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Pd(II)-Mediated Alkynediol Spiroketalization: First Total Synthesis of (−)-Cephalosporolide E and (+)-Cephalosporolide F

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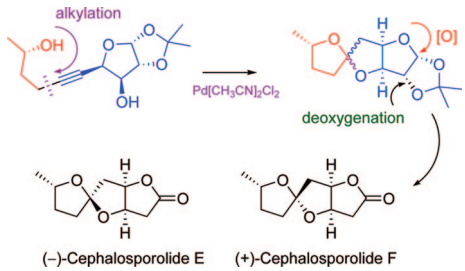
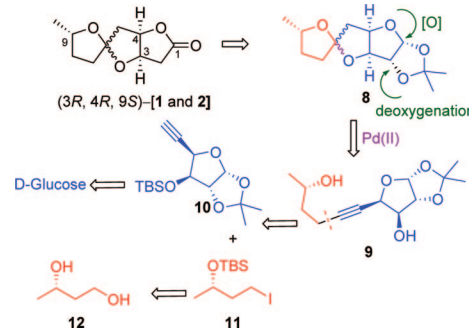


Herein we describe a concise assembly of the central 1,6-dioxaspiro[4.4]nonane core of cephalosporolides E/F by employing a Pd-mediated alkynediol cycloisomerization and their total synthesis. On the basis of spectroscopic data and optical rotation values, the absolute configurations of cephalosporolides E/F were proposed.

Cephalosporolides E (**1**) and F (**2**) were first isolated in 1985 by Hanson and co-workers[1] from industrial fermentation of the fungus *Cephalosporium aphidcola* grown under sulfur limiting conditions and later in 2004 by Rakachaisirikul and co-workers[2] from the entomopathogenic fungus *Cordyceps militaris* BCC 2816. The relative configurations of **1** and **2** were elucidated by extensive NMR studies and by single crystal X-ray analysis of **1**.[1] Cephalosporolides E and F are characterized by a 1,6-dioxaspiro[4.4]nonane in which one of the furan rings is fused with a γ-lactone ring (Figure 1). During their isolation of bassianolone (**3**), Oltra and co-workers noticed that compound **3** can be transformed into a mixture of **1** and **2** by a silica gel promoted spirocyclization and concluded that **1** and **2** are artifacts during the isolation procedures.[3] However, the recent isolation of several other natural products like ascospiroketals

SCHEME 1. Retrosynthetic Disconnections for Cephalosporolides E/F



A (**4**) and B (**5**),[4] cephalosporolides H (**6**) and I (**7**),[5] and penisporolides A and B[6] having the central tricyclic core of **1** and **2** ascertain this tricyclic structural core as unprecedented and of natural origin. The absolute configurations of all the natural products isolated have not yet been established, and no synthetic efforts have been documented.[7] Herein we report a Pd-mediated alkynol cycloisomerization[8−10] for the central tricyclic core construction and the first total synthesis of cephalosporolides E and F establishing the absolute configuration of **1** and **2** as (3*S*,4*S*,6*S*,9*R*) and (3*S*,4*S*,6*R*,9*R*) respectively.

The key retrosynthetic disconnections are outlined in Scheme 1. The C(6)-epimeric tricyclic spiroketals **8** were assumed to arise from cycloisomerization of alkynediol **9**. The spiroketals **8** could be advanced to cephalosporolides E/F by oxidation of

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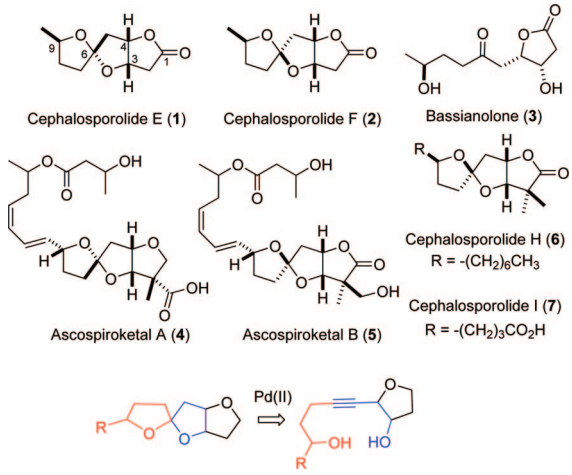


