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Stereoselective synthesis of (-) Cephalosporolide D

Karna Ji Harkala [a], Laxminarayana Eppakayala [a,*] and Thirumala Chary Maringanti [b]

[a] *Department of Physics and Chemistry, Mahatma Gandhi Institute of Technology, Chaitanya Bharati, Gandipet, Hyderabad-500075, India*
[b] *Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad College of Engineering, Nachupally, Karimnagar-505501, India*

**Corresponding author at: Department of Physics and Chemistry, Mahatma Gandhi Institute of Technology, Chaitanya Bharati, Gandipet, Hyderabad-500075, India. Tel.: +91.998.9291441. Fax: +91.40.24193067. E-mail address: elxnkits@yahoo.co.in (L. Eppakayala).*

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ABSTRACT

A simple and efficient synthesis of eight-membered lactone, Cephalosporolide D has been accomplished from inexpensive and commercially available starting materials. This synthesis utilizes α-aminoxylation catalyzed by L-proline reaction, Jacobsen's hydrolytic kinetic resolution and Yamaguchi macrolactonization as key steps.

1. Introduction

The macrolides, which contain medium-sized ring systems, have attracted considerable attention from synthetic chemists due to their interesting biological properties [1-4].

Cephalosporolide D (**3**), a eight-membered lactone, isolated from fermentation fungus, *Cephalosporiumaphidicola*, along with four other cephalosporolides (B, C and E-G) (Figure 1) [5,6]. Among them, cephalosporolide D (**3**) is an eight-membered lactone, cephalosporolides B, C and G are ten-membered ring lactones and the others (cephalosporolide E and F) are spiroketal lactones. Because of their fascinating structural features and interesting biological properties, cephalosporolides have solicited considerable interest among organic chemists [7-12].

In accordance with our interest in the natural product synthesis, herein we report an alternative total synthesis of Cephalosporolide D starting from commercially available starting materials.

2. Experimental

2.1. Instrumentation

Solvents were dried over standard drying agents on freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (60-120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuum. ^1H NMR spectra were acquired at 300 MHz, while, ^{13}C NMR at 75 MHz with TMS as internal standard for solutions in $CDCl_3$. *J* values were given in Hz. IR spectra were recorded on FTIR spectrophotometer with NaCl optics. Optical rotations were measured on digital polarimeter at 25 °C. Mass spectra were recorded on direct inlet system or LC by MSD trap SL, the HRMS data were obtained using Q-TOF mass spectrometry.

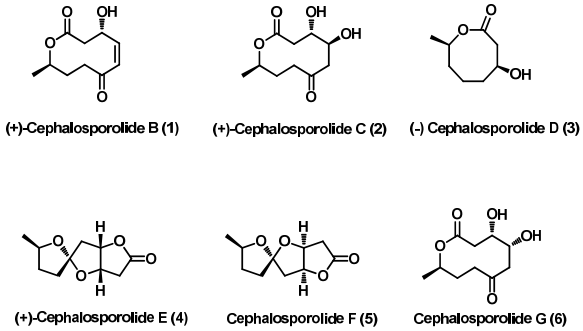

Figure 1. Structures of cephalosporolides.

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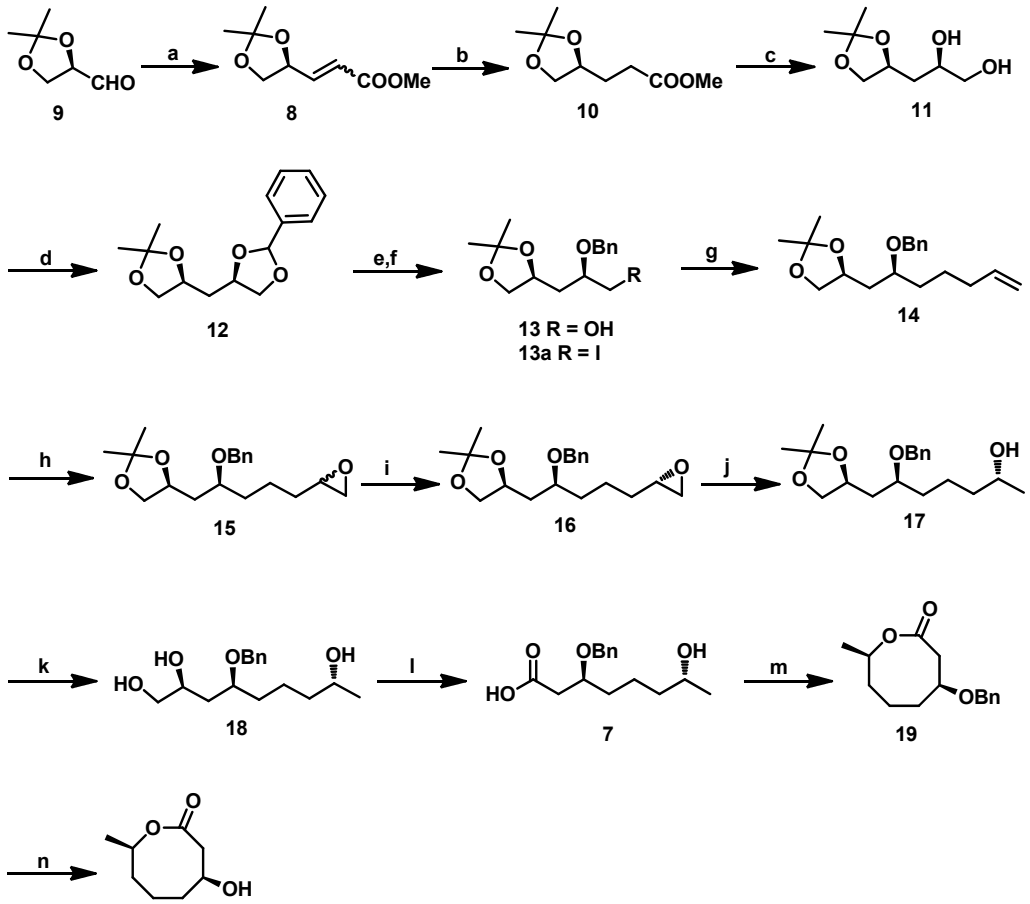


