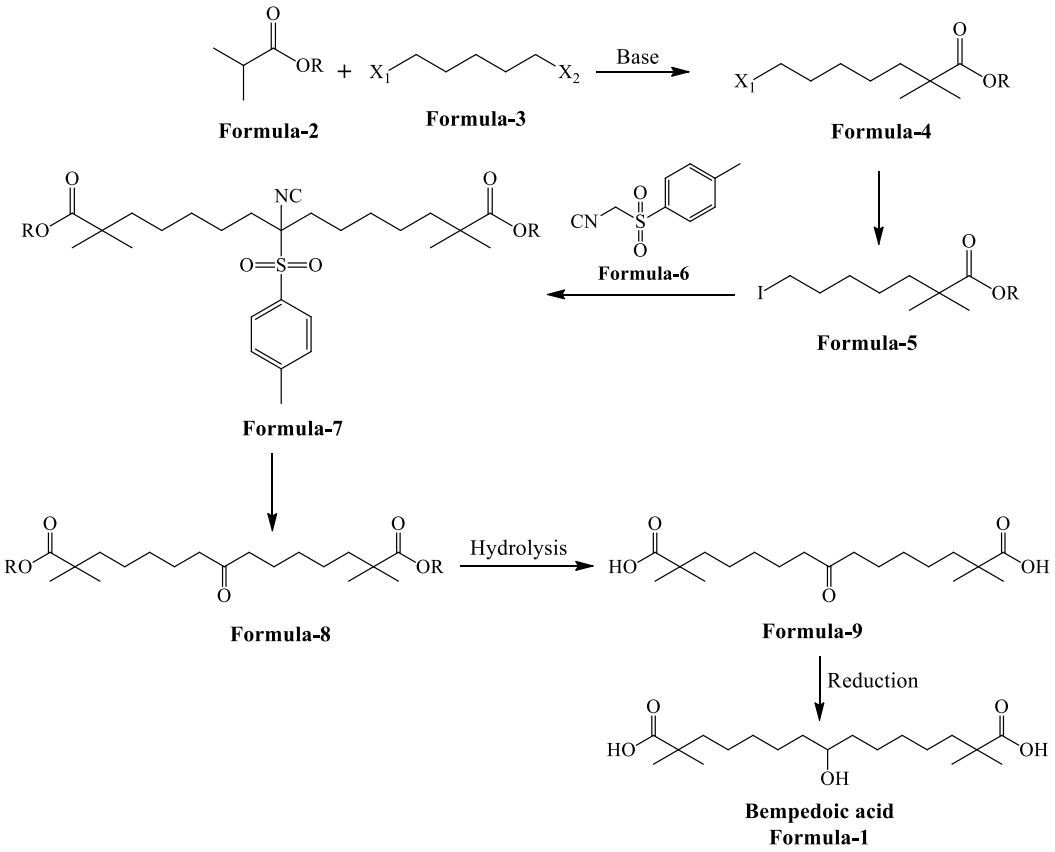
In one aspect of the present invention, the crystalline polymorph of compound of formula-1 may have particle size distribution of D_{90} less than about 100 µm, preferably less than about 50 µm.

The crystalline compound of formula-1 produced by the process of the present invention can be further micronized or milled to get desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction includes but not limited to single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling/micronization may be performed before drying or after drying of the product.

P-XRD Method of Analysis:

The PXRD analysis of compounds of the present invention was carried out by using BRUKER/D8 ADVANCE diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

Scheme-I:



In the above scheme, 'R' represents C_1-C_6 straight chain or branched chain alkyl group; and 'X_1' & 'X_2' are same or different and independently represents Cl, Br.

The best mode of carrying out the present invention is illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be construed as limitation to the scope of the invention.

