Asian Journal of Chemistry; Vol. 33, No. 1 (2021), 210-214

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2021.22934

Identification and Efficient Synthetic Method for Preparation of Cyclopentane-1,3-diol Impurity in Tafluprost Drug

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Received: 6 August 2020; *Accepted*: 2 November 2020; *Published online*: 10 December 2020; AJC-20200

In present work, the isolation, synthesis and characterization of the identified triol impurity present in tafluprost is described. This investigation helps to avoid formation of impurity by control the reaction and its leads to improving high yields of tafluprost. The source of impurity was identified, due to over-reduction of lactone with diisobutyl aluminum hydride (DIBAL-H).

Keywords: Diisobutylaluminium hydride, Lithium aluminum hydride, Sodium borohydride, Tafluprost.

INTRODUCTION

Lithium aluminum hydride (LAH) is a highly reactive and useful reagent due to its broad range of usage in synthetic organic syntheses such as reduction of aldehydes and ketones to corresponding alcohols and to reduce lactones to lactols [1]. However, the usage of $LiAlH_4$ associated with many difficulties such as its explosive nature and not user-friendly handling due to pyrophoric nature. Aldehydes are intermediates during the reduction of esters and lactones with lithium aluminum hydride (LAH), but it is difficult to isolate aldehydes as aldehydes are more reactive than esters. However with outmost care, it is possible to stop at the aldehyde stage. If the desired product is an aldehyde or hydroxyl aldehyde (lactol), it is better to switch over to a less reactive reducing agent, which can stop the reduction at the aldehyde stage. For this purpose, *bis*(2-methylpropyl)aluminum hydride or diisobutylaluminum hydride (DiBAL or DiBAL-H) can be utilized as a reducing agent [2]. DIBAL-H is available as a solution in toluene. The favourable condition for the reduction of lactones to lactols (or hydroxy aldehydes) is at -70 ºC.

Organic fluoro compounds [3] profound in biological activities such as glaucoma [4] and chemotherapy drugs such as gemcitabine, clofarabine, *etc*. Many therapeutic prostaglandin analogs are available for glaucoma treatment such as bimatoprost [5] and latanoprost [6]. More recently, tafluprost [7-9], a 15,15-difluoro analog is multi-fold effectively percribed as compared to the former two analogs.

The synthesis of tafluprost has consistently resulted in a very low level (about 0.02%) due to the presence of unknown impurity. To ensure long-term control, the identity and source of the impurity are desired. In this work, an isolation, synthesis and characterization of an impurity, (*Z*)-isopropyl 7-((1*R*,2*R*,3*R*,5*S*)-2-((1*E*,3*Z*)-3-fluoro-4-phenoxybuta-1,3-dienyl)-3,5-dihydroxycyclopentyl)hept-5-enoate, which was formed during the preparation of tafluprost drug is reported.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer. Tetramethyl silane (TMS) was used as an internal standard and all chemical shifts were reported in parts per million (ppm) while the coupling constant (*J*) values were calculated in hertz (Hz). Deuteriochloroform ($CDCl_3$) was used as solvent for all NMR experiments with residual chloroform as an internal standard for ^{13}C NMR. IR spectra were recorded on a FT-IR spectrophotometer. Mass spectra were obtained by positive chemical ionization (CI) or by fast atomic bombardment (FAB) technique.

Unless otherwise noted, all reactions were carried out in oven-dried glasswares. Dichloromethane was distilled from

calcium hydride. Tetrahydrofuran (THF) was freshly distilled from sodium metal/benzophenone prior to use. All solvents for chromatography were obtained commercially and used as received. Reactions were monitored by analytical thin layer chromatographic (TLC) methods, using pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV_{254} (layer:0.20 mm silica gel 60 with fluorescent indicator UV_{254}) and all spots on TLC plates were either visualized by ultraviolet (UV) light or detected by dipping the plate into a nin hydrin solution in ethanol and heating. The pure products for characterization were isolated by column chromatography with the use of silica gel, 60-120 mesh and 100-200 mesh.