Reagents and conditions: (a) Ph_3P=CHCOOMe, Benzene, reflux, 2 h, 81%; (b) H_2, Pd/C, MeOH, rt, 3 h, 84%; (c) i) DIBAL-H, CH_2Cl_2, 0 °C to rt, 3 h,; ii) PhNO, L-proline, CH_3CN, -20 °C, 24 h then $NaBH_4$, MeOH, 0 °C; iii) 10% Pd/C, H_2, MeOH, 24 h, overall yield for 3 steps 72%; (d) Benzaldehyde dimethyl acetal, PTSA, CH_2Cl_2, 0 °C to rt, 6 h, 83%; (e) DIBAL-H, CH_2Cl_2, 0 °C to rt, 4 h, 79%; (f) I_2, PPh_3, imidazole, 0 °C to rt, THF, 71%; (g) homoallyl bromide, Mg, THF, 0 °C, 8 h, 83%; (h) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 6 h, 76%; (i) (*S,S*)-salen-Co-(OAc) (0.5 mol %), distd H_2O (0.55 equiv), 0 °C, 22 h, 44%; (j) LAH, THF, 0 °C to rt, 1h, 95%. (k) 70% aq. acetic acid, rt, 12 h; (l) i) $NaIO_4$, sat. $NaHCO_3$ soln., CH_2Cl_2, rt, 6 h; ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH:water (2:1), 0 °C to rt, 3 h; (m) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt, 12 h; (n) $TiCl_4$, CH_2Cl_2.

Scheme 1

2.2. Synthesis

2.2.1. (S)-Methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (8)

To a stirred solution of compound **9** (2.7 g, 20.71 mmol) in benzene (50 mL) was treated with (methoxy-carbonyl methylene) triphenyl phosphorane (3.54 g, 10.54 mmol) at reflux temperature. After 2 h, solvent was evaporated and purification of the residue by column chromatography (60-120 Silica gel, 15% EtOAc in petroleum ether) furnished compound **8** (Scheme 1).

(S)-Methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**8**): Color: Yellow liquid. Yield: 81%. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.72 (dd, 1H, *J* = 6.1 Hz, 12.2 Hz, -C*H*=CH_2), 5.72 (d, 1H, *J* = 12.2 Hz, -C*H*=CH_2), 5.34-5.23 (m, 1H, -OC*H*-), 4.25-4.18 (m, 2H, -OCH_2-), 3.68 (s, 3H, OCH_3), 1.37 (s, 3H, -CH_3), 1.35 (s, 3H, CH_3). ESI-MS (*m/z*): 209 $(M+Na)^+$.

2.2.2. (S)-Methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl) propanoate **(10)**

A solution of compound **8** (7.0 g, 24.47 mmol) in methanol (25.0 mL) was treated with 10% Pd-C (0.45 g) for 3 h under hydrogen atmosphere. After completion of reaction, it was filtered, The filtrate was extracted with EtOAc (2 × 50 mL), the organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in petroleum ether) to give compound **10** (Scheme 1).

(S)-Methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (**10**): Color: Pale yellow liquid. Yield: 84%. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.12-4.02 (m, 2H, -OCH_2-), 3.92 (m, 1H, -OC*H*-), 3.64 (s, 3H, OCH_3), 2.48-2.35 (m, 2H, -CH_2-C=O), 1.88-1.77 (m, 2H, -CH_2-), 1.39 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ESI-MS (*m/z*): 211 $(M+Na)^+$.

2.2.3. (R)-3-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)propane-1,2-diol **(11)**

A solution of ester **10** (6.9 g, 36.72 mmol) in dry CH_2Cl_2 (30 mL) was cooled to -78 °C and DIBAL-H (18 mL, 25.82 mmol, 20 mol% in toluene) was added. The resultant solution was stirred at the same temperature for 2 h and quenched with MeOH (5 mL). The reaction mixture was diluted with EtOAc (20 mL) aq. potassium sodium tartrate (5 mL) and stirred vigorously at room temperature for an additional 1 h. It was filtered through celite, the filtrate was dried (Na_2SO_4), concentrated to give the crude aldehyde.

