An Improved and Efficient Process for the Preparation of (+)-cloprostenol

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ABSTRACT An improved and efficient synthesis of (+)-cloprostenol has been accomplished in nine steps and 26% overall yield from commercially available (–)-Corey lactone 4-phenylbenzoate alcohol **1**. The present route avoids tedious purifications and requires only one column chromatography operation, which reduces the generation of waste and is suitable for large-scale preparation. *Chirality 27:392–396, 2015.*

KEY WORDS: Corey lactone; prostaglandin; (+)-cloprostenol; synthesis; process development; asymmetric reduction

INTRODUCTION

Cloprostenol is a synthetic analog of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Fig. 1).[1] It is an FP receptor agonist and has the ability to elicit luteolysis.[2–4] It is used for the induction of parturition in pregnant animals by promoting uterine contraction. It has also been demonstrated that only the (+)-enantiomer of cloprostenol exhibits luteolytic activity.[5–7]

Although a large number of the literature involves the synthesis of prostaglandins,[8–13] the synthetic method of (+)-cloprostenol was rarely described. As a synthetic analog of $PGF_{2\alpha}$, the synthesis of (+)-cloprostenol from Corey lactone derivatives could be a well-established approach.[14–16]

As part of our drive to develop an efficient process for the preparation of prostaglandins, we recently initiated a systematic investigation to improve the existing chemical schemes, to enhance the yield, and to minimize the tedious purification operations. In this report we discuss our improved synthesis of (+)-cloprostenol, which was simple and suitable for large-scale preparation.

EXPERIMENTAL

General

All reagents were used as received without further purification. The solvents were distilled from standard drying agents. The final product was purified by flash chromatography using Qing Dao Sea Chemical Reagent silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Bruker (Billerica, MA) Avance III 400 (400 MHz) spectrometer and referenced internally to the residual proton resonance in $CDCl_3$ ($\delta = 7.26$ ppm), or with tetramethylsilane (TMS, $\delta = 0.00$ ppm) as the internal standard. Chemical shifts are reported as parts per million (ppm) in the δ scale downfield from TMS. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), dd (doublet of doublet), bs (broad singlet). ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker spectrometer with complete proton decoupling, and chemical shifts are reported in ppm from TMS with the solvent as the internal reference ($CDCl_3$, $\delta = 77.0$ ppm). High-resolution mass spectrometry (HRMS) spectra were recorded on an ESI-ion trap mass spectrometer (Shimadzu LCMS-IT-TOF) or an EI mass spectrometer (Thermo Trace DSQ). High-performance liquid chromatography (HPLC) analyses were carried out using a Shimadzu LC-20AT liquid chromatography system equipped with a Shiseido Chiral CD-Ph column.

Preparation of Corey Aldehyde (2). To a solution of dicyclohexyl carbodiimide (DCC, 7.2 g, 34.0 mmol) in 2,2-dimethoxy ethane (DME, 120 mL) was successively added Corey lactone **1** (3.0 g, 8.5 mmol), phosphoric acid (0.30 mL, 5.1 mmol), and dimethyl sulfoxide (DMSO) (4.9 mL, 68.0 mmol) at room temperature. After the reaction was completed (about 30 min), the unwanted dicyclohexyl urea was filtered off and washed with DME (60 mL). The organic phase was washed with water (60 mL × 2) and saturated brine (60 mL) subsequently, then concentrated under reduced pressure to afford Corey aldehyde **2** in quantitative yield (4.17 g). The crude product was used for the next step without further purification.

Preparation of (3aR,4R,5R,6aS)-4-((E)-4-(3-chlorophenoxy)-3-oxobut-1-enyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl [1,1′-biphenyl]-4-carboxylate (3). Triethylamine (1.8 mL, 12.9 mmol) and anhydrous lithium chloride (0.9 g, 21.4 mmol) were added to a solution of aldehyde **2** (2.9 g, 2.8 mmol) and phosphonate **12** (3.0 g, 10.3 mmol) in tetrahydrofuran (THF) (120 mL) at –10°C. After stirring for 30 min at –10°C, the mixture was warmed to room temperature and stirred for another 8 h. Then ethyl acetate (60 mL) and saturated sodium bicarbonate (90 mL) were added. The organic phase was washed with saturated brine and concentrated in vacuo to afford crude product **3** (4.8 g).

