JOC The Journal of Organic Chemistry

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Structural Revision of Cephalosporolide J and Bassianolone

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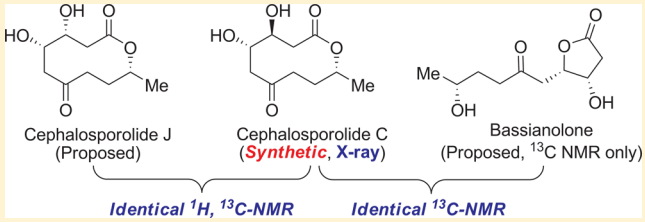
Supporting Information

ABSTRACT: The NMR spectra for three "natural" products: cephalosporolide C (Ces-C), cephalosporolide J (Ces-J), and bassianolone were found to be identical, and we proposed that Ces-C was the correct structure for the reported spectra. The first total synthesis of the proposed structure for Ces-J was achieved to support our structural revision for Ces-J. Chemical transformations of bassianolone and computational prediction of ^{13}C NMR spectra allowed us to conclude that Ces-C was the correct structure for bassianolone. Our synthetic and computational studies suggested that these "different" natural products Ces-C, Ces-J, and bassianolone have the same structure: Ces-C.



Natural products have been playing a major role in drug discovery[1] and served as a great impetus for the development of organic synthesis.[2] The unambiguous molecular structures including relative and absolute configurations of natural products are of great importance and essential to the subsequent studies. However, there are many natural products whose structures have been misassigned or could not be unambiguously established by spectroscopic methods without the assistance of single-crystal X-ray diffraction analysis, despite the fact that modern strategies and methods in structural elucidation are greatly developed.[3,4] In such cases, total synthesis has played an increasing role in definite structural proof or revision.[4] More recently, computational prediction of NMR chemical shifts and coupling constants has emerged as a new tool for structure elucidation.[5] For instance, the original structures of hexacyclinol[6] and aquatolide[7] were revised on the basis of predicting NMR spectra by computational methods, and the revised structures were subsequently confirmed by total synthesis[8] and X-ray diffraction analysis, respectively. Nevertheless, structural misassignments of natural products could not be easily detected until relevant synthetic and/or computational studies were performed. The occurrence of identical NMR spectra of two nonenantiomeric molecules definitely warrants re-examination of their originally proposed structures. A recent unexpected observation of identical ^{13}C NMR spectra for three "natural" products: cephalosporolide C, cephalosporolide J, and bassianolone triggered our interest in re-examining the structural assignments of these molecules. We herein report the structural revisions of cephalosporolide J and bassianolone by synthetic and computational studies (Figure 1).

Cephalosporolides C, E, and F were reported in 1985 by Hanson[9] and co-workers from the fungus *C. aphidicola*, ACC 3490 (Figure 1), and the relative configuration of Ces-C and Ces-E was further confirmed by single-crystal X-ray diffraction analysis. Interestingly, Ces-E and Ces-F were also found unexpectedly in 2005 by Oltra[10] and co-workers from the broth culture of *Beauveria bassiana* under a low-nitrogen medium, along with an unknown metabolite named (+)-bassianolone. The structure of bassianolone was proposed mainly on the basis of ^{1}H and ^{13}C NMR, COSY, and HMBC studies of its diacetate derivative and its easy chemical conversion to the spiroisomeric mixture of Ces-E and Ces-F. More recently, Nanayakkara[11] and co-workers isolated the Ces-E and Ces-J (**3**) from antimicrobial ethyl acetate extracts of wood decay fungus *Armillaria tabescens* (strain JNB-OZ344). It is noteworthy that the structure of Ces-J was proposed as an isomer of natural Ces-C by comparison of their NMR data. Surprisingly, we noticed that the proposed natural Ces-J and bassianolone, whose constitutions were proposed to be different, possessed identical ^{13}C NMR spectra.

