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Improved Process for the Preparation of Naloxegol Oxalate, an Opiod Receptor Antagonist

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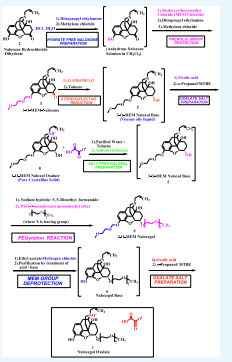
ABSTRACT: The present article discloses an improved and robust commercial process of the modern medicine naloxegol oxalate, which is used to treat opioid-induced constipation. The synthesis originates from the easily available key starting material, viz., naloxone, and ends with the oxalate salt of naloxegol (a pharmaceutically acceptable salt). This novel route has a very high yield and purity greater than 99.5%, substantially free from impurities (less than 1%).



INTRODUCTION

Naloxegol oxalate (Figure 1) is chemically known as (5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate and has a structure of compound (**1**). Naloxegol is a PEGylated derivative of naloxone.[1−4]

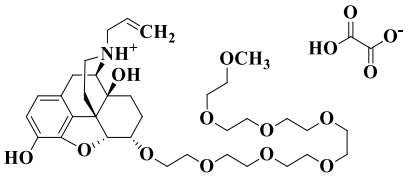


Figure 1. Naloxegol oxalate (**1**).

Naloxegol oxalate (Figure 1) was approved by the U.S. Food and Drug Administration (FDA) on September 16, 2014, and then approved by the European Medicine Agency (EMA) on December 8, 2014. It was developed and marketed as Movantik (in the US)/Moventig (in EU) by AstraZeneca.

Naloxegol is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancerous pain. Naloxegol works by treating constipation without reducing the pain-relieving effects. Naloxegol antagonizes μ- and κ-opioid receptors and displays low affinity to δ-opioid receptors in the GI tract, thereby decreasing opioid-induced bowel dysfunction symptoms without reversing central analgesic effects. Naloxegol is metabolized through CYP3A4 to six metabolites, with the majority of the dose (68%) excreted with feces and less (16%) with urine.[5−7]

Naloxegol is a peripherally selective opioid antagonist acting μ-opioid receptor antagonist used to treat OIC in adult patients with chronic noncancerous pain.[8−10]

PEGylation confers increased oral bioavailability and peripheral selectivity to the naloxone moiety by a reduction in passive permeability across the blood−brain barrier. Naloxegol is also a substrate of the P-glycoprotein transporter, which promotes efflux of naloxegol and serves to further restrict its entry into the central nervous system. The advantage of naloxegol over the opioid antagonist naloxone is that its PEGylated structure allows for high selectivity for peripheral opioid receptors and lack of entry into the central nervous system through the blood−brain barrier.[11,12]

Naloxegol was previously a Schedule II drug in the United States because of its chemical similarity to opium alkaloids but was recently reclassified as a prescription drug after the FDA concluded that the impermeability of the blood−brain barrier for this compound made it non-habit-forming and thus without the potential for abuse—specifically, naloxegol was officially decontrolled on January 23, 2015.[13]

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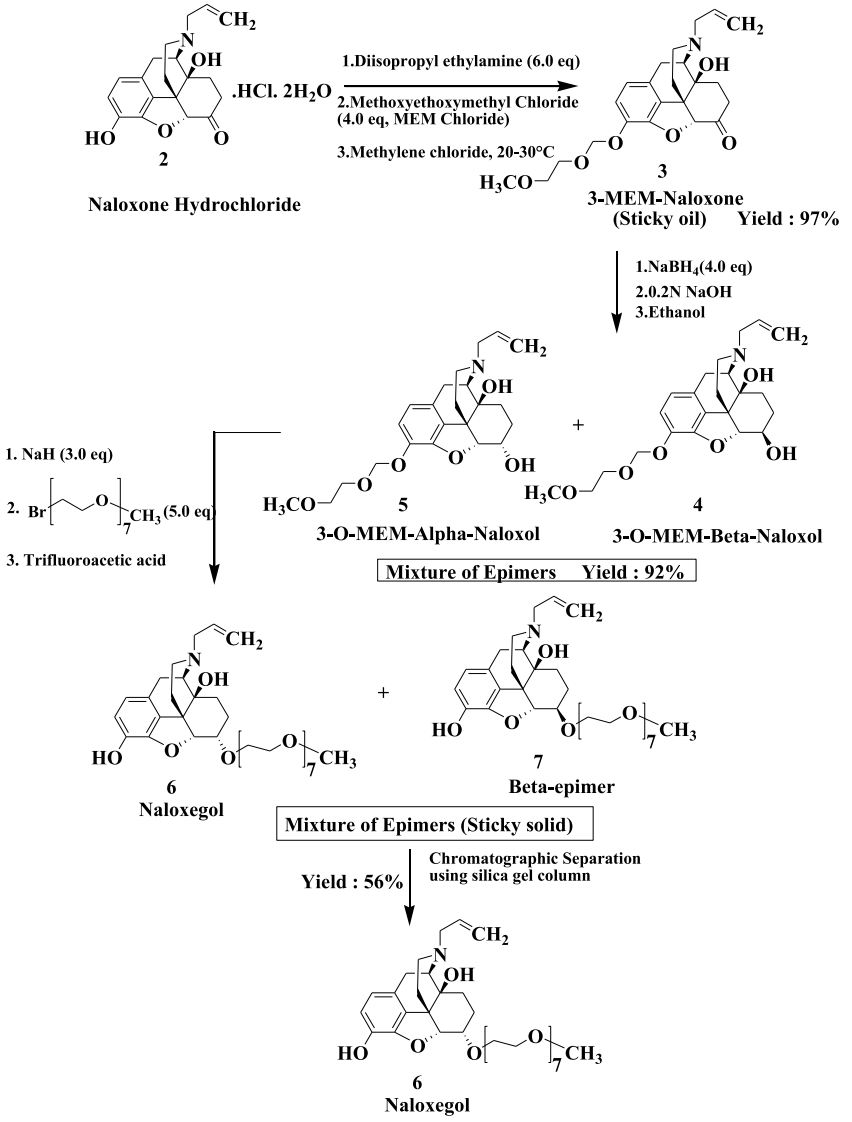
Scheme 1. Naloxegol Synthetic Process (Disclosed in US Patent No. 7,786,133 B2)



RESULTS AND DISCUSSION

The present article is published as a patent by our team. IN application, 201741022942, has been granted as IN389154 and US 11,077,103 B2.

