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ORIGINAL PAPER

A concise stereoselective total synthesis of (−)-cephalosporolide D

Gurrala Alluraiah[1] · Reddymasu Sreenivasulu[1] · Palle Sadanandam[2] · Kowthalam Anitha[3] · Rudraraju Ramesh Raju[1]

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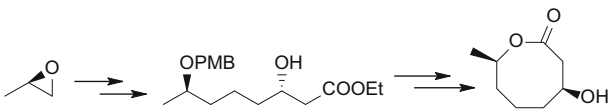
Abstract A concise stereoselective total synthesis of eight-membered lactone (−)-cephalosporolide D has been derived from inexpensive and commercially available starting material (*S*)-propylene epoxide. This concise synthesis utilizes Grignard reaction, Noyori asymmetric reduction, and Yamaguchi macrolactonization as key steps.

Graphical abstract



Keywords (*S*)-Propylene epoxide · Noyori asymmetric reduction · Yamaguchi macrolactonization · Stereoselective synthesis · (−)-Cephalosporolide D

Introduction

The interesting biological properties of medium-sized ring systems tend to attract the scientists from worldwide toward the synthesis of macrolides [1–4]. The various cephalosporolides represent very important attractive target molecules for the synthesis due to their biological activities which include mild inhibitory activity toward xanthine oxidase and 3α-hydroxysteroid dehydrogenase and also showed antimicrobial activity against gram-positive cocci, fungi, and structural profiles [5–9]. Among them, the eight-membered ring lactone (−)-cephalosporolide D (**1**) was isolated from fermentation fungus, *Cephalosporium aphidicola* ACC 3490 [5] and shown in Fig. 1. The absolute configuration of **1** was assigned as (4*R*, 8*S*) with chemical, spectroscopic, and X-ray analyses. The first stereoselective total synthesis of (−)-cephalosporolide D (**1**) was done by Shiina et al. [10, 11].

The reported synthetic routes [12, 13] to (−)-cephalosporolide D that mainly involve the low yielding steps, multiple step sequences, and dependence on the chiral pool reagents are some of the disadvantages associated with the earlier methods. We previously reported stereoselective total synthesis of (+)-cephalosporolide D from inexpensive starting material racemic propylene epoxide which includes α-aminoxylation catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ and Yamaguchi macrolactonization as key steps. This synthesis compromises the long chain reaction with low yields. In continuation of our research work on the synthesis of biologically active natural products, herein we report an efficient straightforward and concise stereoselective total synthesis of (−)-cephalosporolide D starting from commercially available starting material (+)-propylene epoxide with overall high yield.

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✉ Rudraraju Ramesh Raju
rrraju1@gmail.com

[1] Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar, 522 510 Guntur, Andhra Pradesh, India

[2] Centre for Chemical Sciences and Technology, Institute of Science and Technology, Jawaharlal Nehru Technological University, Hyderabad 500 085, India

[3] Department of Chemistry, Sri Krishnadevaraya University, 515 003 Anantapur, Andhra Pradesh, India

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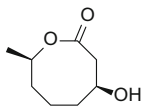
Fig. 1 Structure of (−)-cephalosporolide D



(-)-Cephalosporolide D (**1**)

Results and discussion

Our retrosynthetic analysis of **1** is outlined in Scheme 1. The macrolide **1** could be obtained by Yamaguchi macrolactonization followed by reductive cleavage of benzyl ether of hydroxyl acid **3** which in turn could be synthesized from corresponding ester **4**. The ester **4** could be obtained from (*S*)-propylene epoxide.

