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Total synthesis of naturally occurring cephalosporolides E/F

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ABSTRACT

A modular total synthesis of cephalosporolides E/F featuring sequential epoxide–alkyne coupling and subsequent highly regioselective gold catalyzed alkynolcycloisomerization of the resulting alkynetetrol to construct the central spiroketal core has been documented.

1. Introduction

Cephalosporolides E and F were isolated from the industrial fermentation of the fungus *Cephalosporium aphidcola* in 1985 and later in 2004 from fungus *Cordyceps militaris* BCC 2816.[1,2] Cephalosporolides E and F belong to a special class of natural products possessing a rare spiral lactone skeleton. Ascospiroketals A/B,[3] penisporolides A/B,[4] cephalosporolides H/I[5] also possess the similar spiral lactone skeleton with variations mainly either in the side chain and/or the groups at the C2-methylene group. The cephalosporolides E and F are epimeric at the spiro-carbon center and have a similar configuration at the other three stereogenic centers. In 2009, we documented the total synthesis of unnatural enantiomers of the cephalosporolides E and F and proposed the absolute configuration of these two natural products.[6] The naturally occurring cephalosporolides E/F have been synthesized first by Fernandez's group followed by the groups of Brimble, Dudley, and Britton.[7–11]

In our synthesis of cephalosporolides E/F, a Pd-catalyzed alkynediol cycloisomerization[12] has been used as the key reaction to construct the central spirocyclic ketal unit. The D-glucose and L-maleic acids have been employed as chiral-pool starting materials in order to address the stereochemistry of the C(4), C(5), and C(10) centers.[6] In continuation, we have been interested in developing a general strategy for the synthesis of the cephalosporolides E/F (1/2) and other related natural products. As shown in Fig. 1, keeping the metal-mediated spiroketalization[13,14] of an alkynediol as the key skeletal construct and considering the fact that all these natural products differ mainly either in the side chain and/or the groups at the C2-methylene group, the complete carbon framework has been disconnected into two key oxirane fragments with the plan being to couple the two by an ethylene unit by employing sequential epoxide–alkyne couplings. The glucose-diacetonide **3** has been selected as the starting chiral-pool material for the synthesis of key oxirane fragments. The functional group manipulations at C3 of this acetonide should address the variations required at the C2 of these natural products. On the other hand, the constitution and configuration of the R group will be addressed by the oxirane fragment employed. Fig. 1 reveals the general retrosynthetic scheme for these natural products. To start in this direction, the total synthesis of cephalosporolides E/F has been selected as an exploratory example. The epoxides **4** and **5** have been identified as the key building blocks in this context.

The complementary stereochemical relation between the C3/C4 in glucose acetonide **3** (used for the synthesis of *ent*-cephalaosporolides E/F) with that of C4/C5 in **4** (with a simple inversion at C5) has been considered as a handle for the stereo-divergent synthesis of naturally occurring cephalosporolides E/F(**1**/**2**).

2. Results and discussion

The synthesis commenced with the opening of the known epoxide **4**[15] with lithiated trimethylsilylacetylene in the presence of $BF_3 \cdot Et_2O$. The treatment of the resulting TMS alkynol **6** with NaH