US patent no. 7,786,133 B2 discloses a process for preparing naloxegol. The process is depicted in Scheme 1:

We have observed that the process reported will give a thick viscous liquid of MEM-naloxone and 3-*O*-MEM α naloxol, which contains un-reacted reagents of the process as well as the process impurity, 3,14-di-*O*-MEM-naloxone.

These impurities are carried forward in subsequent steps to naloxegol. These impurities are generated during the preparation of intermediates and are undesirable and require a tedious purification process, for example, column chromatography, at the naloxegol base, which is the penultimate stage of drug substance, which leads to more yield loss and high non-operation in a bulk scale.

Therefore, there is a need to develop an improved process for naloxegol, which involves isolation of MEM-naloxone and 3-*O*-MEM α-naloxol or a pharmaceutically acceptable salt in the solid form; the purification of 3-*O*-MEM naloxegol and naloxegol base is required to obtain pure naloxegol oxalate.

The synthetic route to make naloxegol oxalate is divided into two parts.

(A) Synthesizing naloxegol oxalate from naloxone hydrochloride (Scheme 2).

(B) Synthesizing the PEG-7 side chain (Scheme 3).

Part A: Synthesis of Naloxegol Oxalate (1). The 3-MEM protective group is the same in both the schemes, but the main difference is stereoselective reagent in addition to an additive; we used lithium tri-*tert*-butoxy aluminium hydride (LTBA) reagent to get more selectivity and to avoid column chromatography. 3-*O*-MEM naloxone and 3-*O*-MEM naloxol intermediates were isolated as solids instead of an oil mass/residue in Scheme 1, and we got a pure form of naloxegole base by acid−base work-up without column chromatography.

The process of making naloxegol oxalate begins with the synthesis of 3-*O*-MEM naloxone (**3**). The synthesis of 3-*O*-MEM-naloxone involves the protection of the phenolic group in naloxone hydrochloride dihydrate (**2**) to prevent naloxone from undergoing any other functional group transformation. The protecting group should be stable under basic conditions and non-labile under mildly acidic reduction conditions. We

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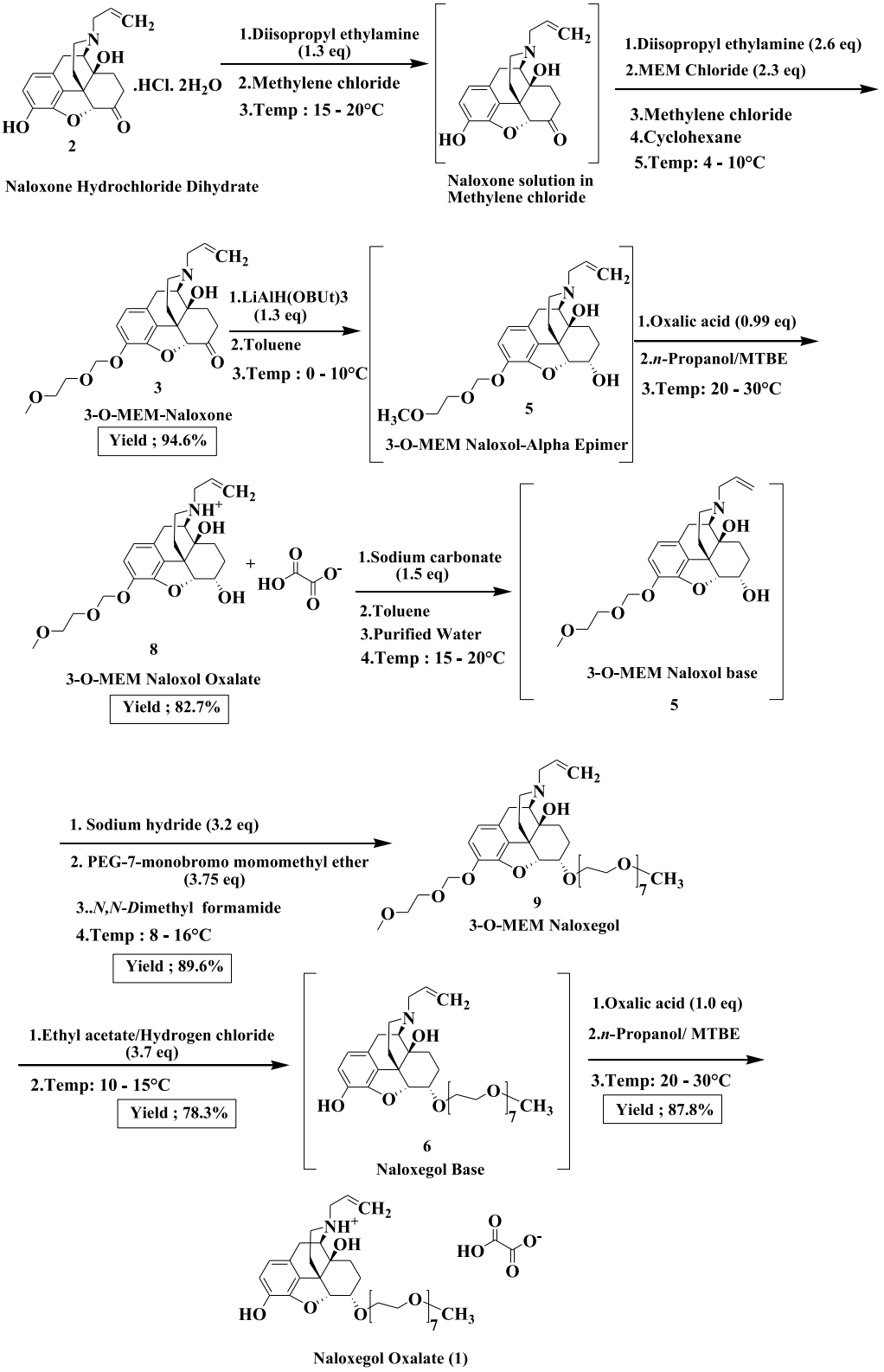
ACS Omega 2023, 8, 3415−3422