The total synthesis of **1** was initiated with (*S*)-propylene epoxide (**5**) which was obtained from (±)-propylene oxide [14–16] and shown in Scheme 2. Regeoselective ring opening of epoxide **5** with the Grignard reagent derived from homoallyl bromide at −78 °C for 2 h gave secondary alcohol **6** [17], which on subsequent treatment with PMBBr and NaH in tetrahydrofuran solvent at 0 °C to 25 °C for 8 h afforded **7** in 81 % yield. Further extension of the olefin **7** by ozonolysis and subsequent addition reaction with EtOAc on the resulting aldehyde (EtOAc/LiHMDS/THF/−78 °C) afforded a mixture of secondary alcohol product (72 %). In order to increase the diastereoselectivity in favor of the requisite stereocenter (*anti* to the existing one), an oxidation–reduction protocol was undertaken. Hence, secondary alcohol **4** was oxidized with PDC in dry CH_2Cl_2 at reflux temperature for 10 h afforded the corresponding keto compound, which was subjected to Noyori asymmetric hydrogenation reduction [18] with $RuCl_2$ [(*S*)-binap] in MeOH at 30 °C for 36 h afforded alcohol **9** in 81 % (94 % de). The above obtained alcohol **9** on treatment with NaH and benzyl bromide at 0 °C gave the Bn ether **10** in 89 % yield. Hydrolysis of **10** in the basic condition (LiOH in THF:MeOH:H_2O-3:1:1) afforded acid **11**, which on selective cleavage of PMB ether in the presence of DDQ in aq. CH_2Cl_2 gave the hydroxyacid **3** in 81 % yield [13]. Hydroxyacid **3** was subjected to macrolactonization under Yamaguchi high dilution conditions [19] using 2,4,6-trichlorobenzoyl chloride and Et_3N in dry THF to afford the lactone **12** in 69 % yield [13]. Finally, oxidative deprotection of Bn group in **12** using $TiCl_4$ in CH_2Cl_2 gave (−)-cephalosporolide D (**1**) in 79 % yield. The ^1H NMR and ^{13}C NMR spectral data and optical rotation value of synthetic **1** were in good accord with those of the natural product [12] (Scheme 2).

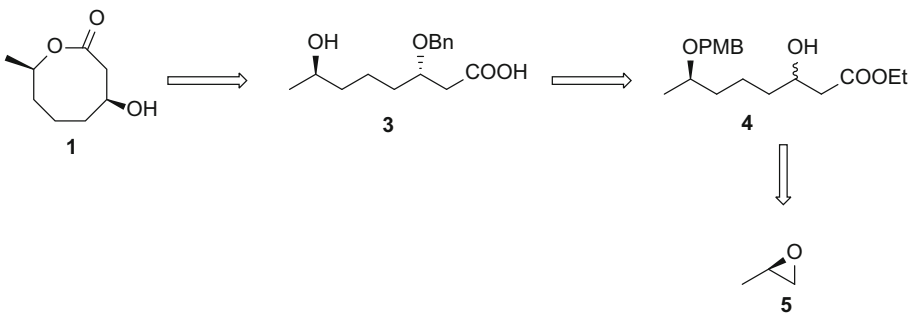
Conclusion

We developed a concise route for the synthesis of (−)-cephalosporolide D (**1**) by a common synthetic strategy. The synthesis of this lactone has been achieved by convergent approach starting from (*S*)-propylene oxide followed by Grignard reaction, Noyori Asymmetric reduction, and Yamaguchi macrolactonization as key steps.

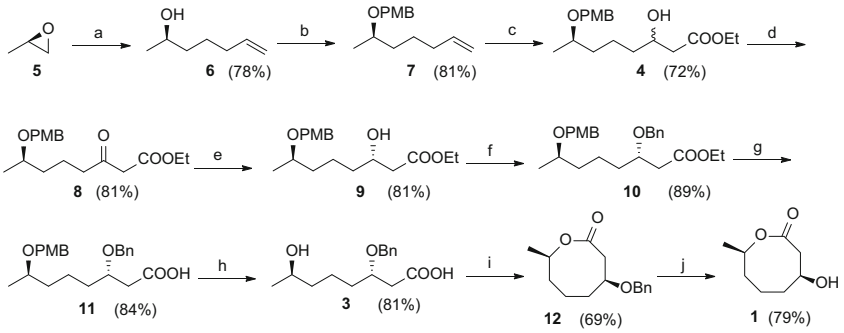
Experimental

All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^1H and ^{13}C NMR spectra were recorded on INOVA (400 MHz) or Gemini Varian-VXR-unity (300 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI^+ software with capillary voltage 3.98 kV and

Scheme 1



Scheme 2



(a) Homoallyl bromide, Mg, dry ether, -78 °C, 2 h; (b) PMBBr, NaH, THF, 0 °C to 25 °C, 8 h; (c) i) O_3, CH_2Cl_2, -78 °C, 15 min; ii) EtOAc, LiHMDS, THF, -78 °C, 1 h; (d) PDC, CH_2Cl_2, reflux, 10 h; (e) $RuCl_2$ [(*S*)-binap], MeOH, 30 °C, 36 h; (f) benzyl bromide, NaH, THF, 0 °C to 25 °C, 4 h; (g) LiOH, THF:MeOH:H_2O (3:1:1), 25 °C, 4 h; (h) DDQ, CH_2Cl_2:H_2O (19:1), 25 °C, 3 h; (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, 25 °C, 12 h; (j) $TiCl_4$, CH_2Cl_2, 0 °C to 25 °C, 3 h.