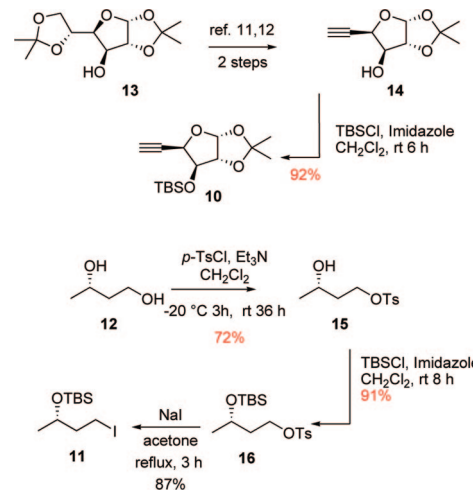
FIGURE 1. Representative natural products having the central tricyclic core of cephalosporolides E/F and the key alkyne diol cycloisomerization strategy for the central 1,6-dioxaspiro[4.4]nonane core construction.

the C(1) lactol unit to lactone and the subsequent deoxygenation at C(2). By selecting a tentative 3*R*,4*R*,9*S* configuration for the targeted **1**/**2**, the alkynediol **9** was identified as an advanced intermediate. The central carbon chain of **8** has been disconnected between C(6) and C(7), identifying the alkyne **10** and iodo compound **11** as the coupling units. On the basis of the requisite absolute configurations at C(3), C(4) of alkyne **10**, D-glucose was identified as a suitable chiral pool precursor. Compound **11** could be elaborated from known (3*S*)-butane-1,3-diol (**12**) by selective functional group manipulations, which in turn can readily be obtained from L-malic acid.

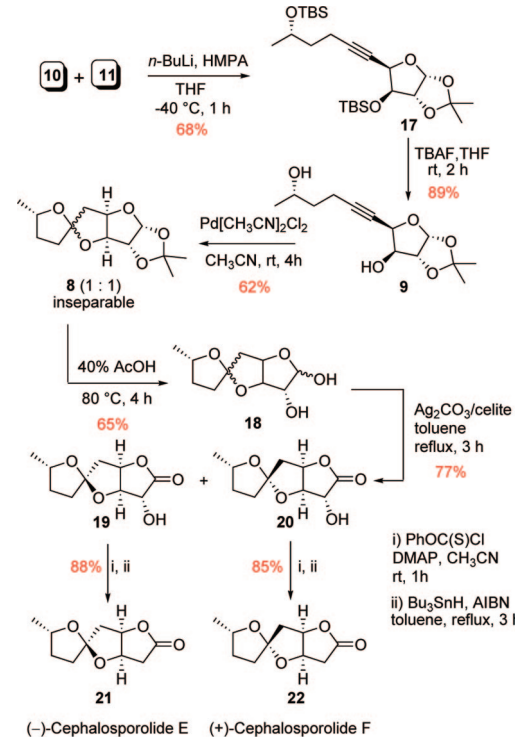
The synthesis was initiated with the preparation of coupling partners **10** and **11**. By following the reported two-step sequence that involves a one-pot C(6)-chlorination and terminal acetonide migration[11] and subsequent *n*-BuLi-mediated double elimination,[12] glucose diacetonide **13** afforded the alkynol **14**. The TBS protection of compound **14** gave the alkyne fragment **10** (Scheme 2). The known (*S*)-butane-1,3-diol (**12**)[13] was advanced to the iodo derivative **11** in an overall yield of 57% following a three-step sequence: (i) the selective tosylation of the primary hydroxyl group, (ii) protection of the secondary hydroxyl group as its TBS ether, followed by (iii) nucleophilic substitution of the tosylate group with sodium iodide (Scheme 2).

