*molbank*

MDPI

*Short Note*

# (1*R*,5*S*)-6-(4-Methyl-2-oxo-2,5-dihydrofuran-3-yl)-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one

**Dong-Jun Fu [1,2], Victor Pham [2], Matthew-Alexander Tippin [2], Liankun Song [2], Xiaolin Zi [2], En Zhang [1] and Hong-Min Liu [1,*]**

1 School of Pharmaceutical Sciences & Collaborative Innovation Center of New Drug Research and Safety Evaluation, Zhengzhou University, Zhengzhou 450001, China; zzufdj@sina.com (D.-J.F.); zhangen@zzu.edu.cn (E.Z.)

2 Department of Urology, University of California, Irvine, Orange, CA 92868, USA; victorp1@uci.edu (V.P.); matthew.tippin@gmail.com (M.-A.T.); liankuns@uci.edu (L.S.); xzi@uci.edu (X.Z.)

* Correspondence: liuhm@zzu.edu.cn; Tel.: +86-371-67781739

Received: 11 August 2018; Accepted: 28 August 2018; Published: 30 August 2018


**Abstract:** Efficient large-scale and feasible industrial synthesis of the 1-oxacephem core structure from 6-aminopenicillanic acid (6-APA) has been reported for several decades. Via the industrial synthesis route, a byproduct (compound **9**) containing a butenolide unit was purified and characterized by NMR and HRMS in this work. It is worth noting that compound **9** is an entirely new compound. Additionally, a plausible mechanism and effects on the formation of **9** by different Lewis acids were proposed. The discovery of compound **9** could improve the purity of this feasible industrial synthesis and provide considerable cost savings.

**Keywords:** industrial feasible synthesis; 6-APA; butenolide; 1-oxacephem

## 1. Introduction

Antibacterial substances are of great importance and necessity in treating infectious diseases caused by pathogenic bacteria [1–3]. Due to its unique antimicrobial activity and novel structure among the synthetic antibiotics, the 1-oxacephem core structure as an important pharmaceutical scaffold has attracted immense interest from medicinal chemists [4–6]. A variety of synthetic compounds prepared from the 1-oxacephem intermediate, including prominent antibiotics such as Flomoxef, Moxalactam, and OCP-9-176 (Figure 1), have a broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria [7–9].

A feasible industrial route by which to synthesize 1-oxacephem **8** in good yield starting from commercially available 6-aminopenicillanic acid (6-APA) (Figure 2) was reported by Nagata of the Shionogi company [10,11]. In this sophisticated method designed to retain all the carbon atoms, preparing epioxazolinoazetidinones having an unconjugated ester moiety at the β-lactam nitrogen was a breakthrough. However, byproducts of and probable mechanisms in this industrial synthesis of 1-oxacephem **8** have not been systematically explored. In this work, we focused on the byproduct **9** ((1*R*,5*S*)-6-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one).

