Synthesis of (−)-Cephalosporolide D Using an Iterative Acetylene–Epoxide Coupling Strategy

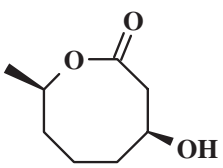
Gowravaram Sabitha,* Teega Rammohan Reddy, Muddala Ramesh, Chitti Srinivas, and Jhillu Singh Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received October 4, 2010
E-mail: gowravaramsr@yahoo.com

The synthesis of an eight-membered lactone, cephalosporolide D is described using an iterative acetylene–epoxide coupling strategy. The terminal triple bond compound prepared in situ from the known epoxy chloride was coupled with (*R*)-methyloxirane to afford the propargyl alcohol. The selective protection of the propargylic hydroxy group as TBS ether followed by reduction of the triple bond gave the saturated alcohol. Removal of THP group followed by selective oxidation of the primary hydroxy group was achieved using BAIB–TEMPO to furnish the aldehyde, which was converted to the corresponding acid by Pinnick oxidation, followed by Yamaguchi lactonization and finally removal of the TBS group afforded the target molecule. A concise synthesis of (−)-cephalosporolide D is described. The salient features are the utilization of acetylene–epoxide coupling strategy and Yamaguchi lactonization.

Medium ring systems (eight- to twelve-membered rings) are often found in biologically active natural products, and as a consequence, methods for their synthesis are of considerable interest.[1] Cephalosporolides,[2–4] a group of lactones, were produced by fermentation of the fungus *Cephalosporium aphidicola*, and their structures were elucidated by a combination of spectroscopic, chemical, and X-ray analyses.[2] Among them, cephalosporolide D (Figure 1) is an eight-membered lactone, three of these metabolites are ten-membered lactones (cephalosporolides B, C, and G), and the others (cephalosporolides E, F, H, and I) are spiroketal lactones. The relative and absolute stereochemistry of (−)-cephalosporolide D, was determined by its synthesis[5] followed by a recent report utilizing the cross-metathesis reaction.[6] The unnatural (+)-cephalosporolide D was synthesized by Buszek et al.[7] in 2001 using the Corey–Nicolaou lactonization method.[8]



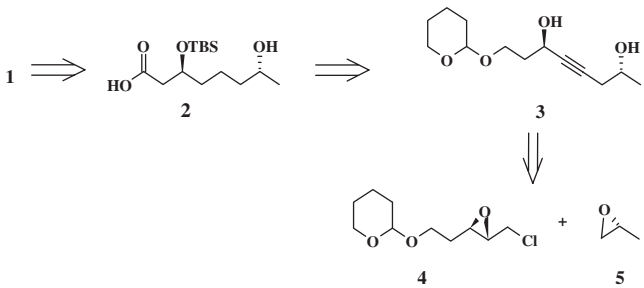
1

Figure 1. (−)-Cephalosporolide D.

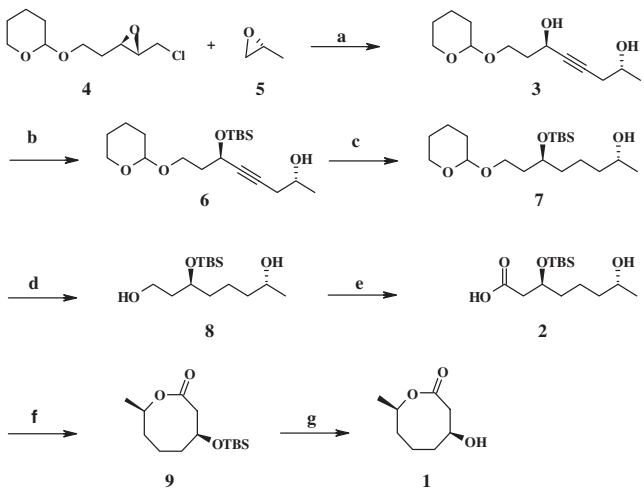
In continuation of our studies on the synthesis of naturally occurring macrolides,[9] we herein report an alternate and a concise synthesis of (−)-cephalosporolide D using an iterative acetylene–epoxide coupling methodology and Yamaguchi lactonization.

