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Total Synthesis and Structural Reassignment of (±)-Cereoanhydride

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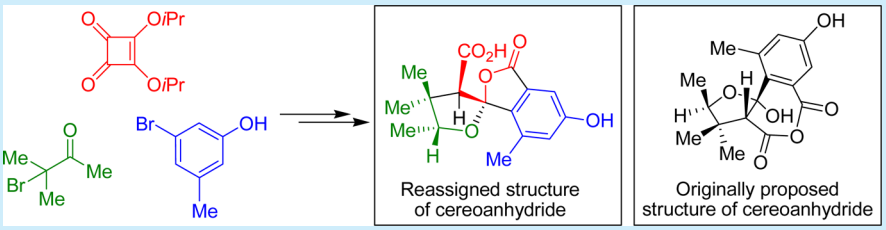
Supporting Information



ABSTRACT: The first total synthesis of (±)-cereoanhydride has been achieved under the inspiration of its biosynthetic hypothesis. The tricyclic skeleton of trypethelone, the proposed biosynthetic precursor of cereoanhydride, was constructed by an interesting ring expansion of cyclobutenone in one step in which the introduced acetyl group is pivotal to avoid the following aerial oxidation. On the basis of X-ray crystallographic analysis, the structure of cereoanhydride is reassigned to a spiroketal structure **2**, which should be formed through an isomerization of the originally proposed structure **1**.

Marine algae derived fungi afford a specific but important source for the discovery of secondary metabolites with promising bioactivities and unusual molecular structures.[1] On the basis of extensive studies on marine endophytic fungus *Coniothyrium cereale* isolated from green algae *Enteromorpha* sp. in the Baltic sea, König and co-workers reported the isolation of a new secondary metabolite, cereoanhydride, in 2012.[2] Through NMR spectroscopic and mass spectrometric analysis, the structure of cereoanhydride was originally assigned as **1** (Figure 1). It features a very rare seven-membered cyclic

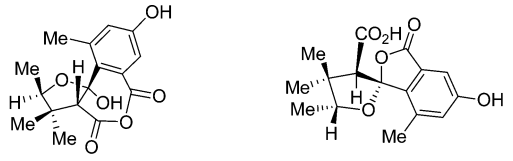


Figure 1. Structures of originally proposed and reassigned cereoanhydride.

anhydride, a polysubstituted aromatic ring, and a *trans*-fused trimethyltetrahydrofuran ring bearing three stereogenic centers, making it an attractive synthetic target. Additionally, cereoanhydride displayed weak inhibition (IC_{50} = 16 μg mL^{-1}) to serine protease human leukocyte elastase in preliminary biological studies. Due to the limited amount of this compound from the natural source, development of synthetic pathways to cereoanhydride will build up an important foundation for further biological evaluations of this secondary metabolite. Herein, we report the first total synthesis and the structural reassignment (**2**) of cereoanhydride.

König and co-workers postulated that cereoanhydride might be formed from the oxidation of trypethelone (**4**), which was isolated from cultivation of the same fungus in their earlier work.[3] It was also demonstrated that this homologous natural product **4** possesses cytotoxicity against mouse fibroblast cells and inhibitory activities toward *Mycobacterium phlei*, *Staphylococcus aureus*, and *Escherichia coli*. Inspired by the biosynthetic hypothesis, our synthetic plan to the originally proposed cereoanhydride (**1**) is illustrated in Scheme 1. Because that *trans* relationship between C1 and C15 and *trans* fusion on C1−C14 of **1** should cause less steric hindrance compared with its epimers, we envisioned that the expected stereochemistry at C1 and C14 could be established via a diastereoselective hydration of the enol ether motif on C1−C14 of **3** under thermodynamic conditions. Cyclic anhydride **3** could be obtained through a Baeyer−Villiger oxidation of **4**, which could potentially be generated from **5** through deprotection and oxidation. For the synthesis of **5**, a ring-expansion process on **6**, via an interesting four-electron electrocyclic ring-opening/6π-electrocyclization cascade of cyclobutenones, was envisaged. Such chemistry was initially developed by Moore[4] and Liebeskind[5] for related arene ring construction. Commercially available **7**, **8** ,and **9** were considered suitable building blocks for synthesis of **6**.