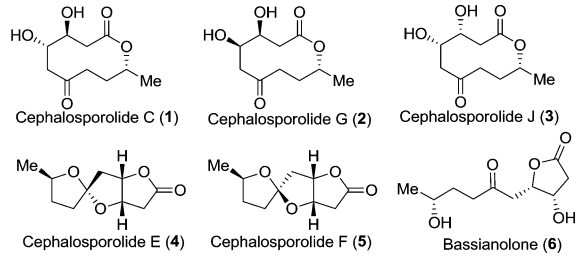


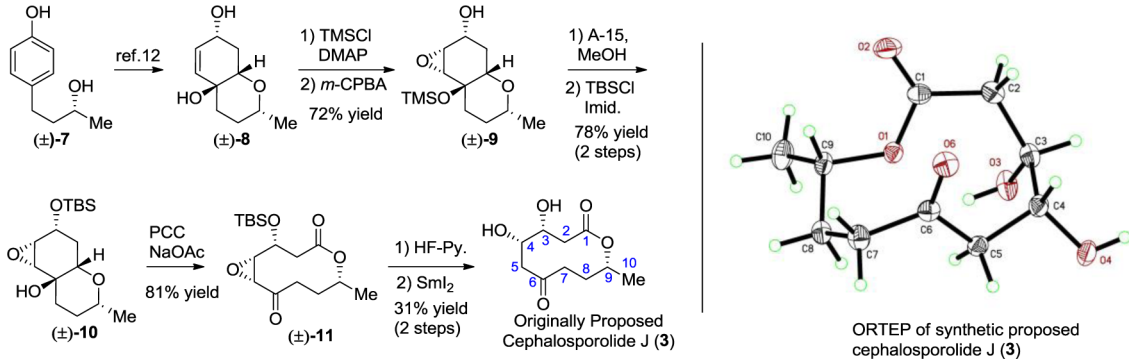
Figure 1. Representative cephalosporolides.

Recently, we have achieved asymmetric biomimetic total syntheses of cephalosporolides and reported new NMR data for Ces-C, which was also confirmed by X-ray diffraction analysis of both natural and synthetic samples.[12] Interestingly, we observed that the NMR data of our synthetic Ces-C were in good agreement with those of Ces-J and bassianolone. This surprising coincidence prompted us to cast doubt on the structural assignments of cephalosporolide J and bassianolone and initiate our synthetic and computational studies.

Received: November 22, 2013
Published: January 13, 2014

dx.doi.org/10.1021/jo402602h | J. Org. Chem. 2014, 79, 1493−1497

Scheme 1. Total Synthesis of the Proposed Cephalosporolide J



Our studies were first prompted by the coincidence of identical NMR data (^{1}H and ^{13}C NMR) from two supposed diastereomers: Ces-C and Ces-J. It is well-known that NMR spectra of enantiomers should be identical, but diastereomers are far less likely to have identical NMR spectra.[13] The possibility of similar or identical NMR spectra for diastereomers often exists for complex natural products with remote stereocenters.[14] There is no precedent that diastereomers with different vicinal chiral centers on either cyclic or linear framework have identical NMR spectra. However, we could not rule out the possibility that the supposed diastereomers of Ces-J and Ces-C have identical NMR spectra. Therefore, we started a total synthesis of the proposed Ces-J (Scheme 1) using a similar synthetic strategy developed previously for the total syntheses of cephalosporolides.[12] (±)-Rhododendrol (**7**) was elaborated into bicyclic ether **8** in five steps.[12] Silylation of **8** with TMSCl followed by *m*-CPBA epoxidation gave the bicyclic epoxy alcohol **9** as a single diastereomer. The excellent diastereoselectivity may be attributed to in situ unmasking of the secondary alcohol by desilylation with *m*-CPBA (>85% purity) and subsequent hydroxyl-directed epoxidation. After desilylation with Amberlyst 15 (A-15) in methanol and TBS protection of the secondary alcohol, PCC-promoted oxidative ring expansion provided the decanolide **11**, which upon removal of TBS with HF−pyridine underwent SmI_2-promoted reductive epoxide opening to furnish the proposed Ces-J (**3**) in seven steps with 8.9% overall yield from **8**. The relative structural configuration of the synthetic Ces-J (**3**) was further substantiated by X-ray diffraction analysis.

The NMR analysis of our synthetic Ces-J and Ces-C (new NMR data) indicated several significant differences (Table 1). For instance, the difference of chemical shifts on C-4 in the ^{1}H NMR spectra was 0.72 ppm and in the ^{13}C NMR spectra was 4.0 ppm. The methylene protons (2a and 2b) on C-2 also have very distinct ^{1}H NMR chemical shifts: the chemical shift difference between 2a and 2b was 0.54 ppm for Ces-C and only 0.23 ppm for our synthetic Ces-J. In addition, the NMR spectra of our synthetic Ces-J were not identical to those of another diastereomer, Ces-G (**2**).[15] This evidence suggested that the NMR spectra for diastereomers of these decanolides were not identical, and we concluded that the originally isolated compound named Ces-J was in fact the known Ces-C.