Having synthesized the alkyne **10** and the iodo compound **11**, our next concern was the synthesis of the key cycloisomerization substrate **9**. By using *n*-BuLi as base, several combinations of THF−HMPA were explored to bring about the alkylation of compound **10** with iodo derivative **11**, and under optimized conditions (Scheme 3) the di-TBS protected alkynediol was obtained in 68% yield.[14] The TBS deprotection of compound **17** employing TBAF in THF gave the alkynediol **9**

SCHEME 2. Synthesis of Coupling Partners 10 and 11



SCHEME 3. The Central Alkynol Cycloisomerization Reaction and the Total Synthesis of Enantiomers of Cephalosporolides E and F



in 89% yield. The central cycloisomerization reaction of **9** could be conducted smoothly with 10 mol % of $Pd[CH_3CN]_2Cl_2$ complex in acetonitrile at room temperature and the C(6) epimeric (1:1) tricyclic ketals **8** were obtained in 62% yield (Scheme 3) as an inseparable mixture.

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(16) The diffraction data measurements were carried out for both compounds **19** and **22** at room temperature (297 K) on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo Kα = 0.71073 Å) radiation. SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[17] Hydrogen atoms for both compounds were included in the refinement as per the riding model except for the hydroxyl H-atom for compound **19**, which was located in difference Fourier map and refined isotropically.
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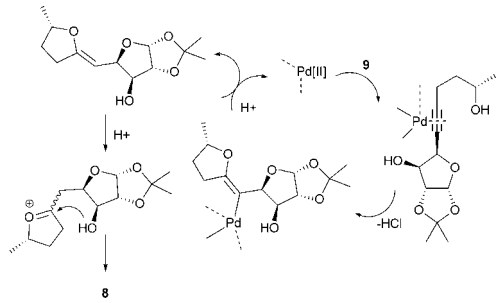
SCHEME 4. Tentative Mechanism for Pd(II)-Mediated Alkynediol Spiroketalization



A tentative mechanism for Pd-mediated spiroketalization of **9** is given in Scheme 4. The reaction will be initiated by the π-activation of the alkyne. A 5-*exo*-dig mode of addition of the C(9)−OH and subsequent protodepalladation of the resulting vinylpalladium intermediate leads to the formation of the *exo*-enol ether intermediate and thus regenerates the Pd(II) catalyst.[10] The regiochemistry of the nucleophilic addition could be explained by considering the $-I$ effect of the furanosyl ring.[8i] The *exo*-enol ether intermediate upon exposure to in situ generated acid leads to the formation of an oxy-carbenium cation. The addition of the C(3)−OH to the incipient oxy-carbenium cation affords the spiroketals **8**. The lack of regioselectivity in spiroketalization is indicative of the conformational flexibility along the C(5)−C(6) bond.

After examining a set of reaction conditions, the deprotection of 1,2-acetonide could be conducted successfully by using 40% acetic acid at 80 °C (oil bath temperature) for 4 h to obtain a mixture of lactols **18** in 65% yield along with 20% of unreacted **8**. Selective oxidation of lactols **18** under Fétizon's conditions[15] employing Ag_2CO_3/Celite gave lactones **19** and **20** which were separated and characterized. The relative configuration of the newly created spiro center in compounds **19** and **20** was assigned by comparing the multiplicity and coupling constants of H−C(4) and H−C(5) with the reported values of **1**, **2**, and **4** − **7** (Table 1, Supporting Information). The assigned configuration of compound **19** was further confirmed with the help of single crystal X-ray analysis (Supporting Information).[16,17] The α-hydroxy function of **19** and **20** was subjected to Barton−McCombie deoxygenation[18] through the phenylthionocarbonate intermediates to afford **21** and **22**, respectively.