Examples:

Example-1: Preparation of ethyl 7-chloro-2,2-dimethylheptanoate (Formula-4a)

Ethyl isobutyrate compound of formula-2a (81.41 gm) was added to a pre-cooled mixture of tetrahydrofuran (500 ml) and NaHMDS (377.37 ml) at -50°C to -55°C and stirred the reaction mixture for 30 min at the same temperature. 1-Bromo-5-chloropentane compound of formula-3a (100 gm) was slowly added to the reaction mixture at -50°C to -55°C and stirred the reaction mixture for 20 min at the same temperature. Raised the temperature of the reaction mixture to 0-5°C and stirred for 4 hr 30 min at the same temperature. Aqueous ammonium chloride solution was added to the reaction mixture at 0-5°C and stirred the reaction mixture for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C, methyl tert.butyl ether was added to it and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. Cooled the organic layer to 15-20°C and washed with aqueous HCl solution. Aqueous sodium bicarbonate solution was added to the organic layer at 15-20°C and stirred the reaction mixture for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound.

Yield: 108.0 gm.

Example-2: Process for preparation of compound of formula-1

A mixture of ethyl 7-chloro-2,2-dimethylheptanoate compound of formula-4a (100 gm), toluene (400 ml), NaI (81.48 gm) and dimethylformamide (100 ml) was heated to 100-105°C and stirred for 9 hr at the same temperature. Cooled the reaction mixture to 25-30°C, water was added and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the

solvent from the organic layer under reduced pressure. Tetrahydrofuran (600 ml), tetra butyl ammonium bromide (14.6 gm) and tosylmethyl isocyanide compound of formula-6 (TosMIC, 48.64 gm) were added to the obtained compound at 25-30^{o}C. Cooled the reaction mixture to -15^{o}C to -20^{o}C. Potassium tert.butoxide (61 gm) was slowly added lot wise to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 3 hr at the same temperature. Methyl tert.butyl ether followed by aqueous ammonium chloride solution was added to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Cooled the organic layer to 0-5^{o}C, conc.HCl (100 ml) was added to it and stirred the reaction mixture for 4 hr at the same temperature. Water was added to the reaction mixture at 0-5^{o}C. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. n-Heptane (600 ml) was added to the obtained compound at 25-30^{o}C and stirred the mixture for 10 min at the same temperature. Charcoal (5 gm) was added to the mixture at 25-30^{o}C and stirred for 30 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with n-heptane. Cooled the filtrate to 5-10^{o}C, aqueous NaOH solution was added to it and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C. Both organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. Ethanol (200 ml) and aqueous potassium hydroxide solution (58.45 gm of KOH in 200 ml water) were added to the obtained compound at 25-30^{o}C. Heated the reaction mixture to 75-80^{o}C and stirred for 7 hr at the same temperature. Cooled the reaction mixture to 5-10^{o}C, water and methyl tert.butyl ether were added to it. Acidified the reaction mixture by using aqueous HCl solution at 5-10^{o}C. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Aqueous sodium bicarbonate solution was added to the organic layer at 25-30^{o}C and stirred the reaction mixture for 1 hr at the same temperature. Both the organic

and aqueous layers were separated. Methyl tert.butyl ether was added to the aqueous layer at 25-30^{o}C and stirred the reaction mixture for 30 min at the same temperature. Both the organic and aqueous layers were separated and cooled the aqueous layer to 5-10^{o}C. Acidified the aqueous layer with aqueous HCl solution at 5-10^{o}C and stirred the reaction mixture for 45 min at the same temperature. Filtered the solid, washed with water and dried. Isopropyl acetate (75 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 40-45^{o}C and stirred for 10 min at the same temperature. Cooled the mixture to -5^{o}C to -10^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with chilled isopropyl acetate and suck dried. Ethyl acetate (60 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 55-60^{o}C and stirred for 15 min at the same temperature. Cooled the mixture to -5^{o}C to -10^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with chilled ethyl acetate and dried.

The PXRD pattern of the obtained compound is shown in figure-1.