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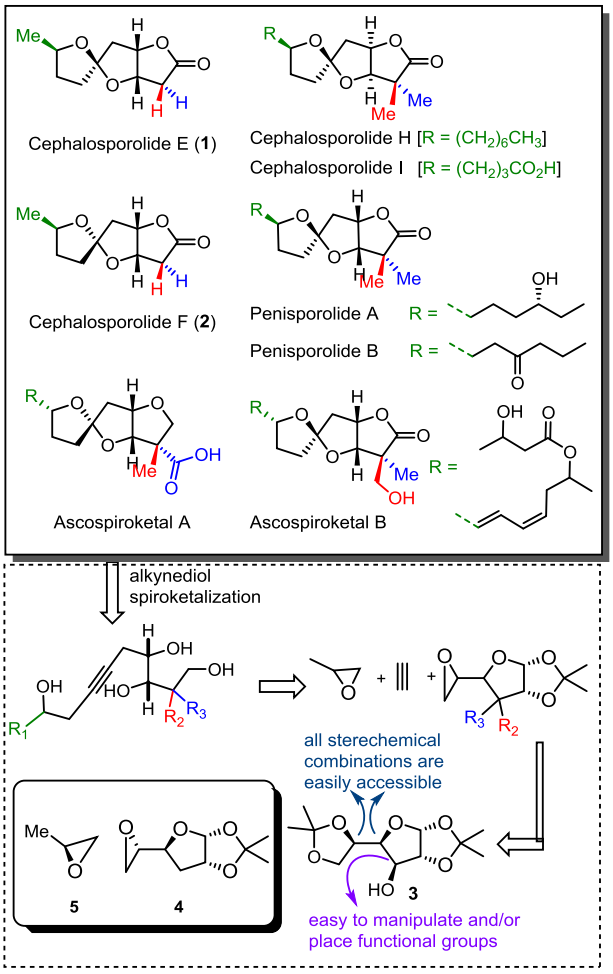
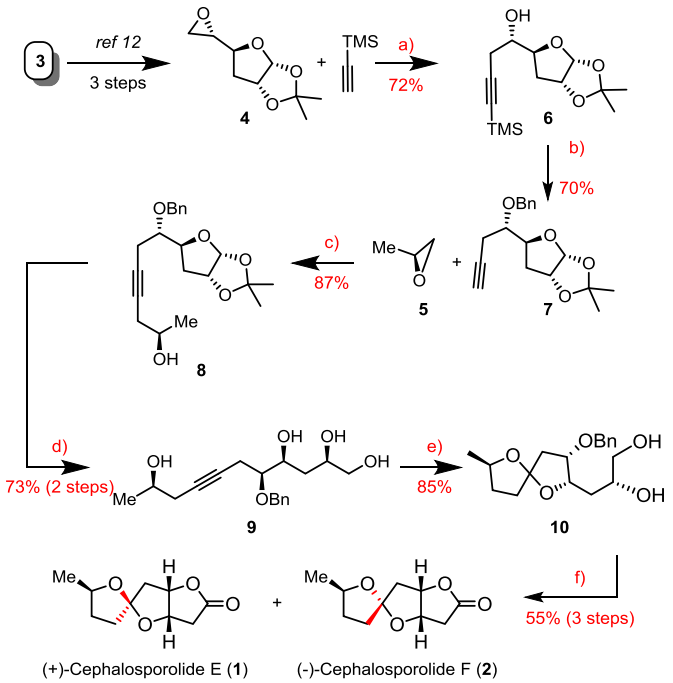


Fig. 1. Spiral lactone natural products & a unified modular approach.



Scheme 1. Total synthesis of cephalosporolides E/F—Reagents and conditions: (a) BuLi, $BF_3{\cdot}Et_2O$, THF, 1 h; (b) BnBr, NaH, THF, 3 h; (c) BuLi, $BF_3{\cdot}Et_2O$, THF, 1 h; (d) [i] 60% AcOH, reflux, 6 h; [ii] $NaBH_4$, MeOH, 3 h; (e) (5 mol %) $Au(PPh_3)Cl$, (5 mol %) $AgSbF_6$, CH_2Cl_2, 2 h, 0 °C; (f) [i] $NaIO_4$, CH_2Cl_2, H_2O, 1.5 h; [ii] $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl 2-butene, $^tBuOH{+}H_2O$, 5 h [iii] $Pd(OH)_2/C/H_2$, MeOH, 3 h.

and benzyl bromide in DMF gave the benzyl ether **7** resulting from the deprotection of the *C*-trimethylsilyl group during the benzylation. Subsequently, the alkyne **7** and the commercially available (2*S*)-porolyene oxide **5** were subjected for the alkyne-epoxide coupling under the established conditions to procure the alkynol **8**. Alkynol **8** was converted to the alkynetetrol intermediate **9** (73% over two steps) by following a sequence of acetonide hydrolysis and subsequent reduction of the intermediate lactal with $NaBH_4$ (Scheme 1).