ESI mode-positive ion trap detector. Melting points were determined with an Electrothermal melting point apparatus.

*(R)-Hept-6-en-2-ol (**6**) [17]*

A suspension of 3.8 g Mg (165.51 mmol, 3.0 eq) and 30 cm^3 dry ether was treated with 8.4 cm^3 homoallyl bromide (82.75 mmol, 1.5 eq) at 25 °C and stirred for 30 min. It was cooled to −78 °C, and a solution of 4 cm^3 **5** (55.17 mmol, 1.0 eq) in 10 cm^3 dry ether was added dropwise and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with 10 cm^3 aq. NH_4Cl solution and extracted with ether (2 × 50 cm^3). Combined extracts were washed with 30 cm^3 brine, dried (Na_2SO_4), and concentrated and purified the residue by column chromatography (silica gel, 60–120 mesh, 7 % EtOAc in pet. ether) to afford alcohol **6** (4.9 g, 78 %) as a colorless liquid.

(R)-1-[(Hept-6-en-2-yloxy)methyl]-4-methoxybenzene (**7**, $C_{15}H_{22}O_2$)

To a cooled (0 °C) solution of 4.8 g **6** (42.10 mmol, 1.0 eq) in 30 cm^3 dry THF, 4.0 g NaH (168.4 mmol, 4.0 eq) was added, stirred for 30 min, and treated with a solution of 10.0 g PMBBr (50.52 mmol, 1.2 eq) in 40 cm^3 dry THF. After 7.5 h stirring at 25 °C, the reaction mixture was quenched with 30 cm^3 sat. NH_4Cl solution and extracted with ethyl acetate (2 × 100 cm^3). The organic layers were washed with water (2 × 50 cm^3), 50 cm^3 brine, and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (silica gel, 60–120 mesh, 5 % EtOAc in pet. ether) to furnish **7** (8.01 g, 81 %) as a yellow liquid. $[\alpha]_D^{25} = +43.8$ ($c = 0.91$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.18$ (d, 2H, $J = 8.5$ Hz, ArH-PMB), 6.79 (d, 2H, $J = 8.5$ Hz, ArH-PMB), 5.84 (dddd, 1H, $J = 6.6$, 10.2, 13.4, 16.8 Hz, olefinic), 4.98–4.89 (m, 2H, olefinic), 4.46 (d, 1H, $J = 11.3$ Hz, benzylic), 4.34 (d, 1H, $J = 11.3$ Hz, benzylic), 3.78 (s, 3H, –OCH_3), 3.46 (m, 1H, –OCH), 2.01 (m, 2H, –CH_2), 1.61–1.41 (m, 4H, 2 CH_2), 1.14 (d, 3H, $J = 6.0$ Hz, –CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.0$, 138.9, 129.7, 129.1, 114.4, 113.7, 74.3, 69.9, 55.2, 36.1, 33.8, 24.8, 19.6 ppm; IR (neat):$\bar{V} = 3070$, 2932, 2829, 1635, 1466, 1134, 1015 cm^{-1}; ESI–MS: $m/z = 257$ [$(M + Na)^+$].

(R)-Ethyl 3-hydroxy-7-(4-methoxybenzyloxy)octanoate (**4**, $C_{18}H_{28}O_5$)

Ozone was bubbled through a cooled (−78 °C) solution of 5.0 g **7** (21.36 mmol, 1.0 eq) in 50 cm^3 CH_2Cl_2 until the pale blue color persisted. Excess ozone was removed with 2 cm^3 Me_2S and stirred for 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give aldehyde, which was used for further reaction. To a stirred solution of 10.5 g HMDS (65.24 mmol, 3.5 eq) in 25 cm^3