Our retrosynthetic analysis is shown in Scheme 1. The macrolide **1** could be obtained by Yamaguchi lactonization of **2**, which in turn could be made from **3** prepared by iterative coupling of triple bond compound (made in situ from epoxy chloride **4**) with (*R*)-methyloxirane (**5**).

Accordingly, the known epoxy chloride **4**[10d] was subjected to $LiNH_2$ in liquid ammonia to furnish the desired terminal acetylene,[10] which was coupled in situ with 5 equiv of compound **5** to get the chiral propargyl alcohol **3** in one-pot reaction in 80% yield (Scheme 2). The propargylic hydroxy group was selectively converted to the TBS ether **6** in the presence of the other secondary hydroxy group. Now, the triple bond in compound **6** was reduced with H_2 over 10% Pd/C in



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: a) Li, liq NH_3, $Fe(NO_3)_3$ (catalyst), dry THF, 2 h then propylene oxide, −33 °C, 5 h, 80%; b) TBDMSCl, imidazole, dry CH_2Cl_2, 0 °C, 4 h, 86%; c) 10% Pd/C, EtOAc, H_2, rt, 15 h, 90%; d) NH_4Cl, MeOH, reflux, 15 h, 91%; e) i. BAIB, TEMPO, CH_2Cl_2, 0 °C, 2 h; ii. $NaClO_2$, NaH_2PO_4, DMSO, 0 °C to rt 1 h, 83%; f) 2,4,6-trichlorobenzoyl chloride, Et_3N, 3 h then DMAP, toluene, reflux, 6 h, 70%; g) TBAF, dry THF, 0 °C, 6 h, 90%.

Published on the web February 4, 2011; doi:10.1246/bcsj.20100283

EtOAc providing saturated compound **7**. Removal of the tetrahydropyran protecting group by using NH_4Cl in MeOH at reflux temperature resulted in diol **8** in 91% yield. Selective oxidation of primary alcohol in diol **8** to aldehyde was achieved with bisacetoxyiodobenzene–TEMPO[11] in CH_2Cl_2 at 0 °C which without purification was converted to the corresponding acid **2** by Pinnick oxidation,[12] followed by Yamaguchi lactonization (2,4,6-trichlorobenzoyl chloride in refluxing toluene) to provide the eight-membered lactone **9**.[5b] Finally, removal of the TBS group provided the target molecule **1** in good yield. The ^{1}H NMR and ^{13}C NMR spectral data and optical rotation value of synthetic **1** were in good accord with those of the natural product.

In conclusion, an iterative acetylene–epoxide coupling, selective protection of a propargylic hydroxy group and Yamaguchi's protocols were successfully applied leading to the synthesis of (−)-cephalosporolide D.

Experimental

General. Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). Light petroleum ether (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS (δ 0.0) as an internal standard. Mass spectra were recorded under E1 conditions at 70 eV on LC-MSD (Agilent technologies) spectrometers. All high-resolution spectra were recorded on a QSTAR XL hybrid ms/ms system (Applied Biosystems/MDS sciex, Foster city, USA), equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with a JASCO DIP-370 Polarimeter at 25 °C.

(2*R*,6*R*)-8-(Tetrahydro-2*H*-2-pyranyloxy)-4-octyne-2,6-diol (3). To freshly distilled ammonia (50 mL) in a 250 mL two-necked round-bottomed flask fitted with a cold finger condenser was added a catalytic amount of $Fe(NO_3)_3$, followed by the piece-wise addition of lithium metal (0.55 g, 79.2 mmol) at −33 °C and the resulting gray-colored suspension was stirred for 30 min. To this suspension epoxy chloro compound **4** (2.5 g, 11.3 mmol) in dry THF (20 mL) was added over 20 min. The reaction mixture was stirred for 2 h at −33 °C. After 2 h, the addition of a catalytic amount of $BF_3 \cdot Et_2O$ followed by **5** (4.1 mL, 56.7 mmol) was carried out successively, stirred for 5 h at the same temperature, and quenched by the addition of solid NH_4Cl (10 g) and the ammonia was then allowed to evaporate. The reaction mixture was diluted with water (10 mL) and EtOAc (50 mL) and filtered on a small pad of Celite. The filtrate was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography to afford **3** (2.19 g, 80%) as a pale yellow-colored viscous liquid