Crude product **3** (4.8 g) was dissolved in ethyl acetate (30 mL) and MTBE (100 mL) at room temperature. The solution was cooled to –5°C for 4 h. The formed precipitate was filtered, washed with cold MTBE, and dried to afford pure **3** as a white solid (3.8 g, 87% yield for two steps).

Mp 176.1–178.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, $J = 8.3$ Hz, 2H), 7.67 (d, $J = 8.3$ Hz, 2H), 7.62 (d, $J = 7.2$ Hz, 2H), 7.47 (t, $J = 7.4$ Hz, 2H), 7.40 (t, $J = 7.3$ Hz, 1H), 7.18 (t, $J = 8.2$ Hz, 1H), 6.98-6.87 (m, 3H), 6.75 (m, 1H), 6.59 (d, $J = 15.8$ Hz, 1H), 5.36 (m, 1H), 5.11 (t, $J = 5.4$ Hz, 1H), 4.67 (s, 2H), 3.00-2.88 (m, 3H), 2.64 (m, 1H), 2.51 (m, 1H), 2.34 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 194.5, 175.8, 165.7, 158.3, 146.3, 145.5, 139.8, 135.1, 130.5, 130.2, 129.0, 128.3, 127.8, 127.3, 126.5, 122.1, 115.2, 113.0, 83.1, 78.4, 72.2, 54.3, 42.7, 37.9, 34.9; HRMS (ESI) calcd. for $C_{30}H_{25}ClO_6Na$ $[M + Na]^+$ 539.1232, found 539.1213.

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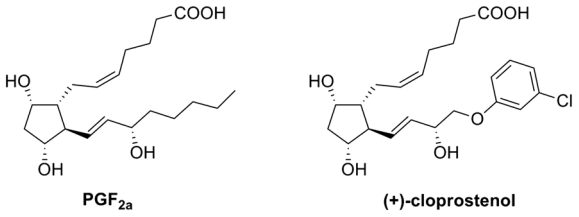


Fig. 1. Structures of $PGF_{2\alpha}$ and (+)-cloprostenol.

Preparation of (3aR,4R,5R,6aS)-4-((R,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl [1,1′-biphenyl]-4-carboxylate (4). (–)-DIP-Cl as reductant. **3** (3.0 g, 5.8 mmol) in THF (60 mL) was added to a solution of (–)-B-chlorodiisopinocampheylborane (10.2 mL, 1.7 M in heptane, 17.4 mmol) in THF (15 mL) at –40°C. The reaction mixture was stirred at –15°C for 18 h, then acetone (6 mL) was added. The solution was stirred at 25°C for 1 h, then concentrated under reduced pressure. The residue was dissolved in dichloromethane (60 mL), washed with saturated NH_4Cl (45 mL × 3), and saturated brine (45 mL × 1) in turn, then cooled to –5°C for 8 h. The formed precipitate was filtered off, the filtrate was concentrated in vacuo to give crude product **4** (2.7 g, 88% yield, 92:8 *dr*).

(R)-Me-CBS as reductant. (*R*)-2-Methyl-CBS-oxazaborolidine (1.16 mL, 1.0 M in toluene, 1.16 mmol) was charged along with THF (30 mL) under nitrogen atmosphere. *N,N*-Diethylanilineborane (DEANB, 2.6 mL, 14.5 mmol) was added in a slow stream and stirred for 30 min at 25°C. The solution was cooled to –15°C, then **3** (3.0 g, 5.8 mmol) in THF (15 mL) was added in about 5 min. The mixture was stirred at 0°C for 1 h, then quenched with methanol (30 mL) and stirred for 10 min. Hydrochloric acid (1.5 N, 60 mL) was added, and the mixture was stirred at 25°C for 10 min, diluted with ethyl acetate (60 mL) and water (30 mL). The organic layer was separated, washed with 1.5 N hydrochloric acid (30 mL), water (30 mL), and saturated brine (30 mL) in turn, dried over anhydrous sodium sulfate, concentrated under vacuum to give crude product **4** (2.7 g, 89% yield, 91:9 *dr*).