Our synthesis commenced with the preparation of **12** (Scheme 2). In the presence of magnesium, **9** reacted with **8** smoothly,[6] affording **10** in 83% yield following rearrangement under acidic conditions. The efficient bromine−lithium exchange of *n*-butyllithium with **11**, which was obtained from the TBS protection of phenolic hydroxyl of **7**, ensured the

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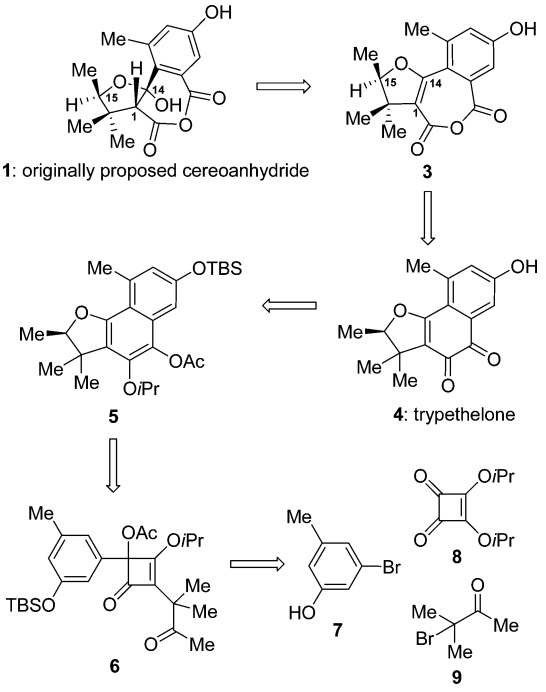
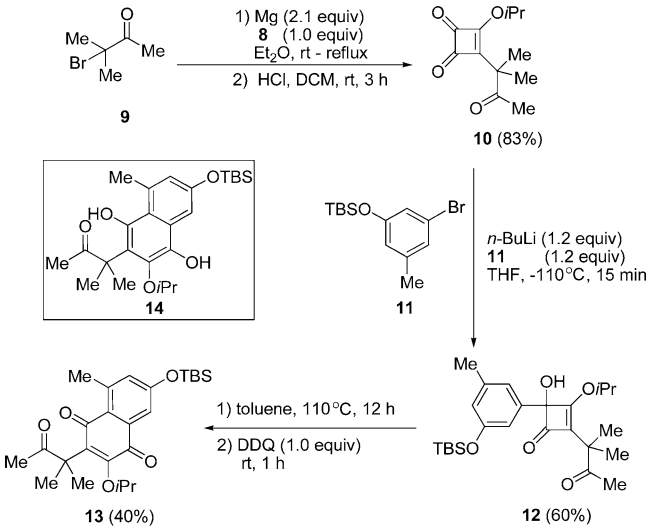
Scheme 1. Synthetic Plan to Proposed Cereoanhydride (1)



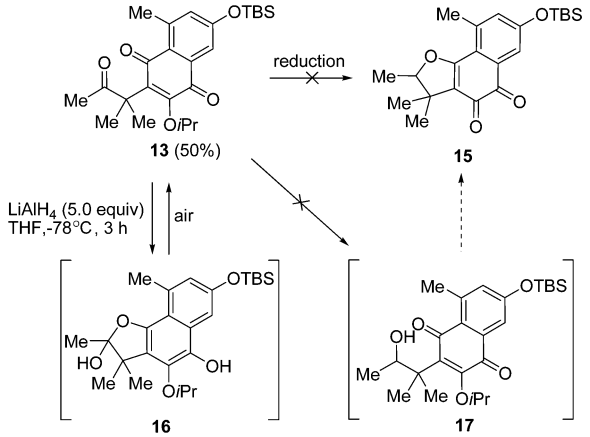
Scheme 2. Synthesis and Ring Expansion of 12



nucleophilic addition to one carbonyl of **10** and generated cyclobutenone **12** with high regioselectivity. The latter was the first substrate submitted to the ring-expansion process under thermal conditions. However, **13** was obtained consistently as the major product in poor yields (less than 15%). There was no formation of expected product **14** observed. It was thought that the 1,4-diphenol motif in intermediate **14** could be readily oxidized by air. The application of DDQ at the later stage of the reaction increased the yield of **13** to 40%.[7]