$[\alpha]_D^{25}$ +11.9 (*c* 3.2, $CHCl_3$); IR (neat): ν_{max} 3392, 2925, 2854, 1736, 1649, 1455, 1373, 1264, 1203, 1120, 1069, 1027, 983, 939, 867 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.63–4.51 (m, 2H), 4.17–4.04 (m, 1H), 3.97–3.76 (m, 2H), 3.73–3.64 (m, 1H), 3.61–3.44 (m, 1H), 2.46–2.25 (m, 2H), 2.11–1.43 (m, 8H), 1.24 (d, $J = 6.04$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.8, 83.1, 81.8, 66.2, 64.6, 62.2, 61.1, 37.1, 30.5, 29.2, 25.2, 22.2, 19.6. ESI mass: m/z 265 $[M + Na]^+$.

(2*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-8-(tetrahydro-2*H*-2-pyranyloxy)-4-octyn-2-ol (6). To a stirred solution of alcohol **3** (2.0 g, 8.25 mmol) and imidazole (0.84 g, 12.3 mmol) in dry CH_2Cl_2 (20 mL) was added TBDMSCl (1.24 g, 8.25 mmol) portion wise at 0 °C. The reaction mixture was stirred at the same temperature for 4 h and then quenched with saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 40 mL). The DCM layer was separated and the aqueous layer extracted with additional CH_2Cl_2 (2 × 30 mL). Combined organic layers were washed with water (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo and the residue was purified by silica gel column chromatography to afford **6** (2.53 g, 86% yield) as a colorless liquid.

$[\alpha]_D^{25}$ +6.0 (*c* 2.6, $CHCl_3$); IR (neat): ν_{max} 3439, 2929, 2857, 1734, 1462, 1356, 1254, 1201, 1083, 1029, 839, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61–4.51 (m, 2H), 3.96–3.77 (m, 3H), 3.55–3.42 (m, 2H), 2.45–2.25 (m, 2H), 1.98–1.32 (m, 8H), 1.24 (d, $J = 6.0$ Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.8, 84.4, 80.8, 66.4, 63.4, 62.3, 60.1, 38.9, 30.7, 29.4, 25.8, 25.4, 22.3, 19.5, 18.2, −4.6, −5.1; ESI mass: m/z 379 $[M + Na]^+$.

(2*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-8-(tetrahydro-2*H*-2-pyranyloxy)octan-2-ol (7). To a solution of compound **6** (2.40 g, 6.73 mmol) in ethyl acetate (15 mL) was added a 10% Pd/C (0.250 g) and the mixture was kept under a H_2 atmosphere for 15 h at room temperature. After the reaction was completed (monitored by TLC), the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography afforded the desired product **7** (2.18 g) in 90% yield.

$[\alpha]_D^{25}$ −10.1 (*c* 2.8, $CHCl_3$); IR (neat): ν_{max} 3444, 2933, 2858, 1644, 1463, 1372, 1253, 1124, 1072, 1030, 835, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.56–4.51 (m, 1H), 3.87–3.69 (m, 4H), 3.51–3.36 (m, 2H), 1.77–1.32 (m, 14H), 1.18 (d, $J = 6.8$ Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.9, 69.2, 68.0, 64.1, 62.3, 39.5, 37.4, 36.9, 30.7, 25.9, 25.5, 23.4, 21.2, 19.7, 18.1, −4.4, −4.6; ESI mass: m/z 383 $[M + Na]^+$.