The obtained compound was added to a mixture of water (500 ml) and NaOH (11.59 gm) at 25-30^{o}C. $NaBH_4$ (5.48 gm) was slowly added to the reaction mixture at 25-30^{o}C and stirred for 3 hr at the same temperature. Methyl tert.butyl ether was added to the reaction mixture at 25-30^{o}C. Acidified the reaction mixture with aqueous HCl solution at 25-30^{o}C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent completely from the organic layer. Diisopropyl ether (60 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 60-65^{o}C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at the same temperature. Filtered the solid and washed with diisopropyl ether. Diisopropyl ether (50 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 60-65^{o}C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with diisopropyl ether and suck dried. Diisopropyl ether (50 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 60-65^{o}C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with diisopropyl ether and dried to get the title compound.

Yield: 25 gm; Purity by HPLC: 99.89%.

Example-3: Preparation of compound of formula-1

A mixture of ethyl 7-chloro-2,2-dimethylheptanoate compound of formula-4a (100 gm), acetone (1000 ml) and NaI (135.8 gm) was heated to 55-60^{o}C and stirred for 42 hr at the same temperature. Cooled the reaction mixture to 25-30^{o}C, filtered and washed with acetone. Distilled off the solvent from the filtrate under reduced pressure. Methyl tert.butyl ether was added to the obtained compound at 25-30^{o}C. Cooled the reaction mixture to 10-15^{o}C and stirred for 1 hr at the same temperature. Filtered the reaction mixture and washed with methyl tert.butyl ether. Distilled off the solvent from the filtrate under reduced pressure. Tetrahydrofuran (600 ml), TBAB (14.6 gm) and TosMIC (44.22 gm) were added to the obtained compound at 25-30^{o}C. Cooled the reaction mixture to -15^{o}C to -20^{o}C. KOBt (61 gm) was slowly added lot wise to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 5 hr at the same temperature. Methyl tert.butyl ether and aqueous ammonium chloride solution were added to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Cooled the organic layer to 0-5^{o}C, conc.HCl (100 ml) was added to it and stirred the reaction mixture for 3 hr at the same temperature. Water was added to the reaction mixture at 0-5^{o}C. Raised the temperature of the reaction mixture to 30-35^{o}C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. n-Heptane (600 ml) was added to the obtained compound at 25-30^{o}C and stirred the mixture for 10 min at the same temperature. Charcoal (5 gm) was added to the mixture at 25-30^{o}C and stirred for 30 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with n-heptane. Cooled the filtrate to 5-10^{o}C, aqueous NaOH solution was added to it and stirred the mixture for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. Ethanol (200 ml) and aqueous potassium hydroxide solution (58.45 gm of KOH in 200 ml water) were added to the obtained compound at 25-30^{o}C. Heated the reaction mixture to 75-80^{o}C and stirred for 7 hr at

the same temperature. Cooled the reaction mixture to 5-10^{o}C, water and methyl tert.butyl ether were added to it. Acidified the reaction mixture by slowly adding aqueous HCl solution at 5-10^{o}C. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Aqueous sodium bicarbonate solution was added to the organic layer at 25-30^{o}C and stirred the reaction mixture for 1 hr at the same temperature. Both the organic and aqueous layers were separated, methyl tert.butyl ether was added to the aqueous layer and stirred for 15 min. Both the organic and aqueous layers were separated. Acidified the aqueous layer with aqueous HCl solution at 5-10^{o}C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 1 hr at the same temperature. Filtered the solid, washed with water and dried. Isopropyl acetate (100 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 40-45^{o}C and stirred for 20 min at the same temperature. Cooled the mixture to -5^{o}C to -10^{o}C and stirred for 3 hr at the same temperature. Filtered the slid, washed with chilled isopropyl acetate and dried. Ethyl acetate (75 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 55-60^{o}C and stirred for 15 min at the same temperature. Cooled the mixture to -5^{o}C to -10^{o}C and stirred for 2 hr at the same temperature. Filtered the solid, washed with chilled ethyl acetate and dried. The obtained compound was added to a mixture of water (500 ml) and NaOH (11.7 gm) at 25-30^{o}C. $NaBH_4$ (5.5 gm) was slowly added to the reaction mixture at 25-30^{o}C and stirred for 3 hr at the same temperature. Methyl tert.butyl ether was added to the reaction mixture at 25-30^{o}C. Acidified the reaction mixture with aqueous HCl solution at 25-30^{o}C stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. Diisopropyl ether (100 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture 60-65^{o}C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with diisopropyl ether. Diisopropyl ether (75 ml) was added to obtained compound at 25-30^{o}C. Heated the mixture to 60-65^{o}C and stirred for 30 min at same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at same temperature. Filtered the solid, washed with diisopropyl ether. Diisopropyl ether (75 ml) was

