July 2020

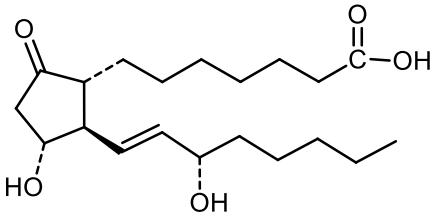
Process for the preparation of (11α,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid

Srinivasan Thirumalai Rajan

Process for the preparation of (11α,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid

Field of the invention:

The present application relates a process for the preparation of (11α,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid.



Formula-1

Background of the invention:

(11α,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid is generally known as Prostaglandin E1 (PGE1) or Alprostadil. Alprostadil was approved in US and Europe under the brand name of CAVERJECT® and indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

Biosynthetic PGE1, is formed from dihomo-γ-linolenic acid was disclosed in Prostaglandin 20, 187, 1980. Syntheses of PGE1 was disclosed in J. Chem. Soc. Chem. Comm 304, 1972; J. Chem. Soc. Chem. Comm. 180, 1973; J Am. Chem. Soc. 94, 3643, 1972; J. Am. Chem Soc. 95, 1676, 1973; J. Org. Chem. 37, 2921, 1972.

Another possible approach is the regioselective saturation of the cis double bonds of the prostanoid structure containing cis and trans double bonds. Hydrogenation of 5(Z), 11α, 13E, 15(S)-11,15-dihydroxy-9-oxoprosta-5,13-diene-1-oic-acid (PGE2) of formula in ethyl acetate yields only 6% of PGE1 (J Biol. Chem 239, 4091 1964).

Journal of Medicinal Chemistry, 29(10), 1826-32, 1986 discloses the preparation of protected Alprostadil analogous compound. US4024174A; American Chemical Society, 92(8), 2586-7, 1970; WO1997022581A1 discloses reduction of double bond at C5-C6 position in Prostaglandin acid compound.

The present inventors developed a process for the preparation of compound of (11α,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid with higher yield and purity by reducing the impurities.

Brief description of the invention:

The present invention provides a process for the preparation of Alprostadil of formula-1.

Detailed description of the Invention:

As used herein the term “suitable solvent” or “solvent” used in the present invention refers to “hydrocarbon solvents” such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; “ether solvents” such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; “ester solvents” such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; “polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), 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 isobutylketone and the like; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and the like; “alcohol solvents” such as methanol,

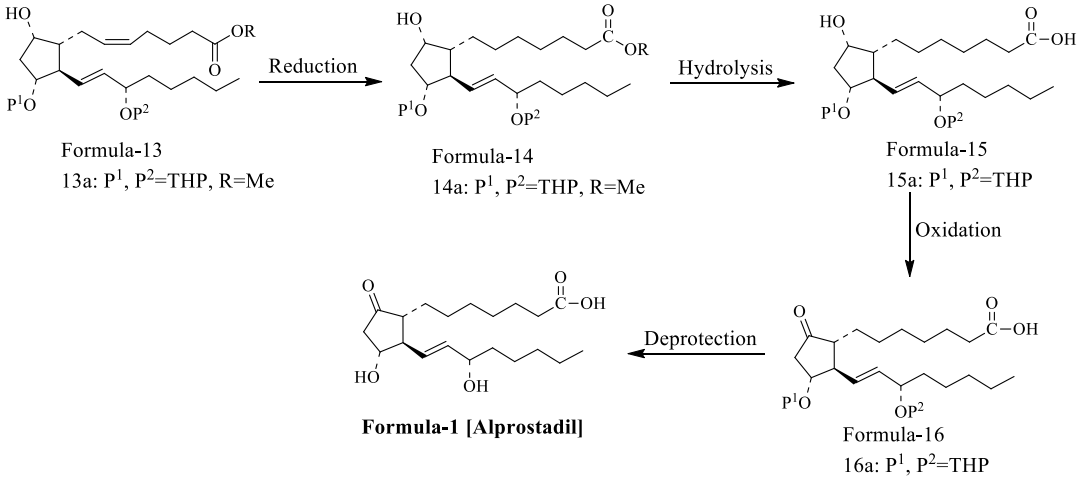
ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; water or mixtures or any other suitable solvent known in the art.