Crude product **4** (3.0 g) was then dissolved in methanol (6 mL) and isopropyl ether (12 mL) at room temperature. The formed precipitate was filtered, washed with cold isopropyl ether, and dried to afford pure **4** as a white solid (2.5 g, 81% yield, 98:2 *dr*). Mp 110.0–113.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (m, 2H), 7.72-7.64 (m, 2H), 7.64-7.57 (m, 2H), 7.51-7.43 (m, 2H), 7.40 (m 1H), 7.16 (t, J = 8.2 Hz, 1H), 6.98-6.90 (m, 1H), 6.90-6.84 (m, 1H), 6.74 (m, 1H), 5.85 (m, 1H), 5.74 (m, 1H), 5.31 (m, 1H), 5.09 (m, 1H), 4.53 (d, J = 3.5 Hz, 1H), 3.94 (m, 1H), 3.83 (m, 1H), 2.95-2.77 (m, 3H), 2.61 (m, 2H), 2.41 (d, J = 4.1 Hz, 1H), 2.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.3, 165.9, 159.1, 146.1, 139.8, 135.0, 130.9, 130.2, 128.9, 128.2, 127.2, 121.5, 115.0, 113.1, 83.3, 79.0, 71.8, 70.0, 54.3, 42.7, 37.6, 34.9; HRMS (ESI) calcd. for $C_{30}H_{27}ClO_6Na$ $[M+Na]^+$ 541.1388, found 541.1387.

Preparation of 2-((1R,2R,3R,5S)-2-((R,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)acetic acid (5). **4** (2.5 g, 4.8 mmol) was added to a solution of potassium hydroxide (2.7 g, 74.0 mmol) in methanol (60 mL) and water (1.3 mL) at room temperature. The solution was stirred at 80°C for 2 h, then concentrated in vacuo. Water (50 mL) and MTBE (50 mL) were added and the organic phase was discarded, the aqueous phase was acidized to pH ≈ 1.0–1.5 with 1 N hydrochloric acid. The acidic solution was stirred for 30 min, then extracted with MTBE (50 mL). The organic phase was washed successively with water (25 mL) and saturated brine (25 mL), then concentrated in vacuo. The residue was dissolved in dichloromethane (10 mL) and cooled to 5°C for 4 h. The formed precipitate was filtered off, the filtrate was concentrated in vacuo to give crude product **5** (1.9 g, 87% yield).

Preparation of (3aR,4R,5R,6aS)-4-((R,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one (6). A solution of **5** (1.9 g) in toluene (35 mL) was refluxed for 30 min, then concentrated at atmospheric pressure to a volume of about 10 mL. The mixture was cooled to 80°C and ethyl acetate (10 mL) was added. The solution was further cooled to 30°C and *n*-heptane (10 mL) was added to form some seed crystal in the mixture. The mixture was stirred at 25°C for 10 min, then *n*-heptane (15 mL) was added over 5 min. After stirring for another 1 h, the formed precipitate was filtered and dried to give compound **6** (1.4 g, 95% yield). Mp 117.9–120.8°C; $[a]_D^{20}$ = –7.6 (c = 0.5, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (s, 1H), 6.95 (d, J = 25.7 Hz, 2H), 6.81 (s, 1H), 5.71 (s, 2H), 4.92 (s, 1H), 4.53 (s, 1H), 4.01 (s, 2H), 3.89 (d, J = 7.4 Hz, 1H), 2.74 (d, J = 17.6 Hz, 2H), 2.64 (s, 1H), 2.50 (d, J = 15.8 Hz, 3H), 2.37 (s, 1H), 1.99 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.1, 159.1, 134.9, 132.9, 131.3, 130.4, 121.5, 115.1, 113.1, 82.6, 76.3, 71.7, 70.6, 56.2, 42.4, 39.7, 34.2; HRMS (ESI) calcd. for $C_{17}H_{19}ClO_5Na$ $[M+Na]^+$ 361.0813, found 361.0811.