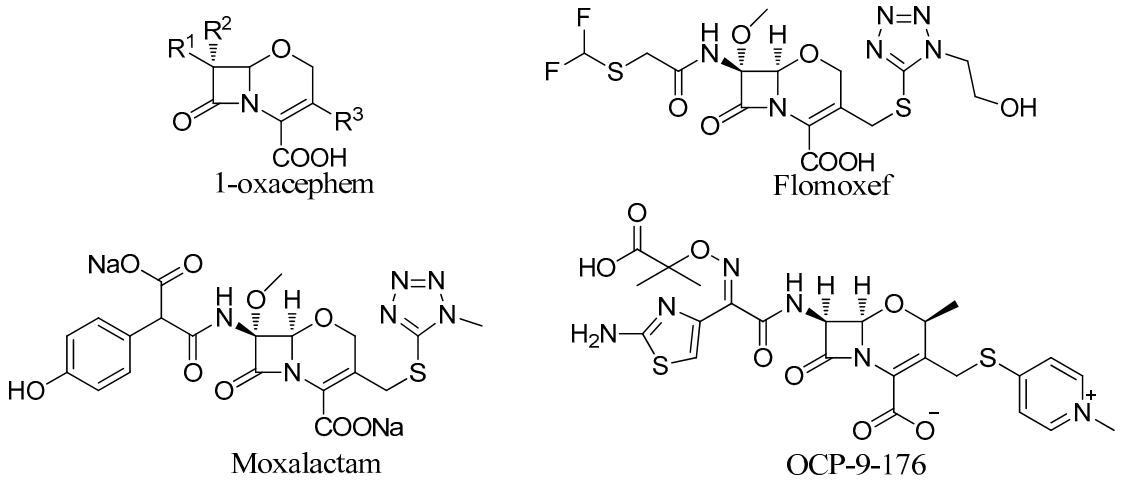



**Figure 1.** Synthetic 1-oxacephem antibiotics.

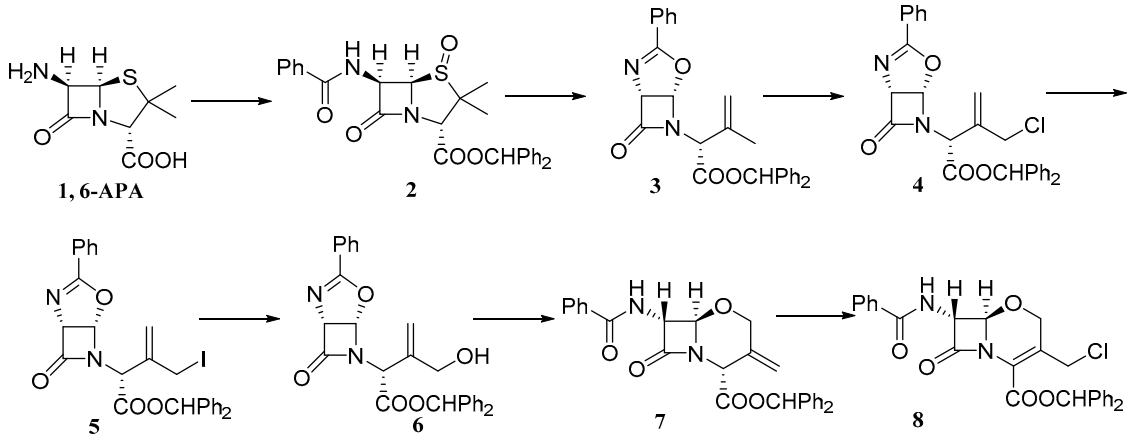


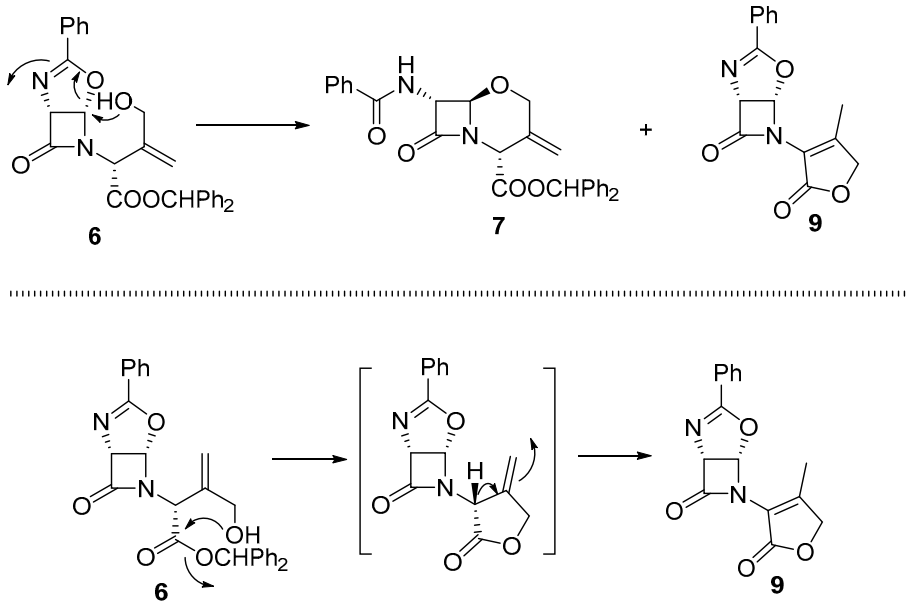

**Figure 2.** Feasible industrial synthesis of 1-oxacephem **8**.

## 2. Results and Discussion

Intramolecular etherification proceeded from the less-hindered $\beta$ side with stereoselectivity to furnish a versatile exomethylene intermediate **7** in 79% yield and accompanied by a byproduct **9** in 15% yield. The probable mechanism which afforded the butenolide **9** catalyzed by boron fluoride ethyl ether involved two reactions: (a) an intramolecular transesterification and (b) isomerization of the double bond promoted by a Lewis acid (Scheme 1).