added to obtained compound at 25-30°C. Heated the mixture to 60-65°C and stirred for 30 min at same temperature. Cooled the mixture to 25-30°C and stirred for 3 hr at same temperature. Filtered the solid, washed with diisopropyl ether and dried.

Yield: 26 gm.

Example-4: Purification of compound of formula-1

A mixture of compound of formula-1 (50 gm), water (250 ml) and ammonia (75 ml) was stirred for 20 min at 25-30°C. Filtered the reaction mixture under reduced pressure and washed with water. Hydrochloric acid (37.5 ml) was added to the filtrate at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Filtered the precipitated solid and washed with water. Water (250 ml) was added to the obtained compound at 25-30°C and stirred the mixture for 2 hr at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound. The PXRD pattern of the obtained compound is shown in figure-2.

Yield: 45 gm; Purity by HPLC: 99.93% by HPLC.

Example-5: Preparation of compound of formula-1

Ethyl isobutyrate compound of formula-2a (75.15 gm) was added to a pre-cooled mixture of tetrahydrofuran (500 ml) and NaHMDS (400 ml) at -50°C to -55°C and stirred the reaction mixture for 15 min at the same temperature. 1-Bromo-5-chloro pentane compound of formula-3a (100 gm) was slowly added to the reaction mixture at -50°C to -55°C. Raised the temperature of the reaction mixture to 0-5°C and stirred for 5 hr at the same temperature. Aqueous ammonium chloride solution was slowly added to the reaction mixture at to 0-5°C. Raised the temperature of the reaction mixture to 25-30°C. Methyl tert.butyl ether was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. Cooled the organic layer to 20-25°C and washed with aqueous HCl solution. Aqueous sodium bicarbonate solution was added to the organic layer at 20-25°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure. Acetone (1000 ml) and NaI (224 gm) were added to the obtained compound at 25-30°C. Heated the reaction mixture to

50-55^{o}C and stirred for 24 hr at the same temperature. Cooled the reaction mixture to 25-30^{o}C. Filtered the reaction mixture and washed with acetone. Distilled off the solvent from the filtrate under reduced pressure. Methyl tert.butyl ether was added to the obtained compound at 25-30^{o}C. Cooled the mixture to 10-15^{o}C and stirred for 1 hr at the same temperature. Filtered the reaction mixture and washed with methyl tert.butyl ether. Distilled off the solvent from the filtrate under reduced pressure. Tetrahydrofuran (600 ml), tetra butyl ammonium bromide (16 gm) and TosMIC (48.64 gm) were added to the obtained compound at 25-30^{o}C. Cooled the reaction mixture to -15^{o}C to -20^{o}C, KOBt (67.1 gm) was slowly added lot wise to it and stirred for 6 hr at the same temperature. Methyl tert.butyl ether and aqueous ammonium chloride solution were added to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Cooled the organic layer to 0-5^{o}C, conc.HCl (100 ml) was added to it and stirred the reaction mixture for 4 hr at the same temperature. Water was added to the reaction mixture at 0-5^{o}C. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. n-Heptane (600 ml) was added to the obtained compound at 25-30^{o}C and stirred the mixture for 15 min at the same temperature. Charcoal (5 gm) was added to the reaction mixture at 25-30^{o}C and stirred for 45 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with n-heptane. Cooled the filtrate to 5-10^{o}C and aqueous NaOH solution was added to it. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. Ethanol (200 ml) and aqueous potassium hydroxide solution (64.29 gm of KOH in 200 ml water) were added to the obtained compound at 25-30^{o}C. Heated the reaction mixture to 75-80^{o}C and stirred for 6 hr at the same temperature. Cooled the reaction mixture to 5-10^{o}C, water and methyl tert.butyl ether were added and acidified the reaction mixture with aqueous HCl solution at the same temperature. Raised the temperature