The term "suitable base" used in the present invention refers 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 and the like; "alkyl metals" such as n-butyl lithium and like; "metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal phosphates" such as disodium hydrogen phosphate, dipotassiumhydrogen phosphate; and "organic bases" selected from but not limited to methyl amine, ethyl amine, dimethylamine, diethylamine, diisopropylamine, diisopropylethyl amine (DIPEA), diisobutylamine, triethylamine, tert.butylamine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), 2,6-lutidine, lithium diisopropylamide, nmethyl pyridine (NMP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), imidazole; "organo lithium bases" such as methyl lithium, n-butyl lithium, tert-Butyllithium, phenyl lithium and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; "alkali metal amides" such as sodium amide, potassium amide, lithium amide, lithium diisopropyl amide (LDA) and the like; ammonia such as aqueous ammonia, ammonia gas, alcoholic ammonia; organosilicon bases such as sodium bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide, lithium bis(trimethysilyl)amide (LiHMDS), potassium

hexamethyldisilazide (KHMDS) and the like; or mixtures or any other suitable base known in the art.

As used herein term, "an alcohol protecting group" is a functional group that protects the alcohol group from participating in reactions that are occurring in other parts of the molecule. Suitable alcohol protecting groups that are used in step (a) include, acetyl, benzoyl, benzyl, β-methoxyethoxymethyl ether, methoxymethyl ether, dimethoxytrityl, p-methoxybenzyl ether, methylthiomethyl ether, allyl ether, *t*-butyl ether, pivaloyl, trityl, silyl ether (e.g., trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBDMS), *t*-. butyldiphenylsilyl (TBDPS), *t*-butyldimethylsilyloxymethyl (TOM) or triisopropylsilyl (TIPS) ether), tetrahydropyranyl (THP), methyl ether and ethoxyethyl ether (EE) or any suitable alcohol protecting group known in the art.

Scheme-1



Wherein R is selected from straight or branched C_1-C_{10} “alkyl” or optionally “alkenyl” or optionally substituted C_5-C_{12} “aryl”; P^1, P^2 are H or “an alcohol protecting group” which may be the same or different groups.

The first embodiment of present invention provides a process for the preparation of Alprostadil of formula-1 comprising;

a) converting compound of formula-13 to compound of formula-14,
b) ester hydrolysis of compound of formula-14 with a base in a solvent to provide compound of formula-15,
c) converting compound of formula-15 to Alprostadil of formula-1.

Converting compound of formula-13 to compound of formula-14 in step-a) of the second embodiment can be done by reduction of double bond at C_5-C_6 position of the compound of formula-13 with hydrogenating agent in a solvent optionally in presence of a base to provide compound of formula-14.

Wherein the hydrogenating agent is selected from Pd/C, Pd(OH)2/C (Pearlman's catalyst), palladium acetate, platinum oxide, platinum black, sodium borohydride, Na-liquid ammonia, Raney-Ni, tri(C1-C6)alkylsilanes, tri(C1-C6)alkylsilyl halides and the like optionally in presence of hydrogen gas; the solvent is selected from alcohol solvents, ester solvents, chloro solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, polar solvents such as water and/or mixtures thereof; the base is selected from organic or inorganic bases.

The second embodiment of present invention provides a process for the preparation of Alprostadil of formula-1 comprising;