Synthesis of (3a*R*,4*R*,5*R*,6a*S*)-2-oxo-4-((E)-3-oxo-4-phenoxybut-1-enyl) hexahydro-2*H*-cyclopenta[*b*]furan-5-yl benzoate (2): Arranged a clean dry round bottom flask, charged dimethyl 2-oxo-3-phenoxypropylphosphonate (47.1 g, 0.182 mol) and tetrahydrofuran (500 mL) under nitrogen atmosphere at 30 ± 5 °C. Charged $ZnCl_2$ (29.7g, 0.218 mol) into reaction mass under nitrogen atmosphere at 27 ºC. Charged NaOH (8.74 g, 0.218 mol) into reaction mass under nitrogen atmosphere at 30 ± 5 ºC. Stirred the reaction mass for 45-60 min under nitrogen atmosphere at 27 ºC. Added Corey aldehyde (**10**, 50 g, 0.182 mol) into reaction mass under nitrogen atmosphere and then stirred the reaction mass for 15 h under nitrogen atmosphere at 27 ºC. Filtered the reaction mass through Hyflow bed after adding ethyl acetate (500.0 mL) and sodium chloride solution (50.0 g in 500 mL). The separated organic layer was washed with sodium chloride solution (10%) and then finally washed with water (250 mL). Dry the organic layer with Na_2SO_4 and distilled under vacuum at 40 ºC to obtain the crude compound. The crude compound was recrystallized from methanol, produce compound **2**.

Yield 50%. FT-IR (KBr, cm^{-1}): 3405 (=C-H *str.*), 3042 (-C-H *str.*), 1772 (cyclic anhydride -O-C=O), 1726 (anhydride O-C=O), 1493 (C=C *str.*), 1336 (-C-H scissoring), 1309, 1225, 758, 717; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.99-7.96 (dd, 2H, *J* = 1.2 Hz, 7.6-7.55 (m, 1H), 7.46-7.43 (m, 2H), 7.29-7.25 (m, 2H), 7.00-6.84 (m, 4H), 6.58-6.58 (1H, d, *J* = 0.8 Hz, 5.32-5.30 (1H, q), 5.09-5.06 (1H, m), 4.67 (s, 2H), 2.96-2.83(m, 3H), 2.63-2.56 (1H, m), 2.51-2.43 (m, 1H), 2.31-2.26 (m, 1H); MS: *m/z*: 442 (M^+H).

Synthesis of (3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-5-phenylpent-1-enyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]-furan-5-yl benzoate (3): Charged dichloromethane (1000 mL) and compound **2** (100 g, 0.246 mol) into a clean round bottom flask at 25 ºC. Slowly added 4-N,N′-dimethylamino-*N*-methyl-4-stilbazolium toyslate (DAST) (478 g, 2.955 mol) to the reaction mass and then stirred the reaction mass for 70 h at 25 ºC. After completion of the reaction, quenched the reaction mass by slowly adding it into aqueous $NaHCO_3$ solution (20%), separated the organic layer and extracted aqueous layer with CH_2Cl_2 (360 mL). Combined both organic layers and washed with water (200 mL) followed by the separation of organic and aqueous layers. Dried the organic layer with Na_2SO_4 and then distilled it under vacuum at below 40 ºC to afford compound **3**. Yield: 97.25% (102.0 g); FT-IR (KBr, cm^{-1}): 3022 (=C-H *str.*), 1773 (cyclic anhydride -O-C=O), 1771 (-O-C=O), 1600 (-C=C *str.*), 1452 (-C-H scissor), 1273, 758 (-C-F *str.*); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.97 (d, 2H, *J* = 16.8 Hz, 7.55 (t, 1H), 7.4 (m, 2H), 7.26 (m, 2H), 7.0 (t, 1H), 6.88 (m, 2H), 5.9 (m, 1H), 5.07 (m, 1H), 4.15 (m, 2H), 2.9 (m, 2H), 2.4 (m, 3H), 2.3 (m, 1H).