Having the key alkynetetrol **9** in hand the next concern was metal-catalyzed alkynediol spiroketalization. Our initial experiments dealing with $Pd[CH_3CN]Cl_2$ as a complex gave the desired spiroketals **10** in poor yields along with the formation of various unidentifiable products. The reactions with the other [Pd]-complexes are either sluggish or gave the products in poor yields. In this context, we next screened various gold complexes (See Table 1, SI) amongst, which the $AuCl(PPh_3)/AgSbF_6$ combination has been found to be the best for this purpose and the required spiroketals **10** were obtained in excellent yield. As the resulting epimeric spiroketals are not separable, the mixture was subjected for the next reaction directly. To this end, the cephalosporolides E/F (**1**/**2**) have been synthesized (3 steps, 55% overall yields) from **10** by following a sequence of reactions—i. diol cleavage with $NaIO_4$; ii. oxidation of intermediate aldehyde to acid using Pinnic conditions; and iii. hydrogenation over 20% $Pd(OH)_2/C$ in methanol. Both the cephalosporolides E and F were separated and their spectral and physical data was in agreement with the data reported.

3. Conclusion

In summary, a concise and short total synthesis of cephalosporolides E and F has been documented. The central bicyclic ketal core has been constructed through a gold-catalyzed spiroketalization of an alkynetetrol **9** with complete regioselectivity.

4. Experimental section

4.1. General

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine over KOH; Acetone on $KMnO_4$. Commercial reagents were used without purification. Column chromatography was carried out by using *Spectrochem* silica gel. Optical rotations were determined on a *Jasco* DIP-370 digital polarimeter. Specific optical rotations $[\alpha]_D$ are given in $10^{-1}\times deg\times cm^2\times g^{-1}$. ^1H and ^{13}C NMR spectroscopy measurements were carried out on *Bruker* AC 200 MHz, *Bruker* DRX 400 MHz, and *Bruker* DRX 500 MHz spectrometers, and TMS was used as an internal standard. ^1H and ^{13}C NMR chemical shifts are reported in parts per million downfield from Chloroform-*d* (δ=7.25) or TMS or acetone-d_6 (δ=2.05) and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. The multiplicity of ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used: s=singlet, d=doublet, t=triplet, and q=quartet, represent C (quaternary), CH, CH_2, and CH_3, respectively. Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and 4800 plus MALDI TOF/TOF *Applied Biosystem* spectrometer.

4.2. Synthesis of oxirane 4

To a solution of 3-*deoxy*-1,2-*O*-isopropylidiene-6-(*tert*-butyldimethylsilyl)-*ribo*-hexopyranose[15] (9.0 g, 28.3 mmol) in CH_2Cl_2 (100 mL), Et_3N (15.7 mL, 113.0 mmol) followed by CH_3SO_2Cl (3.32 mL, 42.4 mmol) were added at 0 °C and stirred for 3 h at rt. The reaction mixture was poured into 100 mL of water and extracted with CH_2Cl_2 (2×100 mL). The combined organic layer was washed with saturated solution of $NaHCO_3$ (100 mL), brine (50 mL), and dried over (Na_2SO_4), evaporated under reduced pressure. The resulting crude mesylate (10.2 g, 25.7 mmol) dissolved in THF (100 mL), was added TBAF (16.8 g, 64.3 mmol) and allowed to stir for 2 h at room temperature. THF removed under reduced pressure and extracted with ethyl acetate. Organic layer was concentrated, crude product was purified by column chromatography (30:70% ethyl acetate/petroleum ether) to afford compound **4** (4.1 g, 78% yield overall two steps) as a colorless oil. R_f (25% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ −26.9 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) ν: 3438, 2990, 2063, 1634, 1456, 1383, 1324, 1217, 1021, 928, 855, 765, 649, 600, 501 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.46 (s, 3H), 1.73–1.87 (d, *J*=8.1 Hz, 1H), 2.08–2.17 (dd, *J*=4.7, 13.4 Hz, 1H), 2.75–2.80 (m, 2H), 2.97–3.03 (m, 1H), 4.08–4.18 (dt, *J*=4.6, 1H), 4.71 (t, *J*=4.2 Hz, 1H), 5.77 (d, *J*=3.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1 (q), 26.7 (q), 35.5 (t), 44.3 (t), 52.2 (d), 76.9 (d), 80.2 (d), 105.5 (d), 111.3 (s) ppm; HRMS (ESI+): calcd for $C_9H_{14}O_4Na$ [M^++Na] 209.0784; found 209.0784.