anhydrous THF at 0 °C, 39 cm^3 *n*-BuLi (2.0 M in *n*-hexane, 74.56 mmol, 4.0 eq) was added and reaction mixture stirred for 30 min at the same temperature, after that reaction mixture taken to −78 °C and 6.5 g EtOAc (74.56 mmol, 4.0 eq) was added in one pot by syringing. Stirring was continued at −78 °C for 1 h, and then 4.4 g aldehyde (18.64 mmol, 1.0 eq) dissolved in 25 cm^3 dry THF was added to above reaction mixture at −78 °C and reaction mixture stirred at the same temperature for 1 h. The reaction mixture was quenched with 50 cm^3 sat. aq. NH_4Cl solution at 0 °C, extracted with EtOAc (2 × 100 cm^3), washed with 50 cm^3 water, 50 cm^3 brine, concentrated the organic layer, and purified by column chromatography (silica gel, 60–120 mesh, 12 % EtOAc in pet. ether) to afford **4** (2.17 g) in 72 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.21$ (d, 2H, $J = 8.8$ Hz, ArH-PMB), 6.81 (d, 2H, $J = 8.8$ Hz, ArH-PMB), 4.44 (d, 1H, $J = 11.1$ Hz, benzylic), 4.38 (d, 1H, $J = 11.1$ Hz, benzylic), 4.14 (q, 2H, $J = 7.0$ Hz, –OCH_2), 3.74 (s, 3H, –OCH_3), 3.66 (m, 1H, –OCH), 3.44 (m, 1H, –OCH), 2.76 (m, 2H, –CH_2), 1.58–1.21 (m, 6H, 3 –CH_2), 1.27 (t, 3H, $J = 7.0$ Hz, –OCH_2CH_3) 1.12 (d, 3H, $J = 6.1$ Hz, –CH_3) ppm; ESI–MS: $m/z = 325$ $[(M + H)^+]$.

(R)-Ethyl 7-(4-methoxybenzyloxy)-3-oxooctanoate (**8**, $C_{18}H_{26}O_5$)

To the stirred solution of 2.5 g **4** (7.71 mmol, 1.0 eq) in 25 cm^3, anhydrous CH_2Cl_2 MS powder and 8.7 g PDC (23.14 mmol, 3.0 eq) were added, to that (4–5 drops) Ac_2O was added and the whole reaction mixture was put for reflux for 10 h. The reaction mixture was concentrated and purified by column chromatography (silica gel, 60–120 mesh, 10 % EtOAc in pet. ether) to afford **8** (2.01 g, 81 %) as a yellow colored thick syrup. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$ (d, 2H, $J = 8.6$ Hz, ArH-PMB), 6.87 (d, 2H, $J = 8.6$ Hz, ArH-PMB), 4.47 (s, 2H, $J = 10.8$ Hz, benzylic), 4.11 (q, 2H, $J = 6.9$ Hz, –OCH_2), 3.67 (s, 3H, –OCH_3), 3.36 (m, 1H, –OCH), 3.31 (s, 2H, –CH_2), 2.19 (t, 2H, $J = 6.6$ Hz, –CH_2), 1.44–1.24 (m, 4H, 2 CH_2), 1.21 (t, 3H, $J = 6.9$ Hz, –OCH_2CH_3) 1.11 (d, 3H, $J = 6.1$ Hz, –CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.8$, 170.8, 158.3, 130.1, 129.3, 113.3, 79.1, 62.2, 56.1, 49.3, 44.6, 36.7, 22.8, 22.3, 14.6 ppm; ESI–MS: $m/z = 323$ $[(M + H)^+]$.

(3S,7R)-Ethyl 3-hydroxy-7-(4-methoxybenzyloxy)octanoate (**9**, $C_{18}H_{28}O_5$)