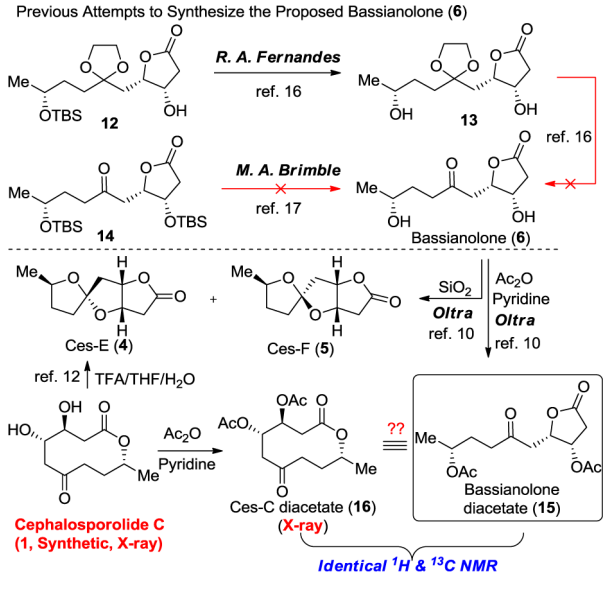
Next, our attention was attracted by our unexpected observation of identical ^{13}C NMR data of our synthetic Ces-C and bassianolone, reportedly two compounds with different skeletons. In analogy to the case of Ces-J, we suspected that the Ces-C was isolated again by Oltra from a different source but proposed as bassianolone due to significant discrepancies of ^{13}C NMR data when compared to those of Ces-C reported by Hanson. Previous synthetic studies by Fernandes[16] and Brimble[17] suggested that the proposed bassianolone (**6**) was too labile to be isolated from reactions of its direct precursors such as **12**, **13**, or **14** under various conditions (Scheme 2). Therefore, we did not attempt to undertake a total synthesis for the structural confirmation of bassianolone. However, acetylation of Ces-C permitted us to directly compare the NMR data of Ces-C diacetate (**16**) and the proposed bassianolone

Table 1. ^{1}H and ^{13}C NMR Data for Ces-C and Synthetic Ces-J

position	Ces-C (ppm)	synthetic Ces-J (ppm)	Δδ (ppm)
2a	2.89 (38.9)	2.75 (37.6)	0.14 (1.3)
2b	2.35	2.52	0.17
4	**3.38 (75.0)**	**4.10 (71.0)**	**0.72 (4.0)**
5a	2.76 (43.5)	2.96 (43.1)	0.20 (0.4)
5b	2.69	2.70	0.01
8a	2.05 (33.7)	2.14 (33.1)	0.09 (0.6)
8b	2.05	2.01	0.04

Note: ^{13}C NMR data are in parentheses.

Scheme 2. Previous Synthetic Studies of Proposed Bassianolone and Chemical Conversions to its Derivatives and Cephalosporolides E and F



dx.doi.org/10.1021/jo402602h | J. Org. Chem. 2014, 79, 1493−1497

diacetate (**15**), which was obtained by Oltra via acetylation of bassianolone (**6**) and used for confirmation of the structure for bassianolone through extensive NMR studies (^{1}H and ^{13}C NMR, COSY, HMQC, and HMBC). Not surprisingly, **15** and **16** had identical ^{1}H and ^{13}C NMR data,[18] which suggested that they were identical compounds and one of them may be misassigned. X-ray diffraction analysis of the Ces-C diacetate (**16**) confirmed its molecular structure, and therefore, **15** should be the misassigned one. The X-ray diffraction analysis of **16** also ruled out the possibility that rearrangement of Ces-C (**1**) to bassianolone (**6**) occurred in the course of acetylation to give bassianolone diacetate (**15**). In addition, Ces-C and bassianolone were reported to undergo the identical rearrangement:[19] acid-catalyzed dehydrative rearrangement to a 3:1 mixture of Ces-E and Ces-F. The combination of chemical transformations and NMR studies of its derivatives clearly supported that the natural product isolated by Oltra and named as bassianolone should be the known Ces-C.