4.3. (*S*)-1-((3a*R*,5*S*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-4-(trimethylsilyl)but-3-yn-1-ol (6)

At −78 °C, to a solution of TMS alkyne (1.5 mL, 10.7 mmol) in THF (7.0 mL) were added *n*-BuLi (6.7 mL, 1.6 M in hexane, 10.7 mmol) and $BF_3\cdot Et_2O$ (1.14 mL, 10.7 mmol) followed by a solution of the epoxide **4** (1.0 g, 5.37 mmol) in THF (8 mL) with a 15 min interval. The stirring was continued for another 30 min at −78 °C and then quenched with NH_4Cl (5 mL). The reaction mixture was allowed to reach room temperature and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2×25 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by column chromatography (silica 230–400 mesh, 20:80 ethylacetate/petroleum ether) afford the alkynol **6** (1.1 g, 72% yield) as a white color solid. Mp=243 °C; R_f (25% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +12.3 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) ν: 3418, 2989, 2170, 1634, 1381, 1251, 1162, 1027, 924, 842, 760, 498 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.13 (t, *J*=3.5 Hz, 9H), 1.32 (s, 3H), 1.51 (s, 3H), 1.79–1.87 (m, 1H), 2.06–2.10 (dd, *J*=4.6 Hz, 1H), 2.24 (d, *J*=6.8 Hz, 1H), 2.45–2.51 (dd, *J*=7.0, 17.0 Hz, 1H), 2.52–2.58 (dd, *J*=6.5, 16.8 Hz 1H), 3.64–3.70 (m, 1H), 4.32–4.36 (dt, *J*=4.3 Hz, 1H), 4.75 (t, *J*=4.2 Hz, 1H), 5.80 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 0.0 (q), 25.8 (t), 26.3 (q), 26.8 (q), 34.8 (t), 70.7 (d), 79.4 (d), 80.8 (d), 87.2 (s), 102.5 (s), 105.4 (d), 111.5 (s) ppm; HRMS (ESI+): calcd for $C_{14}H_{24}O_4NaSi$ [M^++Na] 307.1336; found 307.1334.

4.4. (3a*R*,5*S*,6a*R*)-5-((*S*)-1-(Benzyloxy)but-3-yn-1-yl)-2,2-dimethyl tetrahydrofuro[2,3-*d*][1,3]dioxole (7)