(3*S*,7*R*)-3-(*tert*-Butyldimethylsilyloxy)octane-1,7-diol (8). Compound **7** (2.0 g, 5.54 mmol) was taken in 30 mL of MeOH. To this NH_4Cl (1.48 g, 27.73 mmol) was added. The reaction mixture was vigorously refluxed for 15 h and purification by chromatography gave **8** (1.39 g, 91% yield).

$[\alpha]_D^{25}$ −0.7 (*c* 2.1, $CHCl_3$); IR (neat): ν_{max} 3381, 2927, 2855, 1646, 1462, 1374, 1252, 1110, 1061, 836, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (q, $J = 6.1$ Hz, 1H), 3.82–3.74 (m, 2H), 3.71–3.65 (m, 1H), 1.70–1.23 (m, 8H), 1.19 (d,

$J = 6.1$ Hz, 3H), 0.91 (9H, s), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.8, 67.9, 60.2, 39.3, 37.7, 25.8, 23.5, 21.5, 18.0, −4.4, −4.7; ESI mass: m/z 299 $[M + Na]^+$.

(3*S*,7*R*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxyoctanoic Acid (2). BAIB (1.53 g, 4.77 mmol) was added to a solution of alcohol **8** (1.20 g, 4.34 mmol) and TEMPO (0.067 g, 0.43 mmol) in 4 mL of CH_2Cl_2 at 0 °C. The rection mixture was stirred until the alcohol was no longer detectable (TLC), and then it was diluted with CH_2Cl_2 (20 mL). The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The unstable crude aldehyde was immediately used for the next reaction.

A solution of $NaClO_2$ (0.59 g, 6.54 mmol) in 2 mL of water was added dropwise to a stirred solution of the above crude aldehyde (1.2 g, 4.36 mmol) in 5 mL of DMSO and NaH_2PO_4 (8.72 g, 4.87 mmol) in 5 mL of water over 5 min at 0 °C. The mixture was stirred for 1 h at 0 °C to room temperature and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted (3 × 30 mL) with CH_2Cl_2 (3 × 30 mL) and washed with brine (30 mL), then dried over (Na_2SO_4). Solvent was removed in vacuo and the residue was purified by silica gel column chromatography to afford the acid **2** (1.04 g) as a yellowish liquid (83% yield for two steps).

$[a]_D^{25}$ −0.09 (*c* 3.1, $CHCl_3$); IR (neat): ν_{max} 3405, 2934, 2859, 1713, 1462, 1375, 1254, 1198, 1094, 940, 834, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.12 (q, $J = 6.0$ Hz, 1H), 3.84–3.72 (m, 1H), 2.47 (d, $J = 6.0$ Hz, 2H), 1.61–1.32 (m, 6H), 1.19 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.1, 69.2, 67.9, 41.9, 39.1, 37.2, 25.7, 23.4, 21.2, 17.9, −4.6, −4.9; ESI mass: m/z 313 $[M + Na]^+$.

(4*S*,8*R*)-4-(*tert*-Butyldimethylsilyloxy)-8-methyloxocan-2-one (9). 2,4,6-Trichlorobenzoyl chloride (1.58 mL, 10.1 mmol) was added to the solution of **2** (0.980 g, 3.37 mmol), triethylamine (0.23 mL, 1.67 mmol), and THF (3 mL). The solution was stirred at room temperature for 3 h, diluted with toluene (6 mL), and added to a refluxing solution of 4-dimethylaminopyridine (4.16 g, 34.1 mmol) and toluene (50 mL). The reaction mixture was refluxed for 6 h, cooled to room temperature, then to it was added sat. aq. $NaHCO_3$. The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with water (20 mL), and sat'd. brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography to give **9** (0.681 g, 70%).

$[a]_D^{25}$ +0.8 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} 3446, 2933, 2858, 1732, 1459, 1370, 1265, 1216, 1170, 1125, 1088, 1055, 992, 838, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.92–4.81 (m, 1H), 4.01–3.95 (m, 1H), 2.61 (dd, $J = 4.9$, 11.7 Hz, 1H), 2.42 (dd, $J = 8.8$, 10.7 Hz, 1H), 1.90–1.64 (m, 4H), 1.59–1.49 (m, 1H), 1.32 (d, $J = 5.9$ Hz, 3H), 1.20–1.10 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 75.0, 71.4, 42.3, 38.5, 36.6, 29.7, 25.7, 21.3, 18.6, −4.8, −4.9; ESI mass: m/z 295 $[M + Na]^+$.