of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. Isopropyl acetate (100 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 45-50°C and stirred for 30 min at the same temperature. Cooled the mixture to -5°C to -10°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with chilled isopropyl acetate and dried. Ethyl acetate (100 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 50-55°C and stirred for 15 min at the same temperature. Cooled the mixture to -5°C to -10°C and stirred for 2 hr at the same temperature. Filtered the solid, washed with chilled ethyl acetate and dried. Water (500 ml) and NaOH (12.87 gm) were added to the obtained compound at 25-30°C. $NaBH_4$ (6.12 gm) was added slowly to the reaction mixture at 25-30°C and stirred the reaction mixture for 2 hr at the same temperature. Methyl tert.butyl ether was added to the reaction mixture at 25-30°C and acidified with aqueous HCl solution. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer. Ethyl acetate (100 ml) was added to the obtained compound at 25-30°C. Heated the mixture 60-65°C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30°C and stirred for 3 hr at the same temperature. Filtered the solid and washed with ethyl acetate. Ethyl acetate (75 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 60-65°C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with ethyl acetate and dried. Ethyl acetate (75 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 60-65°C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with ethyl acetate and dried the material to get the title compound.

Yield: 32 gm.

Example-6: Purification of compound of formula-1

A mixture of compound of formula-1 (50 gm), water (250 ml) and ammonia (75 ml) was stirred for 1 hr at 25-30°C. Filtered the reaction mixture under reduced pressure and washed with water. HCl (37.5 ml) was added to the filtrate at 25-30°C and stirred the reaction

mixture for 6 hr at the same temperature. Filtered the precipitated solid and washed with water. Water (250 ml) was added to the obtained compound at 25-30^{o}C and stirred the mixture for 3 hr at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound.

Yield: 44 gm.

Example-7: Preparation of ethyl 7-chloro-2,2-dimethylheptanoate (Formula-4a)

Ethyl isobutyrate compound of formula-2a (75.15 gm) was added to a pre-cooled mixture of tetrahydrofuran (300 ml) and NaHMDS (377 ml) at -50^{o}C to -55^{o}C and stirred the reaction mixture for 15 min at the same temperature. 1-Bromo-5-chloropentane compound of formula-3a (100 gm) was slowly added to the reaction mixture at -50^{o}C to -55^{o}C. Raised the temperature of the reaction mixture to 0-5^{o}C and stirred for 6 hr at the same temperature. Water was slowly added to the reaction mixture at 5-10^{o}C and acidified the reaction mixture by using aqueous HCl solution at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C, toluene was added to it and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound.

Yield: 119 gm.

Example-8: Preparation of compound of formula-1

A mixture of compound of formula-4a obtained in example-7, toluene (300 ml), NaI (76.76 gm) and dimethylformamide (50 ml) was stirred for 5 min at 25-30^{o}C. Heated the reaction mixture to 110-115^{o}C and stirred for 9 hr at the same temperature. Cooled the reaction mixture to 45-50^{o}C, water was added to it and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Tetrahydrofuran (300 ml), tetra butyl ammonium bromide (16.16 gm) and compound of formula-6 (TosMIC, 53 gm) were added to the obtained organic layer at 25-30^{o}C and stirred for 10 min at the same temperature. Cooled the reaction mixture to -15^{o}C to -20^{o}C. KOBt (60.4 gm) was slowly added lot wise to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 2 hr at the same temperature. Aq.NH_4Cl solution was slowly added to the reaction mixture at 5-10^{o}C and stirred for 15 min at the same temperature. Raised the