To a solution of alcohol **6** (2 g, 7.0 mmol) in anhydrous THF (15 mL), sodium hydride (60% oil suspension, 562 mg, 14.1 mmol) was added at 0 °C and allowed to stir for 20 min. To this cooled reaction mixture, benzyl bromide (1.25 mL, 10.5 mmol) was added slowly and stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (10:90% ethyl acetate/petroleum ether) affords compound **7** (1.5 g, 70% over all yield from two steps) as a yellow syrup. R_f (10% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ −23.3 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) ν: ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.49 (s, 1H), 1.72–1.81 (ddd, *J*=4.8, 10.6,13.3 Hz, 1H), 1.84–1.96 (dd, *J*=4.8, 20.0 Hz, 1H), 2.0 (t, *J*=2.7 Hz, 1H), 2.51–2.55 (dd, *J*=2.7 Hz, 2H), 3.53–3.61 (ddd, *J*=4.3, 6.3, 12.5 Hz, 1H), 4.37–4.47 (dt, *J*=4.6 Hz, 1H), 4.61–4.79 (m, 3H), 5.82 (d, *J*=3.7 Hz, 1H), 7.29–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (t), 26.3 (q), 26.9 (q), 33.8 (t), 70.2 (d), 73.3 (t), 77.4 (d), 79.5 (d), 80.5 (d), 80.5 (s), 105.3 (d), 111.3 (s), 127.7 (d), 127.9 (d, 2C), 128.3 (d, 2C), 138.2 (s) ppm; HRMS (ESI+): calcd for $C_{18}H_{22}O_4Na$ [M^++Na] 325.1410; found 325.1408.

4.5. (2*R*,7*S*)-7-(Benzyloxy)-7-((3a*R*,5*S*,6a*R*)-2,2-dimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)hept-4-yn-2-ol (8)

At −78 °C, to a solution of alkyne **7** (1.0 g, 3.31 mmol) in THF (10.0 mL) were added n-BuLi (2.1 mL, 1.6 M in hexane, 3.31 mmol) and $BF_3\cdot Et_2O$ (0.4 mL, 3.31 mmol) followed by a solution of the epoxide **5** (76 mg, 1.32 mmol) in anhydrous THF (1.0 mL) with a 15 min interval. The stirring was continued for another 30 min at −78 °C and then quenched with NH_4Cl (5 mL). The reaction mixture was allowed to reach room temperature and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2×25 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by column chromatography (silica 230–400 mesh, 25:75 ethyl acetate/petroleum ether) to afford compound **8** (418 mg, 87% yield) as a colorless liquid. R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{23}$ −12.4 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) ν: 3565, 2928, 1722, 1373, 1217, 849, 754, 468 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$): δ 1.21 (d, *J*=6.2 Hz, 3H), 1.30 (s, 3H), 1.48 (s, 3H), 1.71–1.85 (m, 1H), 1.92–2.01 (m, 1H), 2.15–2.23 (m, 1H), 2.25–2.33 (m, 2H), 2.49–2.52 (dd, *J*=4.0 Hz, 1H), 2.53–2.55 (dd, *J*=2.0, 2.3 Hz, 1H), 3.48–3.58 (ddd, *J*=4.3, 6.3, 10.6 Hz, 1H), 3.80–3.95 (m, 1H), 4.37–4.46 (ddd, *J*=4.4, 9.1, 10.5 Hz, 1H), 4.59 (d, *J*=12.0 Hz, 1H), 4.67–4.76 (m, 2H), 5.81 (d, *J*=3.8 Hz, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4 (t), 22.3 (q), 26.2 (q), 26.7 (q), 29.4 (t), 34.5 (t), 66.3 (d), 72.5 (t), 77.5 (d), 78.3 (s), 79.0 (d), 80.2 (d), 105.3 (d), 111.1 (d), 127.7 (d), 127.9 (d, 2C), 128.3 (d, 2C), 138.02 (d), ppm; HRMS (ESI+): calcd for $C_{21}H_{28}O_5Na$ [M^++Na] 383.1829; found 383.1826.

4.6. (2*R*,4*S*,5*S*,10*R*)-5-(Benzyloxy)undec-7-yne-1,2,4,10-tetraol (9)