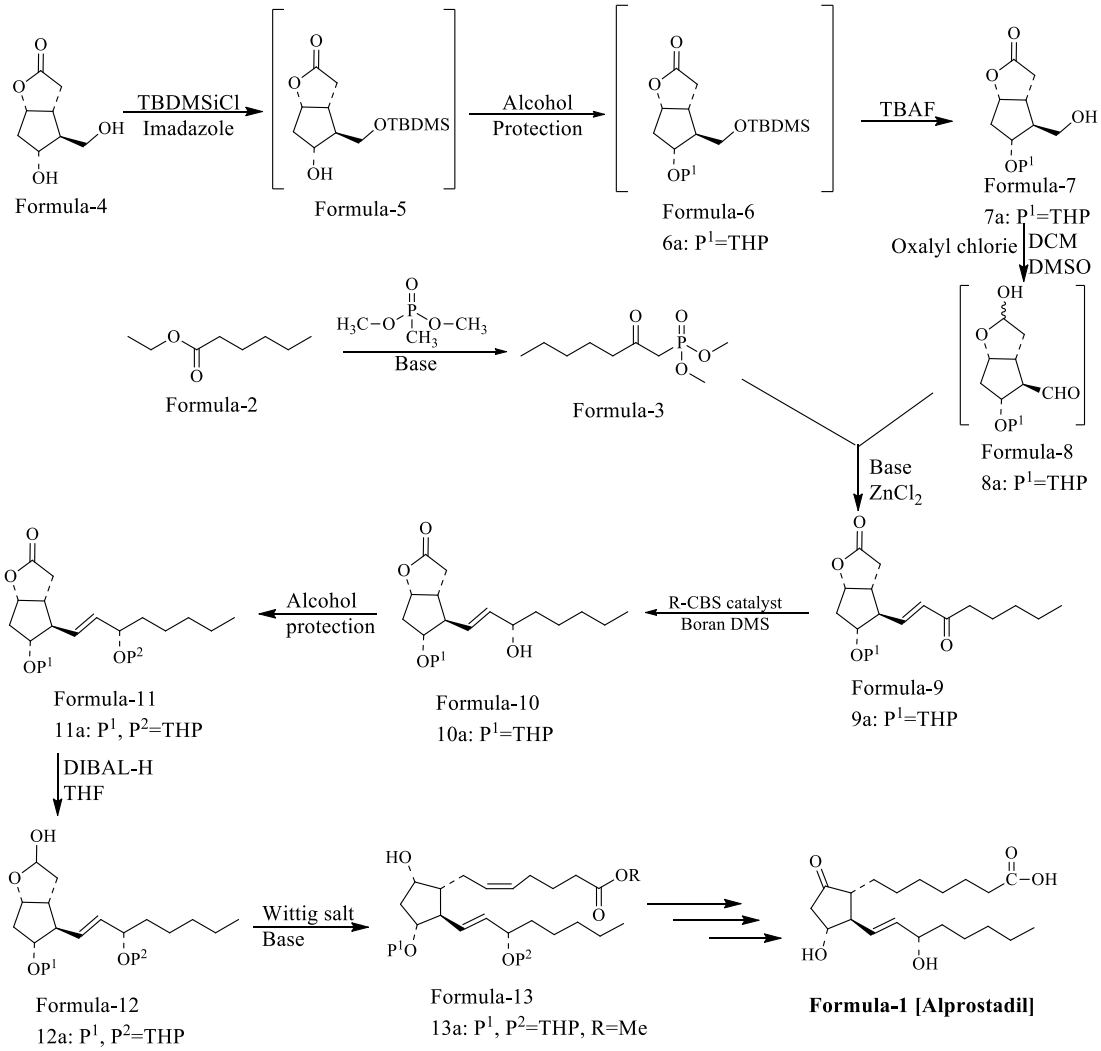
a) converting compound of formula-13 to compound of formula-14,
b) ester hydrolysis of compound of formula-14 with a base in a solvent to provide compound of formula-15,
c) oxidation of the compound of formula-15 with an oxidizing agent in a solvent to provide the compound of formula-16,
d) deprotecting the hydroxyl protecting group of formula-16 in a solvent to provide Alprostadil of formula-1.

