ORGANIC LETTERS

2013
Vol. 15, No. 22
5850–5853

Cephalosporolide B Serving as a Versatile Synthetic Precursor: Asymmetric Biomimetic Total Syntheses of Cephalosporolides C, E, F, G, and (4-OMe-)G

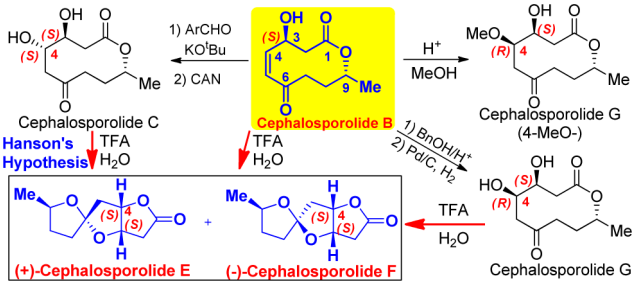
Liyan Song, Yuan Liu, and Rongbiao Tong*

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China

rtong@ust.hk

Received October 9, 2013

ABSTRACT



Cephalosporolide B (Ces-B) was efficiently synthesized and exploited for the first time as a versatile biomimetic synthetic precursor for the chemical syntheses of not only cephalosporolides C, G, and (4-OMe-) G via a challenging diastereoselective oxa-Michael addition but also the structurally unprecedented cephalosporolides E and F via a novel biomimetic ring-contraction rearrangement. These findings provide the first direct chemical evidence that Ces-B may be the true biosynthetic precursor of cephalosporolides.

Biomimetic synthesis inspired by a biosynthesis (or biosynthetic hypothesis) of natural products has been well recognized as a highly efficient synthetic tactic for chemical synthesis of complex molecules (e.g., natural products).[1] It provides not only chemical evidence for its biogenesis origin but also a new venue for synthesis of other structure-related naturally occurring products. However, it is still a formidable synthetic task to mimic an enzyme-mediated transformation that involves a cascade reaction process or rearrangement of structural skeletons. Another challenge for biomimetic synthesis is to imitate the strategy used in nature for construction of natural product collections from a common intermediate or interconversions of natural products within a family.[2] This natural synthetic strategy received less attention from synthetic communities due to the structural diversity and scarcity of the parent natural products. In this context, we herein report a strategy that led to asymmetric biomimetic total syntheses of five natural products from a parent natural product within the family, which successfully mimicked two biosynthesis-inspired processes: (i) a novel ring-contraction rearrangement of 10-membered lactones (cephalosporolides B, C, and G) to 5,5-spiroketal-*cis*-fused-γ-lactone (cephalosporolides E and F) and (ii) a diastereoselective intermolecular oxa-Michael addition (Scheme 1).

Cephalosporolides B–G (Figure 1) were isolated by Hanson[3] and co-workers from the industrial fermentation of the fungus *Cephalosporium aphidicola*, ACC 3490.

(1) For selected reviews on biomimetic synthesis of natural products, see: (a) Poupon, E.; Nay, B. *Biomimetic Organic Synthesis*; Wiley-VCH: Weinheim, 2011. (b) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254. (c) de la Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 160.

(2) For selected examples, see: (a) Flyer, A. N.; Si, C.; Myers, A. G. *Nat. Chem.* **2010**, *2*, 886. (b) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (c) Wang, J.; Chen, S.-G.; Sun, B.-F.; Lin, G.-Q.; Shang, Y.-J. *Chem.—Eur. J.* **2013**, *19*, 2539. (d) Li, H.; Wang, X.; Hong, B.; Lei, X. *J. Org. Chem.* **2013**, *78*, 800.