A solution of alkynol **8** (500 mg, 1.39 mmol) in 60% aq acetic acid (10 mL) was refluxed for 7 h. Acetic acid was evaporated under reduced pressure and resulting crude (320 mg) was dissolved in 15 mL methanol and sodium borohydride (113 mg, 3 mmol) was added at 0 °C in portion wise and allowed to stir for 4 h at rt. The reaction mixture was quenched with satd NH_4Cl solution (2 mL) and methanol was evaporated under reduced pressure. The crude product was purified by column chromatography (100–200 silica gel, 1:9% methanol/CH_2Cl_2) afford tetrol **9** (210 mg, 73% yield over two steps) as a colorless gum; R_f (100% EtOAc) 0.3; $[\alpha]_D^{25}$ +7.0 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) ν: 3400, 2924, 1645, 1401, 1069, 939, 755, 698, 665, 505, 466 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6): δ 1.18 (d, *J*=6.1 Hz, 3H), 1.62–1.58 (m, 1H), 1.80 (dt, *J*=3.66, 1H), 2.23–2.18 (m, 1H), 2.33–2.28 (m, 1H), 2.47–2.41 (m, 1H), 2.56 (dq, *J*=5.2, 2.7 Hz, 1H), 3.48–3.41 (m, 2H), 3.54–3.50 (dd, *J*=6.1, 10.7 Hz, 1H), 3.86–3.82 (m, 1H), 3.91 (d, *J*=4.9 Hz, 1H), 4.01 (m, 1H), 4.13 (d, *J*=4.9 Hz, 1H), 4.17 (d, *J*=3.4 Hz, 1H), 4.61(d, *J*=11.6 Hz, 1H), 4.77 (d, *J*=11.6 Hz, 1H), 7.41–7.25 (m, 5H); ^{13}C NMR (acetone-d_6, 50 MHz): 20.7 (t), 23.0 (q), 30.1 (t), 36.5 (t), 67.1 (d), 67.3 (t), 72.2 (d), 72.4 (d),

73.0 (t), 79.4 (s), 79.9 (s), 81.8 (d), 128.3 (d), 128.7 (d, 2C), 129.1 (d, 2C), 140.1 (s) ppm; HRMS (ESI+): calcd for $C_{18}H_{26}O_5Na$ [M^++Na] 345.1672; found 345.1670.

4.7. 3-((2*S*,3*S*,7*R*)-3-(Benzyloxy)-7-methyl-1,6-dioxaspiro[4.4]nonan-2-yl)propane-1,2-diol (10)

To a solution of alkynetetrol **9** (140 mg, 0.43 mmol) in dichloromethane (20 mL) was added catalyst solution prepared by dissolving $Au(PPh_3)Cl$ (10.7 mg, 21.7 μmol) and $AgSbF_6$ (7.4 mg, 21.7 μmol) in CH_2Cl_2 (10 mL)] at 0 °C and the reaction mixture was allowed to stir for 1 h at room. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (20:80% ethyl acetate/petroleum ether) gave the spiroketal diols **10** (120 mg, 85% yield) as yellow oil. R_f (50% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{23}$ +7.0 (*c* 0.03, $CHCl_3$); IR ($CHCl_3$) ν: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (d, *J*=6.1 Hz, 1H), 1.26 (d, *J*=6.1 Hz, 3H), 1.63–1.78 (m, 4H), 1.88–1.98 (m, 2H), 2.0–2.09 (m, 2H), 2.12–2.16 (m, 2H), 2.18–2.30 (m, 2H), 2.32–2.37 (m, 1H), 3.51–3.55 (m, 2H), 3.59–3.64 (m, 1H), 3.90–3.94 (m, 1H), 4.10–4.17 (m, 2H), 4.19–4.22 (m, 0.3H), 4.26–4.35 (m, 1H), 4.39 (d, *J*=11.9 Hz, 1H), 4.43 (d, *J*=12.3 Hz, 0.3H), 4.54 (d, *J*=11.9 Hz, 1H), 4.61 (d, 12.3 Hz, 0.3H), 7.28–7.35 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4 (q), 22.9 (q), 31.4 (t), 32.5 (t), 32.8 (t), 33.0 (t), 37.4 (t), 37.8 (t), 40.7 (t), 41.3 (t), 66.6 (t), 66.7 (t), 70.8 (d), 70.9 (d), 71.3 (t), 71.4 (t), 75.3 (d), 76.4 (d), 78.1 (d), 79.1 (d), 79.3 (d), 79.9 (d), 113.9 (s), 127.5 (d, 2C), 127.7 (d), 128.4 (d, 2C), 137.9 (s) ppm: HRMS (ESI+): calcd for $C_{18}H_{26}O_5Na$ [M^++Na] 345.1672; found 345.1670.