With **13** in hand, we anticipated that the carbonyl on the side chain of **13** could be selectively reduced. The product **17** might transform into **15** through an intramolecular 1,3-alkoxyl exchange (Scheme 3). However, the formation of **15** or **17** was not observed under reductive conditions, such as $NaBH_4$ and $LiAlH_4$. After reaction workup and column chromatography, the major component obtained was the starting material

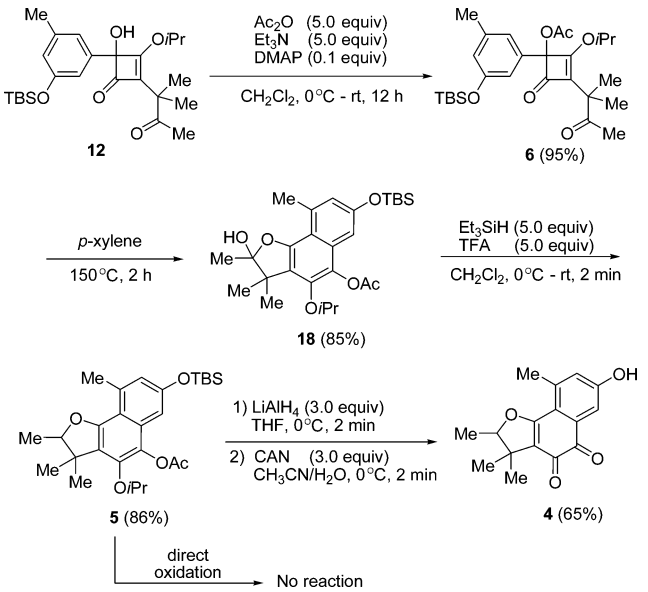
Scheme 3. Reduction of 13



13. We postulated that the reduction of **13** only happened on the more electron-poor 1,4-benzoquinone motif. Rather than be reduced, the side-chain carbonyl of **13** was attacked by one phenolic hydroxyl generated from the reduction, affording intermediate **16**. The formed hemiketal motif in **16** completely inhibited further reduction. Moreover, **16** could be easily oxidized by air, which led to the formation of **13** at the end of the operation. Besides, there is a high possibility that intermediate **14** generated from the ring-expansion of **12** would exist in its hemiketal form **16**.

At this point, our synthetic route was adjusted as depicted in Scheme 4. With the purpose of inhibiting the facile aerial

Scheme 4. Synthesis of 4



oxidation, an acetyl protecting group was introduced on the hydroxyl of **12**, affording **6**. To our delight, the ring expansion of **6** was not followed by oxidation, compound **18** being obtained in 85% yield. The introduction of the acetyl group not only successfully inhibited the oxidation of the 1,4-diphenol motif but also significantly increased the yield of the ring-expansion product. The reduction of the hemiketal motif of **18** was achieved using Et_3SiH and TFA and gave **5** in 86% yield.[8] For the synthesis of **4**, we envisioned removing the protecting groups from the middle ring of **5** and following this by an