Synthesis of (3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)-5-hydroxyhexahydro-2*H*-cyclopenta-[*b*]furan-2-one (4): Charged methanol (440 mL) and (3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-5-phenylpent-1-enyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl benzoate (**3**) (36.0 g, 0.084 mol) in to a clean and dry round bottom flask under nitrogen atmosphere. Cool the reaction mass to 0-5 ºC under nitrogen atmosphere and then added K_2CO_3 lot wise into reaction mass. Raised the reaction mass temperature to 25 ºC and stirred the reaction for 60-90 min under nitrogen atmosphere followed by the addition of NaCl solution (10%) and dichloromethane into the reaction mass. Separated the organic layer and extracted aqueous layer with dichloromethane (360 mL). Combined both organic layers and washed with water (200 mL) followed by the separation of the organic and aqueous layers. Distilled the organic layer under vacuum at below 40 ºC to obtain the crude product. Crude product was purified by column chromatography by eluting column with petroleum ether and ethyl acetate. Disti-lled the pure fractions under vacuum at below 40 ºC to obtain compound **4**. Yield 76%; FT-IR (KBr, cm^{-1}): 3449 (-OH *str.*), 3018 (-C-H *str.*), 2938 (=C-H *str.*), 1765 (cyclic anhydride –O-C=O), 1599, 1590, 1496 (-C-H scissor), 1458, 755 (-C-F *str.*); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): δ 7.32-7.30 (m, 2H), 7.03-6.99 (m, 1H), 6.91-6.89 (m, 2H), 6.09-6.02 (m, 1H), 5.88-5.81 (m, 1H), 4.956-4.915 (1H, dt, *J* = 7.0 Hz, 2.4 Hz, 4.22-4.16 (t, 2H, *J* = 11.2 Hz, 4.10-4.04 (q, 1H, *J* = 6.4 Hz, 2.72-2.39 (m, 5H).

Synthesis of (3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)hexahydro-2*H*-cyclopenta[*b*]furan-2,5-diol (5): Charged (3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)-5-hydroxyhexahydro-2*H*-cyclopenta[*b*]-furan-2-one (**4**) (3.8 g,0.0117 mol) and THF (38 mL) into clean and dry round bottom flask under nitrogen atmosphere. Cooled the reaction mass to −70 ºC under nitrogen atmosphere followed by the addition of DIBAL-H (28% in toluene, 24.6 mL, 0.043 mol) slowly to the reaction mass at -70 ºC under nitrogen atmosphere for 20-30 min and then stirred the reaction mass for another 20-30 min. Quenched the reaction mass with methanol (10.0 mL) slowly at below -50 ºC in 30 min followed by the addition of water (36 mL) and ethyl acetate (36 mL) to the reaction mass at below -40 ºC. Now allow to cool the reaction mass at 25 ºC and stirred the reaction mass for 30 min. Separated the organic layer and extract the aqueous layer with ethyl acetate (36 mL). Total organic layer was washed with water (36 mL), separated the organic layer and dry over Na_2SO_4. Concentrated the organic layer at below 40 °C under vacuum to obtain compound **5**. Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): δ 7.30 (t, 2H, *J* = 8.0 Hz, 7.02(m, 1H), 6.91(dd, 2H), 6.16 (d, 1H), 5.58 (m, 1H), 4.72 (m, 1H), 4.37 (m, 2H), 4.05 (m, 1H), 2.58 (m, 1H), 2.2 (m, 4H), 1.98 (m, 1H); MS: *m/z* 309.3 (M-H_2O).

Synthesis of (1*S*,3*R*,4*R*,5*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)-5-(2-hydroxyethyl)cyclopentane-1,3-diol (triol) (6)

Method-1: Charged (3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)hexahydro-2*H*-cyclopenta[*b*]furan-2,5-diol (**5**) (3.8 g, 0.0117 mol) and methanol (38.0 mL) into a clean and dry round bottom flask at 25 °C. Cooled the reaction mass to 0-5 °C, slowly added sodium borohydride (0.44 g, 0.0117 mol) into reaction mass at 0-5 ºC. Stirred the reaction mass for 60 min at below 5 °C and monitored by TLC. Quenched the reaction mass by adding acetone (5.0 mL) into reaction mass. Charged water (50 mL) into reaction mass followed by ethyl acetate (50.0 mL) and agitated the mixture for 10 min. Separated the upper organic layer and the aqueous layer was reextracted with ethyl acetate (25.0 mL). Combined organic layer washed twice with water (2 × 25 mL), dried over sodium sulphate, concentrated the organic layer under reduced pressure at below 35 °C affords (1*S*,3*R*,4*R*,5*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)-5-(2-hydroxyethyl)cyclopentane-1,3-diol(triol) (**6**) as white crystalline powder in a quantitative yield.

