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Total Synthesis of Cephalosporolide E via a Tandem Radical/Polar Crossover Reaction. The Use of the Radical Cations under Nonoxidative Conditions in Total Synthesis

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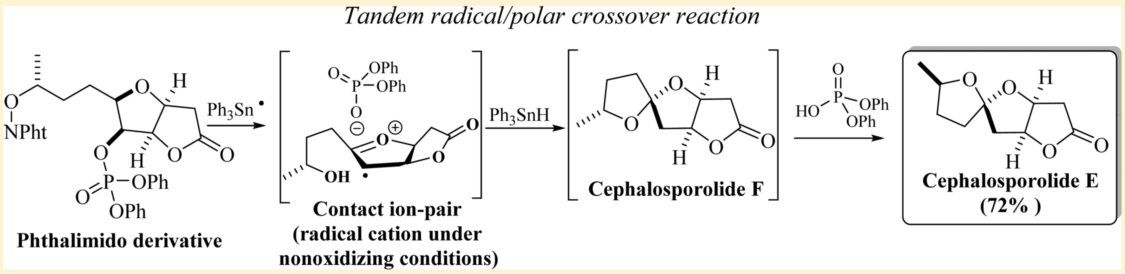
Supporting Information



ABSTRACT: The present work reports the first example of the use of the chemistry of radical cations under nonoxidative conditions in total synthesis. Using a late-stage tandem radical/polar crossover reaction, a highly stereoselective total synthesis of cephalosporolide E (which is typically obtained admixed with cephalosporolide F) was accomplished. The reaction of a phthalimido derivative with triphenyltin radical in refluxing toluene engenders a contact ion-pair (radical cation) that leads, in the first instance, to the cephalosporolide F, which is transformed into the cephalosporolide E via a stereocontrolled spiroketal isomerization promoted by the diphenylphosphate acid that is formed during the tandem transformation.

INTRODUCTION

Unlike conventional olefin radical cations, which are formed by one-electron oxidation of an olefin in high polar media (eq 1),[1] the nonoxidative radical cations are similar charged species generated by a C−O bond heterolysis (even in nonpolar media) of a suitable leaving group placed at the β-position of an alkyl free radical (eq 2).[2] Despite that this C−O bond heterolysis was first reported in 1972 by Norman and co-workers,[3] it was not until the beginning of this century that the nature of this heterolysis was fully recognized.[4] In conjunction with the physical organic chemical studies of these species,[4] synthetic applications were documented, wherein an intramolecular nucleophilic attack to the cation by heteroatoms like oxygen and nitrogen has permitted the development of new methodologies for the synthesis of lactones,[5] tetrahydrofurans,[5,6] pyranes,[5] and pyrrolidines,[5,7] with moderate and good yields, and also acceptable stereoselectivities (eq 3). The origin of the stereoselectivities is generally explained in terms of a stereocontrolled nucleophilic attack on the contact ion-pair, on the opposite side of the leaving group (eq 3, Scheme 1).[5,7]

Inspired by the synthetic sequence described in eq 3, we developed a tandem radical/polar crossover reaction for the synthesis of a carbohydrate-derived spiroketal (Scheme 2).[8a] Accordingly, when phthalimide derivative **1** was treated with Ph_3SnH/AIBN in refluxing benzene, spiroketal **2** was obtained in 70% yield. The stereochemical outcome of the reaction was rationalized based on the contact ion-pair model described in Scheme 1 (eq 3), wherein a stereocontrolled attack of the hydroxyl group on the intermediate **A**, on the opposite face to that shielded by the phosphate ion, gave exclusively a single stereoisomer (Scheme 2). Although this methodology appears as an attractive solution for overcoming the problem of the stereoselective construction of 5,5-spiroketal centers, no synthetic application has been reported yet. On this basis, we believe that this tandem transformation can be utilized as an expedient chemical transformation for the total synthesis of compounds that contain the 5,5-spiroketal moiety.

Among the wide variety of 5,5-spiroketal-containing natural products, chalcogran sex-pheromones[9] and cephalosporolides[10] have received special attention due to their biological importance and structural complexity, especially the latter, because of the lack of stereocontrolled methods for the formation of the spiroketal center (Figure 1).[11]

Unlike the 5,6- or 6,6-spiroketal compounds, the 5,5-spiroketal analogues are weakly dependent on the anomeric effect;[12] therefore, the classical acid-catalyzed method generally provides unpredictable mixtures of spiroketals. Consequently, all of the total syntheses of cephalosporolides have required separation from their respective spiro-diastereoisomers.[13] Moreover, an interesting approach for the stereocontrolled synthesis of cephalosporolides H[14] and E[11] was reported. This

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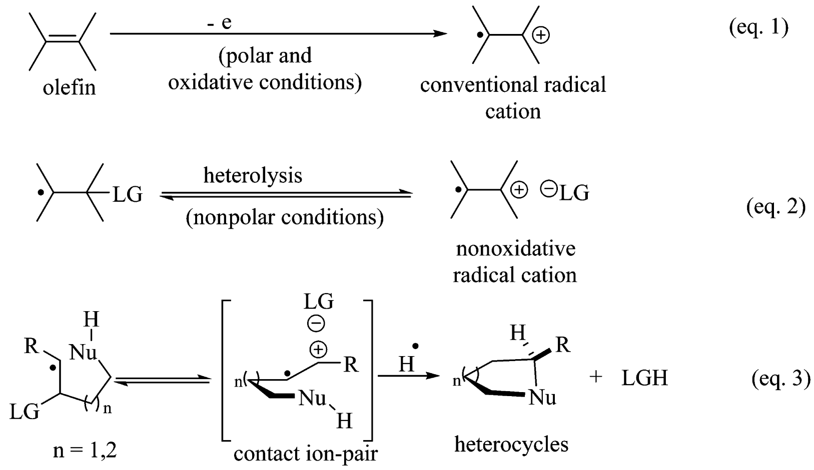
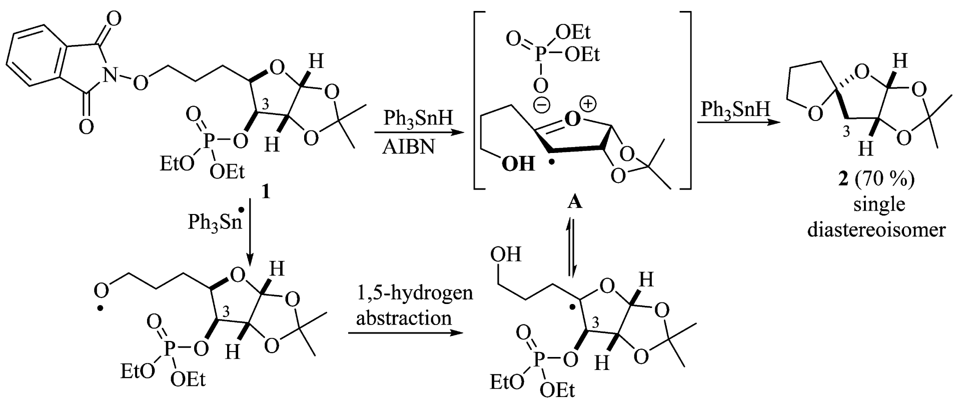
Scheme 1. Radical Cations: Conventional (eq. 1) and Nonclassical (Nonoxidative, eqs 2 and 3)[a]



[a]Abbreviations: LG = leaving group; Nu = nucleophile.