Scheme 2. Synthesis of Naloxegol Oxalate (Part A)



tried with the benzyl protecting group, while the deprotection of benzyl group, the allylic functional group in naloxegol, also got reduced. We chose methoxyethoxymethyl chloride (MEM-Cl) for the protection of the free phenolic group based on the literature report.[1] The synthesis of MEM chloride was done by reacting 2-methoxy ethanol with paraformaldehyde.[14,15]

After exploring several bases and reaction conditions, the protection of the phenolic group was optimized using MEM chloride and di-isopropylethylamine as a base; the results of various bases and their purity are shown in Table 1.

Our next challenge was to obtain a pure 3-*O*-MEM naloxol α-epimer; we started performing stereoselective reduction and

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ACS Omega 2023, 8, 3415−3422

Scheme 3. Synthesis of PEG-7 Side Chain (Part B)

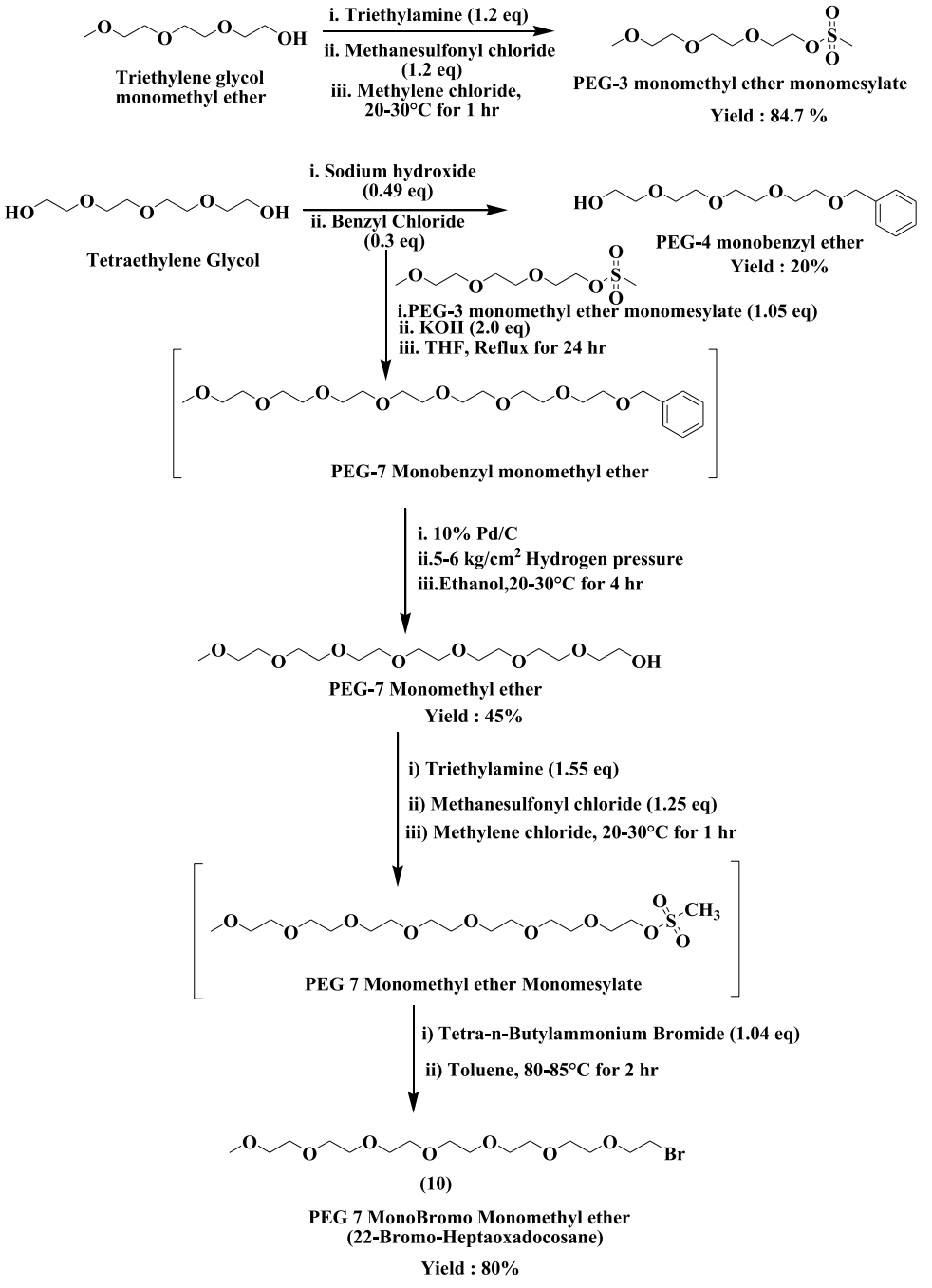

Table 1. Selection of a Base

entry	name of the base used	solvent	temperature (°C)	HPLC purity
1	potassium *tert*-butoxide	THF	0−10	pure compound was not obtained
2	sodium carbonate	MDC	23−28	95.68%
3	di-isopropylethylamine	MDC	10−15	99.32%

targeted a good reagent that must be a reagent of choice for stereoselective reduction and the best condition for reduction, and a series of experiments were executed. The results of these experiments with α/β epimer ratios tabulated are shown in Table 2.