To further support our structural revision of bassianolone, we relied on computational prediction[20] of ^{13}C NMR chemical shifts of Ces-C and the proposed bassianolone. A computational method for accurately predicting ^{13}C NMR chemical shifts[5] was used in our studies: (i) the low energy structural conformers (minimum) were optimized at the B3LYP/6-311+G(2d,p) level; (ii) the isotropic shielding constants were calculated with the GIAO option at the mPW1PW91/6-311+G(2d,p)/CPCM(chloroform) level.[18] We performed ^{13}C NMR calculations of Ces-C and bassianolone separately, and the difference between experimental and calculated (corrected) chemical shifts was plotted, respectively (Figure 2). The

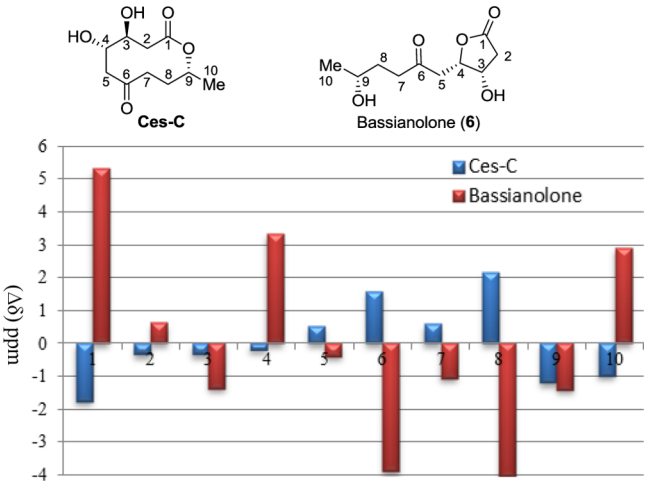


Figure 2. Structure and ppm difference between calculated and experimental ^{13}C NMR chemical shifts for Ces-C (**1**) and bassianolone (**6**). The average $|\Delta\delta|$ for Ces-C was 0.97 ppm, maximum $|\Delta\delta|$ was 2.15 ppm. The average $|\Delta\delta|$ for bassianolone was 2.44 ppm, maximum $|\Delta\delta|$ was 5.31 ppm.

predicted ^{13}C NMR for Ces-C was in excellent agreement with those obtained by experiments, with an average deviation of 0.97 ppm and maximum deviation of 2.15 ppm. On contrast, the predictions for the reported structure of bassianolone were poorly correlated with the experimental results. The average chemical shift difference was 2.44 ppm and the maximum difference was 5.31 ppm. In correlation plots, Ces-C with an R^2 value of 0.999630 has a better linear relationship with the experimental value than bassianolone with an R^2 value of 0.997687.[18] These computational studies suggested that the ^{13}C NMR spectra reported for bassianolone did not match the proposed structure of bassianolone but were consistent with the sturcture of Ces-C. Taking the synthetic and computational studies into consideration, we concluded that Ces-C was the correct structure for the reported bassianolone, which may not exist as a natural product. Consequently, the biosynthetic hypothesis[10] of Ces-E and Ces-F based on the wrong structure of bassianolone should be revised accordingly.

These two unusual examples of structural misassignments warrant some comments. The discovery of the identical NMR spectra for three reportedly different natural products was quite unexpected and unprecedented in the literature. Scepticism on these proposed structures invoked the obvious questions about the true structure and the causes of mistakes, which may be a mystery forever. Fortunately, our previous synthetic studies suggested that the original ^{13}C NMR data for Ces-C were erroneously reported, and the new ^{13}C NMR spectra for Ces-C were identical to those reported for Ces-J and bassianolone. The mistake reported for the natural Ces-C was believed to cause the structure misassignments of Ces-J and bassianolone because the NMR spectra for Ces-J and bassianolone were compared with and different from those reported for Ces-C by Hanson.

In conclusion, we discovered the identical NMR spectra reported for three "different natural" products: Ces-C, Ces-J, and bassianolone and proposed that Ces-C was the correct structure for the reported spectra. The first total synthesis of the proposed structure for cephalosporolide J was achieved to support our structural revision of Ces-J, which also ruled out the possibility of identical NMR spectra for the diastereomeric Ces-C and Ces-J. Chemical transformations and computational prediction of ^{13}C NMR chemical shifts enabled us to conclude that Ces-C was the correct structure for the antimicrobial bassianolone. The structural revisions of Ces-J and bassianolone would have significant implications in the subsequent research including synthetic studies and drug discovery.