Method-2: Charged compound **5** (3.8 g,0.0117 mol) and THF (38 mL) into clean and dry round bottom flask under nitrogen atmosphere. Cooled the reaction mass to -70 ºC under nitrogen atmosphere followed by the addition of DIBAL-H (28% in toluene, 49.2 mL and 0.086 mol) slowly to the reaction mass at -20 ºC under nitrogen atmosphere for 20-30 min and finally stirred the reaction mass at 0 ºC for 20-30 min. After completion of the reaction, the reaction mixture was quenched with methanol (10.0 mL) slowly at below -50 ºC in 30 min and then added water (36 mL) and ethyl acetate (36 mL) to the reaction mass at below -40 °C. Allowed the reaction mass to attain the room temperature (25 ºC) and stirred the reaction mass again for 30 min. Separated the organic layer and extract aqueous layer with ethyl acetate (36 mL) and washed total organic layer with water (36 mL). Separated the organic layer and dry over sodium sulphate and then removed the low volatiles at below 40 ºC to afford (1*S*,3*R*,4*R*,5*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)-5-(2-hydroxyethyl)cyclopentane-1,3-diol (triol) (**6**) (Yield: in 3.0 g, 79.0%).

Method-3: Charged compound **5** (3.8 g, 0.0117 mol) and anhydrous tetrahydrofuran (38 mL) into clean and dry round bottom flask under nitrogen atmosphere. Cooled the reaction mass to 0 ºC under N_2 atmosphere and added $LAlH_4$ (0.0117 mol) slowly to the reaction mass at 0 ºC. Stirred the reaction mass at 0 °C for 20-30 min and then quenched the reaction mass with 10% sodium sulphate solution (10.0 mL) slowly at >5 °C. Added water (36 mL) and ethyl acetate (36 mL) into reaction mass and then raise the reaction mass temperature 25 ºC. Stirred the reaction mass for 30 min and filtered the mass through celite bed, washed the bed with ethyl acetate (20 mL). Separated the organic layer and then extracted the aqueous layer with ethyl acetate (36.0 mL). Washed total organic layer with water (36 mL). Separated the organic layer and dried over with sodium sulphate. Removed the low volatiles at below 40 ºC yields compound **6**. Yield 99.0% (3.8 g); ^{19}F NMR: 102.565, 102.838; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): δ 7.25-7.31 (dt, 2H), 6.976-7.013 (t, 1H), 6.89-6.91 (dd, 2H), 4.15-4.21 (t, 2H), 6.02-6.09 (m, 1H), 5.74-5.83 (m, 1H), 2.40-2.46 (q, 1H), 3.93-3.98 (1H, m), 1.73-1.82 (m, 2H), 3.60-3.64 (m, 1H), 2.18-2.24 (m, 1H), 1.61-1.69 (m, 2H), 3.76-3.79 (m, 2H), 4.29 (s, 1H), 3.02-3.04 (d, 1H), 2.78 (s, 2H); ^{13}C NMR: 30.15, 42.33, 49.01, 55.80, 61.63, 69.03, 69.76, 72.96, 77.32, 138.44, 138.61, 123.57, 124.06, 118.13, 129.60, 114.76, 121.83, 157.90; Mass (ESI/MS positive mode): (*m/z*): 329 (M+H).

RESULTS AND DISCUSSION

During the synthesis of tafluprost from Corey aldehyde (**1**) [10] (**Scheme-I**), while DIBAL-H reduction of lactone **4** to lactol **5** (or hydroxy aldehyde), one more new impurity formation is observed, and this impurity is carried forwarded to final drug substance and resulted in the less yields of tafluprost. As per ICH quantification threshold of 0.15% [11] for known impurities and unspecified impurities are controlled to the ICH level of not more than (NMT) 0.10%.

To identify the impurity, which is formed during the reduction, few experiments were carried out with different mol ratio of DIBAL-H during the reduction of lactone to lactol. The observed results are tabulated below (results are measured by quantitative TLC). In present investigation, when lactone **4** reacted with 2, 3.5, 4.5, 6 and 10 mol ratio of DIBAL-H, yielded lactol **5** in 70%, 80%, 60%, 40% and 20%, respectively apart from obtained triol impurity 2%, 5%, 20%, 30% and 60%, respectively. It is also observed that when the usage of mole ratio of DIBAL-H increased the desired product yields decrease and simultaneously the impurity conversion also increases.