When we were performing stereoselective reduction with traces of 2-methoxy ethanol, we found that the use of a small amount of additive such as 2-methoxyethanol improves the α/β ratio in the range of about 99:1 to 100:0 or about 99:1 to 99.6:0.4.

From the above results, we concluded that LTBA is the best reagent compared with sodium borohydride to improve the diastereoselectivity and avoid column chromatography for separation of isomers. Remaining reagents are very difficult to handle in a bulk scale in terms of safety aspects. The best condition for the conversion of 3-*O*-MEM naloxone to 3-*O*-MEM α-naloxol is using 1.3 equiv of LTBA as a stereoselective reagent, toluene as a solvent, and an additive such as 2-methoxyethanol at lower temperatures (0−8 °C). 3-*O*-MEM

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ACS Omega 2023, 8, 3415−3422

Table 2. Selection of a Stereoselective Reducing Agent

entry	reducing agent	reaction condition	yield (%)	α/β epimer ratio
1	sodium borohydride	$NaBH_4$ 1.66 equiv, ethanol, 15−20 °C	80	70:30
2	sodium tri-*sec*-butylborohydride (N-selectride)	N-selectride 1.5 equiv, THF, 20 °C	95	100:0
3	potassium tri-*sec*-butylborohydride (K-selectride)	K-selectride 1.5 equiv, THF, 20 °C	94	100:0
4	sodium triethylborohydride	$NaBHEt_3$ 1.5 equiv, THF, 0 °C	85	100:0
5	sodium bis(2-methoxyethoxy)aluminium hydride (vitride)	vitride 2.5 equiv, THF, 22−28 °C	86	85:15
6	sodium triacetoxyborohydride	$NaBH(OAc)_3$ 2.0 equiv, acetic acid 1 equiv, toluene, 22−28 °C	99.6	97.34:2.66
7	sodium triacetoxyborohydride	$NaBH(OAc)_3$ 2.0 equiv, acetic acid 1.0 equiv, toluene, 22−28 °C	99.6	97.34:2.66
8	lithium tri-*tert*-butoxy aluminium hydride (LTBA)	LTBA 1.3 equiv, THF, 13−15 °C	91	99.78:0.22
9	lithium tri-*tert*-butoxy aluminium hydride (LTBA)	LTBA 1.3 equiv, toluene, 2-methoxyethanol, 0−8 °C	99	99.91:0.09

α-naloxol is a viscous oily liquid; to make the 3-*O*-MEM α-naloxol into a solid form and free from volatile organic impurities, various salts of 3-*O*-MEM α-naloxol were made, but finally oxalic acid was chosen for making oxalate salt, among the hydrochloride, fumarate, and maleate salts. As oxalic acid is a mild acid and deprotection of the MEM group does not happen, the resulting salt has better filterability and good purity profile with respect to the 6-α-naloxol impurity formation.

O-Alkylation of 3-*O*-MEM α-naloxol oxalate salt (**8**) was attempted using excess mole equivalents of sodium hydride as a base and leaving the reaction for longer hours, but the PEGylation did not go for completion. This prompted us to release the free base (3-*O*-MEM α-naloxol). After performing several alkylation reactions with PEG-7 monobromo monomethyl ether using various bases and several reaction conditions, we found that sodium hydride is the best base and a mixture of dimethylformamide (DMF) and toluene is an appropriate solvent mixture for alkylation. The O-alkylation product 3-*O*-MEM naloxegol is treated with oxalic acid; the solution of oxalic acid addition salt is washed with toluene to remove excess PEG-7 monobromo monomethyl ether and its related impurities, which is further treated with a base sodium carbonate with a pH of about 7.5−9.0 and extracted into methylene chloride to improve the purity greater than 95.5%.

Several hit-and-trail reactions were performed on 3-*O*-MEM naloxegol for the deprotection of MEM chloride. When deprotection was attempted using a mixture of trifluoroacetyl and MDC, it resulted in the formation of several impurities. There was no product formation when the deprotection was tried using CBr_4 and methanol as the reagent and solvent, respectively. Using HBr in acetic acid as a deprotecting agent resulted in the dealkylation of the side chain. The reaction was very slow, with several impurities formed when aqueous HCl was used for the removal of MEM chloride. There was no deprotection, and the reaction did not proceed when aqueous acetic acid was used for deprotection. HCl in ethyl acetate emerged as a suitable reagent for deprotecting MEM chloride in 3-*O* MEM naloxegol (**9**), without any side products. 6% HCl in ethyl acetate is optimal for the deprotection of MEM chloride. The MEM deprotection product naloxegol base is treated with hydrobromic acid, and the aqueous solution of naloxegol hydrobromide is washed with methylene chloride to remove dialkylated naloxegol impurities, which is further treated with a base sodium carbonate with a pH of about 7.5−9.0 and extracted into methylene chloride to obtain the naloxegol free base in a pure form.