(4*S*,8*R*)-4-Hydroxy-8-methyloxocan-2-one (1). To a solution of **9** (0.660 g, 2.28 mmol) in THF (10 mL) was added TBAF (1.31 mL, 4.57 mmol, 1 M solution in THF) at 0 °C. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc (3 × 10 mL). The organic layer was washed with water (20 mL), and brine (20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel to give **1** (0.358 g, 90%).

$[a]_D^{25}$ −41.8 (*c* 0.6, $CHCl_3$); IR (neat): ν_{max} 3408, 2925, 2857, 1728, 1646, 1439, 1283, 1163, 1122 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67–4.60 (m, 1H), 4.16–3.95 (m, 1H), 2.93 (dd, $J = 4.8$, 11.8 Hz, 1H), 2.6 (dd, $J = 5.8$, 11.9 Hz, 1H), 1.89–1.52 (m, 6H), 1.33 (d, $J = 5.9$ Hz, 3H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 172.1, 75.1, 71.4, 43.3, 38.5, 36.6, 25.7, 19.1; ESI mass: m/z 181 $[M + Na]^+$.

T. R. M. R and Ch. S thanks UGC, New Delhi for the award of Fellowships.

References

1 I. Shiina, *Chem. Rev.* **2007**, *107*, 239.
2 M. J. Ackland, J. R. Hanson, P. B. Hitchcock, A. H. Ratcliffe, *J. Chem. Soc., Perkin Trans. 1* **1985**, 843.
3 A. Farooq, J. Gordon, J. R. Hanson, J. A. Takahashi, *Phytochemistry* **1995**, *38*, 557.
4 X. Li, Y. Yao, Y. Zheng, I. Sattler, W. Lin, *Arch. Pharmacal Res.* **2007**, *30*, 812.
5 a) I. Shiina, Y. Fukuda, T. Ishii, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **1998**, 831. b) I. Shiina, H. Fujisawa, T. Ishii, Y. Fukuda, *Heterocycles* **2000**, *52*, 1105.
6 G. V. Reddy, R. S. C. Kumar, E. Sreedhar, K. S. Babu, J. M. Rao, *Tetrahedron Lett.* **2010**, *51*, 1723.
7 K. R. Buszek, Y. Jeong, N. Sato, P. C. Still, P. L. Muiño, I. Ghosh, *Synth. Commun.* **2001**, *31*, 1781.
8 E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974**, *96*, 5614.
9 a) G. Sabitha, P. Padmaja, K. Sudhakar, J. S. Yadav, *Tetrahedron: Asymmetry* **2009**, *20*, 1330. b) G. Sabitha, K. Yadagiri, R. Swapna, J. S. Yadav, *Tetrahedron Lett.* **2009**, *50*, 5417. c) G. Sabitha, C. Srinivas, C. Maruthi, J. S. Yadav, *Helv. Chim. Acta* **2010**, *93*, 1634.
10 a) J. S. Yadav, P. K. Deshpande, G. V. M. Sharma, *Pure Appl. Chem.* **1990**, *62*, 1333. b) G. Sabitha, E. V. Reddy, M. Bhikshapathi, J. S. Yadav, *Tetrahedron Lett.* **2007**, *48*, 313. c) G. Sabitha, E. V. Reddy, K. Yadagiri, J. S. Yadav, *Synthesis* **2006**, 3270. d) G. Sabitha, N. Fatima, R. Swapna, J. S. Yadav, *Synthesis* **2006**, 2879.
11 T. Mathew Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. C. Abrams, C. J. Forsyth, *Tetrahedron Lett.* **2003**, *44*, 57.
12 B. S. Bal, W. E. Childers, Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.