10.1021/ol402913m
Published on Web 11/06/2013

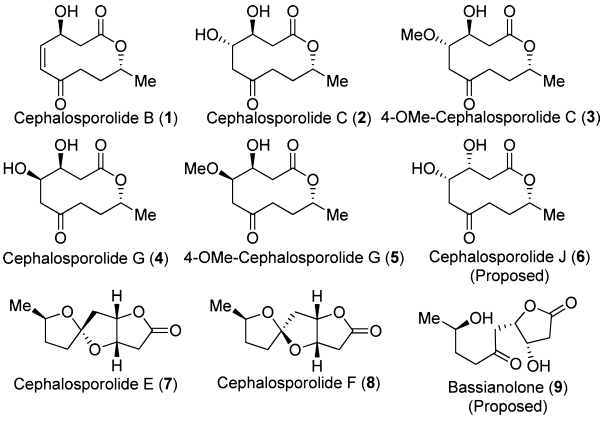
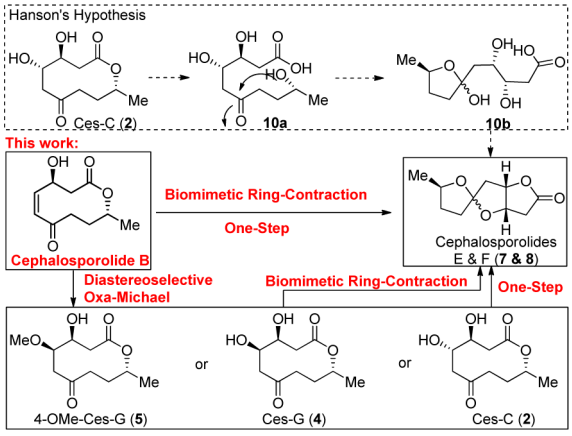


Figure 1. Representative cephalosporolides.

The molecular structures of cephalosporolides were elucidated by extensive NMR studies, and the relative configuration of Ces-C (**2**) and Ces-E (**7**) was unambiguously determined by single-crystal X-ray diffraction. Interestingly, some of these cephalosporolides were also isolated recently from other natural sources such as *Cordyceps militaris* BCC 2816,[4] *Beauveria bassiana*,[5] and/or wood decay fungus *Armillaria tabescens* (strain JNB-OZ344).[6] Structurally, these cephalosporolides (**1**–**6**) are 10-membered lactones (namely decanolides) with a methyl group at C9, resembling to other bioactive decanolides.[7] However, the structural skeleton of cephalosporolides E and F (Ces-E, **7**, and Ces-F, **8**) characterized by the presence of 5,5-spiroketal-*cis*-fused-γ-lactone was unprecedented at the time of their isolation but found in other recently isolated natural products such as cephalosporolides H and I, penisporolides, and ascospiroketals.[8]

Although the biological activity profiles of cephalosporolides have not been fully demonstrated, they have received considerable synthetic attention[9,10] partly because of the novel structural skeleton of Ces-E and Ces-F and/or

Scheme 1. Synthetic Plans and Hanson's Biosynthetic Hypothesis of Cephalosporolides E and F



the synthetically challenging 10-membered lactone. However, it has not been reported that a unified synthetic strategy would lead to total syntheses of both 10-membered cephalosporolides and the unique 5,5-spiroketal-*cis*-fused-γ-lactones Ces-E and Ces-F. The combination of the wide occurrence in nature and potential biological activity coupled with the structural novelty and complexity of Ces-E and Ces-F prompted us to develop a biomimetic divergent synthetic strategy for the cephalosporolide family, especially the potential transformations of the 10-membered lactones to 5,5-spiroketal-*cis*-fused-γ-lactones.

Our synthetic strategy (Scheme 1) was primarily inspired by Hanson's biogenetic hypothesis[3] of Ces-E and Ces-F, which might arise from dehydrative ring contraction of Ces-C via hydrolysis, lactonization, and acetalization.[11] However, their attempts to the chemical conversion of Ces-C into Ces-E and Ces-F in the laboratory were unsuccessful. Intrigued by the employment of Ces-B for hypothetic biosynthesis of tenuipyrone[12] and pyridomacrolidin,[13] we envisioned that Ces-B could also be the biosynthetic precursor of cephalosporolides via a diastereoselective intermolecular oxa-Michael addition[14] and/or Hanson's ring-contraction rearrangement (Ces-E and Ces-F, Scheme 1). In addition, Ces-C and Ces-G, if available from Ces-B, could be explored to verify Hanson's biosynthetic hypothesis under the conditions optimized for ring contraction rearrangement of Ces-B.

(3) (a) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 843. (b) Farooq, A.; Gordon, J.; Hanson, J. R.; Takahashi, J. A. *Phytochemistry* **1995**, *38*, 557.

(4) Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953.