To a stirred solution of aldehyde (5.8 g, 30.85 mmol) and nitrosobenzene (3.3 g, 30.85 mmol) in DMSO (20 mL) was added L-proline (0.71 g, 6.17 mmol, 20 mol %) in one portion at 25 °C. After 24 h, the temperature was lowered to 0 °C, followed by dilution with anhydrous MeOH (30 mL) and the careful addition of excess $NaBH_4$ (2.46 g, 61.7 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1 M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography over silica gel using ethyl acetate:petroleum ether (40:60, *v*:*v*) as eluent to give pure aminoxy alcohol as a pure diastereomer. The aminoxy alcohol (6.7 g, 25.09 mmol) was dissolved in EtOAc (30 mL) and to the solution was added 10% Pd/C (0.35 g). The reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC), It was filtered through celite pad. The filtrate was dried (Na_2SO_4) concentrated and residue purified by column chromatography using petroleum ether:ethyl acetate (3:2, *v*:*v*) as eluent to give pure diol **11** (Scheme 1).

(R)-3-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)propane-1,2-diol (**11**): Color: Yellow liquid. Yield: 72%. IR (Neat, ν, cm^{-1}): 3412, 3018, 2938, 1612, 1513, 1248, 1215. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.09-3.92 (m, 4H, 2 x -OC*H*$_2$), 3.87-3.79 (m, 2H, 2 x -OC*H*), 2.08 (br s, 2H, 2 x -O*H*), 1.74-1.59 (m, 2H, -C*H*$_2$), 1.38 (s, 3H, -C*H*$_3$), 1.33 (s, 3H, -C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 109.1 (1C, -O-*C*-O-), 74.3 (2C, -O-*C*H-), 72.6 (1C, -*C*H$_2$-OH), 66.8 (1C, -O-*C*H$_2$-), 66.1(1C, -*C*H-OH), 36.5 (1C, -*C*H$_2$-), 25.7 (1C, -*C*H$_3$). ESI-MS (*m/z*): 199 $(M+Na)^+$. $[\alpha]_D^{25}$: -66.8 (*c* 0.5, $CHCl_3$).

2.2.4. (4S)-2,2-Dimethyl-4-(((4R)-2-phenyl-1,3-dioxolan-4-yl)methyl)-1,3-dioxolane (12)

To a stirred solution of compound **11** (3.1 g, 17.61 mmol) in dry CH_2Cl_2 (20 mL), benzaldehyde dimethylacetal (3.2 mL, 21.13 mmol) followed by *p*-toluedine sulphonic acid (PTSA, catalytic) were added at 0 °C. After stirring of 6 h the reaction mixture was treated with aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL) and both the organic layers were dried over anhydrous Na_2SO4 and concentrated. Crude product was purified by column chromatography (60-120 Silica gel, 10% EtOAc in petroleum ether) to afford compound **12** (Scheme 1).

(4S)-2,2-Dimethyl-4-(((4R)-2-phenyl-1,3-dioxolan-4-yl) methyl)-1,3-dioxolane (**12**): Color: Pale yellow syrup. Yield: 83%. IR (Neat, ν, cm^{-1}): 3010, 2900, 1250, 852. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.35-7.29 (m, 5H, -C$_6$*H*$_5$), 5.77 (s, 1H, -OC*H*Ph), 4.07-3.88 (m, 4H, 2 x -OC*H*$_2$-), 3.99-3.89 (m, 2H, -OC*H*-), 1.78-1.54 (m, 2H, -C*H*$_2$-), 1.36 (s, 3H, -C*H*$_3$), 1.31 (s, 3H, -C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 140.6 (1C, Ar-*C*), 129.8 (2C, Ar-*C*), 128.6 (1C, Ar-*C*), 126.3 (2C, Ar-*C*), 108.3 (1C, -O-*C*-O-), 104.3 (1C, -O-*C*H-O-), 78.1 (1C, -O-*C*H-), 74.2 (1C, -O-*C*H-), 72.2 (1C, -O-*C*H$_2$-), 66.7(1C, -O-*C*H$_2$-), 36.4 (1C, -*C*H$_2$-), 25.8 (2C, -*C*H$_3$). ESI-MS (*m/z*): 287 $(M+Na)^+$.

2.2.5. (R)-2-(Benzyloxy)-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (13)

To a stirred solution of compound **12** (3.6 g, 13.63 mmol) in dry CH_2Cl_2 (20 mL) DIBAL-H (11.6 mL, 16.36 mmol, 2 M solution in toluene) was added at 0 °C. After 4 h the reaction mixture was quenched with MeOH and aq. sodium potassium tartrate (5 mL), filtered through celite. The residue was washed with CH_2Cl_2 (2 x 50 mL) and both the organic layers were dried over anhydrous Na_2SO4 and concentrated. Crude product was purified by column chromatography (60-120 Silica gel, 30% EtOAc in petroleum ether) to afford compound **13** (Scheme 1).