The spectral and analytical data of synthetic cephalosporolide E (**21**) were in agreement with the reported data and the observed optical rotation {$[\alpha]^{25}_D$ −48.2 (*c* 0.50, $CHCl_3$); lit.[1] $[\alpha]^{30}_D$ +51.3 (*c* 0.42)} indicated that the enantiomer of the cephalosporolide E has been synthesized. While the spectral data for **22** were found to be in excellent agreement with that for cephalosporolide F, the opposite sign and a large deviation in the magnitude of specific rotation {$[\alpha]^{25}_D$ synthetic +95.2 (*c* 0.9, $CHCl_3$); lit.[2] $[\alpha]^{25}_D$ −33.3 (*c* 0.79, $CHCl_3$)} was noticed. The constitution and the relative stereochemistry of compound **22** were further established by single crystal X-ray analysis (Supporting Information),[16,17] which, along with the observed opposite sign of specific rotation, confirmed that it was the enantiomer of the natural cephalosporolide F.

In summary, a Pd-mediated alkynediol cycloisomerization approach to the central tricyclic core of cephalosporolides E/F and related congeners has been developed. A concise synthesis of cephalosporolide E (**1**) and cephalosporolide F (**2**) has been executed, which established their absolute configurations as (3*S*,4*S*,6*S*,9*R*) and (3*S*,4*S*,6*R*,9*R*), respectively. As a result of convergence at an advanced stage and the late stage installation of the key spirocyclic core, the present approach leaves ample room for the synthesis of related natural products.

Experimental Section

Coupling of 10 and 11. At −40 °C, a solution of **10** (1.6 g, 5.37 mmol) in THF (40 mL) and HMPA (5 mL) was treated with *n*-BuLi (4 mL, 1.6 M in hexanes, 6.44 mmol) and stirred for 20 min. A solution of compound **11** (2.0 g, 6.44 mmol) in THF (5 mL) was added dropwise and the mixture was stirred for 1 h at −30 °C. The reaction was quenched by saturated NH_4Cl solution (10 mL) then the mixture was extracted with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (7% ethyl acetate in petroleum ether) gave **17** (1.77 g, 68% yield) as a colorless oil. $[\alpha]^{25}_D$ +15.3 (*c* 1.7, $CHCl_3$). IR ($CHCl_3$) ν 2956, 2931, 2828, 2238, 1472, 1376, 1256, 1218, 1131, 1082, 1018, 838 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.03 (2s, 6H), 0.12, 0.13 (2s, 6H), 0.86 (s, 9H), 0.91 (s, 9H), 1.10 (d, J = 6.1 Hz, 3H), 1.29 (s, 3H), 1.46 (s, 3H), 1.60 (dd, J = 1.7, 5.9 Hz, 1H), 1.62 (d, J = 17.4 Hz, 1H), 2.22 (ddt, J = 2.0, 8.0, 16.8 Hz, 1H), 2.31 (ddt, J = 2.0, 7.2, 16.8 Hz, 1H), 3.86 (sextet, J = 6.1 Hz, 1H), 4.12 (d, J = 2.5 Hz, 1H), 4.37 (d, J = 3.6 Hz, 1H), 4.78 (dd, J = 2.1, 4.3 Hz, 1H), 5.93 (d, J = 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.0 (q), −4.9 (q), −4.8 (q), −4.4 (q), 15.2 (t), 18.0 (s), 18.3 (s), 23.5 (q), 25.7 (3q, 3C), 25.8 (3q, 3C), 26.2 (q), 26.8 (q), 38.0 (t), 67.1 (d), 72.5 (d), 74.1 (s), 77.3 (d), 85.2 (d), 88.7 (s), 104.5 (d), 111.6 (s) ppm. ESI-MS *m*/*z* 485 (6%, $[M + 1]^+$), 502 (21%, $[M + NH_4]^+$), 507 (100%, $[M + Na]^+$), 523 (13%, $[M + K]^+$). Anal. Calcd for $C_{25}H_{48}O_5Si_2$: C, 61.93; H, 9.98. Found: C, 61.84; H, 10.03.