The resultant pure naloxegol base (**6**) is transformed into oxalate salt using anhydrous oxalic acid and a mixture of *n*-propanol and methyl-*tert*-butylether (MTBE) solvents for salt preparation. The resulting naloxegol oxalate (**1**) has a purity of >99.5%.

Part B: Synthesis of PEG-7 Side Chain (10): (PEG-7 Monobromo Monomethyl Ether). The synthesis of naloxegol side chain (Scheme 3) was achieved by performing the synthetic procedure mentioned in the literature.[1,2]

EXPERIMENTAL SECTION

All the solvents and reagents were obtained from commercial sources and were used without purification. The IR spectra (ϑ_{max}, cm^{-1}) were recorded in a solid-state KBr dispersion using a PerkinElmer Fourier transform infrared (FTIR) spectrometer. The ^1H NMR spectra were recorded on Bruker Advance 300 and 500 MHz spectrometers. The chemical shifts were reported in δ/ppm relative to tetramethylsilane. The mass spectra were recorded on an API 2000 PerkinElmer PESciex mass spectrometer. The reactions were monitored by high-performance liquid chromatography (HPLC). HPLC analysis was performed on a Waters instrument with a UV detector (230 nm) using a Ascentis Express C18 (150 mm × 4.6 mm, 2.7 μm) column. The column oven temperature was 30 °C. Mobile phase A was prepared using a degassed mixture of buffer pH 2.0, acetonitrile, and tetrahydrofuran (THF) in the ratio 940:20:40 v/v/v; buffer pH 2.0 was prepared by dissolving 1.1 g of octane-1-sulfonic acid sodium salt in 1000 mL of water. The pH was adjusted to 2.0 ± 0.05 with orthophosphoric acid. Mobile phase B was prepared using a degassed mixture of acetonitrile and THF in the ratio 960:40 v/v. The flow rate was 1.0 mL/min. A gradient (A/B) of 95:05 (0−10 min), 90:10 (5−20 min), 80:20 (20−35 min), 60:40 (35−55 min), and 95:05 (55−70 min) was used. Melting points were determined on a Polman melting point apparatus (model no. MP96) by the open capillary method and were uncorrected.

Preparation of 3-*O*-MEM Naloxone (3). *N*,*N*′-Diisopropylethylamine (21.4 g, 166 mmol) was added slowly to a solution of naloxone hydrochloride dihydrate (50 g, 125 mmol) in dichloromethane (350 mL) at 15−20 °C. Purified water (110 mL) was added, and the biphasic solution was stirred. The layers were separated, and the aqueous layer was extracted with dichloromethane. The organic layers were combined and concentrated by distillation under reduced pressure at a temperature less than 40 °C until the volume reached ∼200 mL and the dichloromethane solution got dehydrated and dried. Diisoproplethylamine (42 g, 325 mmol) was added to the dichloromethane solution at 4−10 °C; a solution of MEM chloride in dichloromethane (36 g, 289

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ACS Omega 2023, 8, 3415−3422

mmol MEM chloride in 100 mL of dichloromethane) was added to the mass over 55−65 min at 4−10 °C. After reaction completion, purified water was added and the biphasic solution was stirred. The layers were separated, and the aqueous layer was extracted with dichloromethane. Two organic layers were combined, and the combined extract was washed with aqueous sodium hydroxide solution to remove the unreacted naloxone. The dichloromethane extract was concentrated to an oily residue. Last traces of dichloromethane were removed by co-distilling with a small amount of cyclohexane. The residue was stirred for 6 h with cyclohexane (400 mL) at about 16 °C for the complete precipitation of the product; the slurry was filtered and washed with cyclohexane (100 mL, 24 °C) and then dried at about 40 °C under reduced pressure until constant weight. The yield was 49.1 g (94.6%). Melting range: 58−62 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.58 & 1.84 (2m, 2H), 1.61 & 2.11 (2m, 2H), 1.64 & 2.20 (2m, 2H), 2.40 & 2.55 (2m, 2H), 2.60 & 3.14 (2m, 2H), 2.97 (m, 1H), 3.05 (m, 2H), 3.36 (s, 3H), 3.57 (m, 2H), 3.88 (m, 2H), 4.66 (s, 1H), 5.02 (br s, 1H), 5.23 (m, 2H), 5.28 & 5.35 (2d, 2H, J = 6.6 Hz), 5.81 (m, 1H), 6.62 (d, 1H, J = 8.1 Hz), 6.93 (d, 1H, J = 8.1 Hz); FT-IR (KBr, cm^{-1}): 3104, 3067, 2341, 2125, 1906, 1643, 1291, 785, 709; HRMS (ESI-QTOF) for $C_{23}H_{29}NO_6$ $[M + H]^+$: m/z calcd, 416.2073; found, 416.2273. Purity (by HPLC): 99.85%.

Preparation of 3-*O*-MEM Naloxol α-Epimer (5). LTBA (19.93 g, 78.35 mmol) was added to toluene at 0−10 °C. 3-*O*-MEM naloxone (∼200 mL, prepared by dissolving 25 g, 60.24 mmol 3-*O*-MEM naloxone in a mixture of 187 mL toluene and 1 g of 2-methoxyethanol) was added slowly drop-wise to the above-obtained pre-cooled suspension of LTBA in toluene at 0−10 °C. After addition, the temperature of the reaction mass was raised to 20−30 °C and the reaction mass was stirred for 1 h. The reaction was then stopped by adding ethyl acetate (2.5 mL) to the reaction mass at 5−10 °C. Further aqueous ammonium sulfate solution (10 g ammonium sulfate dissolved in 15 mL demineralized water) was added to the reaction mass at 5−10 °C and stirred for 10 min. The reaction mixture was treated with hyflo at 20−30 °C, filtered through a thin hyflo bed, and washed with toluene. The toluene layer was separated and washed with demineralized water and then butylated hydroxy toluene (BHT) was added to the toluene extract. The solvents were removed using a rotary evaporator at temperatures less than 60 °C to give a viscous oily liquid (25.1 g, 100% isolated yield). HPLC analysis indicated that 3-*O*-MEM naloxol-α-epimer was about 99.4% and 3-*O*-MEM naloxol-β-epimer was about 0.3%.