To the stirred solution of 1.9 g **8** (4.96 mmol, 1.0 eq) in 5.0 cm^3, anhydrous methanol was treated with catalytic amount of $RuCl_2$ [(*S*)-binap] [17] at 30 °C for 36 h under hydrogen atmosphere. After completion of the reaction, it was filtered, evaporated, and purified by column chromatography (silica gel, 60–120 mesh, 15 % EtOAc in pet. ether) to give **9** (1.56 g, 81 %) as a pale yellow syrup. $[\alpha]_D = -114.3$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.20$ (d, 2H, $J = 8.6$ Hz, ArH-PMB), 6.79 (d, 2H, $J = 8.6$ Hz, ArH-PMB), 4.47 (d, 1H, $J = 11.1$ Hz, benzylic), 4.36 (d, 1H, $J = 11.1$ Hz, benzylic), 4.14 (q, 2H, $J = 7.0$ Hz, –OCH_2), 3.74 (s, 3H, –OCH_3), 3.63 (m, 1H, –OCH), 3.39 (m, 1H, –OCH), 2.71 (dd, 1H, $J = 8.0$, 15.3 Hz, –CH), 2.50 (dd, 1H, $J = 5.2$, 15.3 Hz, –CH), 1.58–1.29 (m, 6H, 3 CH_2), 1.27 (t, 3H, $J = 7.1$ Hz, –OCH_2CH_3) 1.11 (d, 3H, $J = 6.1$ Hz, –CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.3$, 159.3, 141.2, 130.1, 129.8, 114.3, 75.6, 72.2, 66.8, 59.8, 56.1, 42.4, 37.3, 34.7, 26.0, 23.2, 20.9, 14.7 ppm; IR (neat): $\bar{V} = 3354$, 2928, 2862, 2105, 1613, 1514 cm^{-1}; ESI–MS: $m/z = 347$ $[(M + Na)^+]$.

(3S,7R)-Ethyl 3-(benzyloxy)-7-(4-methoxybenzyloxy) octanoate (**10**, $C_{25}H_{34}O_5$)

To a cooled (0 °C) suspension of 0.41 g NaH (17.28 mmol, 4.0 eq 60 % w/w dispersion in paraffin oil) in 15 cm^3 dry THF, a solution of 1.4 g **9** (4.32 mmol, 1.0 eq) in 5 cm^3 dry THF was added and stirred for 30 min. After that 0.78 cm^3 BnBr (6.48 mmol, 1.2 eq) was added dropwise at 0 °C and stirred for 4 h at 25 °C. Saturated aq. NH_4Cl solution (20 cm^3) was added dropwise at 0 °C followed by 30 cm^3 EtOAc. Organic layers were washed with 20 cm^3 water, 20 cm^3 brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 60–120 mesh, 8 % EtOAc in pet. ether) to give **10** (1.59 g, 89 %) as a light yellow syrup. $[\alpha]_D = -166.3$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.27$ (m, 5H, ArH-Bn), 7.18 (d, 2H, $J = 8.3$ Hz, ArH-PMB), 6.84 (d, 2H, $J = 8.3$ Hz, ArH-PMB), 4.56 (d, 1H, $J = 11.4$ Hz, benzylic), 4.48 (s, 2H, benzylic), 4.36 (d, 1H, $J = 11.4$ Hz, benzylic), 4.11 (q, 2H, $J = 7.3$ Hz, –OCH_2), 3.69 (s, 3H, –OCH_3), 3.59 (m, 1H, –OCH), 3.39 (m, 1H, –OCH), 2.71 (dd, 1H, $J = 8.1$, 15.1 Hz, –CH), 2.53 (dd, 1H, $J = 5.1$, 15.1 Hz, –CH), 1.66–1.31 (m, 6H, 3 CH_2), 1.27 (t, 3H, $J = 7.0$ Hz, –OCH_2CH_3), 1.14 (d, 3H, $J = 6.1$ Hz, –CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 170.9$, 159.6, 146.7, 139.3, 129.8, 129.6, 129.1, 128.5, 128.0, 127.8, 114.0, 75.9, 73.1, 71.3, 69.9, 60.3, 55.4, 40.4, 36.8, 36.0, 23.3, 21.2, 14.9 ppm; IR (neat): $\bar{V} = 2928$, 2862, 2105, 1613, 1514 cm^{-1}; ESI–MS: $m/z = 437$ $[(M + Na)^+]$.

(3S,7R)-3,7-Bis(4-methoxybenzyloxy)octanoic acid (**11**, $C_{23}H_{30}O_5$)