Converting compound of formula-13 to compound of formula-14 in step-a) of the second embodiment can be done by reduction of double bond at C5-C6 position of the compound of formula-13 with hydrogenating agent in a solvent optionally in presence of a base to provide compound of formula-14, wherein the hydrogenating agent is selected from Pd/C, Pd(OH)2/C (Pearlman's catalyst), palladium acetate, platinum oxide, platinum black, sodium borohydride, Na-liquid ammonia, Raney-Ni, tri(C1-C6)alkylsilanes, tri(C1-C6)alkylsilyl halides and the like optionally in presence of hydrogen gas; oxidizing agent in step-c) is selected from but is not limited to nitric acid, hydrogen peroxide, per acids such as peracetic acid, trifluoro per acetic acid, per benzoic acid, m-chloroperbenzoic acid and the like, ozone, manganese dioxide, sodium periodate, dinitrogen tetroxide, hydroperoxide, iodobenzene acetate, t-butyl hypochlorite, sulfuryl chloride, potassium peroxymonosulfate, potassium permanganate, chromic acid, chromium trioxide, selenium dioxide, sodium hypochlorite, sodium metaperiodate, ruthenium trichloride, TEMPO, DABCO, Dess-martin reagent, oxaloyl chloride in DMSO and the like or any other suitable oxidizing agent known in the art.; deprotecting agent in step-d) is selected from but not limited to acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, aq.phosphoric acid, trifluoroacetic acid, methane sulfonic acid, p-toluenesulfonic acid, acetic acid and the like; acetyl chloride in combination with alcohols; bases such as alkali metal hydroxides, alkali metal alkoxides, alkali metal carbonates, cesium carbonate/imidazole, ammonia, cerium(IV) ammonium nitrate (CAN); organic bases such as methylamine, ethylamine, diethylamine, triethylamine, piperidine and the like or any other suitable deprotecting agent known in the art; the solvent is selected from alcohol solvents, ester solvents, chloro solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, polar solvents such as water and/or mixtures thereof; the base is selected from organic or inorganic bases.

Compound of formula-13 used in the present invention can be prepared by any of the processes disclosed in literature such as US 6359181B1 or other references such as Journal of the Chemical Society Chemical communications, 1975, 658; J. Am. Chem. Soc. 1974, 96, 18, 5876–5894; J. Org. Chem. 1979, 44, 13, 2194–2199 or as per the present application.

The third embodiment of the present invention schematically provides the preparation of Alprostadil of formula-1 as shown in below scheme-2:

Scheme-2



The fourth embodiment of the present invention provides substantially pure Alprostadil of formula-1 and its intermediates. The term “substantially pure” refers to the compound obtained according to the present invention having purity of greater than about 95%; preferably greater than about 97.5%; more preferably greater than about 99.0% as measure by HPLC.

Alprostadil of formula-1 prepared according to 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 include 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 or micronization may be performed before drying or after drying of the product.

The fifth embodiment of the present invention provides a pharmaceutical composition comprising the crystalline form of Alprostadil of formula-1 and at least one pharmaceutically acceptable excipient. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

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

Examples:

Example-1: Preparation of dimethyl-(2-oxoheptyl)phosphonate (Formula-3)

n-Butyl lithium (119 ml) was slowly added to a pre-cooled mixture of dimethyl phosphonate (22.07 ml) and tetrahydrofuran (140 ml) at -65 to -70°C and stirred the resultant solution at the same temperature. A solution of ethyl hexanoate (14 g) in tetrahydrofuran was added to the above reaction mixture at the same temperature and stirred. The reaction mixture was quenched with aqueous ammonium chloride solution and extracted with ethyl acetate. Combined the organic layers and washed with water and distilled off the solvent from the organic layer to get the title compound.

Yield: 20 g.

Example-2: Preparation of Formula-7a

A mixture of imidazole (29.65 g) and tert-butyldimethylsilyl chloride [TBDMSiCl] (48.07 g) were added to pre-cooled solution of Corey lactone compound of formula-4 (50 g) in dichloromethane (750 ml) at 0-5°C and stirred the resultant mixture at the same temperature. Water was added to the above reaction mixture. The organic layer was washed with water and followed by aqueous sodium chloride solution. Distilled off solvent completely from the organic layer under reduced pressure. Dichloromethane (500 ml) is added to obtained residue at 25-30°C and cooled to 0-5°C. Camphor sulphonic acid (1.68 g), 3,4-dihydropyran (34.35 g) are added to the resultant mixture and followed by added 10% of aqueous sodium bicarbonate solution at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred. Both the aqueous and organic layers were separated. The