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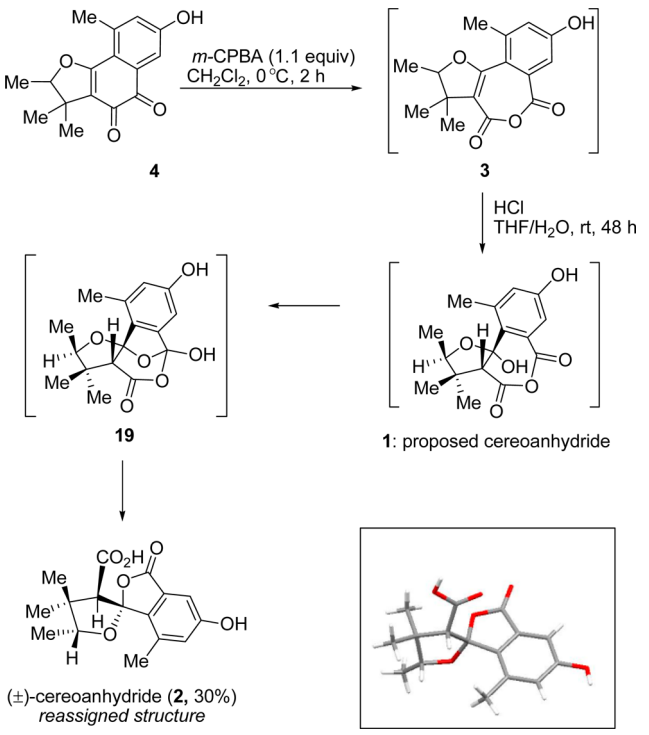
oxidative treatment. However, no reaction occurred with **5** using $KMnO_4$, CAN (ceric ammonium nitrate), and PhI(OAc)$_2$. Obviously, it is difficult to remove the acetyl group of **5** under oxidative conditions. Thus, we turned our attention to reductive conditions. To our disappointment, the reduction of **5** with $LiAlH_4$ gave a complex mixture, and no reasonable product was obtained after column chromatography. Luckily, treating the crude reduction products with 3 equiv of CAN led to the formation of **4** in 65% yield over two steps.[9]

The synthesis of cereoanhydride is demonstrated in Scheme 5. Baeyer–Villiger oxidation of **4** took place smoothly with *m*-CPBA.[10] Due to its poor stability, intermediate **3** was treated directly with HCl in a mixture of THF and H_2O. To our surprise, cereoanhydride was obtained as the major product with good diastereoselectivity. The spectroscopic data (HRMS analysis, ^{1}H and ^{13}C NMR spectra) of the synthesized sample are identical to those reported for natural cereoanhydride. We next secured a crystal of synthesized cereoanhydride and submitted it to X-ray crystallographic analysis. However, it was not the proposed structure **1** containing a seven-membered cyclic anhydride unit, but a new structure **2** with a spiroketal skeleton. To exclude the possibility that synthetic cereoanhydride may change the structure during the crystallization process, ^{1}H and ^{13}C NMR spectra of the crystal of synthesized cereoanhydride were collected, and no change was observed. Moreover, all three stereogenic centers in **2** have the same stereochemistry as those of **1**. Therefore, we propose that **1** should be formed first from the diastereoselective hydration of intermediate **3**. Intermediate **19** will be generated through the attack of the hemiketal hydroxyl on the carbonyl on the right side of the seven-membered cyclic anhydride unit of **1**. Finally, **2** was reached through ring opening of the cyclic anhydride moiety.

Scheme 5. Synthesis and Structural Reassignment of Cereoanhydride



In summary, we have developed a concise approach for the first total synthesis of cereoanhydride under the inspiration of the biosynthetic hypothesis from König and co-workers. The entire synthetic route requires nine steps starting from commercially available materials. Salient features of our route include two key transformations: (a) the Moore/Liebeskind ring expansion of cyclobutenone **6** through a four-electron electrocyclic ring-opening/6π-electrocyclization cascade and (b) the synthesis of cereoanhydride through Baeyer–Villiger oxidation of trypethelone, diastereoselective hydration, and subsequent isomerization in one pot. With the aid of X-ray crystallographic analysis of the synthesized cereoanhydride, the structure of the natural product was serendipitously reassigned[11] to **2** with a spiroketal skeleton. It is postulated that the originally proposed structure **1** should be an integral precursor for the formation of **2**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02424.