Scheme 2. Synthesis of a Carbohydrate-Derived Spiroketal 2 under Nonoxidizing Conditions[a]



[a]Abbreviation: AIBN = azobisisobutyronitrile; Et = ethyl.

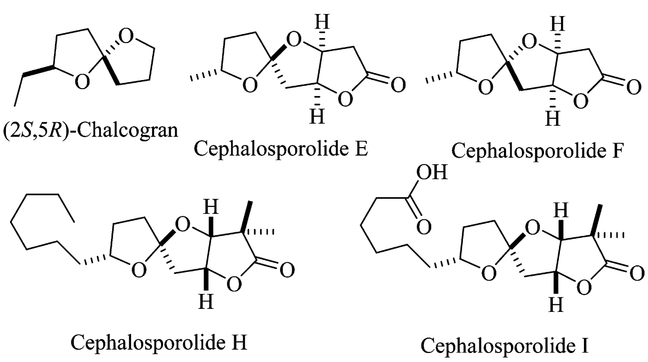


Figure 1. Representative 5,5-spiroketal-containing natural products.

approach is based on the use of zinc salts as key reagents for the formation of the spiro-center via either steric biases or chelation control. Although certainly this zinc-mediated isomerization represents an attractive strategy for the total synthesis of cephalosporolides H and E, the crucial step for the construction of the 5,5-spiroketal center is not stereoselective; an additional step is required.

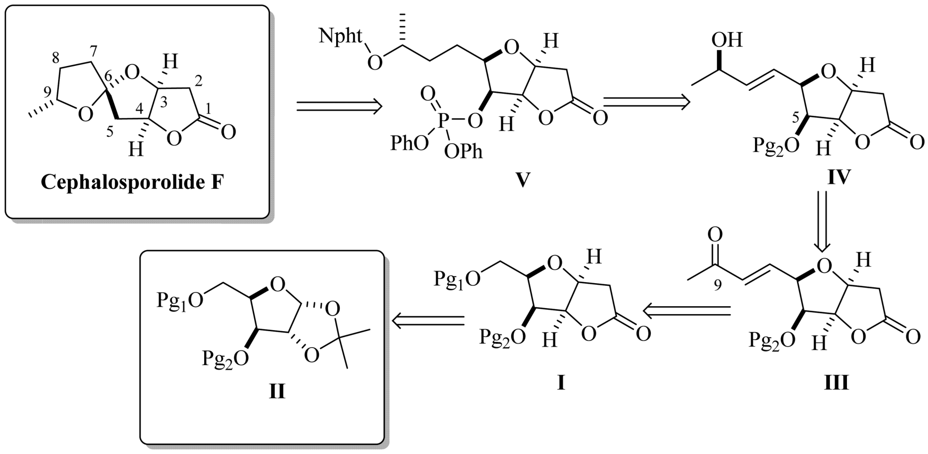
With this background in mind, we envisioned that our stereocontrolled tandem radical/polar crossover reaction might conduct to the first direct synthesis of a single cephalosporolide. Although the present work was designed to achieve the direct stereoselective total synthesis of cephalosporolide F, an interesting and unexpected behavior during the tandem radical/polar reaction (*vide infra*) led to the direct stereocontrolled total synthesis of cephalosporolide E. In order to avoid isomerization in the spiroketal center at earlier stages of the total synthesis, we planned to perform the tandem radical/polar reaction at the late stage of the total synthesis.

■ RESULTS AND DISCUSSION

Our retrosynthetic plan focused on the stereoselective construction of the bicyclic furan-γ-lactone framework (**I**) from the xylofuranose derivative **II** via a sequential procedure, which includes the stereoselective nucleophilic substitution at the anomeric position (NSAP).[15] We planned to use the stereoselective Corey–Bakshi–Shibata (CBS) reduction[16] to install the correct stereochemistry of the hydroxyl group at the C9 position ((*S*)-alcohol **IV** from α,β-unsaturated ketone **III**). Then, after introduction of the *N*-hydroxyphthalimide group under Mitsunobu conditions[17] and phosphorylation at the C5 position, the radical precursor **V** could be obtained. Finally, after the reaction of **V** with Ph_3SnH and AIBN,[18] the direct stereocontrolled total synthesis of cephalosporolide F is expected to be completed (Scheme 3).

This total synthesis began with the transformation of xylofuranose derivative **3**[19] into allylated product **4** via the

Scheme 3. Retrosynthetic Plan for the First Total Synthesis of Cephalosporolide F[a]



[a]Abbreviations: NPht = phthalimide; Ph = phenyl; Pg_1 = protecting group 1; Pg_2 = protecting group 2.

NSAP reaction;[15] however, under standard reaction conditions (allyltrimethylsilane/$BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C), the expected product **4** was obtained in low yield (24%) along with desylilated and debenzylated byproducts. This forced us to prepare another xylofuranose derivative (**5**) with a more robust protecting group at the C5 position. To this end, diacetone-D-glucose **6** was benzylated and transformed into xylofuranose derivative **7** by using the Robins's dehomologation protocol (H_5IO_6 in ethyl acetate, then $NaBH_4$ in ethanol at room temperature).[20] Xylofuranose derivative **5** was obtained by simple acetylation of **7**. Then, compound **5** was submitted to NSAP under the same reaction conditions as for compound **3**, and allylated product **8** was stereoselectivelly obtained in 82% yield. The stereochemical outcome of the reaction can be rationalized based on the Woerpel's "*inside attack*" model,[21] which predicts the formation of the 1,3-*cis* stereoisomer as the major product. Deprotection of **8** with K_2CO_3 in methanol and reprotection with TBSCl gave **4** (94% yield from **8**). Mesylation of the secondary hydroxyl group afforded compound **9** (85% yield).

Conversion of **9** to the bicyclic furan-γ-lactone **10** was accomplished by transforming the double bond into a carboxylic acid in three sequential steps ((1) OsO_4/NMO; (2) $NaIO_4$; (3) $NaClO_2$, **11** in 75% overall yield), followed by an intramolecular S_N2 substitution with triethylamine at the reflux temperature of the solvent (Scheme 4). Compound **10** was transformed into the α,β,-unsaturated ketone **12** by applying another sequential three-steps reaction: silyl deprotection with $BF_3{\cdot}OEt_2$, then oxidation of the respective primary hydroxyl group with Dess–Martin perioidinane,[22] and finally *trans*-selective Wittig olefination at −45 °C with the commercially available 1-(triphenylphosphoranylidene)-2-propanone (60% overall yield). Since the absolute stereochemistry at the C9 position of the cephalosporolides E and F is *R*, and the incorporation of the *N*-hydroxyphthalimide would occur with inversion of the configuration, then the stereoselective reduction of the unsaturated ketone **12** would have to provide the corresponding *S*-stereoisomer. Therefore, the stereoselective keto reduction was conducted with the appropriate Corey–Bakshi–Shibata (CBS) catalyst.[16] After screening reaction conditions, it was found that the use of 0.6 equiv of the (*R*)-MeCBS and 1.0 equiv of $BH_3{\cdot}SMe_2$ at −50 °C provided the best yield and stereoselectivity (70%, dr = 9:1, respectively). Allylic alcohol **13** was subjected to Mitsunobu conditions[17] with *N*-hydroxyphthalimide, DIAD, and triphenyl phosphine; its corresponding *N*-phthalimido derivative **14** was obtained in 60% yield. The reduction of the double bond and removal of the benzyl group was conducted simultaneously over $Pd(OH)_2$ in 40% (by weight) and H_2 during 14 h. Finally, phosphorylation of **15** with phenyldichloro phosphate in the presence of 4-dimethylamino pyridine gave the radical precursor **16** (Scheme 4).