Preparation of (3aR,4R,5R,6aS)-4-((3R,E)-4-(3-chlorophenoxy)-3-(1-ethoxyethoxy)but-1- enyl)-5-(1-ethoxyethoxy)hexahydro-2H-cyclopenta[b]furan-2-one (7). **6** (2.0 g, 5.9 mmol) was dissolved in dichloromethane (30 mL) and placed in a sealable pressure tube. Then trichloroacetic acid (0.06 g in 10 mL dichloromethane) and vinyl ethyl ether (17.0 mL, 177.0 mmol) were added successively. The tube was closed and heated at 45°C for 8 h. Triethylamine (1.0 mL) was added, the mixture was stirred for 10 min, then concentrated in vacuo to give crude product **7** (3.7 g, >99% yield).

Preparation of (3aR,4R,5R,6aS)-4-((3R,E)-4-(3-chlorophenoxy)-3-(1-ethoxyethoxy)but-1- enyl)-5-(1-ethoxyethoxy)hexahydro-2H-cyclopenta[b]furan-2-ol (8). A solution of **7** (3.7 g, 5.9 mmol) in THF (10 mL) was cooled to –40°C and a solution of diisobutylaluminium hydride (DIBAL-H, 6.6 mL, 1.5 M in THF, 9.9 mmol) was added. The mixture was stirred for 30 min at –40°C, then quenched by the addition of ethyl acetate (30 mL) and aqueous potassium sodium tartrate (20 g in 60 mL H_2O). The mixture was heated at 45°C for 1 h, then cooled to room temperature. The organic layer was separated and concentrated in vacuo to give crude product **8** (3.7 g, 95% yield).

Preparation of (Z)-7-((1R,2R,3R,5S)-2-((3R,E)-4-(3-chlorophenoxy)-3-(1-ethoxyethoxy)but-1-enyl)-3-(1-ethoxyethoxy)-5-hydroxycyclopentyl)hept-5-enoic acid (9). A suspension of 4-carboxybutyltriphenylphosphonium bromide (9.6 g, 21.7 mmol) in THF (60 mL) was cooled to –10°C and potassium *tert*-butoxide (7.8 g, 69.5 mmol) was added slowly. The mixture was stirred for 1 h, followed by a slow addition of crude **8** (3.7 g, 5.5 mmol) in THF (20 mL) at –10°C. After stirring for 3 h at 0°C, water (30 mL) was added dropwise followed

by the addition of ethyl acetate (60 mL) and aqueous tris (hydroxymethyl)metyl aminomethane (THAM) solution (15 wt%, 30 mL). The organic layer was separated and washed with aqueous THAM solution (15 wt%, 30 mL × 2). The aqueous phase was combined and washed with ethyl acetate (45 mL), then adjusted to pH = 3 with phosphoric acid solution (40%) and extracted with MTBE (50 mL × 3). The organic layer was combined and concentrated in vacuo to give crude product **9** (7.2 g, 65% yield).