Preparation of 3-*O*-MEM α-Naloxol Oxalate Salt (8). 3-*O*-MEM α-naloxol (5 g, 11.99 mmol) was dissolved in *n*-propanol (20 mL) at 20−30 °C under nitrogen atmosphere. Oxalic acid (anhydrous) (1.07 g, 11.88 mmol) was dissolved in *n*-propanol (10 mL) and added slowly drop-wise to the above reaction mass at 20−30 °C and stirred for 30 min. Further, methyl *tert*-butyl ether (30 mL) was added slowly drop-wise to the above reaction mass at 20−30 °C. Oxalate salt precipitated out during addition, which was stirred for 90 min at 20−30 °C. The product was filtered under nitrogen atmosphere and washed with methyl *tert*-butyl ether (20 mL) and dried under vacuum at 20−25 °C to afford a white solid. Yield: 5.02 g (82.7%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.50 & 1.65 (2m, 2H), 1.53 & 1.60 (2m, 2H), 2.06 & 3.63 (2m, 2H), 2.64 & 2.73 (2m, 2H), 3.02 & 3.17 (2m, 2H), 3.34 (s, 3H), 3.35 (m, 1H), 3.51 (m, 2H), 3.76 & 3.91 (m, 2H), 3.78 (m, 1H), 3.79 & 4.19 (m, 2H), 4.66 (d, 1H, J = 6.6 Hz), 5.10 & 5.67 (2d, 2H, J = 6.6 Hz), 5.51 (m, 2H), 6.07 (m, 1H), 6.68 (d, 1H, J = 8.4 Hz), 6.91 (d, 1H, J = 8.4 Hz); FT-IR (KBr, cm^{-1}): 3084, 2837, 1364, 1313, 823, 763, 732; HRMS (ESI-QTOF) for $C_{23}H_{31}NO_6$ $[M + H]^+$: m/z calcd, 418.2229; found, 418.2452.

Preparation of 3-*O*-MEM Naloxegol (5). Sodium carbonate (3.14 g, 29.6 mmol) was dissolved in water (50 mL), and to this solution was added toluene (45 mL) and 3-*O*-MEM-α-naloxol oxalate (10 g, 19.7 mmol) at 15−20 °C. The resulting solution was stirred at 20−30 °C for 30 min, and the organic layer was separated and an aqueous layer was extracted with toluene. The combined organic layer was washed with water. BHT (0.4 g, 1.81 mmol) was added to the organic layer and then concentrated at a temperature less than 60 °C until the volume reached ∼20 mL. In another reaction vessel, sodium hydride (1.5 g, 64.6 mmol) was added into a mixture of DMF (4 mL) and toluene (16 mL) at 5−10 °C. To this slurry was added diluted solution of 3-*O*-MEM-α-naloxol base (∼20 mL) diluted with DMF (2 mL) in 30 min and then stirred for 30 min under nitrogen atmosphere. Thereafter, a solution of 22-bromo-heptaoxadocosane (**10**) (30 g, 74 mmol) in sodium hydride and a mixture of toluene (24 mL) and DMF (12 mL) were added for 3−4 h at 8−16 °C. After reaction completion, aqueous ammonium chloride (15% w/w, 100 mL) was added to the reaction mass and extracted with toluene (70 mL). The combined organic extracts were washed with brine (30 mL). Thereafter, the washed organic layer was diluted with purified water and then cooled to 15−20 °C. This solution was acidified with an aqueous oxalic acid solution (10% w/w) at 15−20 °C. The organic layer was separated and the aqueous layer was washed with dichloromethane. The resulting aqueous layer containing 3-*O*-MEM-naloxegol oxalate salt was added to dichloromethane (50 mL) followed by neutralization with an aqueous sodium carbonate solution (20% w/w) and stirred for 20 min at 20−30 °C. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was concentrated by distillation under reduced pressure to afford 3-*O*-MEM-naloxegol, as a pale-yellow liquid. Yield: 13 g (89.6%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 & 1.60 (2m, 2H), 1.47 & 2.19 (2m, 2H), 1.56 & 1.72 (2m, 2H), 2.21 & 2.54 (2m, 2H), 2.58 & 3.08 (2dd, 2H, J = 6.6 Hz), 2.88 (d, 1H, J = 6.3 Hz), 3.10 (d, 2H, J = 6.3 Hz), 3.35 (s, 3H), 3.36 (s, 3H), 3.51−3.69 (m, 28H), 3.53 (m, 1H), 3.74 & 3.93 (2m, 2H), 3.87 (m, 2H), 4.71 (d, 1H, J = 4.2 Hz), 4.88 (br s, 1H), 5.16 & 5.26 (2m, 2H), 5.23 & 5.29 (2d, 2H, J = 6.6 Hz), 5.79 (m, 1H), 6.53 (d, 1H, J = 8.1 Hz), 6.91 (d, 1H, J = 8.1 Hz); MASS (PE SCIEX-API 2000) ESI for $C_{38}H_{61}NO_3$ $[M + H]^+$: m/z calcd, 740.9; found, 740.2. HPLC purity: 95.76% by HPLC; impurities: 1.44% (3-*O*-MEM α naloxol) and 0.83% (6,14-dialkylated 3-*O*-MEM naloxegol).