EXPERIMENTAL SECTION

NMR spectra were recorded on a 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), and the reported chemical shifts in parts per million (ppm) are relative to the internal chloroform (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Infrared (IR) spectra were recorded as neat samples (liquid films on KBr plates). HRMS spectra were recorded with a TOF detector and direct inert probe. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as indicator. Dichloromethane (CH_2Cl_2) was freshly distilled before use from calcium hydride (CaH_2). All other anhydrous solvents were dried over 3 or 4 Å molecular sieves. Compounds **1** and **8** are known compounds that were prepared according to the literature procedure.[12]

(±)-9. To a solution of alcohol (±)-**8** (550 mg, 3.0 mmol) in dry CH_2Cl_2 (6 mL) were added imidazole (816 mg, 12.0 mmol) and 4-dimethylaminopyridine (DMAP, 37.0 mg, 0.30 mmol). The resulting solution was cooled to 0 °C with an ice−water bath, and then trimethylsilyl chloride (TMSCl, 980 mg, 9.0 mmol) dissolved in CH_2Cl_2 (2 mL) was added dropwise. After completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by addition of water (10 mL). The organic fractions were collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the bis-silyl ether of **9** as a colorless oil, which was used directly in the next step without further purification. To a solution of silyl ether obtained above in dichloromethane (30 mL) at 0 °C was added *meta*-chloroperox-

dx.doi.org/10.1021/jo402602h | J. Org. Chem. 2014, 79, 1493−1497

ybenzoic acid (*m*-CPBA, 1.22 g, 6.0 mmol). After the addition was completed, the reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction mixture was cooled to 0 °C again. A second portion of *m*-CPBA (1.22 g, 6.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. After TLC analysis indicated the complete consumption of starting materials, the reaction mixture was cooled to 0 °C and quenched with satd Na_2SO_3 (10 mL). The organic fractions were collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with satd $NaHCO_3$ (10 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using eluents (hexane/ethyl acetate = 10/1) to give the bicyclic epoxy alcohol (±)-**9** (587 mg, 72% yield over two steps) as a colorless oil. IR (neat, cm^{-1}): 3535, 2956, 2932, 2858, 1437, 1416, 1252, 1116, 1096, 1074, 1010, 941, 872, 840. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.10 (m, 1H), 4.46−4.45 (m, 1H), 3.43−3.37 (m, 1H), 3.34 (t, J = 4.0 Hz, 1H), 3.23 (br, 1H), 3.11 (dd, J = 3.6, 2.4 Hz, 1H), 2.33−2.23 (m, 1H), 1.93 (ddd, J = 14.8, 5.2, 2.4 Hz, 1H), 1.86−1.76 (m, 3H), 1.61−1.54 (m, 1H), 1.14 (d, J = 6.4 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 79.0, 73.6, 67.7, 63.3, 59.0, 52.1, 37.2, 30.9, 30.8, 21.6, 2.8 (3 × C). HRMS (TOF, CI^-): m/z calcd for $C_{13}H_{23}O_4Si$ $[M - H]^-$ 271.1366, found 271.1366.

(±)-10. To a solution of the bicyclic epoxy alcohol (±)-**9** (272 mg, 1.0 mmol) in methanol (5 mL) was added Amberlyst-15 (A-15, 544 mg), and the mixture was stirred at room temperature for an additional 1 h and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford epoxy diol as a colorless solid, which was used directly in the next step without further purification. To a solution of epoxy diol obtained above in dry DMF (1 mL) was added imidazole (136 mg, 2.0 mmol). The resulting solution was cooled to 0 °C with an ice−water bath, and then *tert*-butyldimethylsilyl chloride (TBSCl, 226 mg, 1.5 mmol) was added in one portion. After the completion of addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by addition of water (5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic fractions were washed with 1.0 M citric acid (5 mL), satd $NaHCO_3$ (5 mL), and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using eluents (hexane/ethyl acetate = 10/1) to give the epoxide (±)-**10** (245 mg, 78% yield over two steps) as a colorless solid. Mp = 132−134 °C. IR (neat, cm^{-1}): 3440, 2959, 2929, 2900, 2858, 1460, 1379, 1252, 1135, 1087, 1045, 1021, 984, 865, 839. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.21 (ddd, J = 10.4, 5.2, 1.2 Hz, 1H), 3.81 (ddt, J = 12.0, 8.8, 6.4 Hz, 1H), 3.43 (dd, J = 10.8, 5.2 Hz, 1H), 3.24 (d, J = 3.6 Hz, 1H), 2.96 (d, J = 4.0 Hz, 1H), 2.02 (ddd, J = 13.6, 10.0, 7.6 Hz, 1H), 1.88−1.79 (m, 2H), 1.76−1.64 (m, 3H), 1.56−1.47 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 79.0, 68.8, 68.4, 67.2, 59.3, 56.9, 32.0, 27.3, 27.2, 25.9 (3 × C), 22.3, 18.3, −4.4, −4.5. HRMS (TOF, CI^-) m/z calculated for $C_{16}H_{29}O_4Si$ $[M - H]^-$ 313.1835, found 313.1835.