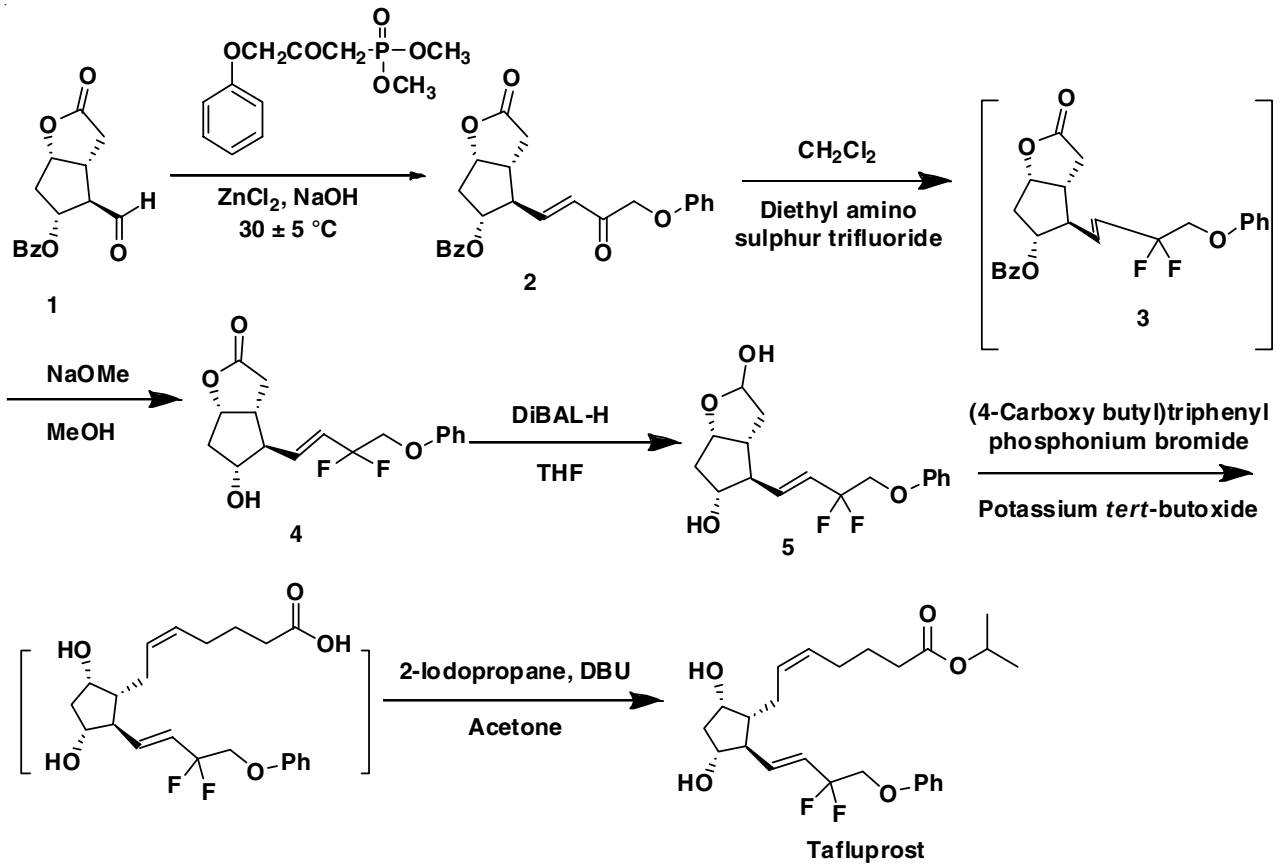
Lactone requires minimum of three equivalents DIBAL-H to convert lactol due to free hydroxyl group, hence good conversion was observed with 3.5 mol ratio of DIBAL-H when compared with 2.5 mol ratio of DIBAL-H. The over reduction impurity was increased due to the increased mole ratio of DIBAL-H above 3.5 mol ratio, since the obtained lactol further reacts with excess of DIBAL-H.