aqueous layer was extracted with dichloromethane. Combined the organic layers and washed with aqueous sodium bicarbonate solution and followed by aqueous sodium chloride solution. Distilled off solvent completely from the organic layer under reduced pressure. Tetrahydrofuran (600 ml) was added to the above obtained residue at 25-30°C. Cooled the mixture to 0-5°C and a solution of tetrabutyl ammonium fluoride (106.28 g) in tetrahydrofuran (600 ml) was slowly added to the above mixture and stirred. Water and dichloromethane were added to the above reaction mixture. The aqueous layer was extracted with dichloromethane and combined the organic layers. The organic layer was washed with aqueous sodium chloride solution. Distilled off solvent completely from the organic layer to get the title compound.

Yield: 49.3 g

Example-3: Preparation of Formula-9a

Oxalyl chloride (41.44 g) was slowly added to pre-cooled mixture of dichloromethane (400 ml) and dimethyl sulfoxide (37.80 g) at -70°C and stirred at the same temperature. The solution of compound of formula-7a (40 g) in dichloromethane was added to the above mixture at the same temperature and stirred. Raised the temperature of the reaction mixture to -40°C to -45°C and stirred at the same temperature. Cooled the mixture to -70°C to -75°C. Triethylamine (89.85 g) was added the above mixture at the same temperature and stirred. Water was added to the above mixture at 25-30°C. The aqueous layer was extracted with dichloromethane. Combined the organic layers and washed with water. Distilled off solvent completely from the organic layer under reduced pressure. The obtained residue was dissolved in tetrahydrofuran and kept a side. Dimethyl-(2-oxoheptyl)phosphonate of formula-3 (34.69 g) and zinc chloride (27.99 g) was added to the mixture of tetrahydrofuran (400 ml) and sodium hydroxide (9.36 g) mixture at 25-30°C and stirred. The above obtained solution was added to this reaction mixture at 25-30°C and stirred at the same temperature. 10% sodium chloride solution was added to the reaction mixture at 25-30°C. The aqueous layer was extracted with ethyl

acetate. Combined the organic layers and washed with water. Distilled off solvent completely from the organic layer and the obtained compound was purified by column chromatography using petroleum ether and ethyl acetate as eluents. Distilled off solvent from the pure fractions to get pure title compound.

Yield: 20.0 g

Example-4: Preparation of Formula-10a

(R)-2-Methyl-CBS-oxazaborolidine catalyst (13.84 g) was slowly added to the mixture of compound of formula-9a (35 g) and tetrahydrofuran (350 ml) at 25-30°C and stirred at the same temperature. Cooled the mixture to -25°C to -30°C and borane-dimethyl sulfide (5.68 g) was slowly added to the above mixture at the same temperature and stirred. Quenched the reaction mixture with methanol. Aqueous ammonium chloride solution and ethyl acetate were added to the above mixture. The aqueous layer was extracted with ethyl acetate and combined the organic layers. The organic layer was washed with aqueous citric acid solution and followed by water. Distilled off solvent completely from the organic layer. The obtained compound is purified by silica column chromatography with cyclohexane and ethyl acetate as eluents and distilled the pure fractions to get the pure title compound.

Yield: 27.0 g

Example-5: Preparation of Formula-11a

Para toluenesulfonic acid (6.595 g) was added to the pre-cooled mixture of dichloromethane (270 ml) and sodium sulphate (5 g) and compound of formula-10a (27 g) at 0-5°C. 3,4-Dihydropyran (32.21 g) was added to the above reaction mixture at the same temperature and stirred at the same temperature. Water was added to the mixture. The aqueous layer was extracted with dichloromethane and combined the organic layers. The organic layer was washed with aqueous sodium bicarbonate solution and followed by water and aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer. The obtained compound was purified

by silica column chromatography using cyclohexane and ethyl acetate as eluents and distilled off the solvent from pure fractions to get pure title compound.