The title compound was also prepared by using 22-OMs-heptaoxadocosane instead of 22-bromo-heptaoxadocosane (**10**) in a manner similar to that described above.

Preparation of Naloxegol Base (6). Hydrogen chloride (∼6% w/w) solution in ethyl acetate (31 g, 51 mmol) was slowly added to the solution of 3-*O*-MEM naloxegol (10 g, 13.5 mmol) in ethyl acetate (20 mL) containing BHT (0.1 g, 0.45 mmol) at 10−15 °C, and the mixture was stirred for ∼90 min at 10−15 °C. After reaction completion, purified water (50 mL) was added at 10−20 °C. The organic layer was separated, and the aqueous layer was washed with ethyl acetate (20 mL). The aqueous solution containing naloxegol hydrochloride was neutralized by the addition of an aqueous sodium

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ACS Omega 2023, 8, 3415−3422

carbonate solution (20% w/w) and the product was extracted with dichloromethane (80 mL). The dichloromethane solution was concentrated by distillation under reduced pressure to obtain a pale-yellow viscous liquid/residue. The residue was diluted with purified water (30 mL) and then acidified by the addition of an aqueous hydrobromic acid solution (~20% w/w) at 10−20 °C. The aqueous solution containing hydrobromide salt was washed with dichloromethane. The washed aqueous solution containing naloxegol hydrobromide was neutralized with an aqueous sodium carbonate solution, extracted with dichloromethane, washed with water, and then concentrated to afford a naloxegol base, as a pale-yellow viscous liquid. Yield: 6.9 g (78.3%). ^{1}H NMR (500 MHz, DMSO-d_6): 1.03 & 2.44 (2m, 2H), 1.33 & 1.35 (2m, 2H), 1.46 & 2.11 (2m, 2H), 2.50 & 2.52 (2m, 2H), 2.79 & 3.08 (m, 2H), 3.23 (s, 3H), 2.97 (m, 1H), 3.50−3.63 (m, 28H), 3.57 (m, 1H), 3.65 (d, 2H, J = 6.3 Hz), 3.84 (m, 1H), 4.59 (d, 1H, J = 4.2 Hz), 5.14 (m, 2H), 5.80 (m, 1H), 6.43 (d, 1H, J = 8.1 Hz), 6.54 (d, 1H, J = 8.1 Hz), 8.95 (s, 1H); FT-IR (KBr, cm^{-1}): 3377, 3077, 2873, 1960, 1640, 1613, 1193, 879, 763, 728; MASS (PE SCIEX-API 2000) ESI for $C_{34}H_{53}NO_{11}$ [M + H]$^+$: m/z calcd, 652.36; found, 652.3.

Preparation of Naloxegol Oxalate (1). Naloxegol (5 g, 7.67 mmol) was dissolved in MTBE (40 mL) and n-propanol (5 mL). The solution of oxalic acid (0.7 g, 7.77 mmol) prepared in MTBE (30 mL) and n-propanol (2 mL) was added slowly to the naloxegol base solution. Naloxegol oxalate was precipitated during addition, and the product slurry was further stirred for about 3 h. It was then cooled to 12−15 °C and further stirred for about 45 min. The product was filtered under nitrogen atmosphere and washed with MTBE and dried under vacuum at 25−30 °C to afford a white solid. Yield: 5.0 g (87.8%). ^{1}H NMR (300 MHz, D_2O): 1.10 & 1.60 (2m, 2H), 1.42 & 1.53 (2m, 2H), 1.64 & 2.33 (2m, 2H), 2.84 & 3.23 (2m, 2H), 2.90 & 3.41 (m, 2H), 3.23 (s, 3H), 3.39−3.58 (m, 28H), 3.55 (m, 1H), 3.66 (m, 2H), 3.86 (m, 1H), 4.69 (d, 1H, J = 4.54 Hz), 5.43 (dd, 2H, J = 10.23 Hz), 5.87 (m, 1H), 6.49 (d, 1H, J = 8.1 Hz), 6.63 (d, 1H, J = 8.1 Hz); FT-IR (KBr, cm^{-1}): 3349, 2877, 1682, 1640, 1616, 1474, 1482, 1089; HRMS (ESI-QTOF) for $C_{34}H_{53}NO_{11}$ [M + H]$^+$: m/z calcd, 652.3697; found, 652.3698. Purity: 98.58% by HPLC; impurities: 0.03% (3-O-MEM naloxegol), 0.05% (dialklated naloxegol), 0.08% (β-epimer), 0.64% (PEG-8 naloxegol), 0.37% (PEG-6 naloxegol), 0.08% (PEG-5 naloxegol) and 0.07% (PEG-3 naloxegol).

Part B: Synthesis of PEG-7 Side Chain (10): (PEG-7 Monobromo Monomethyl Ether). *Preparation of Triethylene Glycol Monomethyl Ether Monomesylate.* Triethylene glycol monomethyl ether (200 g, 1.21 mol) was dissolved in methylene chloride (800 mL). To this solution was added triethylamine (148 g, 1.46 mol) and cooled to 0−5 °C. The solution of methanesulfonyl chloride (167.4 g, 1.46 mol) prepared in methylene chloride (260 mL) was added slowly to the above solution and stirred for 1 h at 20−30 °C. The mixture was then cooled to 5−10 °C, and water (400 mL) was added. The layers were separated, and the organic layer was washed with aqueous $NaHCO_3$ solution followed by water and then concentrated by distillation under reduced pressure to afford the title compound as a pale yellow liquid. Yield: 250 g (84.7%). ^{1}H NMR (500 MHz, $CDCl_3$): 3.07 (s, 3H), 3.37 (s, 3H), 3.53−3.69 (m, 8H), 3.77 (m, 2H), 4.38 (m, 2H); MASS (GC−MS) for $C_8H_{18}SO_6$ [M + H]$^+$: m/z calcd, 243; found, 243.