With the radical precursor **16** in hand, we proceeded to test the crucial tandem radical polar crossover reaction. The slow addition of Ph_3SnH (45 min) in the presence of AIBN at vigorous toluene reflux[23] led to the exclusive formation of cephalosporolide E in 72% yield, and no traces of the cephalosporolide F was observed (Scheme 5). Evidently, this unexpected result seems to be at odds with the radical cation/ion-pair model proposed in Scheme 2. However, a likely explanation would be that the cephalosporolide F is actually formed according to the predicted ion-pair model, and the formation of the cephalosporolide E is the result of an acid isomerization of the cephalosporolide F by the presence of phenylphosphate acid, which is formed during the tandem radical/polar crossover reaction. If this is true, then the isomerization process would be decreased by conducting the radical reaction under basic conditions, and thus to observe the presence of cephalosporolide F. Having this in mind, we proceeded to perform the reaction in the presence of a suitable base. Among the studied bases, we found that both triethylamine and imidazole are compatible with the substrate and the reaction conditions.

When the radical reaction was performed with 3 equiv of triethylamine, a mixture of cephalosporolides E/F (85/15) was observed. A slightly increase of the cephalosporolide F (i.e., ~75/25) is detected when either 6 or 8 equiv of triethylamine was used. Moreover, a more significant decrease of cephalosporolide E at the expense of the formation of cephalosporolide F (i.e., ~51/49) was achieved when either 6 or 8 equiv of imidazole was employed (Scheme 5). Unfortunately, further addition of imidazole did not improve the formation of cephalosporolide F, but degradation of the starting material was observed.

It is worth to remark the extraordinary effectiveness of the phenylphosphate acid for promoting the stereoselective

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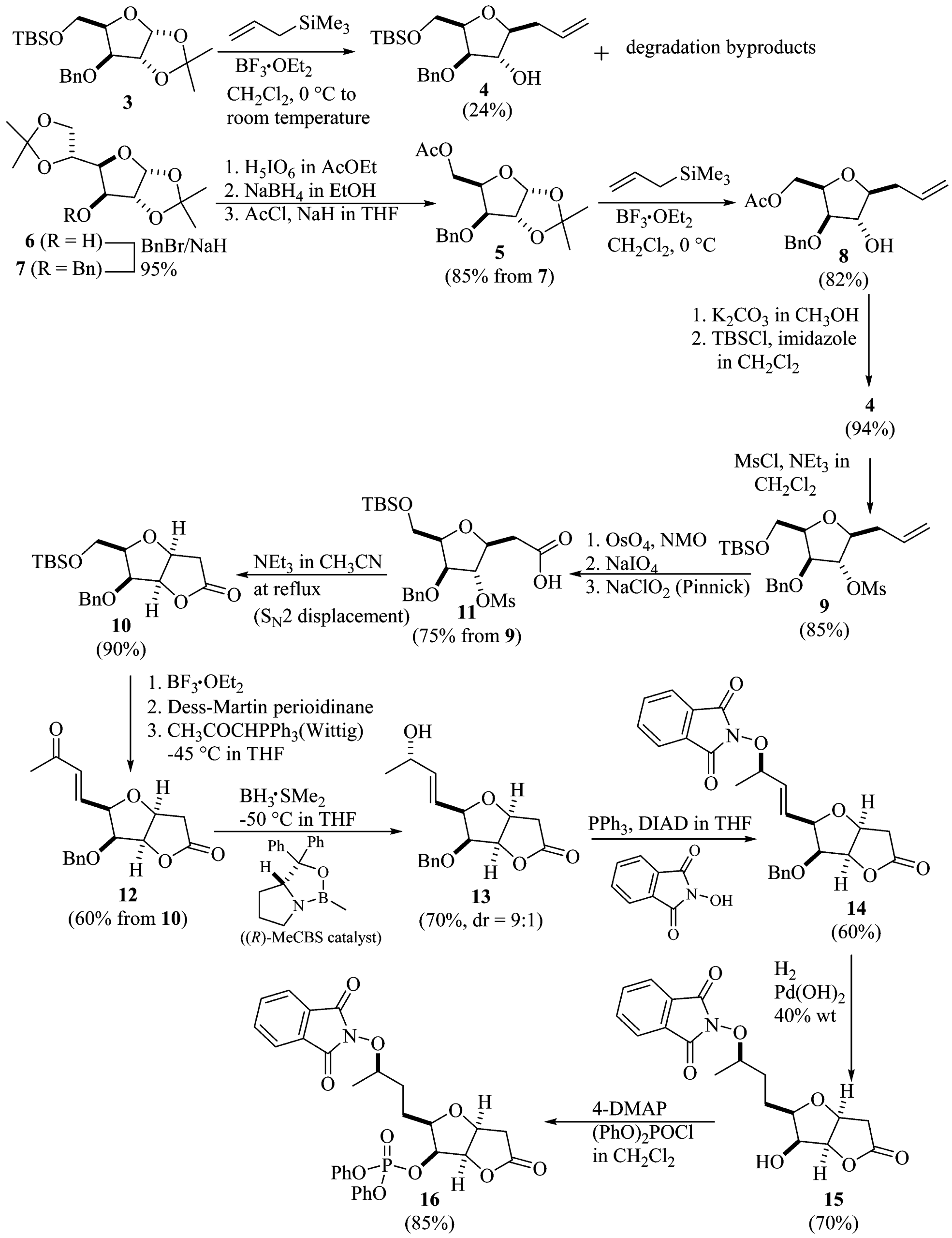
Scheme 4. Synthesis of Precursor of the Cephalosporolide E (16)[a]



[a]Abbreviations: TBS = *tert*-butyldimethylsilyl; Bn = benzyl; Ac = acetyl; Ms = methanesulfonyl; DIAD = diisopropyl azodicarboxylate; NMO = *N*-methylmorpholine-*N*-oxide; CBS = Corey–Bakshi–Shibata; 4-DMAP = 4-dimethylaminopyridine; THF = tetrahydrofuran; dr = diastereomeric ratio.

formation of cephalosporolide E from its stereoisomer congener, since as above-mentioned, similar stereocontrol was only achieved when $ZnCl_2$ is used as catalyst. Also, the presence of a hydroxyl group either protected or unprotected close to the spiroketal nucleus is required.[11,14] Since, in our case, the presence of an additional stereochemical element is not needed for the stereochemical control of the cephalosporolide E, but the presence of phenylphosphate acid and the toluene refluxing temperature, we propose that the cephalosporolide E is the thermodynamic product and the cephalosporolide F the kinetic.[24] Further experimental and theoretical studies in order to prove this proposal are currently underway and will be reported soon.