(R)-2-(Benzyloxy)-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl) propan-1-ol (**13**): Color: Colorless syrup. Yield: 79%. IR (Neat, ν, cm^{-1}): 3450, 3010, 2900, 1250, 1050, 850. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.32-7.27 (m, 5H, -C$_6$*H*$_5$), 4.58 (s, 2H, -OC*H*$_2$Ph), 4.12-4.08 (m, 4H, 2 x -OC*H*$_2$), 3.76-3.68 (m, 1H, -OC*H*), 3.49-3.41 (m, 1H, -OC*H*), 1.78-1.58 (m, 3H, -C*H*$_2$, *OH*), 1.37 (s, 3H, -C*H*$_3$), 1.34 (s, 3H, -C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 138.8 (1C, Ar-*C*), 127.9 (2C, Ar-*C*), 127.6 (3C, Ar-*C*), 109.3 (1C, -O-*C*-O-), 76.5 (1C, -O-*C*H-O-), 74.3 (1C, -O-*C*H-), 72.6 (1C, -O-*C*H$_2$-), 66.7 (1C, -*C*H$_2$-OH), 66.5 (1C, -*C*H$_2$-OH), 36.8 (1C, -*C*H$_2$-), 25.1 (2C, -*C*H$_3$). ESI-MS (*m/z*): 289 $(M+Na)^+$. $[\alpha]_D^{25}$: -70.92 (*c* 0.27, $CHCl_3$).

2.2.6. (S)-4-((S)-2-(Benzyloxy)hept-6-enyl)-2,2-dimethyl-1,3-dioxolane (14)

A solution of alcohol **13** (2.76 g, 10.37 mmol) in dry THF (20 mL), imidazole (1.1 g, 15.55 mmol), Ph_3P (3.25 g, 12.44 mmol) and iodine (1.31 g, 10.37 mmol) were added at 0 °C and allowed to stir for 1 h. After that it was neutralized with aq. $NaHCO_3$ (10 mL) solution and extracted with 10% EtOAc in hexane (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by flash column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in petroleum ether) to afford compound **13a** (2.7 g, 71%) as a yellow colored liquid.

The iodo derivative **13a** (2.7 g, 7.18 mmol) was immediately treated with a solution of CuI (1.36 g, 7.18 mmol) and homoallylmagnesium bromide (prepared from homoallyl bromide (12.6 mL, 97.5 mmol) and Mg (6.08 g, 264.0 mmol) in dry THF) at -40 °C. After stirring at -40 °C for 8 h, it was treated with aq. NH_4Cl (20 mL). The residue was extracted with EtOAc (2 × 30 mL) and the organic layers were dried over anhydrous Na_2SO4 and concentrated. Crude product was purified by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in petroleum ether) to afford compound **14** (Scheme 1).

(S)-4-((S)-2-(Benzyloxy)hept-6-enyl)-2,2-dimethyl-1,3-dioxo lane (**14**): Color: Colorless liquid. Yield: 83%. IR (Neat, ν, cm^{-1}): 3435, 3070, 2932, 2829, 1635, 1466, 1134, 1015. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.32-7.26 (m, 5H, -C$_6$*H*$_5$), 5.79-5.66 (m, 1H, -C*H*=CH$_2$), 4.98-4.89 (m, 2H, -CH=C*H*$_2$), 4.56 (d, 1H, *J* = 11.3 Hz, -OC*H*$_2$Ph), 4.44 (d, 1H, *J* = 11.4 Hz, -OC*H*$_2$Ph), 4.07-3.99 (m, 2H, -OC*H*$_2$), 3.77-3.66 (m, 1H, -OC*H*), 3.52-3.44 (m, 1H, -OC*H*), 2.16-2.09 (m, 2H, -C*H*$_2$), 1.61-1.31 (m, 6H, 3 x -C*H*$_2$), 1.36 (s, 3H, -C*H*$_3$), 1.32 (s, 3H, -C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 138.8 (1C, Ar-*C*), 133.7 (1C, -*C*H=CH$_2$), 128.7 (2C, Ar-*C*), 128.3 (1C, Ar-*C*), 128.1 (2C, Ar-*C*), 114.8 (1C, =CH$_2$), 108.5 (1C, -O-*C*-O-), 77.3 (1C, -O-*C*H-), 74.2 (1C, -O-*C*H-), 72.1 (1C, -O-*C*H$_2$-), 66.5 (1C, -O-*C*H$_2$-), 39.8 (1C, -*C*H$_2$-), 34.2 (1C, -*C*H$_2$-), 33.8 (1C, -*C*H$_2$-), 32.7 (1C, -*C*H$_2$-), 25.2 (2C, -*C*H$_3$). ESI-MS (*m/z*): $(M+Na)^+$ 327. $[\alpha]_D^{25}$: +39.71 (*c* 1.12, $CHCl_3$).

2.2.7. (S)-4-((S)-2-(Benzyloxy)-5-(oxiran-2-yl)pentyl)-2,2-dimethyl-1,3-dioxolane (15)

To a stirred solution of olefin **14** (2.5 g, 8.22 mmol) in $CHCl_3$ (25 mL), *m*-chloroperbenzoic acid (*m*-CPBA) (2.12 g, 12.33 mmol) was added and allowed to stir for 24 h at room temperature. After that the reaction mixture was filtered and the filtrate was washed with saturated $NaHCO_3$ solution (30 mL), dried over Na_2SO_4 and concentrated. Crude product was purified by column chromatography (60-120 Silica gel, 10% EtOAc in petroleum ether) to furnish compound **15** (Scheme 1).