While the synthesis of tafluprost, a new impurity **6** was formed due to the over reduction of lactone **4**. The synthesis of this impurity is mandatory and to establish the controls of this impurity in the final drug substance, tafluprost to qualify the drug. A simple laboratory three different methods were used for the synthesis of this novel impurity.

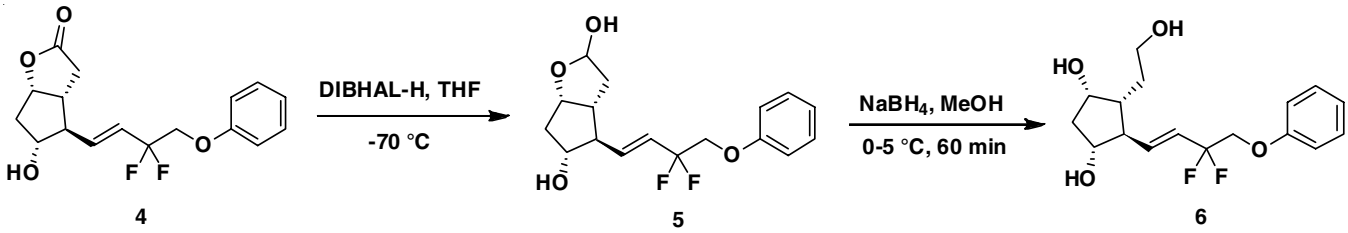
In the first method, the reaction of compound **5** with $NaBH_4$ in methanol at 0-5 ºC afforded a new impurity (1*S*,3*R*,4*R*, 5*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-enyl)-5-(2-hydroxyethyl)-cyclopentane-1,3-diol (triol) (**6**) with 60% yield (**Scheme-II**).

Alternatively, triol impurity **6** was synthesized by reaction with higher molar ratio of DIBAL-H in THF at -78 ºC, under N_2 atmosphere. The reaction mixture was stirred for a period of 30 min gave a product exactly matched with the triol impurity **6** in 78% yield (**Scheme-III**).

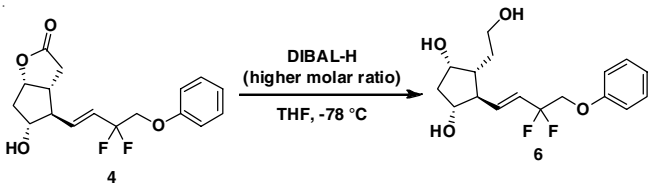
In a third alternative method, which is a single and direct synthesis of triol impurity **6**. The so called lactone **4** was treated with one mole of $LiAlH_4$ in THF under anhydrous conditions at 0 ºC and followed the reaction mixture was stirred for a period of 30 min gave the triol impurity in 99.9% yield (**Scheme-IV**).



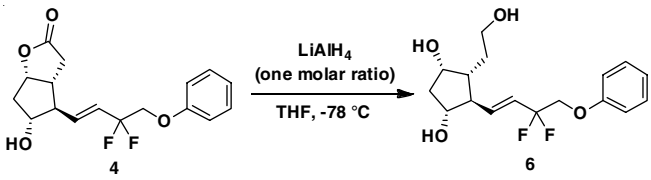
Scheme-I: Synthetic route for tafluprost



Scheme-II: Synthesis of triol impurity by $NaBH_4$



Scheme-III: Alternative synthesis of triol impurity by using higher molar ratio of DIBAL-H



Scheme-IV: Alternative synthesis of triol impurity 6 by using $LiAlH_4$

Conclusion

In summary, a successful attempt is made to isolate, synthesize and characterize the impurity, (*Z*)-isopropyl 7-((1*R*,2*R*,3*R*,5*S*)-2-((1*E*,3*Z*)-3-fluoro-4-phenoxybuta-1,3-dienyl)-3,5-dihydroxycyclopentyl)hept-5-enoate, an important impurity which generally formed during the synthesis of tafluprost. This investigation is more helpful in pharmaceutical industry to avoid formation of impurity and can help to synthesize tafluprost in high yields.

ACKNOWLEDGEMENTS

The authors sincerely thank to the authorities of MSN Laboratories, Hyderabad, India for the financial and analytical support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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