Preparation of (+)-cloprostenol. Crude product **9** (7.2 g, 3.5mmol) was dissolved in THF (140 mL), water (70 mL), and phosphoric acid (3.2 mL, 55.1 mmol) were added. The reaction mixture was refluxed for 2 h, then cooled to 25°C. Ethyl acetate (160 mL) was added, the organic phase was separated, and the aqueous phase was washed with ethyl acetate (80 mL × 2). The organic phase was combined and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20:1 DCM/MeOH) to give (+)-cloprostenol (1.1 g, 72% yield). $[a]_D^{20}$ = +26.0 (c = 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.18 (t, J = 8.1 Hz, 1H), 6.97-6.89 (m, 2H), 6.79 (dd, J = 8.3, 2.3 Hz, 1H), 5.68 (qd, J = 15.4, 6.8 Hz, 2H), 5.49-5.40 (m, 1H), 5.40-5.30 (m, 1H), 4.54 (dd, J = 9.6, 7.0 Hz, 1H), 4.22-4.11 (m, 2H), 4.01-3.87 (m, 4H), 2.46-2.05 (m, 10H), 1.76 (dd, J = 14.7, 3.1 Hz, 1H), 1.70-1.61 (m, 2H), 1.54-1.45 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.2, 159.3, 135.2, 134.9, 130.3, 129.8, 129.7, 129.1, 121.3, 115.2, 113.1, 72.5, 71.8, 70.9, 55.4, 50.1, 42.8, 32.9, 26.3, 25.2, 24.4, 14.2; HRMS (ESI) calcd. for $C_{22}H_{29}ClNaO_6$ $[M+Na]^+$ 447.1545, found 447.1537.

RESULTS AND DISCUSSION

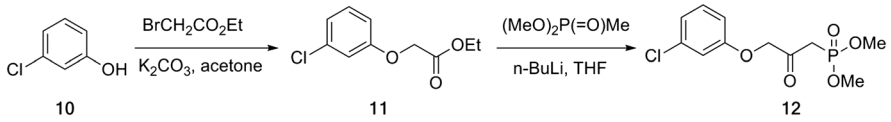
Synthesis of phosphonate ester 12

The requisite phosphonate ester **12** was prepared from 3-chlorophenol (**10**) as shown in Scheme 1.[11] 3-Chlorophenol **10** reacted with methyl bromoacetate to afford the corresponding ether **11** in the presence of K_2CO_3, then **11** was treated with dimethyl methylphosphonate and *n*-BuLi to provide **12** (84% yield for two steps).