(5) Oller-López, J. L.; Iranzo, M.; Mormeneo, S.; Oliver, E.; Cuerva, J. M.; Oltra, J. E. *Org. Biomol. Chem.* **2005**, *3*, 1172.

(6) Herath, H. M. T. B.; Jacob, M.; Wilson, A. D.; Abbas, H. K.; Nanayakkara, N. P. D. *Nat. Prod. Res.* **2012**, 1.

(7) For reviews, see: (a) Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365. (b) Ferraz, H. M. C.; Bombonato, F. I.; Longo, L. S., Jr. *Synthesis* **2007**, 3261. (c) Riatto, V. B.; Pilli, R. A.; Victor, M. M. *Tetrahedron* **2008**, *64*, 2279. For selected syntheses of other decanolides, see: (d) Vadhadiya, P. M.; Puranik, V. G.; Ramana, C. V. *J. Org. Chem.* **2012**, *77*, 2169. (e) Ramana, C. V.; Khaladkar, T. P.; Chatterjee, S.; Gurjar, M. K. *J. Org. Chem.* **2008**, *73*, 3817. (f) Kobayashi, Y.; Asano, M.; Yoshida, S.; Takeuchi, A. *Org. Lett.* **2005**, *7*, 1533.

(8) (a) Li, X.; Yao, Y.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharm. Res.* **2007**, *30*, 812. (b) Li, X.; Sattler, I.; Lin, W. *J. Antibiot.* **2007**, *60*, 191. (c) Seibert, S. F.; Krick, A.; Eguereva, E.; Kehraus, S.; König, G. M. *Org. Lett.* **2007**, *9*, 239.

(9) (a) Krishna, P. R.; Sreeshailam, A. *Synlett* **2008**, 2795. (b) Barradas, S.; Urbano, A.; Carreño, M. C. *Chem.—Eur. J.* **2009**, *15*, 9286. (c) Ma, B.; Zhong, Z.; Hu, H.; Li, H.; Zhao, C.; Xie, X.; She, X. *Chem.—Asian J.* **2013**, *8*, 1391.

(10) (a) Fernandes, R. A.; Ingle, A. B. *Synlett* **2010**, 158. (b) Brimble, M. A.; Finch, O. C.; Heapy, A. M.; Fraser, J. D.; Furkert, D. P.; O'Connor, P. D. *Tetrahedron* **2011**, *67*, 995. (c) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842. (d) Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2012**, *8*, 1287. (e) Chang, S.; Britton, R. *Org. Lett.* **2012**, *14*, 5844.

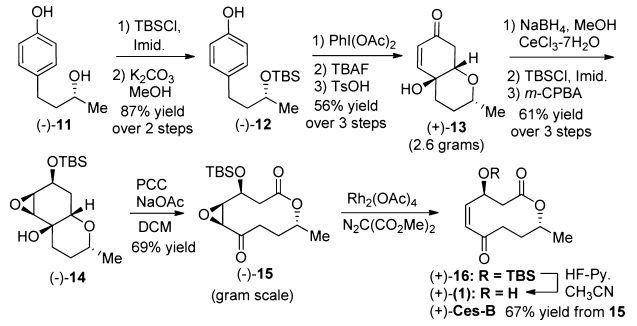
(11) Oltra observed the facile conversion of coisolated bassianolone to Ces-E and Ces-F via acetalization and proposed that bassianolone might be the true biosynthetic precursor. See refs 5 and 25.

(12) (a) Asai, T.; Chung, Y.-M.; Sakurai, H.; Ozeki, T.; Chang, F.-R.; Yamashita, K.; Oshima, Y. *Org. Lett.* **2012**, *14*, 513. (b) Song, L.; Yao, H.; Zhu, L.; Tong, R. *Org. Lett.* **2013**, *15*, 6.

(13) Baldwin, J. E.; Adlington, R. M.; Conte, A.; Irlapati, N. R.; Marquez, R.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 2125.

(14) For recent reviews, see: (a) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218. (b) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988.