(±)-11. To a solution of epoxide (±)-**10** (94 mg, 0.30 mmol) in CH_2Cl_2 (15 mL) were added sodium acetate (590 mg, 7.2 mmol) and pyridinium chlorochromate (PCC, 1.04 g, 4.8 mmol) portionwise over a period of 5 min. The resulting dark mixture was stirred at room temperature overnight and filtered through a pad of Florisil. The filtrate was washed with satd $CuSO_4$ (2 × 5 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using eluents (hexane/ethyl acetate = 20/1 to 10/1) to give the decanolide (±)-**11** (80 mg, 81% yield) as a colorless solid. Mp = 100−102 °C. IR (neat, cm^{-1}): 2976, 2949, 2930, 2901, 2855, 1737, 1708, 1435, 1362, 1251, 1124, 1053, 987, 881. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.15 (dqd, J = 10.4, 6.4, 3.2 Hz, 1H), 4.57−4.54 (m, 1H), 3.48 (d, J = 4.8 Hz, 1H), 3.26 (dd, J = 4.8, 2.0 Hz, 1H), 2.73 (dd, J = 15.2, 4.8 Hz, 1H), 2.68 (ddd, J = 15.2, 10.4, 0.8 Hz, 1H), 2.55 (dd, J = 15.2, 3.2 Hz, 1H), 2.32 (ddd, J = 15.2, 9.6, 1.2 Hz, 1H), 2.15 (dtd, J = 14.4, 10.4, 1.2 Hz, 1H), 1.95 (dddd, J = 14.4, 9.6, 3.2, 0.8 Hz, 1H), 1.22 (d, J = 6.4 Hz, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.9, 170.7, 71.4, 65.3, 60.9, 59.3, 40.1, 36.8, 32.6, 25.8 (3 × C), 19.9, 18.3, −4.6, −5.4. HRMS (TOF, CI^-): m/z calcd for $C_{16}H_{28}O_5Si$ $[M]^-$ 328.1706, found 328.1705.

(±)-3 (Proposed Cephalosporolide J). To a solution of decanolide (±)-**11** (79 mg, 0.24 mmol) in acetonitrile (9 mL) at 0 °C under nitrogen atmosphere was added dropwise a solution of HF−pyridine complex (0.9 mL). The resulting mixture was stirred for 15 min at 0 °C and then warmed to room temperature. After TLC analysis indicated complete consumption of the starting material (2 h), the reaction mixture was cooled with an ice−water bath and quenched by addition of satd $NaHCO_3$ carefully until no gas was released. The mixture was allowed to warm to room temperature and concentrated under reduced pressure. The organic layer was collected, and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were washed with satd $CuSO_4$ (2 × 5 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using eluents (hexane/ethyl acetate = 2/1) to give the epoxide (32 mg, 61% yield) as a colorless oil. IR (neat, cm^{-1}): 3440, 2958, 2934, 2872, 1720, 1641, 1430, 1382, 1269, 1196, 1122, 1044, 971. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.14 (dqd, J = 10.4, 6.4, 3.2 Hz, 1H), 4.63−4.59 (m, 1H), 3.66 (d, J = 4.8 Hz, 1H), 3.38 (dd, J = 4.8, 2.8 Hz, 1H), 3.08 (d, J = 4.4 Hz, 1H), 2.99 (dd, J = 16.0, 3.6 Hz, 1H), 2.76 (ddd, J = 15.2, 11.6, 1.6 Hz, 1H), 2.60 (dd, J = 15.6, 3.6 Hz, 1H), 2.43 (ddd, J = 15.2, 8.0, 1.6 Hz, 1H), 2.31 (dtd, J = 14.4, 11.2, 1.6 Hz, 1H), 1.97 (dddd, J = 14.4, 8.0, 3.2, 1.6 Hz, 1H), 1.27 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.9, 170.2, 72.3, 65.4, 60.9, 59.2, 38.9, 38.0, 32.7, 19.9. HRMS (TOF, CI^-): m/z calcd for $C_{10}H_{14}O_5$ $[M]^-$ 214.0841, found 214.0840.