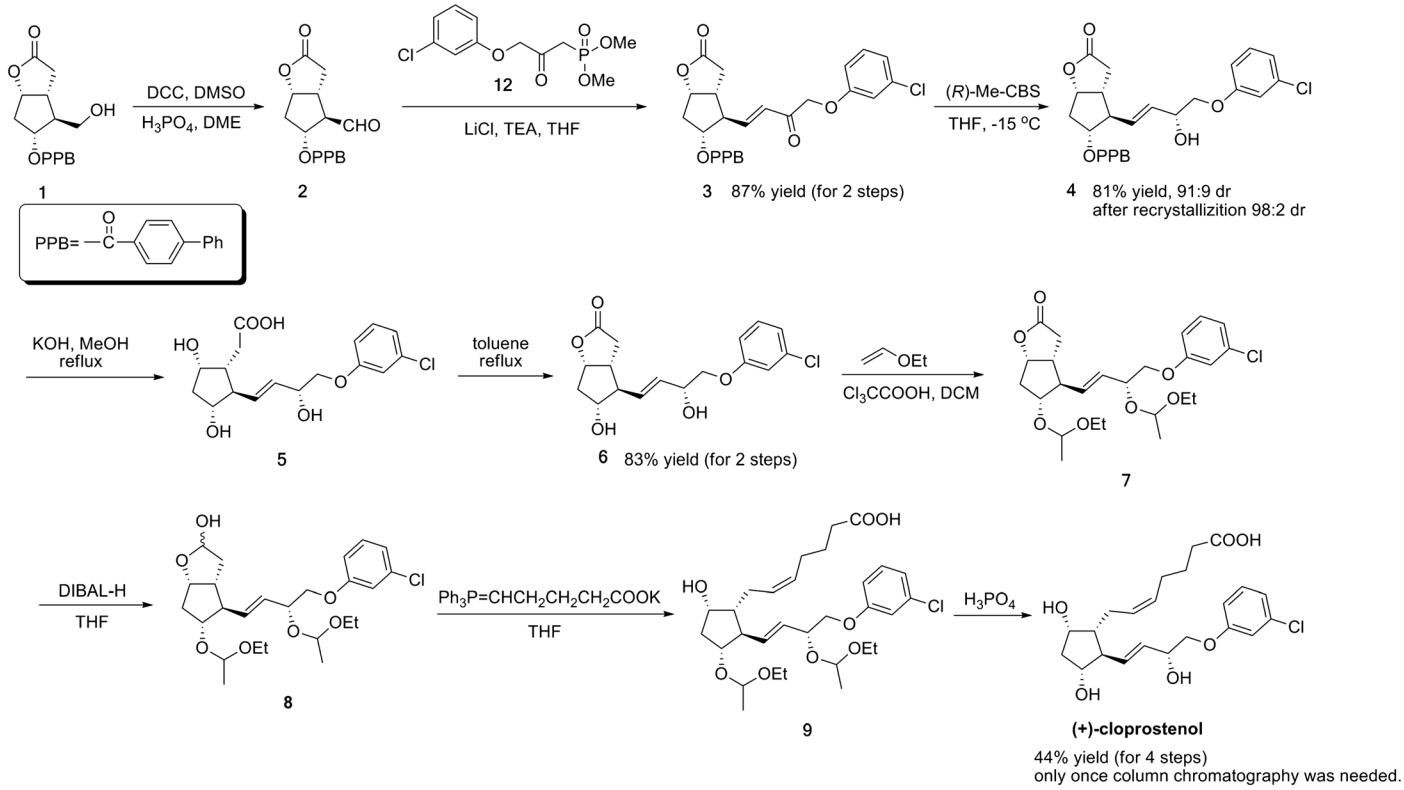
Synthesis of (+)-cloprostenol

The improved synthesis of (+)-cloprostenol commences with the lactone **1** derived from the Corey lactone (Scheme 2). **1** was also commercially available, and the presence of a *p*-phenylbenzoyl protective group in the lactone[11,13] helps to form crystalline intermediates which are easy to purify.

In the first step, the primary alcohol group of lactone **1** was oxidized to the corresponding aldehyde **2**. Several oxidation



Scheme 1. Synthesis of phosphonate ester **12**.



Scheme 2. Improved synthesis of (+)-cloprostenol.

methods, including PCC,[17] IBX,[18,19] Collins reagents,[20] and Pfitzner-Moffat conditions (DCC, DMSO and phosphoric acid)[21,22] were screened and the results are summarized in Table 1. Although both Collins reagents and Pfitzner-Moffat conditions afford aldehyde **2** in nearly quantitative yield, we adopted the latter oxidant for its easy handling and low environmental toxicity.

The ω-side chain of cloprostenol was introduced via the HWE reaction of aldehyde **2** with phosphonate ester **12**. When sodium hydride[20,23] was used as base, 46% yield was achieved. The yield can be further improved to 87% when using triethyl amine/lithium chloride[24] as base. Crude product **3** can be crystallized from ethyl acetate/MTBE.

Next, the regioselective and stereoselective reduction of ketone to the corresponding alcohol was investigated. The alcohol **4** can be isolated in 96% yield via the reduction of $NaBH_4$ at –78°C, but the *dr* value was only 56:44, and it was difficult to separate the diastereoisomers of (*R*)-**4** and (*S*)-**4**.[21] So several chiral boron compounds[25–28] were screened and the results are listed in Table 2. When (–)-diisopinocampheyl chloroborane[29,30] was used as reductant at –15°C, the desired diastereoisomer (*R*)-**4** can be obtained in 88% yield with 92:8 *dr* (Table 2 entry 3). We also tried the catalytic asymmetric reduction using 20 mol% (*R*)-2-methyl-CBS-oxazaborolidine, and obtained 89% yield with 91:9 *dr*. This *dr* can be further improved to 97:3 after recrystallization in MeOH/isopropyl ether with 81% yield (Table 3).