Scheme 2. Total Synthesis of Cephalosporolide B (**1**)[a]

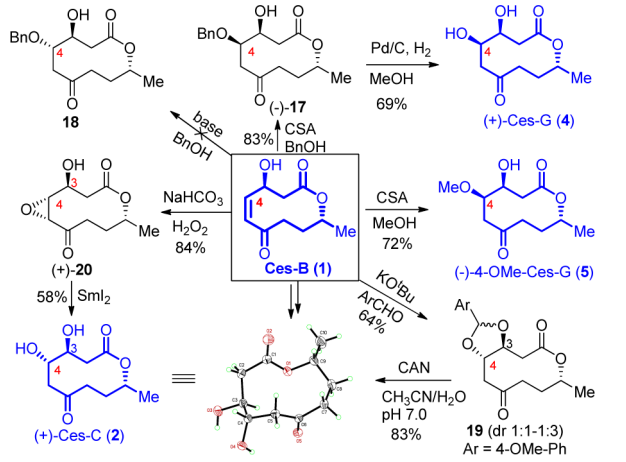


[a] Abbreviations: TBSCl, chloro-*tert*-butyldimethylsilane; TBAF, tetrabutylammonium floride; DEAD, diethyl azodicarboxylate; *m*-CPBA, *meta*-chloroperoxybenzoic acid; PCC, pyridinium chlorochromate.

To achieve a practical total synthesis of the key Ces-B with sufficient quantity for subsequent biomimetic synthetic studies, we chose oxidative ring expansion of β-hydroxyethers developed by Ferraz[15] as the key step to construct the 10-membered lactone (Scheme 2). The enantiomerically pure rhododendrol (**11**)[16] was chemoselectively protected as *tert*-butyldimethylsilyl ether **12**. Phenol dearomatization[17] of **12** with $PhI(OAc)_2$, desilylation, and subsequent TsOH-promoted oxa-Michael cyclization provided bicyclic ether **13** as a single diastereomer.[18] Luche reduction of **13**, chemoselective silylation of the secondary alcohol, and hydroxyl-directed epoxidation with *m*-CPBA provided epoxide **14**, which upon treatment of PCC underwent oxidative ring expansion to give the 10-membered lactone **15**.[9b] Rh-catalyzed deoxygenation[19] of epoxide **15** with dimethyl diazomalonate unmasked the *cis*-alkene to furnish the (+)-Ces-B (**1**)[20] after desilylation with HF-pyridine complex. Noteworthy was the employment of epoxide as an unusual protecting group of *cis*-alkene to avoid oxidative rearrangement of tertiary alcohol in the PCC oxidation. All spectroscopic data of our synthetic Ces-B were in good agreement with those reported in the literature.[3a,9c]

With Ces-B (**1**, ~200 mg) in hand, we set out to exploit it as a biomimetic synthetic precursor for Ces-C, Ces-G, and 4-OMe-Ces-G via diastereoselective intermolecular oxa-Michael addition (Scheme 3). Although it is well recognized that intermolecular oxa-Michael addition has suffered from many drawbacks such as low reactivity, low

Scheme 3. Total Syntheses of Cephalosporolides C and G and 4-OMe-cephalosporolide G from Cephalosporolide B



stereoselectivity, and reversibility issues,[14] we were delighted to know that She[9c] and Xie documented a successful oxa-Michael addition of MeOH to **16**, providing (+)-4-OMe-Ces-G (**5**). Analogously, we found that camphorsulfonic acid (CSA) or Amberlyst-15 (A-15) effectively promoted the *syn*-Michael addition of MeOH to Ces-B, affording (+)-4-OMe-Ces-G (**5**) in 72% yield as a single diastereomer. Encouraged by this result, we employed benzyl alcohol for the similar *syn*-oxa-Michael addition to Ces-B. Not surprisingly, after Pd-catalyzed hydrogenative debenzylation of 4-OBn-Ces-G (**17**), (+)-Ces-G (**4**)[9b] could be obtained in 57.3% yield over two steps.[20] Note: although enzyme-catalyzed Michael addition of water to conjugated carbonyl compounds is well-known,[21] the corresponding nonenzymatic process remains very limited.[22] These exciting findings drove us to explore the possibility of an *anti*-oxa-Michael addition of benzyl alcohol to Ces-B, which after debenzylation would be expected to give Ces-C (**2**), a biosynthetic precursor of Ces-E and Ces-F in Hanson's hypothesis. Unfortunately, in contrast to She's observation,[9c] we were not able to achieve such *anti*-oxa-Michael addition under various basic conditions, which only led to decomposition of Ces-B. Inspired by Evans' example of cascade acetalization/oxa-Michael cyclization,[23] we found that the similar cascade reaction of aromatic aldehyde and Ces-B could proceed smoothly to provide a diastereomeric mixture of bicyclic acetal **19** in good yield. Removal of the aryl acetal by CAN oxidation in a buffered solution produced the expected (+)-Ces-C (**2**) in excellent yield as a single