■ CONCLUSION

By using the Chiron Approach and featuring our tandem radical/polar reaction for the synthesis of 5,5-spiroketals, the total synthesis of cephalosporolide E was accomplished in 20 steps with 4% overall yield from commercially available diaceton-D-glucose. As in the previous total synthesis of cephalosporolides E and F has required the use of either chromatographic purifications from its diastereoisomer congener or the use of an additional step for equilibration to the "apparent" thermodynamic cephalosporolide E, the present work should be considered as the first direct diastereoselective total synthesis of cephalosporolide E. Therefore, the present

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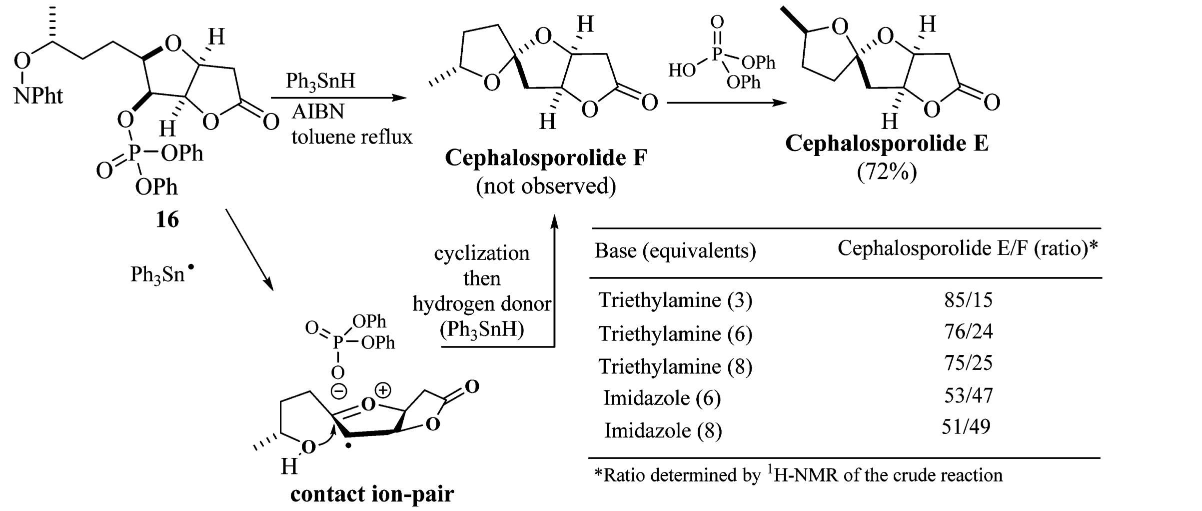
Scheme 5. Synthesis of Cephalosporolide E through a Tandem Radical/Polar Crossover Reaction/Acid-Catalyzed Spiro-isomerization. Evidence of Formation of Cephalosporolide E from Cephalosporolide F via an Ion-Pair Contact Intermediary[a]



Base (equivalents)	Cephalosporolide E/F (ratio)*
Triethylamine (3)	85/15
Triethylamine (6)	76/24
Triethylamine (8)	75/25
Imidazole (6)	53/47
Imidazole (8)	51/49

*Ratio determined by ^{1}H-NMR of the crude reaction

[a]Abbreviations: NPht = phthalimide; AIBN = azobisisobutyronitrile; NMR = nuclear magnetic resonance.

work represents an attractive approach for the total synthesis of other natural products that contain the 5,5-spiroketal nucleus.

■ EXPERIMENTAL SECTION

General. All reagents were obtained from commercial sources and used without purification. Solvents were used as technical grade, and freshly distilled prior to use. NMR studies were carried out with 500, 400, and 300 MHz equipment. Internal references (TMS) for ^{1}H and ^{13}C chemical shifts are stated in parts per million. COSY, HSQC, and NOESY experiments have been carried out in order to assign the ^{1}H and ^{13}C NMR spectra completely. IR spectra were recorded on an FT/IR spectrophotometer (ATR method). High-resolution mass spectra (HRMS, ESI-TOF ion mode).

5-*O*-Acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose (5). To a solution of DAG (**6**) (10 g, 38.4 mmol) and NaH (3.07 g, 128 mmol, 60% dispersion in oil) in dry THF (192 mL) was added BnBr (5.5 mL, 46.3 mmol) at 0 °C. The mixture was warmed up to room temperature and kept stirring for 2 h. The resulting reaction was carefully quenched with H_2O (10 mL) at 0 °C, and the solvent was evaporated under vacuum. The residue was diluted with EtOAc (120 mL), washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent hexane/ethyl acetate: 5/1) to give **7** (12.8 g, 95% yield) as a yellow oil. To a solution of protected product **7** (12.8 g, 36.5 mmol) in EtOAc (256 mL) under an argon atmosphere was added H_5IO_6 (10 g, 43.9 mmol) portion-wise at 0 °C. The reaction mixture was warmed up to room temperature and kept stirring for 2 h.The formed solids were filtered off and washed with ethyl acetate, and the organic phase was evaporated under reduced pressure. The residue was dissolved in methanol (365 mL) and $NaBH_4$ (2.76 g, 73 mmol) was added in small portions with vigorous stirring at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was carefully quenched with H_2O (10 mL) on a bath of ice, the solvent was evaporated, and the residue was diluted with H_2O (50 mL), extracted with EtOAc (3 × 50 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent hexane/EtOAc: 3/1) to give the corresponding alcohol (9.2 g, 90% yield over 2 steps) as a colorless oil. This alcohol (9.2 g, 32.82 mmol) was dissolved in dry THF under an inert atmosphere and added NaH (2.62 g, 109.15 mmol, 60% dispersion in oil) at 0 °C, followed by the dropwise addition of AcCl (4.63 mL, 65.55 mmol). The resulting mixture was warmed up to room temperature and kept stirring for 3 h. Finally, the reaction was carefully quenched with H_2O (5 mL) on a bath of ice. The solvent was evaporated, and the residue was diluted with EtOAc (180 mL), washed with brine (60 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent Hexane/EtOAc: 2/1) to give **5**[25] (9.0 g, 85% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 5H, C*H* arom.), 5.97 (d, 1H, C*H*, *J* = 3.6 Hz), 4.69 (d, 1H, OCH_2Ph, *J* = 12.0 Hz), 4.63 (d, 1H, C*H*, *J* = 4.0 Hz), 4.48 (d, 1H, OCH_2Ph, *J* = 12.0 Hz), 4.37 (m, 2H, CH_2−C*H*), 4.28 (m, 1H, CH_2), 3.96 (d, 1H, C*H*, *J* = 2.8 Hz), 2.05 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.33 (s, 3H,CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1 (COOCH$_3$), 137.0 (*C* arom.), 128.5, 128.0, 127.7 (CH arom.), 105.2 (*C*), 81.9 (CH), 81.5 (CH), 78.0 (CH), 71.8 (CH_2), 62.3 (CH), 26.7 (CH_3), 26.2 (CH_3), 20.9 (CH_3). IR (ATR) ν_{max} 2932, 1738, 1371, 1229 cm^{-1}.