Cycloisomerization of Alkynediol 9. A solution of **9** (300 mg, 1.17 mmol) and $PdCl_2(CH_3CN)_2$ (15 mg, 0.06 mmol) in dry CH_3CN (25 mL) under argon atmosphere was stirred at rt for 4 h. The reaction mixture was concentrated and the crude was purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to afford **8** (186 mg, 62% yield) as a viscous, colorless oil. IR ($CHCl_3$) ν 2980, 1458, 1383, 1218, 1164, 1058, 891 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19, 1.26 (2d, J = 6.2 Hz, 3H), 1.29, 1.32 (2s, 3H), 1.45, 1.46 (2s, 3H), 1.70−2.37 (m, 6H), 4.05−4.21 (m, 1H), 4.52−4.61 (m, J = 3.3, 4.2 Hz, 2H), 4.87 (ddd, J = 1.5, 3.3, 5.2 Hz, 0.5H), 5.00 (t, J = 5.2 Hz, 0.5H), 5.88 (d, J = 3.8 Hz, 0.5H), 6.02 (d, J = 3.6 Hz, 0.5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0 (q), 22.7 (q), 26.6 (q), 27.1 (q, 2C), 27.7 (q), 31.1 (t), 32.5 (t), 35.0 (t), 38.0 (t), 42.3 (t), 43.0 (t), 74.9 (d), 76.2 (d), 83.1 (d), 83.2 (d), 83.7 (d), 85.3 (d), 86.2 (d), 86.4 (d), 106.7 (d), 106.8 (d), 111.6 (s), 112.3 (s), 115.5 (s), 116.5 (s) ppm. ESI-MS *m*/*z* 257 (19%, $[M + 1]^+$), 279 (100%, $[M + Na]^+$), 295 (18%, $[M + K]^+$). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.84; H, 7.94.

Oxidation of Lactols 18. A suspension of lactols **18** (150 mg, 0.69 mmol) and Ag_2CO_3 impregnated on Celite (1.19 g, 2.08 mmol, contains 1 mmol of Ag_2CO_3 per 0.57 g of prepared reagent) in toluene (15 mL) was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite and the Celite pad was washed with ethyl acetate (2 × 10 mL). The combined filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) to afford **19** (78 mg, 53%) as a white crystalline solid and **20** (36 mg, 24% yield) as a colorless oil. **19**: Mp 106−108 °C (EtOAc/*n*-hexane). $[\alpha]^{25}_D$ +5.2 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) ν 3430, 3020, 2929, 1774, 1403, 1216, 1050, 970 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 6.2 Hz, 3H), 1.43−1.47 (m, 1H), 2.06−2.14 (m, 4H), 2.39 (d, J = 14.3 Hz, 1H), 3.06 (br s, 1H), 4.10−4.18 (m, 1H), 4.35 (s, 1H), 4.71 (d, J = 6.2 Hz, 1H), 5.23 (t, J = 6.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8 (q), 31.3 (t), 33.8 (t), 41.2 (t), 74.3 (d), 75.3 (d), 82.2 (d), 83.6 (d), 115.2 (s),

176.5 (s) ppm. ESI-MS *m/z* 215 (40%, $[M + 1]^+$), 237 (100%, $[M + Na]^+$), 253 (13%, $[M + K]^+$). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.92; H, 6.70. **20**: $[\alpha]^{25}_D$ + 81.6 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) ν 3436, 3020, 2930, 1775, 1403, 1216, 1051, 919 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (d, J = 6.2 Hz, 3H), 1.69−1.75 (m, 1H), 1.97−2.01 (m, 1H), 2.05−2.12 (m, 2H), 2.27 (dd, J = 2.7, 14.8 Hz, 1H), 2.50 (dd, J = 6.8, 14.8 Hz, 1H), 3.28 (br s, 1H), 4.20 (tq, J = 6.2, 8.4 Hz, 1H), 4.31 (s, 1H), 4.63 (d, J = 4.7 Hz, 1H), 5.26 (ddd, J = 2.8, 4.7, 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7 (q), 32.3 (t), 36.9 (t), 41.5 (t), 72.8 (d), 77.1 (d), 81.9 (d), 83.0 (d), 115.7 (s), 176.2 (s) ppm. ESI-MS *m/z* 215 (34%, $[M + 1]^+$), 237 (100%, $[M + Na]^+$), 253 (30%, $[M + K]^+$). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.13; H, 6.67.