temperature of the reaction mixture to 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Cooled the organic layer to 0-5°C, conc.HCl (100 ml) was added to it and stirred the reaction mixture for 4 hr at the same temperature. Water was added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. n-Heptane (400 ml) was added to the obtained compound at 25-30°C and stirred for 10 min at the same temperature. Charcoal (2.5 gm) was added to the mixture at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 30 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with n-heptane. Distilled off the solvent from the filtrate under reduced pressure. Ethanol (100 ml) was added to the obtained compound at 25-30°C. Aq.KOH solution (64.29 gm dissolved in water 100 ml) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 75-80°C and stirred for 8 hr at the same temperature. Cooled the reaction mixture to 5-10°C, water and toluene were added to it at the same temperature. Acidified the reaction mixture by using aq.HCl solution at 5-10°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. Aqueous sodium bicarbonate solution was added to the organic layer and stirred the reaction mixture for 1 hr at the same temperature. Both the organic and aqueous layers were separated, toluene was added to the aqueous layer and stirred for 20 min. Both the organic and aqueous layers were separated and cooled the aqueous layer to 5-10°C. Acidified the aqueous layer with aq.HCl solution at 5-10°C and stirred for 30 min at the same temperature. Filtered the solid, washed with water and dried. Isopropyl acetate (97.5 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 10 min at the same temperature. Cooled the mixture to -5°C to -10°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with chilled isopropyl acetate and suck dried. Ethyl acetate (78 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 55-60°C and stirred for 20 min at the same temperature. Cooled the mixture to -5°C to -10°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with

chilled ethyl acetate and dried. The obtained compound was added to a mixture of water (325 ml) and NaOH (11.69 gm) at 25-30°C. $NaBH_4$ (2.65 gm) was slowly added to the reaction mixture at 25-30°C and stirred for 4 hr at the same temperature. Toluene was added to the reaction mixture at 25-30°C. Acidified the reaction mixture with aq.HCl solution at 25-30°C and stirred for 15 min at the same temperature. Heated the mixture to 45-50°C and stirred for 1 hr at the same temperature. Cooled the mixture to 25-30°C and stirred for 1 hr at the same temperature. Filtered the solid, washed with toluene and dried. Ethyl acetate (175 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 60-65°C and stirred for 50 min at the same temperature. Charcoal (0.21 gm) was added to the reaction mixture 60-65°C and stirred for 30 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with ethyl acetate. Distilled off the solvent from the filtrate under reduced pressure. Cooled the mixture to 25-30°C. Ethyl acetate (70 ml) was added to the reaction mixture at 25-30°C. Heated the mixture to 60-65°C and stirred for 35 min at the same temperature. Cooled the mixture to -10°C to -15°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with ethyl acetate and suck dried. Ethyl acetate (70 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 60-65°C and stirred for 1 hr at the same temperature. Cooled the mixture to -10°C to -15°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with ethyl acetate and dried to get the title compound. Yield: 30 gm.

Example-9: Preparation of compound of formula-1

Compound of formula-2a (75.15 gm) was added to a pre-cooled mixture of tetrahydrofuran (500 ml) and NaHMDS (400 ml) at -50°C to -55°C and stirred the reaction mixture for 15 min at the same temperature. Compound of formula-3a (100 gm) was slowly added to the reaction mixture -50°C to -55°C. Raised the temperature of the reaction mixture to 0-5°C and stirred for 6 hr at the same temperature. Aq.NH_4Cl solution was slowly added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C, methyl tert.butyl ether was added to it and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. Cooled the organic layer to 15-20°C and washed with aq.HCl solution. Aq.$NaHCO_3$ solution was added to the organic layer at 15-20°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at