A flame-dried Schlenk tube with nitrogen atmosphere was charged with the epoxide (30 mg, 0.14 mmol) obtained above and dry THF (1 mL). The solution was cooled to −78 °C, and samarium diiodide (3.1 mL, 0.1 M in THF, 0.31 mmol) was added dropwise. The reaction mixture was allowed to warm to −20 °C over a period of 1 h and then quenched with satd $NaHCO_3$ (5 mL). The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using eluents (hexane/ethyl acetate = 1/2) to give the proposed (±)-**3** (proposed cephalosporolide J, 15.4 mg, 51% yield) as a colorless solid. Mp = 98−100 °C. IR (neat, cm^{-1}): 3414, 2929, 1714, 1647, 1445, 1370, 1261, 1159, 1125, 1041, 979, 855. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.08 (dqd, J = 8.4, 6.4, 2.8 Hz, 1H), 4.47 (br, 1H), 4.10 (m, 2H), 3.01 (br, 1H), 2.96 (dd, J = 17.6, 8.4 Hz, 1H), 2.75 (dd, J = 15.2, 9.6 Hz, 1H), 2.70 (dd, J = 17.6, 2.0 Hz, 1H), 2.52 (dd, J = 15.2, 2.0 Hz, 1H), 2.45−2.36 (m, 2H), 2.19−2.09 (m, 1H), 2.04−1.97 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.8, 170.6, 71.9, 71.5, 71.0, 43.1, 40.2, 37.6, 33.1, 19.6. HRMS (TOF, CI^-): m/z calcd for $C_{10}H_{15}O_5$ $[M - H]^-$ 215.0919, found 215.0921.

(+)-16. To a solution of cephalosporolide C ((+)-**1**)[12] (16.0 mg, 0.074 mmol) in pyridine (1 mL) at 0 °C was added acetic anhydride (82 mg, 0.8 mmol). After completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (20 mL). The organic fraction was washed with satd $CuSO_4$ (5 mL × 2) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by short column chromatography on silica gel using eluents (hexane/ethyl acetate = 5/1) to provide the cephalosporolide C diacetate ((+)-**16**) (22.0 mg, 99% yield) as a colorless solid. Mp =78−80 °C. $[\alpha]_D^{25}$ = +12.6 (c 1.1, $CHCl_3$). IR (neat, cm^{-1}): 2980, 2932, 2854, 1739, 1432, 1373, 1241, 1181, 1128, 1066, 1029, 962, 910. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.46 (ddd, J = 11.2, 9.6, 3.2 Hz, 1H), 5.16 (ddd, J = 10.0, 6.8, 2.8 Hz, 1H), 5.05 (dqd, J = 9.2, 6.4, 3.2 Hz, 1H), 3.02 (dd, J = 17.6, 6.8 Hz, 1H), 2.81 (dd, J = 17.2, 3.2 Hz, 1H), 2.67 (dd, J = 17.6, 2.8 Hz, 1H), 2.57 (dd, J = 17.2, 11.2 Hz, 1H), 2.40−2.30 (m, 2H), 2.21−2.09 (m, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 2.04−1.96 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.8, 170.2, 169.7, 167.9, 72.6, 71.0, 68.7, 43.5,

dx.doi.org/10.1021/jo402602h | J. Org. Chem. 2014, 79, 1493−1497

40.0, 38.2, 33.4, 21.1, 21.0, 19.7. HRMS (TOF, CI$^-$): m/z calcd for $C_{14}H_{19}O_7$ $[M - H]^-$ 299.1131, found 299.1134.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Computational studies, X-ray data of compounds **3** and **16**, NMR data comparison of cephalosporolide C, bassianolone, and cephalosporolide J, and copies of ^{1}H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was financially supported by The Hong Kong University of Science and Technology (HKUST, R9309) and Research Grant Council of Hong Kong (DAG12CS03, ECS 605912, and GRF 603313). We are very grateful to Prof. Ian Williams (HKUST) for X-ray diffraction analysis and Profs. Hanson and Oltra for valuable discussions.

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