((2*S*,3*S*,4*R*,5*R*)-2-Allyl-4-(benzyloxy)-5((acetoxy)methyl))-tetrahydrofuran-3-ol (8). To an ice-cooled solution of **5** (2.13 g, 6.6 mmol) and allyltrimethylsilane (5.32 mL, 33.0 mmol) in dry CH_2Cl_2 (133 mL) was dropwise added BF_3·OEt_2 (2.5 mL, 20.0 mmol). The reaction mixture was warmed to room temperature and allowed to react for 30 h. The resulting mixture was treated with saturated aqueous solution of $NaHCO_3$ to adjust pH ∼ 7 and then extracted with CH_2Cl_2 (3 × 30 mL), dried with Na_2SO_4, and evaporated under reduced pressure. Purification by flash chromatography (eluent hexane/EtOAc: 2/1) to afford the **8** (1.65 g, 82% yield) as a yellow oil. $[\alpha]_D^{20}$ = +10.54° (*c* = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (m, 5H, C*H* arom.), 5.84 (dddd, 1H, C*H*=CH$_2$, *J* = 17.0, 10.0, 7.5, 7.0 Hz), 5.11 (m, 2H, CH=CH_2), 4.64 (d, 1H, OC*H*Ph, *J* = 11.7 Hz), 4.51 (d, 1H, OC*H*Ph, *J* = 11.7 Hz), 4.39 (dd, 1H, C*H*, *J* = 10.2, 2.4 Hz), 4.21 (m, 2H, C*H*, C*H*), 4.05 (m, 1H, C*H*), 3.92 (dd, 1H, C*H*, *J* = 4.8, 2.7 Hz), 3.76 (ddd, 1H, C*H*, *J* = 6.6, 6.2, 4.2 Hz), 2.44 (m, 3H, CH_2, O*H*), 2.05 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1 (COOCH$_3$), 137.5 (*C* arom.), 133.9 (CH), 128.3, 127.7, 127.4 (CH arom.), 117.5 (CH_2), 85.0 (CH), 84.0 (CH), 78.4 (CH), 77.6 (CH), 71.7 (CH_2), 63.6 (CH_2), 37.7 (CH_2), 20.8 (CH_3). IR (ATR) ν_{max} 3419, 2905, 1717, 1641, 1234, 1041 cm^{-1}. (HRMS, ESI-TOF) *m*/*z* 307.1535 [M + H]$^+$ calcd for $C_{17}H_{23}O_5$: 307.1525.

(2*S*,3*S*,4*R*,5*R*)-2-Allyl-4-(benzyloxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-ol (4). A solution of **8** (2.1 g, 6.85 mmol) and K_2CO_3 (4.7 g, 34.25 mmol) in MeOH (69 mL) was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was diluted with 60 mL of a mixture of EtOAc/H_2O (10/5 mL). The mixture was neutralized (pH ∼ 7) with HCl (20% aqueous solution) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (69 mL) at

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0 °C, and imidazole (560 mg, 8.22 mmol) was added. The reaction mixture was stirred for 10 min before adding TBSCl (1.13 g, 7.53 mmol). The mixture was warmed to room temperature for 2 h, and 10 mL of water was added, followed by extraction with CH_2Cl_2 (3 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica (eluent hexane/EtOAc: 3/1) to give **4** (2.4 g, 94% yield) as a colorless oil. $[\alpha]_D^{20} = -21.0°$ (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 5H, C*H* arom.), 5.85 (dddd, 1H, C*H*=CH_2, J = 17.2, 9.6, 7.2, 7.0 Hz), 5.10 (m, 2H, CH_2), 4.65 (d, 1H, OC*H*Ph, J = 12.4 Hz), 4.61 (d, 1H, OC*H*Ph, J = 12.0 Hz), 4.07 (dd, 1H, C*H*, J = 10.8, 5.2 Hz), 4.03 (dd, 1H, C*H*, J = 4.4, 2.4 Hz), 3.90 (m, 2H, CH_2−C*H*), 3.78 (dd, 1H, CH_2, J = 10.4, 5.2 Hz), 3.70 (dd, 1H, C*H*, J = 11.4, 6.6 Hz), 2.46 (m, 1H, CH_2), 2.38 (m, 1H, CH_2), 1.73 (br, 1H, O*H*), 0.9 (s, 9H, $(CH_3)_3$), 0.06 (s, 6H, $(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.2 (*C* arom.), 134.4 (CH), 128.3, 127.6, 127.4, 127.3 (CH arom.), 117.3 (CH_2), 84.8 (CH), 83.8 (CH), 80.8 (CH), 79.2 (CH), 72.0 (CH_2), 61.3 (CH_2), 38.0 (CH_2), 25.9 $(CH_3)_3$, 18.3 (*C*), −5.3 (CH_3), −5.4 (CH_3). IR (ATR) ν_{max} 3423, 1641, 1253, 1087, 835 cm^{-1}. (HRMS, ESI-TOF) m/z 379.2296 [M + H]$^+$ calcd for $C_{21}H_{35}O_4Si$: 379.2304.

(2*S*,3*S*,4*S*,5*R*)-2-Allyl-4-(benzyloxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-yl Methanesulfonate (9). To a solution of alcohol **4** (1.8 g, 4.75 mmol) and NEt_3 (3.97 mL, 28.48 mmol) at 0 °C in dry CH_2Cl_2 (95 mL) under an argon atmosphere was added MsCl (0.8 mL, 10.55 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h before adding 10 mL of H_2O, followed by extraction with CH_2Cl_2 (3 × 20 mL), and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc: 6/1) to give **9** (1.8 g, 85% yield) as a yellow pale oil. $[\alpha]_D^{20} = -34.0°$ (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 5H, C*H* arom.), 5.82 (dddd, 1H, C*H*=CH_2, J = 17.2, 10.0, 6.8, 6.8 Hz), 5.15 (dd, 1H, C*H*, J = 1.6, 1.2 Hz), 5.11 (apparent d, 1H, C*H*, J = 9.4), 4.84 (dd, 1H, C*H*, J = 2.8, 1.6 Hz), 4.69 (d, 1H, OC*H*Ph, J = 12.0 Hz), 4.61 (d, 1H, OC*H*Ph, J = 12.0 Hz), 4.15 (dd, 1H, C*H*, J = 2.8, 1.4 Hz), 4.01 (m, 2H, 2(C*H*)), 3.88 (dd, 1H, C*H*, J = 10.2, 6.6 Hz), 3.81 (dd, 1H, C*H*, J = 10.2, 5.4 Hz), 2.95 (s, 3H, CH_3), 2.47 (m, 2H, CH_2), 0.89 (s, 9H, $(CH_3)_3$), 0.06 (s, 3H, CH_3), 0.05 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.4 (*C* arom.), 133.5 (CH), 128.4, 127.8, 127.7 (CH arom.), 118.1 (CH_2), 84.6 (CH), 82.1 (2(CH)), 81.4 (CH), 72.2 (CH_2), 60.7 (CH_2), 38.4 (CH_2), 37.6 (CH_3), 25.8 $(CH_3)_3$, 18.2 (*C*), −5.3 (CH_3), −5.4 (CH_3). IR (ATR) ν_{max} 1641, 1355, 1176, 1253, 1087, 833 cm^{-1}. (HRMS, ESI-TOF) m/z 457.2067 [M + H]$^+$ calcd for $C_{22}H_{37}O_6SSi$: 457.2080.