4.8. Synthesis of (+)-cephalosporolide E and (−)-cephalosporolide F

To an ice cooled solution of spiroketals **10** (120 mg, 0.30 mmol) in dichloromethane $NaIO_4$ (240 mg, 1.13 mmol) was added and stirred for 2 h at room temperature. Then the reaction mixture was filtered through Celite pad and concentrated under reduced pressure. The resulting crude aldehyde (96 mg, 0.33 mmol) was dissolved in a mixture of ^{t}BuOH:H_2O (4:1), $NaH_2PO_4{\cdot}2H_2O$ (154 mg, 0.99 mmol) was added at 0 °C and the contents stirred for 10 min at the same temperature. To this suspension, were added $NaClO_2$ (89.7 mg, 0.99 mmol) followed by 2-methyl 2-butene (0.4 mL, 3.3 mmol) at 0 °C. The reaction temperature was slowly increased to room temperature and was stirred for additional 5 h. After the completion of the reaction as indicated by TLC, ^{t}BuOH was removed under vacuum and extracted with ethyl acetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting crude spiroacid (75 mg) was subjected for hydrogenation with 20% $Pd(OH)_2$/C (10 mg) in methanol (10 mL) under balloon pressure procure the naturally occurring spirolactones (+)-cephalosporolide E (12 mg) and (−)-cephalosporolide F (15 mg) as colorless liquids (total 27 mg, 55% yield over three steps) after chromatography purification.

*4.8.1. (+)-Cephalosporolide E (**1**).* R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +27.4 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) ν: 2969, 1780, 1402, 1303, 1157, 1098, 1056, 918, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, *J*=6.0 Hz, 3H), 1.42–1.48 (m, 1H), 2.03–2.14 (m, 4H), 2.44 (d, 1H), 2.64 (d, 18.5 Hz, 1H), 2.71–2.77 (dd, *J*=7.8 Hz, 1H), 4.13–4.21 (m, 1H), 4.87–4.90 (m, 1H), 5.15 (t, *J*=5.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.9 (q), 31.3 (t), 34.2 (t), 37.6 (t), 41.6 (t), 75.1 (d), 77.3 (d), 83.4 (d), 115.0 (s), 175.9 (s) ppm; HRMS (ESI+): calcd for $C_{10}H_{14}O_4Na$ [M^++Na] 221.0784; found 221.0782.

*4.8.2. (−)-Cephalosporolide F (**2**).* R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ −34.0 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν: 3020, 1781, 1403, 1216, 1167, 1096, 1061, 927 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (d, *J*=6.2 Hz, 3H), 1.68–1.75 (m, 1H), 1.96–2.02 (m, 1H), 2.04–2.09 (m, 1H), 2.12–2.16 (m, 1H), 2.30–2.34 (dd, *J*=2.3, 15.0 Hz, 1H), 2.48–2.52 (dd, *J*=6.6, 14.6 Hz, 1H), 2.66 (d, *J*=18.4 Hz, 1H), 2.71–2.76 (dd, *J*=5.6, 18.7 Hz, 1H), 4.15–4.22 (m, 1H), 4.78 (dt, *J*=4.54, 5.36 Hz, 1H), 5.08 (sp., *J*=2.3, 4.5, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.8 (q), 32.4 (t), 36.0 (t), 36.9 (t), 42.1 (t), 76.5 (d), 76.9 (d), 83.8 (d), 115.5 (s), 175.6 (s) ppm; HRMS (ESI+): calcd for $C_{10}H_{14}O_4Na$ [M^++Na] 221.0784; found 221.0782.

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Supplementary data

NMR spectra of all the new compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.026.

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