Single crystal data for cereoanhydride (**2**) (CIF)
Experimental procedures, spectroscopic data, and images of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Jin, L.; Quan, C.; Hou, X.; Fan, S. *Mar. Drugs* **2016**, *14*, 76. (b) Nazir, N.; El Maddah, F.; Kehraus, S.; Egereva, E.; Piel, J.; Brachmann, A. O.; König, G. M. *Org. Biomol. Chem.* **2015**, *13*, 8071–8079. (c) Elissawy, A. M.; el-Shazly, M.; Ebada, S. S.; Singab, A. B.; Proksch, P. *Mar. Drugs* **2015**, *13*, 1966–1992. (d) Ebel, R. *Mar. Drugs* **2010**, *8*, 2340–2368. (e) Greve, H.; Schupp, P. J.; Eguereva, E.; Kehraus, S.; König, G. M. *J. Nat. Prod.* **2008**, *71*, 1651–1653. (f) Pontius, A.; Mohamed, I.; Krick, A.; Kehraus, S.; König, G. M. *J. Nat. Prod.* **2008**, *71*, 272–274. (g) Bugni, T. S.; Ireland, C. M. *Nat. Prod. Rep.* **2004**, *21*, 143–163.

(2) Elsebai, M. F.; Nazir, M.; Kehraus, S.; Egereva, E.; Ioset, K. N.; Marcourt, L. t.; Jeannerat, D.; Gütschow, M.; Wolfender, J.-L.; König, G. M. *Eur. J. Org. Chem.* **2012**, *31*, 6197–6203.

(3) Elsebai, M. F.; Natesan, L.; Kehraus, S.; Mohamed, I. E.; Schnakenburg, G.; Sasse, F.; Shaaban, S.; Gütschow, M.; König, G. M. *J. Nat. Prod.* **2011**, *74*, 2282–2285.

(4) (a) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821–830. (b) Perri, S. T.; Foland, S. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067–3068. (c) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174–1175. (d) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 3491–3492. (e) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975–989. (f) Enhsen, A.; Karabelas, K.; Heerding, J.

DOI: 10.1021/acs.orglett.6b02424
Org. Lett. XXXX, XXX, XXX–XXX

M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177−1185. (g) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168−9177.
(5) (a) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986**, *51*, 3065−3067. (b) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053−3060.
(6) Castro, J. M.; Linares-Palomino, P. J.; Salido, S.; Altarejos, J.; Nogueras, M.; Sanches, A. *Tetrahedron Lett.* **2004**, *45*, 2619−2622.
(7) Onofrey, T. J.; Gomez, D.; Winters, M.; Moore, H. W. *J. Org. Chem.* **1997**, *62*, 5658−5659.
(8) (a) Yao, X.; Xie, X.; Wang, C.; Zu, L. *Org. Lett.* **2015**, *17*, 4356−4359. (b) Schmitt, A.; Reißig, H.-U. *Eur. J. Org. Chem.* **2000**, *2000*, 3893−3901. (c) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273−1276.
(9) (a) Kimachi, T.; Torii, E.; Kobayashi, Y.; Doe, M.; Ju-ichi, M. *Chem. Pharm. Bull.* **2011**, *59*, 753−756. (b) Inagaki, M.; Matsumoto, S.; Tsuri, T. *J. Org. Chem.* **2003**, *68*, 1128−1131.
(10) Yang, R.-Y.; Kizer, D.; Wu, H.; Volckova, E.; Miao, X.-S.; Ali, S. M.; Tandon, M.; Savage, R. E.; Chan, T. C. K.; Ashwell, M. A. *Bioorg. Med. Chem.* **2008**, *16*, 5635−5643.
(11) For examples of serendipitous structural reassignments of natural products from biomimetic synthesis, see: (a) Calvert, M. B.; Sperry, J. *Chem. Commun.* **2015**, *51*, 6202−6205. (b) Zhao, J.-C.; Yu, S.-M.; Liu, Y.; Yao, Z.-J. *Org. Lett.* **2013**, *15*, 4300−4303. (c) Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. *Org. Lett.* **2012**, *14*, 4537−4539. (d) Matveenko, M.; Liang, G.; Lauterwasser, E. M. W.; Zubía, E.; Trauner, D. *J. Am. Chem. Soc.* **2012**, *134*, 9291−9295. (e) Sharma, P.; Griffiths, N.; Moses, J. E. *Org. Lett.* **2008**, *10*, 4025−4027.

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Org. Lett. XXXX, XXX, XXX−XXX