Preparation of Tetraethylene Glycol Monobenzyl Ether. Sodium hydroxide powder (47.5 g, 1.18 mol) was slowly added to tetraethylene glycol (460 g, 2.37 mol) at 20−25 °C. Benzyl chloride (100 g, 0.79 mol) was added slowly to the mixture and stirred for 6 h. Water (1 L) was added slowly, and the pH of the reaction was adjusted to 9.5−10 with an aqueous HCl solution. The aqueous layer was extracted with cyclohexane to remove the tetraethyleneglycol dibenzylether. The aqueous layer was again extracted with toluene, and the organic layer was washed with an aqueous NaCl solution and then concentrated to afford a titled compound. Yield: 135 g (20%). ^{1}H NMR (500 MHz, DMSO): 3.40−3.55 (m, 16H), 4.48 (s, 2H), 7.32−7.34 (m, 5H); FT-IR (KBr, cm^{-1}): 3087, 3005, 2135, 1815, 1758, 1644, 1603, 1586; MASS for $C_{15}H_{24}O_5$ [M + Na]$^+$: m/z calcd, 307; found, 307.

Preparation of Heptaethylene Glycol Monomethyl Ether. Potassium hydroxide (40 g, 0.71 mol) was added to THF (600 mL), and then, tetraethylene glycol monobenzyl ether (100 g, 0.352 mol) was added; the temperature was raised to 60−70 °C, and the solution was stirred for 30 min. The solution of triethyleneglycol monomethyl ether monomesylate (90 g, 0.371 mol) prepared in THF (100 mL) was added slowly to the above solution and stirred for 24 h at reflux. The reaction mixture was concentrated under reduced pressure and water was added. The concentrated aqueous reaction mass was extracted with cyclohexane followed by toluene to remove the nonpolar impurities. The separated organic layer was washed with aqueous sodium chloride solution and then concentrated to afford heptaethyleneglycol monobenzyl monomethylether (120 g) as a reddish-brown residue (HPLC purity 96.2%).

The above concentrate mass was dissolved in ethanol and treated with carbon. To the filtrate, conc. HCI (1.2 mL) was added and then the solution was taken in an autoclave and 10% palladium on a carbon paste (2.50 g, contains ~50% w/w water) was added and 5−6 kg/cm^2 hydrogen pressure was used for 4 h. Sodium bicarbonate (3.6 g) was added to neutralize the hydrochloric acid and filtered through a hyflo pad; the residue was washed with ethanol. The combined ethanol filtrate was concentrated to a yellow oily residue. The concentrated mass was dissolved in water and washed with ethyl acetate. Two layers were separated, and the aqueous layer was again extracted with methylene chloride, and the organic layer was washed with purified water and concentrated under reduced pressure to afford the titled compound as a pale-yellow liquid. Yield: 54 g (45%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.38 (s, 3H), 3.53−3.75 (m, 28H); MASS (GC−MS) for $C_{15}H_{32}O_8$ [M + H]$^+$: m/z calcd, 341; found, 341.

*Preparation of 22-Bromo-2,5,8,11,14,17,20-heptaoxadocosane (**10**).* The above-obtained compound (200 g, 0.588 mol) was dissolved in methylene chloride (700 mL) and cooled to 0−5 °C. To this solution, triethyl amine (92 g, 0.91 mol) was added, and then a solution of methanesulfonyl chloride (84 g, 0.733 mol) prepared in methylene chloride (240 mL) was added slowly to the above solution and stirred for 30 min. The temperature was raised to 20−30 °C, and the solution was stirred for 1 h and then cooled to 5−10 °C. The reaction mixture was diluted with dichloromethane, followed by water; the organic layer was separated and washed with an aqueous sodium bicarbonate solution and water and then concentrated under reduced pressure to afford heptaethylene glycol monomethylether monomesylate (240 g) as a yellow liquid. The concentrated residue was dissolved in toluene (1000 mL), and tetra-n-butylammonium bromide (197 g,

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ACS Omega 2023, 8, 3415−3422

0.611 mol) was added at 20−30 °C. The reaction mass was heated to 80−85 °C and maintained for 2 h. The mixture was cooled and water was added, the organic layer was separated, and the aqueous solution was extracted with toluene. The combined organic layers were washed with an aqueous sodium chloride solution, and then the toluene layer was concentrated under reduced pressure to afford the titled compound as a pale-yellow liquid. Yield: 190 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.38 (s, 3H), 3.45−3.79 (m, 26H), 3.83 (m, 2H); FT-IR (KBr, cm^{-1}): 2867, 1453, 1281, 1248, 1198, 1039, 948, 568; MASS (GC−MS) for $C_{15}H_{31}BrO_7$ $[M]^+$: m/z calcd, 403; found, 403.

CONCLUSIONS

We developed a novel, efficient, commercially feasible, and fruitful manufacturing method for naloxegol oxalate API. This novel process balances safety, efficiency, and economics and mitigates the risk tolerance.

The solid of 3-*O*-MEM-naloxone (**3**) and acid addition salt of 3-*O*-MEM α naloxol (**8**) is crystalline or amorphous; these properties make the intermediate useful for the preparation of naloxegol oxalate. The acid−base purification technique is efficient for improving the purity of the naloxegol base instead of purification by column chromatography.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07305.

Details of the spectroscopic data including ^{1}H NMR, MS, and IR for the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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