Systematic studies of the reaction conditions to obtain byproduct **9** in highest yield revealed that Lewis acids played key roles (Table 1). When the reaction was catalyzed by $BF_3{\cdot}Et_2O$ and $Yb(OTf)_3$, the major product was compound **7** (Table 1, entries 1 and 6) with yields of 90% and 56%, respectively. Our best result was achieved with $BF_3{\cdot}Et_2O$ at 25 °C, conditions in which **7** was formed in 90% yield, along with only a small amount of readily separable **9** (Table 1, entry 1). When the Lewis acid was changed to LiCl or $ZnCl_2$, byproduct **9** was obtained as a dominant product (Table 1, entries 2, 3, 4).

To our surprise, when EtOH was used as the solvent instead of EtOAc (Table 1, entry 3), the yield of byproduct **9** increased to 92%. These results suggested that ethyl alcohol and Lewis acid LiCl were suitable for this transformation to generate the byproduct **9** in an excellent yield.




**Scheme 1.** The probable mechanism of formation of **9** catalyzed by a Lewis acid ($BF_3 \cdot Et_2O$).

**Table 1.** Screening of the reaction conditions.

| Entry | Lewis Acid [a] | Temperature | Solvent | Yields of 7 [b] | Yields of 9 [b] |
|---|---|---|---|---|---|
| 1 | $BF_3 \cdot Et_2O$ | 25 °C | EtOAc | 90% | 1% |
| 2 | LiCl | 25 °C | EtOAc | 33% | 60% |
| 3 | LiCl | 25 °C | EtOH | 1% | 92% |
| 4 | $ZnCl_2$ | 25 °C | EtOAc | 29% | 65% |
| 5 | $FeCl_3$ | 25 °C | EtOAc | 46% | 42% |
| 6 | $Yb(OTf)_3$ | 25 °C | EtOAc | 56% | 36% |

[a] 1 mol % Lewis acid was used. [b] Isolated yields.

## 3. Materials and Methods

### *3.1. General Information*

All the reactions were monitored by thin-layer chromatography. The byproducts were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 200–300 mesh, Qingdao, China). Melting points were determined on a Beijing Keyi XT4A apparatus (Beijing synthware glass, Beijing, China). All NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer (Agilent, Santa Clara, CA, USA) with TMS as the internal standard. Chemical shifts are given as δ ppm values relative to TMS. Mass spectra (MS) were recorded on an Esquire 3000 mass spectrometer (Varian, Palo Alto, CA, USA) by electrospray ionization (ESI).

### *3.2. Synthesis of (1R,5S)-6-(4-Methyl-2-oxo-2,5-dihydrofuran-3-yl)-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0] hept-2-en-7-one (9)*

A solution of LiCl (1 mol %) was added to intermediate **6** (1 eq, 1 g) in EtOH (10 mL) in a round-bottom flask and reacted at room temperature for 7 h. The reaction system was evaporated to give a residue, which was purified by silica gel flash column chromatography (EtOAc/*n*-hexane = 1:7) to afford the product **9**, yield 92%. White solid; m.p. 199.2–200.3 °C; $[\alpha]_D^{25}$ + 18.9° (C 1.05, $CHCl_3$); $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.81 (d, *J* = 3.3 Hz, 1H), 5.45 (d, *J* = 3.3 Hz, 1H), 4.73 (s, 2H), 2.18 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ

168.64, 167.16, 163.73, 148.48, 132.40, 128.59, 128.50, 126.73, 119.77, 84.70, 82.26, 71.77, 13.17; HRMS (ESI): $m/z$ calcd for $C_{15}H_{12}N_2O_4$ $(M + H)^+$, 285.0875; found, 285.0880.

## 4. Conclusions

In summary, byproduct **9** was obtained in the industrial synthesis of the 1-oxacephem core structure from 6-aminopenicillanic acid. To the best of our knowledge, this is the first report about the byproduct **9**. We explored the effects on the formation of azetidinone-fused butenolide **9** caused by different Lewis acids and explored its probable mechanism of formation. The study of byproduct **9** is valuable for efficient large-scale and feasible industrial synthesis of the 1-oxacephem core structure.