(−)-Cephalosporolide E (21). To a cooled solution of α-hydroxy lactone **19** (50 mg, 0.23 mmol) and DMAP (57 mg, 0.47 mmol) in CH_3CN (5 mL) was added phenyl chlorothionoformate (50 μL, 0.35 mmol) then the mixture was stirred for 1 h at rt. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to obtain phenylthiocarbonate intermediate (77 mg). A solution of thiocarbonate intermediate (77 mg, 0.22 mmol), tri-*n*-butyl tinhydride (87 μL, 0.33 mmol), and AIBN (0.7 mg) in toluene (10 mL) was deoxygenated by purging argon for 20 min and refluxed for 3 h under argon atmosphere. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) to afford (−)-cephalosporolide E **21** (41 mg, 88%) as colorless needles. Mp 96−98 °C (EtOAc/*n*-hexane). $[\alpha]^{25}_D$ −48.2 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) ν 2969, 1780, 1402, 1303, 1157, 1098, 1056, 918, 825 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, J = 6.2 Hz, 3H), 1.36−1.39 (m, 1H), 1.98−2.08 (m, 4H), 2.38 (d, J = 14.3 Hz, 1H), 2.59 (d, J = 18.8 Hz, 1H), 2.68 (dd, J = 7.5, 18.8 Hz, 1H), 4.09−4.14 (m, 1H), 4.82 (t, J = 6.2 Hz, 1H), 5.09 (t, J = 5.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 31.3 (t), 34.2 (t), 37.6 (t), 41.6 (t), 75.1 (d), 77.2 (d), 83.4 (d), 115.1 (s), 175.8 (s) ppm. ESI-MS *m/z* 199 (13%, $[M + 1]^+$), 221 (100%, $[M + Na]^+$), 237 (44%, $[M + K]^+$). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.45; H, 7.19.

(+)-Cephalosporolide F (22). To a cooled solution of α-hydroxy lactone **20** (30 mg, 0.14 mmol) and DMAP (34 mg, 0.28 mmol) in CH_3CN (4 mL) was added phenyl chlorothionoformate (30 μL, 0.21 mmol) then the mixture was stirred for 1 h at rt. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to give phenylthiocarbonate intermediate (47 mg). A solution of thiocarbonate intermediate (47 mg, 0.134 mmol) tributyl tinhydride (53 μL, 0.20 mmol) and AIBN (0.3 mg) in toluene was deoxygenated by purging argon for 20 min and refluxed for 3 h under argon atmosphere. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) gave (+)-cephalosporolide F **22** (24 mg, 85%) as a crystalline solid. Mp 62−64 °C (EtOAc/*n*-hexane). $[\alpha]^{25}_D$ +95.2 (*c* 0.9, $CHCl_3$). IR ($CHCl_3$) ν 3020, 1781, 1403, 1216, 1167, 1096, 1061, 927 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, J = 6.3 Hz, 3H), 1.64−1.69 (m, 1H), 1.93 (dd, J = 7.8, 12.3 Hz, 1H), 1.98−2.03 (m, 1H), 2.06−2.11 (m, 1H), 2.27 (dd, J = 1.8, 14.9 Hz, 1H), 2.45 (dd, J = 6.8, 15.0 Hz, 1H), 2.62 (d, J = 18.3 Hz, 1H), 2.68 (dd, J = 5.3, 18.3 Hz, 1H), 4.09−4.17 (m, 1H), 4.73 (t, J = 4.5 Hz, 1H), 5.02 (ddd, J = 2.1, 4.4, 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) 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. ESI-MS *m/z* 199 (16%, $[M + 1]^+$), 221 (100%, $[M + Na]^+$), 237 (46%, $[M + K]^+$). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.51; H, 7.07.

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Supporting Information Available: General experimental methods and experimental procedures for preparation and compound characterization data of **9**, **10**, **11**, **15**, **16**, and **18**, copies of NMR spectra of compounds **8**−**11** and **15**−**22**, and crystal structure determination and crystallographic information files (CIF) of **19** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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