(S)-4-((S)-2-(Benzyloxy)-5-(oxiran-2-yl)pentyl)-2,2-dimethyl-1,3-dioxolane (**15**): Color: Colorless liquid. Yield: 76%. IR (Neat, ν, cm^{-1}): 3050, 2932, 1620, 1452, 1034, 950, 860. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.35-7.24 (m, 5H, -C$_6$*H*$_5$), 4.46 (dd, 2H, *J* = 11.6 Hz, 5.8 Hz -OC*H*$_2$Ph), 4.06-3.95 (m, 2H, -OC*H*$_2$), 3.79-3.70 (m, 1H, -OC*H*), 3.49-3.41 (m, 1H, -OC*H*), 2.89-2.81 (m, 1H, epoxy C*H*), 2.68-2.62 (m, 1H, epoxy C*H*), 2.49 (m, 1H, epoxy C*H*), 1.63 (m, 2H, C*H*$_2$), 1.37 (m, 2H, C*H*$_2$), 1.36 (s, 3H, -C*H*$_3$), 1.32 (s, 3H, -C*H*$_3$), 1.24 (m, 2H, C*H*$_2$), 1.22-1.11 (m, 2H, -C*H*$_2$). ESI-MS (*m/z*): 343 $(M+Na)^+$.

2.2.8. (S)-4-((S)-2-(Benzyloxy)-5-((S)-oxiran-2-yl)pentyl)-2,2-dimethyl-1,3-dioxolane (16)

A mixture of (*S,S*)-*N,N-bis*(3,5-di-*tert*-butylsalicylidine)-1,2-cyclohexanediamino Co(III) chloride complex (0.18 g, 0.29 mmol) and AcOH (0.035 g, 0.59 mmol) in toluene (1 mL) was stirred in open air for 1 h at room temperature. Then the solvent was removed by rotary evaporator, and the resulting brown residue was dried under vacuum. To this activated catalyst, epoxide **15** (1.95 g, 5.93 mmol) was added in one portion and it was cooled in an ice-water bath. Then H_2O (0.058 g, 3.26 mmol) was slowly added to the reaction mixture. Stirring was continued for 1h in an ice-water bath. After that, ice-water bath was removed and the reaction mixture was allowed to stir at room temperature for 12 h. The crude reaction mixture was adsorbed on silica gel and purified by column chromatography (60-120 Silica gel, 40% EtOAc in petroleum ether) to give compound **16** (Scheme 1).

(S)-4-((S)-2-(Benzyloxy)-5-((S)-oxiran-2-yl)pentyl)-2,2-dimethyl-1,3-dioxolane (**16**): Color: Yellow liquid. Yield: 44%. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.35-7.23 (m, 5H, -C$_6$*H$_5$*), 4.49 (d, 1H, *J* = 11.5 Hz, -OC*H$_2$*Ph), 4.44 (d, 1H, *J* = 11.5 Hz, -OC*H$_2$*Ph), 4.06-3.95 (m, 2H, -OC*H$_2$*), 3.79-3.71 (m, 1H, -OC*H*), 3.49-3.38 (m, 1H, -OC*H*), 2.89 (dt, 1H, *J* = 4.8, 7.2 Hz, epoxy C*H*), 2.68 (dd, 1H, *J* = 4.8, 5.2 Hz, epoxy C*H*), 2.49 (dd, 1H, *J* = 2.8, 5.2 Hz, epoxy C*H*), 1.61-1.38 (m, 6H, 3 x -C*H$_2$*), 1.36 (s, 3H, -C*H$_3$*), 1.32 (s, 3H, -C*H$_3$*), 1.22-1.17 (m, 2H, -C*H$_2$*). ESI-MS (*m/z*): 343 $(M+Na)^+$.

2.2.9. (2R,6S)-6-(Benzyloxy)-7-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)heptan-2-ol (17)

To a cooled (0 °C) and stirred suspension of lithium aluminium hydride (LAH) (0.052 g, 1.380 mmol) in dry THF (4 mL), at 0 °C was added compound **16** (0.290 g, 0.690 mmol) in THF (2 mL) and allowed to stir at room temperature for 1 h. The reaction mixture was quenched by careful addition of aq. Na_2SO_4 solution at 0 °C, filtered through a pad of celite and filtrate concentrated under reduced pressure. The crude residue was purified by column chromatography (60-120 silica gel, 1:3 EtOAc:*n*-Hexane) to give compound **17** (Scheme 1).