2-((2*S*,3*S*,4*S*,5*R*)-4-(Benzyloxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-((methylsulfonyl)oxy)tetrahydrofuran-2-yl)acetic Acid (11). To a solution of allylated compound **9** (2.4 g, 5.26 mmol) in a mixture of acetone/H_2O 10/1 (58 mL) were added *N*-methylmorpholine *N*-oxide (1.23 g, 10.5 mmol) and OsO_4 (4.2 mL, 0.1 M solution in *tert*-butanol). The reaction mixture was stirred at room temperature for 3 h. Then, an aqueous solution of $NaIO_4$ (2.25 g, 10.5 mmol in 5 mL of water) was added slowly, and the resulting suspension was allowed to react at room temperature for 1 h. Then, a mixture of *tert*-butanol/H_2O 7/3 (53 mL) was added, followed by the addition of $NaH_2PO_4 \cdot H_2O$ (7.26 g, 52.6 mmol) and $NaClO_2$ (3.8 g, 42.1 mmol). The reaction mixture was stirred at room temperature for 2 h at room temperature before adding 20 mL of water and 50 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). Both organic phases were dried Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc: 1/1) to give the acid **11** (1.8 g, 75% yield) as a yellow pale oil. This product is itself somewhat unstable; therefore, only NMR characterization was possible. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 5H, C*H* arom.), 4.95 (apparent t, 1H, C*H*, J = 2.2 Hz), 4.69 (d, 1H, OC*H*Ph, J = 11.6 Hz), 4.62 (d, 1H, OC*H*Ph, J = 12.0 Hz), 4.36 (ddd, 1H, C*H*, J = 7.2, 7.2, 2.8 Hz), 4.19 (dd, 1H, C*H*, J = 4.2, 2.2 Hz), 4.12 (m, 1H, C*H*), 3.83 (dd, 1H, O−CH_2CH, J = 10.4, 6.0 Hz), 3.78 (dd, 1H, O−CH_2CH, J = 10.2, 5.6 Hz), 3.02 (s, 3H, CH_3), 2.82 (apparent d, 2H, CH−CH_2−CO, J = 7.6 Hz), 0.89 (s, 9H, $(CH_3)_3$), 0.056 (s, 3H, CH_3), 0.053 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.8 (COOH), 137.2 (*C* arom.), 128.5, 128.0, 127.8 (CH arom.), 84.7 (CH), 81.8 (CH), 81.3 (CH), 78.5 (CH), 72.7 (CH_2), 60.8 (CH_2), 38.3 (CH_3), 37.8 (CH_2), 25.8 $(CH_3)_3$, 18.2 (*C*), −5.3 (CH_3), −5.4 (CH_3). IR (ATR) ν_{max} 3167, 1715, 1354, 1174, 1254, 833 cm^{-1}.

(3a*S*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (10). A solution of acid **11** (1.7 g, 3.7 mmol) and NEt_3 (1.1 mL, 7.4 mmol) in CH_3CN (74 mL) under an inert atmosphere was refluxed for 1 h and then partitioned between H_2O−EtOAc and extracted. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using (eluents hexane/EtOAc: 3/1) to give the γ-lactone **10** (1.2 g, 90% yield) as a yellow oil. $[\alpha]_D^{20} = -74.4°$ (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 5H, C*H* arom.), 5.03 (dd, 1H, C*H*, J = 6.6, 4.6 Hz), 4.79 (d, 1H, OC*H*Ph, J = 11.6 Hz), 4.7 (ddd, 1H, C*H*, J = 7.0, 7.0, 4.4 Hz), 4.49 (d, 1H, OC*H*Ph, J = 11.6 Hz), 4.13 (apparent t, 1H, C*H*, J = 4.4 Hz), 3.92 (m, 2H, C*H*, CH_{2a}), 3.76 (dd, 1H, CH_{2b}, J = 10.2, 6.2 Hz), 2.73 (dd, 1H, CH_{2a}, J = 16.2, 7.2 Hz), 2.72 (dd, 1H, CH_{2b}, J = 16.4, 4.4 Hz), 0.89 (s, 9H, $(CH_3)_3$), 0.058 (s, 3H, CH_3), 0.055 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.2 (*C*OO), 137.3 (*C* arom.), 128.3, 128.0, 127.9 (CH arom.), 82.7 (CH), 82.2 (CH), 77.0 (CH), 75.8 (CH), 73.6 (CH_2), 61.5 (CH_2), 36.2 (CH_2), 25.8 $(CH_3)_3$, 18.3 (*C*), −5.3 (CH_3), −5.4 (CH_3). IR (ATR) ν_{max} 2931, 2857, 1782, 1253, 834 cm^{-1}. (HRMS, ESI-TOF) m/z 379.1934 [M + H]$^+$ calcd for $C_{20}H_{31}O_5Si$: 379.1940.

(3a*S*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-5-((*E*)-3-oxobut-1-en-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (12). To solution of lactone **10** (1.0 g, 2.6 mmol,) in anhydrous CH_2Cl_2 (53 mL) at 0 °C and under an argon atmosphere was slowly added $BF_3 \cdot OEt_2$ (0.34 mL, 2.6 mmol). After stirring at 0 °C for 1 h, the mixture was treated with a saturated aqueous solution of K_2CO_3 to adjust the pH ∼ 7. Extraction with CH_2Cl_2, followed by drying with Na_2SO_4 and concentrating under reduced pressure, gave the corresponding deprotected alcohol as a yellow oil, which was dissolved in dry CH_2Cl_2 (53 mL) at room temperature and treated with Dess−Martin periodinane (3.3 g, 7.9 mmol). After 3 h of stirring, the reaction was quenched with 20% aqueous $Na_2SO_3 \cdot 5H_2O$ (30 mL) at 0 °C, and the resulting mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous NaCl, dried with Na_2SO_4, and concentrated under reduced pressure. The crude aldehyde was directly used for olefination without further purification. To a solution of phosphorus ylide (1.0 g, 3.2 mmol) in anhydrous THF (13 mL) was slowly transferred a solution of the aldehyde in dry THF (40 mL), and the reaction mixture was stirred 14 h at −45 °C. Finally, the reaction mixture was warmed to room temperature for 2 h and partitioned between H_2O−EtOAc and extracted. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc/MeOH: 75/20/5) to afford **12** (480 mg, 60% yield) as a yellow oil. $[\alpha]_D^{20} = -41.0°$ (c = 0.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (m, 5H, C*H* arom.), 6.8 (dd, 1H, C*H*, J = 16.0, 5.2 Hz), 6.24 (dd, 1H, C*H*, J = 16.2, 1.8 Hz), 5.03 (dd, 1H, C*H*, J = 6.0, 4.4 Hz), 4.80 (d, 1H, OC*H*Ph, J = 12.0 Hz), 4.79 (ddd, 1H, C*H*, J = 6.0, 5.8, 4.0 Hz), 4.56 (ddd, 1H, C*H*, J = 4.8, 4.6, 1.7 Hz), 4.52 (d, 1H, OC*H*Ph, J = 11.6 Hz), 4.21 (dd, 1H, C*H*, J = 5.6, 4.8 Hz), 2.79 (apparent d, 1H, CH_{2a}, J = 1.6 Hz), 2.77 (apparent s, 1H, CH_{2b}), 2.27 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.0 (*C*OCH_3), 174.7 (*C*OO), 141.4 (*C*H=CHCOCH$_3$), 136.8 (*C* arom.), 131.7 (CH=*C*HCOCH$_3$), 128.5, 128.3, 128.3, 128.2, 128.0 (CH arom.), 81.6 (CH), 79.9 (CH), 78.8 (CH), 76.5 (CH), 73.3 (CH_2), 36.6 (CH_2), 27.1 (CH_3). IR (ATR) ν_{max} 2933, 1779, 1728, 1255, 1152, 914 cm^{-1}. (HRMS, ESI-TOF) m/z 303.1230 [M + H]$^+$ calcd for $C_{17}H_{19}O_5$: 303.1232.