To a solution of 1.65 g **10** (3.98 mmol, 1.0 eq) in 10 cm^3 THF: MeOH: water (3:1:1), 0.29 g LiOH (18.48 mmol, 4.6 eq) was added and stirred at 25 °C for 4 h. The pH of reaction mixture was adjusted to acidic with 1 N HCl solution and extracted with 30 cm^3 ethyl acetate. Organic layers were washed with 15 cm^3 water, 15 cm^3 brine, dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120

mesh, 30 % EtOAc in pet. ether) to give **11** (1.29 g, 84 %) as a colorless oil. $[\alpha]_D = +14.6$ ($c = 0.6$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.31$ (m, 5H, ArH-Bn), 7.20 (d, 2H, $J = 8.6$ Hz, ArH-PMB), 6.90 (d, 2H, $J = 8.6$ Hz, ArH-PMB), 4.57 (d, 1H, $J = 11.4$ Hz, benzylic), 4.46 (s, 2H, benzylic), 4.37 (d, 1H, $J = 11.4$ Hz, benzylic), 3.71 (s, 3H, –OCH_3), 3.63 (m, 1H, –OCH), 3.37 (m, 1H, –OCH), 2.59 (m, 2H, –CH_2), 1.63–1.41 (m, 4H, 3 CH_2), 1.32–1.20 (m, 2H, –CH_2) 1.16 (d, 3H, $J = 6.0$ Hz, –CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.8$, 159.8, 138.9, 129.7, 129.4, 128.8, 128.5, 128.0, 114.4, 76.1, 73.8, 72.7, 70.1, 56.3, 41.1, 36.3, 36.1, 22.8, 21.4 ppm; IR (neat): $\bar{V} = 3540$, 3031, 2930, 2857, 1710, 1097 cm^{-1}; ESI–MS: $m/z = 409$ $[(M + Na)^+]$.

*(3S,7R)-3-(Benzyloxy)-7-hydroxyoctanoic acid (**3**) [13]*
To a solution of 1.2 g **11** (3.10 mmol, 1.0 eq) in 10 cm^3 aq. CH_2Cl_2 (19:1), 1.05 g DDQ (4.66 mmol, 1.5 eq) was added and stirred at 25 °C for 3 h. The reaction mixture was quenched with 5 cm^3 sat. $NaHCO_3$ solution, filtered, and washed with 10 cm^3 CH_2Cl_2. The filtrate was washed with 3 cm^3 water, 3 cm^3 brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, 50 % EtOAc in pet. ether) to furnish **3** (0.66 g, 81 %). $[\alpha]_D^{25} = -11.1$ ($c = 1.1$, $CHCl_3$).

*(4S,8R)-4-(Benzyloxy)-8-methyloxocan-2-one (**12**) [13]*
To a stirred solution of 0.42 g **3** (1.57 mmol, 1.0 eq) and 0.66 cm^3 Et_3N (4.71 mmol, 3.0 eq) in 5 cm^3 dry THF, a solution of 0.36 cm^3 2,4,6-trichlorobenzoyl chloride (2.36 mmol, 1.5 eq) in 1 cm^3 dry THF was added. The resulting mixture was stirred for 2 h at 25 °C under nitrogen atmosphere and evaporated to afford the mixed anhydride. It was diluted with 10 cm^3 toluene and filtered quickly through Celite. The filtrate was added dropwise to a stirred solution of 0.38 g DMAP (3.14 mmol, 2.0 eq) in 350 cm^3 toluene at 90 °C over a period of 8 h. After the complete addition, the reaction mixture was stirred at 100 °C for 2 h. It was cooled, washed with 40 cm^3 7 % aq $NaHCO_3$, 40 cm^3 2 M aqueous HCl, 40 cm^3 brine, and dried (Na_2SO_4). The organic layer was evaporated and the obtained residue purified by column chromatography (silica gel, 60–120 mesh, 15 % EtOAc in pet. ether) to give **12** (0.27 g, 69 %) as a syrup. $[\alpha]_D = -69.6$ ($c = 0.9$, $CHCl_3$).

*(−)-Cephalosporolide D (**1**)*
To a stirred solution of 0.14 g **12** (0.56 mmol, 1.0 eq) in 2 cm^3 CH_2Cl_2, 0.11 g $TiCl_4$ (0.56 mmol, 1.0 eq) in 1 cm^3 CH_2Cl_2 was added at 0 °C and stirred at 25 °C for 2 h. The reaction mixture was treated with 5 cm^3 saturated $NaHCO_3$ solution and extracted with $CHCl_3$ (3×10 cm^3). The combined organic layers were washed with 10 cm^3 water, 10 cm^3 brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, 60–120 mesh, 1:3 EtOAc:*n*-hexane) to afford **1** (70 mg, 79 %). $[\alpha]_D = -38.7$ ($c = 1.6$, $CHCl_3$); ^1H NMR and ^{13}C NMR spectra were in agreement with those of the natural product [12].

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