(2R,6S)-6-(Benzyloxy)-7-((S)-2,2-dimethyl-1,3-dioxolan-4-yl) heptan-2-ol (**17**): Color: Colorless syrup. Yield: 95%. IR (Neat, ν, cm^{-1}): 3446, 2933, 1611, 1523, 1455, 1374, 1093, 928. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.36-7.24 (m, 5H, -C$_6$*H$_5$*), 4.51 (d, 1H, *J* = 11.8 Hz, -OC*H$_2$*Ph), 4.46 (d, 1H, *J* = 11.8 Hz, -OC*H$_2$*Ph), 4.09-3.98 (m, 2H, -OC*H$_2$*), 3.76-3.67 (m, 2H, 2 x -OC*H*), 3.51-3.44 (m, 1H, -OC*H*), 1.74-1.58 (m, 7H, 3 x -C*H$_2$, OH*), 1.36 (s, 3H, -C*H$_3$*), 1.34 (s, 3H, -C*H$_3$*), 1.22-1.16 (m, 2H, -C*H$_2$*), 1.14 (d, 3H, *J* = 6.3 Hz, -C*H$_3$*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 139.1 (1C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.3 (1C, Ar-*C*), 128.1 (2C, Ar-*C*), 108.3 (1C, -O-*C*-O-), 78.4 (1C, -O-*C*H-), 74.6 (1C, -O-*C*H-), 72.4 (1C, -O-*C*H$_2$-) 66.4 (1C, -O-*C*H$_2$-), 66.0 (1C, -*C*H-OH), 39.7 (1C, -*C*H$_2$-), 37.8 (1C, -*C*H$_2$-), 33.4 (1C, -*C*H$_2$-), 25.6 (2C, -*C*H$_3$), 22.1 (1C, -*C*H$_3$), 20.3 (1C, -*C*H$_2$-). ESI-MS (*m/z*): 345$(M+Na)^+$. $[\alpha]_D^{25}$: +28.3 (*c* 0.49, $CHCl_3$).

2.2.10. (2S,4S,8R)-4-(Benzyloxy)nonane-1,2,8-triol (18)

A solution of compound **17** (0.350 g, 1.143 mmol) in aq. 60% acetic acid (10 mL) was stirred at room temperature for 12 h. After completion of reaction, it was quenched with $NaHCO_3$ and adjusted to pH = 2-3. The reaction mixture was extracted with ethyl acetate (3 x× 10 mL) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure and purification of the residue by column chromatography (Silica gel, 60-120 mesh, 40% EtOAc in petroleum ether) to afford compound **18** (Scheme 1).

(2S,4S,8R)-4-(Benzyloxy)nonane-1,2,8-triol (**18**): Color: Colorless syrup. Yield: 88%. IR (Neat, ν, cm^{-1}): 3449, 3320, 3049, 2933, 1612, 1512, 1451, 1398, 1075. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.32-7.26 (m, 5H, -C$_6$*H$_5$*), 4.47 (s, 2H, -OC*H$_2$*Ph), 3.92-3.84 (m, 2H, -OC*H$_2$*), 3.79-3.68 (m, 2H, 2 x -OC*H*), 3.49-3.38 (m, 1H, -OC*H*), 2.95 (br.s, 2H, 2 x -O*H*), 1.68-1.49 (m, 7H, 3 x -C*H$_2$, OH*), 1.19-1.13 (m, 2H, -C*H$_2$*), 1.12 (d, 3H, *J* = 6.1 Hz, -C*H$_3$*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 139.3 (1C, Ar-*C*), 127.9 (2C, Ar-*C*), 128.4 (1C, Ar-*C*), 128.1 (2C, Ar-*C*), 76.8 (1C, -O-*C*H-), 72.2 (1C, -O-*C*H$_2$-), 69.8 (1C, -*C*H-OH), 68.3 (1C, -*C*H$_2$-OH), 67.2 (1C, -*C*H$_2$-OH, 40.3 (1C, -*C*H$_2$-), 38.3 (1C, -*C*H$_2$-), 33.4 (1C, -*C*H$_2$-), 23.5(1C, -*C*H$_3$), 22.4 (1C, -*C*H$_2$-). ESI-MS (*m/z*): 305 $(M+Na)^+$. $[\alpha]_D^{25}$: +41.3 (*c* 0.65, $CHCl_3$).

2.2.11. (3S,7R)-3-(Benzyloxy)-7-hydroxyoctanoic acid (7)

To a cooled (0 °C) solution of compound **18** (10.0 g, 37.59 mmol) in CH_2Cl_2 (100 mL), $NaIO_4$ (12.06 g, 56.39 mmol) followed by sat. $NaHCO_3$ (4 mL) were added and stirred it at room temperature for 5 h. After completion of reaction, it was dried over Na_2SO_4, washed with CH_2Cl_2 (2 × 50 mL) filtered and evaporated under reduced pressure to give aldehyde quantitatively.