(3a*S*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-5-((*S*,*E*)-3-hydroxybut-1-en-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (13). To a solution of unsaturated ketone **12** (200 mg, 0.66 mmol) and (*R*)-CBS catalyst (110 mg, 0.4 mmol) in dry THF (7 mL) at −50 °C was added $BH_3 \cdot SMe_2$ (75 μL, 0.79 mmol) dropwise. The reaction mixture was stirred

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overnight before quenching with 0.1 mL of methanol and warming to room temperature. The mixture was diluted with EtOAc and washed with NH_4Cl saturated, and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (eluents hexane/EtOAc: 1/2) to give the alcohol **13** (141 mg, 70% yield) as a yellow oil. $[\alpha]_D^{20}$ = −47.5° (*c* = 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.66 (m, 1H, C*H* arom.), 7.49 (m, 1H, C*H* arom.), 7.33 (m, 3H, C*H* arom.), 5.87 (dd, 1H, C*H*, *J* = 15.6, 5.2 Hz), 5.83 (ddd, 1H, C*H*, *J* = 15.2, 15.2, 5.6 Hz), 5.0 (apparent t, 1H, C*H*, *J* = 5.2 Hz), 4.77 (d, 1H, OC*H*Ph, *J* = 12.0 Hz), 4.74 (dd, 1H, C*H*, *J* = 10.0, 4.8 Hz), 4.56 (d, 1H, OC*H*Ph, *J* = 11.6 Hz), 4.42 (apparent t, 1H, C*H*, *J* = 5.4 Hz), 4.32 (quin, 1H, C*H*, *J* = 6.4 Hz), 4.08 (apparent t, 1H, C*H*, *J* = 5.2 Hz), 2.74 (apparent d, 2H, CH_2, *J* = 4.8 Hz), 1.25 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.6 (COO), 137.9 (CH=CHCOCH$_3$), 137.1 (*C* arom.), 132.1 (CH=CHCOCH$_3$), 128.46, 128.43, 128.0, 127.9, 125.6 (CH arom.), 81.9 (CH), 80.1 (CH), 78.8 (CH), 76.0 (CH), 73.0 (CH_2), 68.2 (CH), 37.1 (CH_2), 22.7 (CH_3). IR (ATR) ν_{max} 3454, 2968, 1777, 1267, 1143, 1051, 974 cm^{-1}. (HRMS, ESI-TOF) *m/z* 305.1399 [M + H]$^+$ calcd for $C_{17}H_{21}O_5$: 305.1389.

2-(((*R*,*E*)-4-((2*R*,3*S*,3a*R*,6a*S*)-3-(Benzyloxy)-5-oxohexahydrofuro[3,2-*b*]furan-2-yl)but-3-en-2-yl)oxy)isoindoline-1,3-dione (14). To a mixture of alcohol **13** (153 mg, 0.5 mmol), PPh_3 (236 mg, 0.9 mmol), and *N*-hydroxyphthalimide (163 mg, 1 mmol) in dry THF (10 mL) at 0 °C was added dropwise DIAD (178 μL, 0.9 mmol). The reaction was allowed to warm at room temperature and stirred overnight. The mixture was partitioned between H_2O−EtOAc, and the organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica gel (eluent from hexane/EtOAc: 2/1 to 1/1) to provide the Mitsunobu product **14** (135 mg, 60% yield) as a white solid. mp = 110−112 °C. $[\alpha]_D^{20}$ = −28.7° (*c* = 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (m, 2H, C*H* arom.), 7.66 (m, 2H, C*H* arom.), 7.23 (m, 3H, C*H* arom.), 7.10 (m, 2H, C*H* arom.), 5.95 (dd, 1H, C*H*, *J* = 15.9, 8.1 Hz), 5.90 (dd, 1H, C*H*, *J* = 15.6, 6.0 Hz), 4.90(dd, 1H, C*H*, *J* = 6.0, 4.8 Hz), 4.83 (m, 1H, C*H*), 4.68 (ddd, 1H, C*H*, *J* = 6.3, 6.3, 3.6 Hz), 4.47 (d, 1H, OC*H*Ph, *J* = 11.4 Hz), 4.34 (apparent t, 1H, C*H*, *J* = 5.4 Hz), 4.14 (d, 1H, OC*H*Ph, *J* = 11.7 Hz), 3.95 (apparent t, 1H, C*H*, *J* = 4.8 Hz), 2.69 (m, 2H, CH_{2a}, CH_{2b}), 1.5 (d, 3H, CH_3, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.9 (COO), 163.9 (2(CON)), 136.8 (*C* arom.), 134.3, 128.7, 128.3, 127.8, 127.6, 123.3 (CH arom.), 133.3 (CH=CHCOCH$_3$), 131.0 (CH=CHCOCH$_3$), 84.4 (CH), 81.9 (CH), 80.6 (CH), 78.7 (CH), 76.0 (CH), 73.0 (CH_2), 36.6 (CH_2), 19.0 (CH_3). IR (ATR) ν_{max} 2923, 1783, 1725, 1459, 1262, 1122, 970 cm^{-1}. (HRMS, ESI-TOF) *m/z* 450.1538 [M + H]$^+$ calcd for $C_{25}H_{24}NO_7$: 450.1552.