TABLE 1. Screening of oxidation conditions

Entry	Conditions	Yield (%)
1	PCC, CH_2Cl_2, rt, 2h	65
2	IBX, DMSO, 95°C, 7h	85
3	CrO_3, pyridine, CH_2Cl_2, rt, 0.5h	99
4	DCC, DMSO, H_3PO_4, DME, rt, 2h	99

TABLE 2. Optimization of asymmetric reduction reaction

Entry	Reductant	Temperature (°C)	Yield (%)	*dr*[a]
1	$NaBH_4$	–78	96	56:44
2[b]	(-)-DIP-Cl	–40	86	92:8
3[b]	(-)-DIP-Cl	–15	88	92:8
4	(*R*)-Me-CBS	–15	89	91:9

[a]The *dr* values were determined by HPLC analysis.
[b]2 equiv. of (–)-DIP-Cl.

TABLE 3. Recrystallization of 4 in various solvents

Entry	Solvents (V/V)	Yield (%)	Purity (%)	*dr*[a]
1	MeOH/IPE = 1:3	83	92.5	93:7
2	MeOH/IPE = 1:2	81	96.9	97:3
3	DCM/MTBE = 1:3	77	94.6	95:5
4	EtOAc/MTBE = 1:3	90	93.2	94:6

[a]The *dr* values were determined by HPLC analysis.

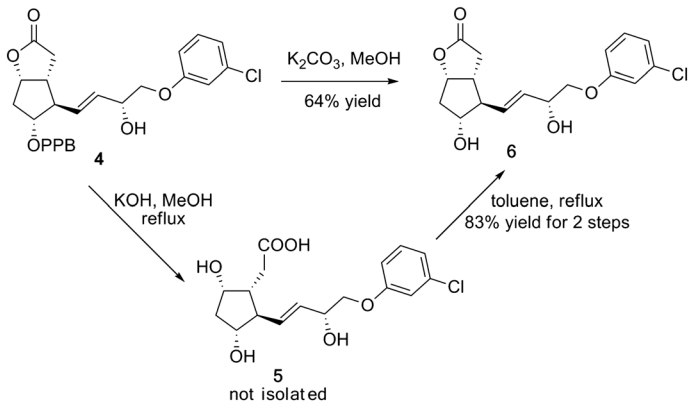
Since the benzoate protective group is labile in basic conditions, next we replaced the protective group of hydroxyl with the more stable acetal group. When the deprotection of benzoate group was carried out in the presence of potassium carbonate, diol **6** was obtained in 64% yield as shown in Scheme 3 (together with 24% by-product **5**[31]). To improve the yield of **6** and to minimize the separation operation, we conducted this reaction with more basic potassium hydroxide to ensure the ring-opening product **5** in quantitative yield. Crude product **5** could easily be purified through acid/base extraction, then transformed to the desired ring-closing product **6** completely.[30] **6** can be further refined via recrystallization in EtOAc/*n*-hexane.

Next, the two hydroxyl groups of **6** were protected by ethyl vinyl ether[32,33] in the presence of trichloroacetic acid. The sequential DIBAL-H reduction of the acetal **7** provided the lactol **8**, which then underwent the Wittig reaction[34,35] with in situ generated ylide $[Ph_3P{=}CH(CH_2)_3CO_2K]$ to afford hydroxyl acid **9**.

Finally, the *O*-EE acetal protective group of **9** was removed in the presence of phosphoric acid[36] to give (+)-cloprostenol in 44% yield (for 4 steps from **6**). The target compound was purified by column chromatography. The spectral data (^{1}H NMR, ^{13}C NMR, HRMS, and optical rotation) of the synthetic cloprostenol was in excellent agreement with the published data.[37]

CONCLUSION

In summary, an efficient and practical synthetic route has been developed for the preparation of (+)-cloprostenol. Highlights of this synthesis include the following: 1) all the intermediates were purified by recrystallization or used in the next step directly, which reduces the purification operations



Scheme 3. Synthesis of lactone **6** via ring-opening/ring-closing sequence.

and the generation of waste; 2) the highly stereoselective reduction of ketone **3** to the corresponding alcohol **4** was achieved with a catalytic amount of (*R*)-Me-CBS reductant; 3) a lactone ring-opening/ring-closing sequence was employed for the removal of benzoate protective group of **4**, which efficiently simplified the purification.

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SUPPORTING INFORMATION

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