**Supplementary Materials:** Supplementary materials are available online.

**Author Contributions:** D.-J.F. and E.Z. designed and synthesized the compounds. V.P., M.-A.T., L.S. and X.Z. revised the manuscript. D.-J.F. wrote the manuscript and H.-M.L. was responsible for the correspondence of the manuscript. All authors read and approved the final manuscript.

**Funding:** Thanks for the funding of Zhengzhou University.

**Acknowledgments:** This work was supported by MEDCHEMEXPRESS. Our thanks to the MCE Award for Scientists Promoting Biology and Medicine Research, and to the CSC scholarship.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Zhao, Z.H.; Zhang, X.X.; Jin, L.L.; Yang, S.; Lei, P.S. Synthesis and antibacterial activity of novel ketolides with 11,12-quinoylalkyl side chains. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2358–2363. [CrossRef] [PubMed]
2. Zhang, L.; Wang, L.; Yi, L.; Wang, X.; Zhang, Y.; Liu, J.; Guo, X.; Liu, L.; Shao, C.; Xin, L. A novel antimicrobial substance produced by Lactobacillus rhamnous LS8. *Food Control* **2016**, *73*, 754–760. [CrossRef]
3. Journal, E.; Pathology, P. Biological control of grapevine crown gall: Purification and partial characterisation of an antibacterial substance. *Eur. J. Plant. Pathol.* **2013**, *124*, 427–437.
4. Hakimelahi, G.H.; Li, P.C.; Moosavimovahedi, A.A.; Chamani, J.; Khodarahmi, G.A.; Ly, T.W.; Valiyev, F.; Leong, M.K.; Hakimelahi, S.; Shia, K.S. Application of the Barton photochemical reaction in the synthesis of 1-dethia-3-aza-1-carba-2-oxacephem: A novel agent against resistant pathogenic microorganisms. *Org. Biomol. Chem.* **2003**, *1*, 2461–2467. [CrossRef] [PubMed]
5. Kobayashi, Y.; Doi, M.; Nagata, H.; Kubota, T.; Kume, M.; Murakami, K. The 7α-methoxy substituent in cephem or oxacephem antibiotics enhances in vivo anti-Helicobacter felis activity in mice after oral administration. *J. Antimicrob. Chemother.* **2000**, *45*, 807–811. [CrossRef] [PubMed]
6. Tombor, Z.; Greff, Z.; Nyitrai, J.; Kajtár-Peredy, M. Simple and condensed β-lactams, XIX. Synthesis of some new 7-acylamino-2-iso-oxacephem-4-carboxylic acids. *Eur. J. Org. Chem.* **2010**, *1995*, 825–835. [CrossRef]
7. Lee, C.H.; Chen, I.L.; Li, C.C.; Chien, C.C. Clinical benefit of ertapenem compared to flomoxef for the treatment of cefotaxime-resistant Enterobacteriaceae bacteremia. *Infect. Drug Resist.* **2018**, *11*, 257–266. [CrossRef] [PubMed]
8. Singh, B.R. Moxalactam is not more active on extended spectrum β-lactamase (ESBL) producing bacteria than on non-ESBL producers. *Infect. Drug Resist.* **2018**, *11*, 427–429. [CrossRef] [PubMed]
9. Shibahara, S.; Okonogi, T.; Murai, Y.; Kudo, T.; Yoshida, T.; Kondo, S.; Christensen, B.G. Synthesis of a novel 2-beta-methyl-1-oxacephalosporin, OCP-9-176. *J. Antibiot.* **1988**, *41*, 1154–1157. [CrossRef] [PubMed]
10. Otsuka, H.; Nagata, W.; Yoshioka, M.; Narisada, M.; Yoshida, T.; Harada, Y.; Yamada, H. Discovery and development of Moxalactam (6059-S): The chemistry and biology of 1-oxacephems. *Med. Res. Rev.* **1981**, *1*, 217–248. [CrossRef] [PubMed]
11. Yoshioka, M.; Tsuji, T.; Uyeo, S.; Yamamoto, S.; Aoki, T.; Nishitani, Y.; Mori, S.; Satoh, H.; Hamada, Y.; Ishitobi, H.; et al. Stereocontrolled, straightforward synthesis of 3-substituted methyl 7α-methoxy-1-oxacephems. *Tetrahedron Lett.* **1980**, *21*, 351–354. [CrossRef]