2-(((*R*)-4-((2*R*,3*S*,3a*S*,6a*S*)-3-Hydroxy-5-oxohexahydrofuro-[3,2-*b*]furan-2-yl)butan-2yl)oxy)isoindoline-1,3-dione (15). A suspension of benzyl ether **14** (81 mg, 0.18 mmol) and $Pd(OH)_2$ (32 mg, 40 wt %) in EtOAc (4 mL) was stirred under a H_2 atmosphere (1 atm) at room temperature. When the starting material was completely consumed (12 h), the mixture was filtered through a neutral alumina pad and washed with EtOAc, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent from hexane/EtOAc: 2/1 to 1/2) to provide the reduced product **15** (46 mg, 70% yield) as a white solid. mp = 150−152 °C). $[\alpha]_D^{20}$ = −25.2° (*c* = 1.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.83 (m, 2H, C*H* arom.), 7.75 (m, 2H, C*H* arom.), 5.0 (dd, 1H, C*H*, *J* = 11.5, 5.5 Hz), 4.6 (ddd, 1H, C*H*, *J* = 6.0, 6.0, 3.3 Hz), 4.36 (m, 2H, 2(C*H*), 3.84 (ddd, 1H, C*H*, *J* = 5.7, 5.7, 3.6 Hz), 2.79 (d, 1H, CH_{2a}, *J* = 18.2, 6.3 Hz), 2.72 (d, 1H, CH_{2b}, *J* = 18.0, 3.1 Hz), 2.43 (br, 1H, O*H*), 1.89 (m, 4H, CH_2−CH_2), 1.36 (d, 3H, CH_3, *J* = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.3 (COO), 164.4 (2(CON)), 134.4 (CH arom.), 128.9 (*C* arom.), 123.5 (CH arom.), 84.5 (CH), 83.0 (2(CH)), 75.5 (CH), 71.2 (CH), 35.8 (CH_2), 31.5 (CH_2), 24.4 (CH_2), 18.9 (CH_3). IR (ATR) ν_{max} 3449, 2923, 1783, 1723, 1460, 1269, 1113 cm^{-1}. (HRMS, ESI-TOF) *m/z* 362.1233 [M + H]$^+$ calcd for $C_{18}H_{20}NO_7$: 362.1239.

(2*R*,3*S*,3a*R*,6a*S*)-2-((*R*)-3-((1,3-Dioxoisoindolin-2-yl)oxy)-butyl)-5 oxohexahydrofuro[3,2-*b*]furan-3-yl Diphenyl Phosphate (16). To a mixture of alcohol **15** (63 mg, 0.17 mmol) and DMAP (128 mg, 1.0 mmol) in dry CH_2Cl_2 (3 mL) under an inert atmosphere at 0 °C was added dropwise $(PhO)_2POCl$ (109 μL, 0.52 mmol). The reaction was allowed to warm at room temperature and was stirred for 3 h before adding a saturated aqueous NH_4Cl solution (1 mL), followed by extraction with CH_2Cl_2 (2 × 3 mL). The organic phase was washed with brine (2 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica gel (eluent CH_2Cl_2/EtOAc 1/1) to afford the phosphorylated product **16** (85 mg, 85% yield) as a yellow oil. $[\alpha]_D^{20}$ = −28.0° (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.81 (m, 2H, C*H* arom.), 7.45 (m, 2H, C*H* arom.), 7.29 (m, 8H, C*H* arom.), 7.17 (m, 2H, C*H* arom.), 5.12 (m, 2H, 2(C*H*)), 4.67 (ddd, 1H, C*H*, *J* = 7.2, 7.2, 3.6 Hz), 4.29 (dd, 1H, C*H*, *J* = 11.6, 6.2 Hz), 3.95 (m, 1H, C*H*), 2.74 (dd, 1H, CH_{2a}, *J* = 18.5, 7.2 Hz), 2.72 (dd, 1H, CH_{2b}, *J* = 18.4, 3.6 Hz), 1.79 (m, 4H, CH_2−CH_2), 1.27 (d, 3H, CH_3, *J* = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.4 (COO), 164.2 (2(CON)), 150.4 (2(*C* arom.)), 134.4, 129.8, 129.7 (CH arom.), 129.0 (2(*C* arom.)), 125.5, 125.4, 123.4, 120.2, 120.18, 120.10 (CH arom.), 83.9 (CH), 81.4 (CH), 81.3 (CH), 77.5 (CH), 75.4 (CH), 35.8 (CH_2), 31.0 (CH_2), 24.7 (CH_2), 18.7 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ: −10.74. IR (ATR) ν_{max} 2926, 1781, 1721, 1485, 1194, 923 cm^{-1}. ESI-HRMS *m/z* 594.1540 [M + H]$^+$ calcd for $C_{30}H_{29}NO_{10}P$: 594.1529.

(+)-Cephalosporolide E. A solution of radical precursor **16** (20 mg, 0.03 mmol) and AIBN (1.6 mg) in dry toluene (5 mL) was refluxed for 5 min under an argon atmosphere. Then, a solution of Ph_3SnH (24 mg, 0.06 mmol) and a catalytic amount of AIBN (1.6 mg) in dry/degassed toluene (5 mL) was slowly added to the refluxing solution (45 min). When the starting material was completely consumed (2 h), the mixture was cooled to room temperature; the solvent was evaporated under reduced pressure. The reaction crude was dissolved in 5 mL of CH_3CN and extracted with hexane to remove tin residues. The acetonitrile phase was evaporated under reduced pressure and purified by flash column chromatography on silica gel (eluent hexane/EtOAc/NEt_3, 60/10/07 to 40/10/0.5) to provide the cephalosporolide E (4.2 mg, 72% yield) as a colorless oil. $[\alpha]_D^{20}$ = +21.5° (*c* = 0.25, $CHCl_3$); lit.[13e] = +27.3 (c 0.41 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.16 (t, 1H, C*H*, *J* = 6.0 Hz), 4.92−4.87 (m, 1H, C*H*), 4.23−4.11 (m, 1H, C*H*), 2.74 (dd, 1H, CH_{2a}, *J* = 18.6, 7.8 Hz), 2.68 (dd, 1H, CH_{2b}, *J* = 18.6, 2.1 Hz), 2.45 (d, 1H, CH_{2c}, *J* = 14.1 Hz), 2.17−2.00 (m, 4H, CH_{2d}, CH_{2e}, CH_2), 1.50−1.42 (m, 1H, CH_{2f}), 1.20 (d, 3H, CH_3, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.8 (COO), 115.08 (*C*), 83.3 (CH), 77.4 (CH), 75.1 (CH), 41.6 (CH_2), 37.5 (CH), 34.2 (CH_2), 31.3 (CH_2), 20.9 (CH_3).

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR and ^{13}C NMR spectra of **4**, **5**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16**, and cephalosporolide E. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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DEDICATION

We respectfully dedicate this manuscript to the 43 missing students of Ayotzinapa. Our prayers and thoughts are with all of them.

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(23) The reaction proceeds very slowly under refluxing benzene or soft refluxing toluene. It is likely that the Stanyl radical addition onto one of the carbonyl group of the secondary *O*-phthalimide is slower than the primary analogues (e.g., phthalimide **1** reacts very well in refluxing benzene; see Scheme 2).

(24) When monitoring the radical reaction by TLC, the formation of cephalosporolide F and its disappearance from the reaction are observed, and the eventual formation of cephalosporolide E is also observed.

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