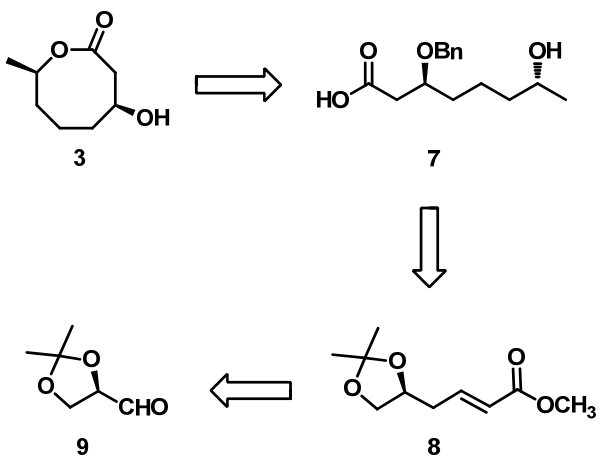
To a cooled (0 °C) solution of the above obtained aldehyde in *t*-butanol (4 mL), 2-methyl-2-butene (2 mL) was added, followed by a solution of $NaClO_2$ (0.26 g, 2.95 mmol) and NaH_2PO_4 (0.46 g, 2.95 mmol) in water (2 mL) and stirred at room temperature for 3 h. *t*-Butanol was evaporated and extracted with ethyl acetate (2 × 10 mL). The organic layers were washed with water (2 × 5 mL), brine (10 mL), dried (Na_2SO_4), evaporated and purified the residue by column chromatography (60-120 Silica gel, 40% EtOAc in petroleum ether) to furnish compound **7** (Scheme 1).

(3S,7R)-3-(Benzyloxy)-7-hydroxyoctanoic acid (**7**): Color: Colorless syrup. Yield: 78%. IR (Neat, ν, cm^{-1}): 3402, 3048, 2984, 1710, 1436, 1258, 1092, 777. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 10.52 (brs, 1H, -COOH), 7.39-7.21 (m, 5H, -C$_6$*H$_5$*), 4.58 (d, 1H, *J* = 11.6 Hz, -OC*H$_2$*Ph), 4.51 (d, 1H, *J* = 11.6 Hz, -OC*H$_2$*Ph), 3.94-3.85 (m, 2H, C*H*), 2.67-2.49 (m, 2H, -C*H$_2$*), 1.73-1.34 (m, 7H, 3 x -C*H$_2$* + *OH*), 1.16 (d, 3H, *J* = 6.3 Hz, -C*H$_3$*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 176.8 (1C, -*C*OOH), 138.1 (1C, Ar-*C*), 128.4 (2C, Ar-*C*), 128.6 (1C, Ar-*C*), 127.9 (2C, Ar-*C*), 75.6 (1C, -*C*H-OH), 71.5 (1C, -*C*H$_2$-OH), 67.8 (1C, -*C*H-OH), 39.5 (1C, -*C*H$_2$-), 34.1 (1C, -*C*H$_2$-), 23.5 (1C, -*C*H$_3$), 21.2 (1C, -*C*H$_2$-). ESI-MS (*m/z*): 289 $(M+Na)^+$. $[\alpha]_D^{25}$: -8.1 (*c* 0.8, $CHCl_3$).

2.2.12. (4S,8R)-4-(Benzyloxy)-8-methyloxocan-2-one (19)

A solution of hydroxy acid **7** (0.19 g, 0.64 mmol) in dry THF (1 mL) was cooled to 0 °C under N_2 atmosphere. Then, triethylamine (0.3 mL, 1.92 mmol) and 2,4,6-trichlorobenzoyl chloride (0.16 mL, 0.96 mmol) were added dropwise and allowed to stirr at room temperature for 2 h. The mixture was then diluted with toluene (10 mL) and stirred at room temperature for further 1.5 h. Subsequently, this mixture was added dropwise over 8 h to a stirred solution of DMAP (0.15 g, 1.28 mmol) in toluene (350 mL) at 90 °C. After the complete addition, the reaction mixture was further stirred at 100 °C for 1 h. It was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by column chromatography (60-120 Silica gel, 6% EtOAc in petroleum ether) to give compound **19** (Scheme 1).

(4S,8R)-4-(Benzyloxy)-8-methyloxocan-2-one (**19**): Color: yellow syrup. Yield: 64%. IR (Neat, ν, cm^{-1}): 2924, 2854, 1719, 1611, 1513, 1458, 1170, 1063. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.38-7.21 (m, 5H, -C$_6$*H$_5$*), 4.77-4.69 (m, 1H, -OC*H*), 4.60 (d, 1H, *J* = 11.6 Hz, -OC*H$_2$*Ph), 4.45 (d, 1H, *J* = 11.6 Hz, -OC*H$_2$*Ph), 3.76-3.66 (m, 1H, -OC*H*), 2.77-2.68 (m, 2H, -C*H$_2$*), 1.88-1.79 (br. m, 4H, 2 x -C*H$_2$*), 1.71-1.62 (m, 2H, -C*H$_2$*), 1.31 (d, 3H, *J* = 6.0 Hz, -C*H$_3$*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 172.8 (1C, -O-*C*=O), 139.4 (1C, Ar-*C*), 130.5 (2C, Ar-*C*), 129.5 (1C, Ar-*C*), 128.1 (2C, Ar-*C*), 75.7 (1C, -O-*C*H-), 72.3 (1C, -O-*C*H$_2$-), 70.1 (1C, -O-*C*H-), 38.7 (1C, -*C*H$_2$-), 38.2 (1C, -*C*H$_2$-), 33.3 (1C, -*C*H$_2$-), 21.6 (1C, -*C*H$_3$, 19.4 (1C, -*C*H$_2$-). ESI-MS (*m/z*): 271 $(M+Na)^+$. $[\alpha]_D^{25}$: -75.4 (*c* 0.16, $CHCl_3$).