the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure. To the obtained compound, acetone (1000 ml) and NaI (224 gm) were added. Heated the reaction mixture 55-60^{o}C and stirred for 24 hr at the same temperature. Cooled the reaction mixture to 25-30^{o}C. Filtered the reaction mixture and washed with acetone. Distilled off the solvent from the filtrate under reduced pressure. Methyl tert.butyl ether (500 ml) was added to the obtained compound at 25-30^{o}C. Cooled the reaction mixture to 15-20^{o}C and stirred for 45 min at the same temperature. Filtered the reaction mixture, washed with methyl tert.butyl ether. Distilled off the solvent from the filtrate under reduced pressure. Tetrahydrofuran (600 ml), tetra butyl ammonium bromide (16 gm) and compound of formula-6 (TosMIC, 48.64 gm) were added to the obtained compound at 25-30^{o}C. Cooled the reaction mixture to -15^{o}C to -20^{o}C. Potassium tert.butoxide (67.1 gm) was slowly added lot wise to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 5 hr at the same temperature. Methyl tert.butyl ether followed by aq.NH_4Cl solution was added to the reaction mixture at -15^{o}C to -20^{o}C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Cooled the organic layer to 0-3^{o}C, conc.HCl (100 ml) was added to it and stirred the reaction mixture for 4 hr at the same temperature. Water was added to the reaction mixture at 0-5^{o}C. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. n-Heptane (600 ml) was added to the obtained compound at 25-30^{o}C and stirred the mixture for 10 min at the same temperature. Charcoal (5 gm) was added to the mixture at 25-30^{o}C and stirred for 30 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with n-heptane. Cooled the filtrate to 5-10^{o}C, aq.NaOH solution was added to it and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C. Both organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. Ethanol (200 ml) and aq.KOH

solution (64.29 gm of KOH in 200 ml water) were added to the obtained compound at 25-30^{o}C. Heated the reaction mixture to 75-80^{o}C and stirred for 6 hr at the same temperature. Cooled the reaction mixture to 5-10^{o}C, water and methyl tert.butyl ether were added to it. Acidified the reaction mixture by using aq.HCl solution at 5-10^{o}C. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer under reduced pressure. Isopropyl acetate (100 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 45-50^{o}C and stirred for 10 min at the same temperature. Cooled the mixture to -5^{o}C to -10^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with chilled isopropyl acetate and suck dried. Ethyl acetate (100 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 55-60^{o}C and stirred for 15 min at the same temperature. Cooled the mixture to -5^{o}C to -10^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with chilled ethyl acetate and dried. The obtained compound was added to a mixture of water (500 ml) and NaOH (12.87 gm) at 25-30^{o}C. $NaBH_4$ (6.12 gm) was slowly added to the reaction mixture at 25-30^{o}C and stirred for 3 hr at the same temperature. Methyl tert.butyl ether was added to the reaction mixture at 25-30^{o}C. Acidified the reaction mixture with aq.HCl solution at 25-30^{o}C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent completely from the organic layer. Ethyl acetate (100 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 60-65^{o}C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at the same temperature. Filtered the solid and washed with ethyl acetate. Ethyl acetate (75 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 60-65^{o}C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with ethyl acetate and suck dried. Ethyl acetate (75 ml) was added to the obtained compound at 25-30^{o}C. Heated the mixture to 60-65^{o}C and stirred for 30 min at the same temperature. Cooled the mixture to 25-30^{o}C and stirred for 3 hr at the same temperature. Filtered the solid, washed with ethyl acetate and dried.

Yield: 32 gm.

Example-10: Preparation of ethyl 7-chloro-2,2-dimethylheptanoate (Formula-4a)

Compound of formula-2a (75.14 gm) was added to a pre-cooled mixture of tetrahydrofuran (500 ml) and NaHMDS (377.37 ml) at -50^{o}C to -55^{o}C and stirred the reaction mixture for 30 min at the same temperature. Compound of formula-3a (100 gm) was slowly added to the reaction mixture at -50^{o}C to -55^{o}C and stirred the reaction mixture for 15 min at the same temperature. Raised the temperature of the reaction mixture to 0-5^{o}C and stirred for 6 hr at the same temperature. Aq. NH_4Cl solution was added to the reaction mixture at 0-5^{o}C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C, methyl tert.butyl ether was added to it and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. Cooled the organic layer to 15-20^{o}C and washed with aq.HCl solution. Aq. $NaHCO_3$ solution was added to the organic layer at 15-20^{o}C and stirred the reaction mixture for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30^{o}C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound.

Yield: 108 gm.