(15) (a) Ferraz, H. M. C.; Longo, L. S., Jr. *Org. Lett.* **2003**, *5*, 1337. (b) Ferraz, H. M. C.; Longo, L. S., Jr. *J. Org. Chem.* **2007**, *72*, 2945.

(16) Yuasa, Y.; Shibuya, S.; Yuasa, Y. *Synth. Commun.* **2003**, *33*, 1469.

(17) (a) For a representative review, see: Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. For selected recent examples, see: (b) Zhao, K.; Cheng, G.-J.; Yang, H.; Shang, H.; Zhang, X.; Wu, Y.-D.; Tang, Y. *Org. Lett.* **2012**, *14*, 4878. (c) Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. *Org. Lett.* **2012**, *14*, 4537.

(18) Note: **13** could be synthesized from **11** in two steps with comparable overall yield on small scale via oxone-mediated dearomatization and TsOH-promoted oxa-Michael cyclization (ref 9b); however, dearomatization on large scale (>18 mmol) was problematic. See ref 17b,17c.

(19) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 251.

(20) See the Supporting Information.

(21) (a) Jin, J.; Oskam, P. C.; Karmee, S. K.; Straathof, A. J. J.; Hanefeld, U. *Chem. Commun.* **2010**, *46*, 8588. (b) Gawron, O.; Fondy, T. P. *J. Am. Chem. Soc.* **1959**, *81*, 6333. (c) Willadsen, P.; Eggerer, H. *Eur. J. Biochem.* **1975**, *54*, 247. (d) Agnihotri, G.; Liu, H. *Bioorg. Med. Chem.* **2003**, *11*, 9. (e) Mohrig, J. R.; Moerke, K. A.; Cloutier, D. L.; Lane, B. D.; Person, E. C.; Onasch, T. B. *Science* **1995**, *269*, 527.

(22) Boersma, A. J.; Coquière, D.; Geerdink, D.; Rosati, F.; Feringa, B. L.; Roelfes, G. *Nat. Chem* **2010**, *2*, 991.

(23) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

Table 1. Ring-Contraction Rearrangement of Cephalosporolide B to Cephalosporolides E and F[a]

entry	acid (equiv)	solvents (ratio)	time (h)	yield (%, **7**/**8**)
1	HCl[b]	THF	1	<10
2	TsOH (5)	THF/H_2O (9/1)	12	NR
3	A-15 (10)	THF/H_2O (9/1)	12	NR
4	TFA/THF/H_2O (1/1/1)		12	40 (3:1)[c]
5	**TFA/THF/H_2O (3/1/1)**		**8**	**79 (3:1)**
6	TFA/THF/H_2O (9/1/1)		2	complex
7	TFA/CH_2Cl_2/H_2O (3/1/1)		2	complex

[a] Reaction with Ces-B (20 mg, 0.1 mmol) was run at 0.05 M at rt; isolated yield. [b] One drop (~5 mg) of concd HCl was added to 2.0 mL of THF solution at 0 °C. [c] Recovery of 42% yield of Ces-B. NR: no reaction.

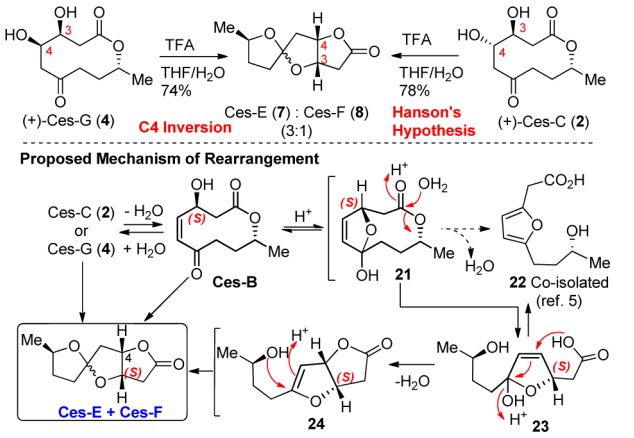
diastereomer. This constitutes the first, asymmetric total synthesis of Ces-C. Alternatively, Ces-C could be synthesized from epoxidation of Ces-B followed by SmI_2-mediated reductive epoxide ring-opening[24] of **20**. Our synthetic (+)-Ces-C was fully confirmed by extensive NMR studies and single-crystal X-ray diffraction. However, we noticed that the NMR data of our synthetic Ces-C were not in well agreement with those reported by Hanson, but with X-ray diffraction analysis of natural and synthetic samples we believed the NMR data for Ces-C might be erroneously reported.[25]