Scheme 2

2.2.13. (-)Cephalosporolide D (3)

To a solution of compound **19** (90 mg, 0.32 mmol) in CH_2Cl_2 (2 mL), $TiCl_4$ (0.02 g, 0.08 mmol) in CH_2Cl_2 (1 mL) was added and it was allowed to stir at room temperature for 3 h. After completion of the reaction, it was quenched with sat. $NaHCO_3$ solution (10 mL), filtered and washed with CH_2Cl_2 (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Purification of the residue by column chromatography (60-120 Silica gel, 20% EtOAc in petroleum ether) furnished compound **3** (Scheme 1).

(-) Cephalosporolide D (**3**): Color: Colorless syrup. Yield: 88%. IR (Neat, ν, cm^{-1}): 3422, 2931, 1721, 1646, 1439, 1283, 1159, 1118. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.67-4.60 (m, 1H, -OC*H*), 4.16-3.95 (m, 1H, -C*H*), 2.92-2.61 (dd, 2H, *J* = 5.8, 11.9 Hz, 2 x -C*H*=CO), 1.89-1.50 (m, 8H, OH, CH, 3 × CH_2), 1.33 (d, *J* = 5.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 172.1 (1C, -O-*C*=O), 75.1 (1C, -O-*C*H-), 71.4 (1C, -*C*H-OH), 43.3 (1C, -*C*H_2-), 38.5 (1C, -CH_2-), 36.6 (1C, -*C*H_2-), 25.7 (1C, -*C*H_3, 19.1 (1C, -*C*H_2-). ESI-MS (*m/z*): 181 $[M + Na]^+$. $[\alpha]_D^{25}$: -40.1 (*c* 0.9, $CHCl_3$).

3. Results and discussion

Our retrosynthetic analysis is outlined in Scheme 2. The macrolide **3** could be obtained by Yamaguchi lactonization followed by deprotection of benzyl ether of hydroxy acid **7**. Compound **7**, in turn, could be obtained from ester **8**. The ester **8** could be prepared from (*R*)-glyceraldehyde derivative **9** by simple chemical transformations.

Accordingly, the known D-glyceraldehyde derivative **9**, prepared from a literature procedure from D-mannitol [13] was subjected to Wittig olefination afforded ester **8** in 81% yield. Ester 8 was subjected to catalytic hydrogenation in the presence of 10% Pd-C in methanol under hydrogen atmosphere to give saturated ester **10** in 84%. Later, ester **10** on further treatment with diisobutylaluminium hydride (DIBAL-H) in dry CH_2Cl_2 at 0 °C for 3 h gave corresponding aldehyde, which was subjected to α-aminoxylation [14] catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ to furnish the required α-amino-substituted diol, which upon reductive hydrogenation using 10% Pd/C in methanol afforded chiral diol 11 in 72% yield (>97% diastereomeric excess). Diol **11** was treated with benzaldehyde dimethyl acetal in the presence of *p*-toluedine sulphonic acid (cat.) in dry CH_2Cl_2 at room temperature for 6 h to afford **12** in 83% yield. Regioselective ring opening of **12** with DIBAL-H (2M solution in toluene) at 0 °C to room temperature for 4 h afforded primary alcohol **13** in 79% yield.

The alcohol **13** on treatment with I_2 in the presence of PPh_3 and imidazole in dry THF afforded iodo-derivative **13a**, which on subsequent treatment with homoallyl bromide and magnesium in THF at 0 °C for 8 h gave **14** in 83% yield, which was then subjected to epoxidation using *m*-chloroperbenzoic acid (*m*-CPBA) in dry CH_2Cl_2 at room temperature for 6 h to afford the racemic epoxide **15** in 70% yield. Hydrolytic kinetic resolution of epoxide **15** using catalyst (*S*,*S*)-salen-Co-OAc catalyst in the presence of AcOH and H_2O at 15 °C to room temperature for 12 h afforded *S*-epoxide **16** in 44% yield [15]. Regioselective opening of epoxide **16** with lithium aluminium hydride in dry THF furnished alcohol **17** in 95% yield. Hydrolysis of **17** with 60% aq. acetic acid at room temperature for 12 h gave diol **18**, which on oxidative cleavage followed by oxidation with $NaClO_2$ and NaH_2PO_4, 2-methyl-2-butene in aq. *t*-butanol afforded hydroxy acid **7** in 78% yield. Hydroxy-acid **7** was subjected to macrolactonisation under Yamaguchi high dilution conditions using 2,4,6-trichlorobenzoyl chloride and Et_3N in dry THF to afford the lactone **19** in 64% yield [16]. Finally, **19** on debenzylation with $TiCl_4$ in CH_2Cl_2 at room temperature for 3 h gave **3** in 88% yield. The ^1H NMR and ^{13}C NMR spectral data and optical rotation value of synthetic **3** were in good accord with those of the natural product (Scheme 1).

4. Conclusion

In conclusion, we have completed the total synthesis of the macrocyclic eight-membered ring lactone, (**-**)-Cephalosporolide D in a regioselective manner from D-glyceraldehyde derivative. The desired stereochemistry was generated by α-amino xylation catalyzed by L-proline reaction, Jacobsen's hydrolytic kinetic resolution.

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