Yield: 27.0 g

Example-6: Preparation of Formula-13a

25% of Diisobutylaluminium hydride (30.78 ml) was added to pre-cooled mixture of compound of formula-11a (27.0 g) and tetrahydrofuran (270 ml) at -70°C to -75°C and stirred. Quenched the above reaction mixture with methanol at the same temperature. Ethyl acetate and water was added to the above mixture. Raised the temperature of the mixture to 25-30°C and stirred. The aqueous layer was extracted with ethyl acetate and combined the organic layers. Distilled off solvent completely from the organic layer. 54 ml of tetrahydrofuran is added to the obtained compound at 25°C-30°C. The solution was added to pre-cooled mixture of tetrahydrofuran (270 ml), (4-carboxybutyl)triphenylphosphonium bromide [Wittig salt] (82.23 g) and potassium tert-butoxide (41.63 g) at 0°C-5°C. Stirred the reaction mixture at 0-5°C. 10% citric acid solution followed by ethyl acetate were added to the above mixture. The aqueous layer was extracted with ethyl acetate and combined the organic layers. The organic layer was washed with water and followed by aqueous sodium chloride solution. Distilled off solvent completely from the organic layer under reduced pressure. The obtained compound was added to acetone (270 ml) at 25-30°C and cooled the above mixture to 0-5°C. Potassium carbonate (25.64 g) and methyl iodide (52.67 g) were added to above mixture at the same temperature and raised the temperature of the reaction mixture to 25-30°C and stirred. Dichloromethane and water were added the mixture. The aqueous layer was extracted with dichloromethane and combined the organic layers. The organic layer was washed with water. Distilled off solvent completely from the organic layer. The obtained compound was purified by silica column chromatography using cyclohexane and ethyl acetate as eluents. Distilled off the solvent from pure fractions and get pure title compound.

Yield: 16.6 g

Example-7: Preparation of Formula-14a

Palladium carbon (3.56 g) was added to the mixture of triethylamine (0.8 ml), compound of formula-13a (16.0 g) and dichloromethane (80.0 ml) at 25-30°C. Applied 4-5 kg hydrogen pressure to the reaction mixture and stirred. The mixture was filtered through hyflow bed and washed with dichloromethane. Dichloromethane & water were added to the obtained filtrate. Both the aqueous and organic layers were separated. The organic layer was washed with water. Distilled off solvent completely from the organic layer and dried to get the compound of formula-14a.

Yield: 15.8 g

Example-8: Preparation of Formula-15a

Aqueous sodium hydroxide solution was added to pre-cooled solution of compound of formula-14a (15.8 g) in methanol (158 ml) at 0-5°C and stirred it at the same temperature. Water and methyl tert-butyl ether were added to the above mixture. Both the aqueous and organic layers were separated. Aqueous citric acid solution was added to the aqueous layer and extracted with methyl tert-butyl ether. The organic layer was washed with water and followed by aqueous sodium chloride solution. Distilled off solvent completely from the organic layer and dried to get the compound of formula-15a.

Yield: 14.0 g

Example-9: Preparation of Formula-16a

Dess-martin periodinane (16.98 g) was added to the pre-cooled solution of compound of formula-15a (14 g) in dichloromethane (140 ml) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred. Water was added to the obtained mixture. Both the aqueous and organic layers were separated. The organic layer was washed with aqueous sodium bicarbonate solution and followed by water. Distilled off solvent completely from the organic layer. The obtained compound was purified by silica gel column chromatography using cyclohexane and ethyl acetate as eluents to get the compound of formula-16a.

Yield: 11.6 g.

Example-10: Preparation of Alprostadil

Acetic acid (114 ml) was slowly added the pre-cooled mixture of compound of formula-16a (6 g), tetrhydrofuran (18 ml) and water (60 ml) at 0-5°C. Heated the reaction mixture to 45-50°C and stirred. Distilled off the solvent completely from the resultant mixture. Aqueous sodium carbonate solution followed by ethyl acetate were added to the resultant mixture at 25-30°C. Both the aqueous and organic layers were separated. The organic layer was washed with water. Distilled off solvent completely from the organic layer. The obtained compound was recrystallized from ethyl acetate and dried to get the title compound.

Yield: 3.1 g