Figures:

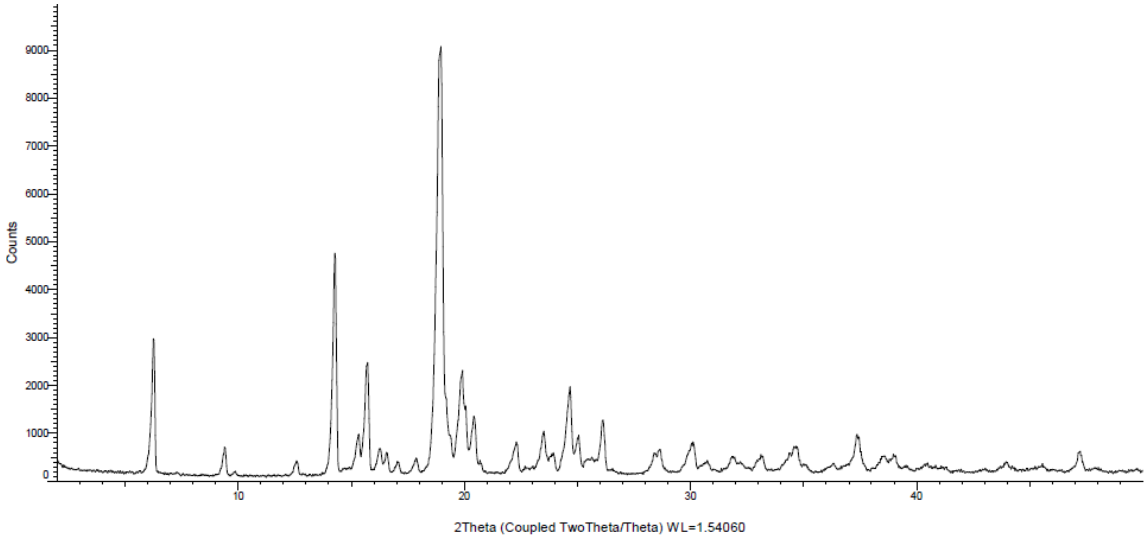


Figure-1: Illustrates the PXRD diffractogram of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid compound of formula-9

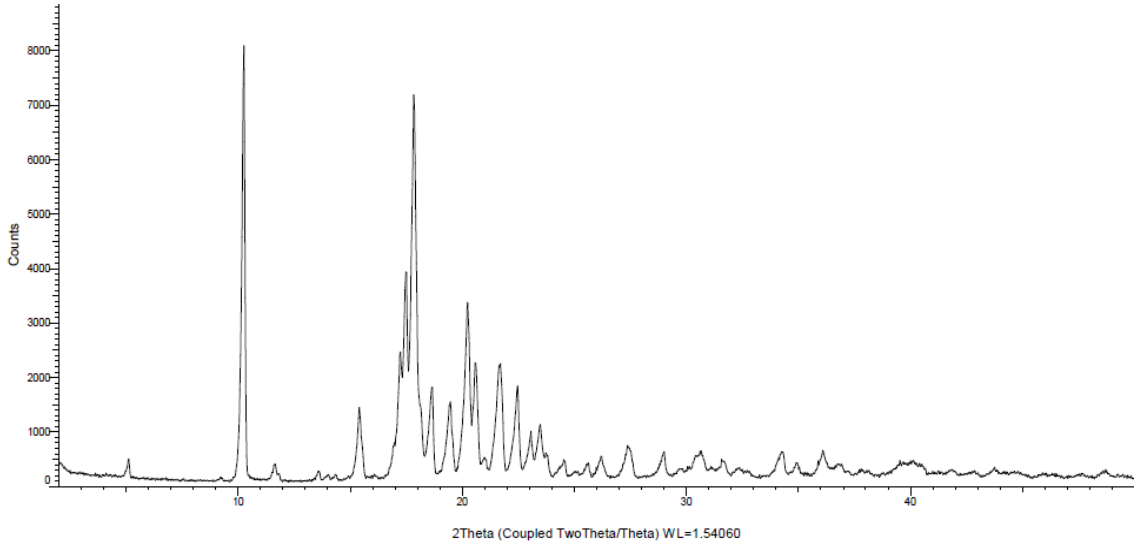


Figure-2: Illustrates the PXRD diffractogram of 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid compound of formula-1