Finally, we set out to verify our key hypothesis that Ces-B could be the direct synthetic precursor of Ces-E and -F (Scheme 1). Because of decomposition under basic conditions, we focused on the ring-contraction rearrangement of Ces-B under acidic conditions (Table 1). To our delight, we observed for the first time that Ces-E and Ces-F could be generated from Ces-B upon addition of one drop of concentrated HCl to the THF solution of Ces-B (entry 1). Further optimization (entries 2−7) led us to identify the trifluoroacetic acid (TFA) as the best acid for the ring-contraction rearrangement of Ces-B (**1**), affording a 3:1 mixture of Ces-E and Ces-F in 79% combined yield (entry 5), favoring the thermodynamically more stable Ces-E. This is the first example that demonstrated a ring-contraction rearrangement of a ten-membered lactone to 5,5-spiroketal-*cis*-fused-γ-lactone, a cascade process mimicking Hanson's hypothesis. This exciting discovery prompted us to further examine Hanson's hypothesis: dehydrative ring contraction of Ces-C into Ces-E and Ces-F (Scheme 4). In sharp contrast to Hanson's results, we found that under our optimized condition Ces-C underwent efficient dehydrative ring contraction to provide a 3:1 mixture of Ces-E and Ces-F in excellent yield. Most strikingly, Ces-G, a diastereomer of Ces-C, was able to rearrange to afford a mixture of Ces-E and Ces-F in comparable yield with the same diastereomeric ratio. The inversion mechanism of C4 stereogenic center of Ces-G

(24) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.

(25) This phenomenon is rare in the literature. Surprisingly, we observed that our NMR spectra for Ces-C were identical to those of Ces-J and bassianolone, and we suspected that Ces-C was the correct structure for Ces-J and bassianolone. For more details, see the Supporting Information.

Scheme 4. Realization of Hanson's Hypothesis and Proposed Mechanism of Dehydrative Ring-Contraction Rearrangement to Cephalosporolides E and F



remains unknown, however, the inconsequence of stereogenic center at C4 in the course of rearrangement (Ces-C and Ces-G) might suggest that Ces-B might be the true biosynthetic precursor of Ces-E and Ces-F. Taking all these evidence together, we proposed that Ces-E and Ces-F might arise from Ces-B through hemiacetal formation (**21**), macrolactone opening to carboxylic acid **23**, γ-lactone formation (**24**) by S_N2' substitution and acid-promoted spiroketalization. This hypothesis also explained the coisolated furan **22**, which may be generated from dehydrative aromatization of **23**.

In conclusion, we have achieved a practical total synthesis of cephalosporolide B, which has been successfully exploited as a versatile synthetic precursor for biomimetic total syntheses of cephalosporolides C, E, F, G, and (4-OMe-)G via an oxa-Michael addition and/or a novel biomimetic ring-contraction rearrangement. These studies suggested that cephalosporolide B might be the true biogenetic precursor of other cephalosporolides, which may imply the biogenetic relationship of the cephalosporolide family and find applications in total syntheses of other bioactive natural products. In addition, the 28-year Hanson's biogenetic hypothesis of cephalosporolides E and F was synthetically verified for the first time in the laboratory.

Acknowledgment. This research was financially supported by startup funding (R9309) from HKUST and Research Grant Council of Hong Kong (ECS 605912 and DAG12CS03). We are also grateful to Prof. Dr. Ian Williams (HKUST) for the single-crystal X-Ray diffraction analysis.

Supporting Information Available. Detailed experimental procedures, characterization, and copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.