HETEROCYCLES, Vol. 99, No. 1, 2019, pp. 111 - 117. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 22nd August, 2018, Accepted, 25th September, 2018, Published online, 31st October, 2018
DOI: 10.3987/COM-18-S(F)40

TOTAL SYNTHESIS OF (–)-ZEPHYRANTHINE

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This paper is dedicated with respect to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – Stereoselective total synthesis of (–)-zephyranthine **1** based on the chiral pool approach starting from D-arabinose is described. The three consecutive chiral centers in (–)-zephyranthine were effectively constructed by the sequential [3,3] sigmatropic rearrangements (Claisen, Overman, and Claisen rearrangements) with chirality transfer of the hydroxy groups in D-arabinose.

(–)-Zephyranthine **1** is an *Amaryllidaceae* alkaloid isolated from *Zephuranthes candida* and *Cyrtanthus elatus*, and structurally classified as a member of the lycorine-type alkaloids.[1] Since alkaloids of the

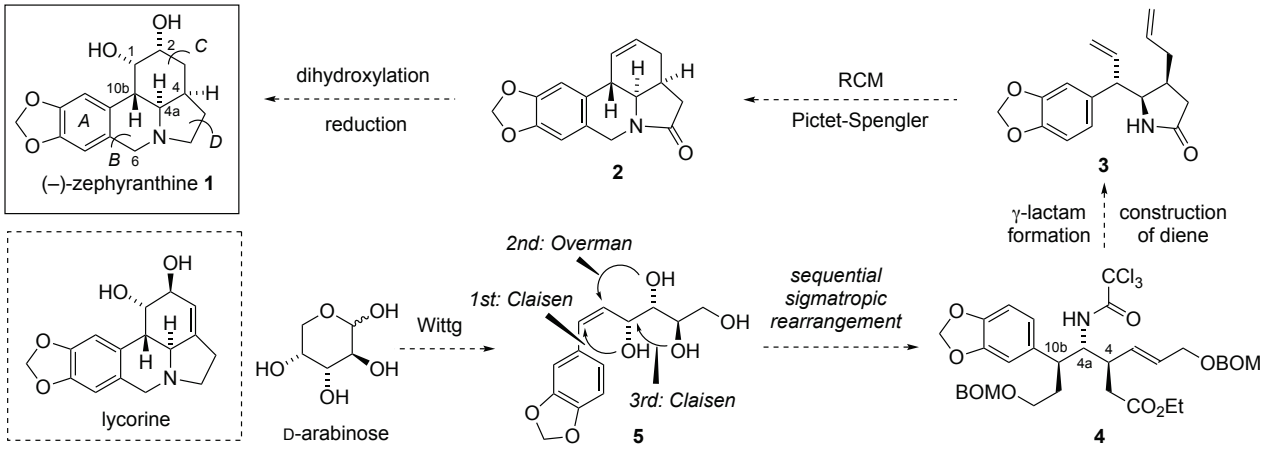

Figure 1. Structure of (–)-zephyranthine **1** and its synthetic plan

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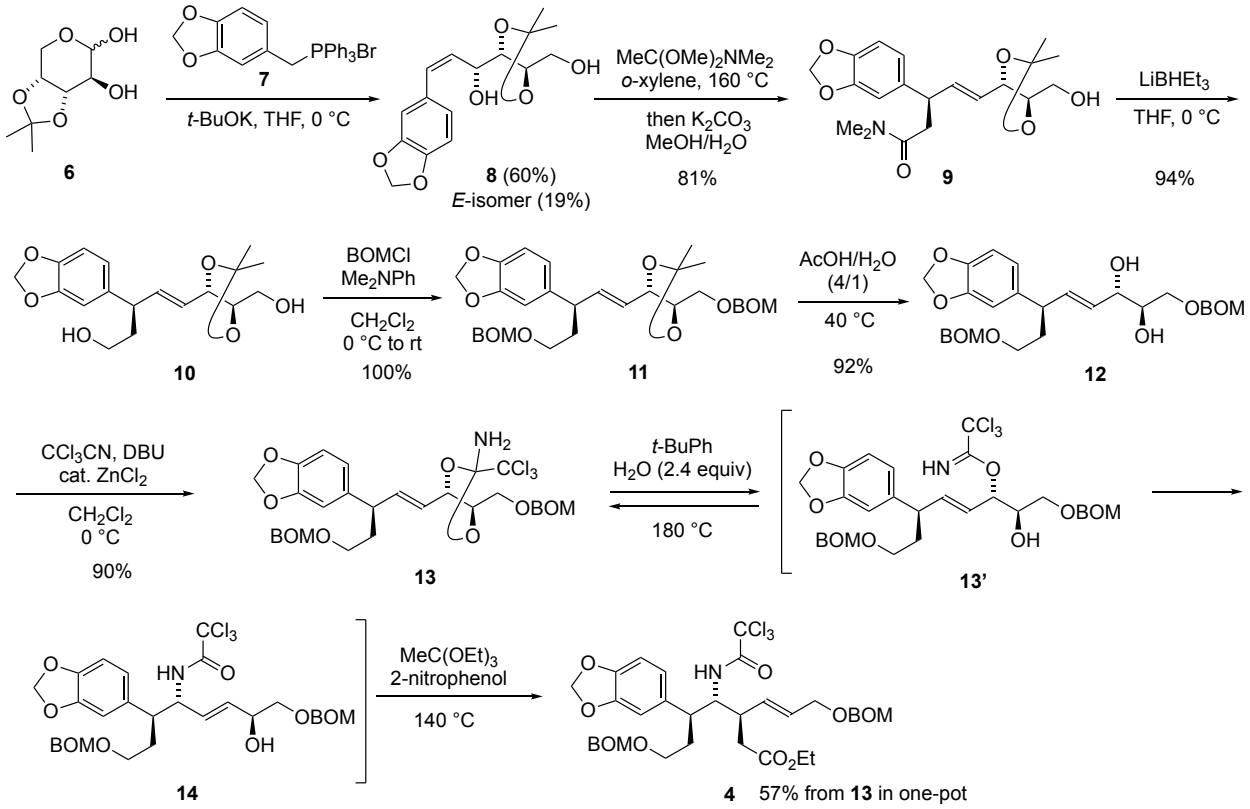
lycorine class have a synthetically attracting tetracyclic ABCD-ring core as well as a wide variety of biological activities,[2] numerous synthetic studies have been reported.[3] However, reports on the synthesis of zephyranthine, possessing five contiguous chiral centers, are limited.[4,5] In 1979, the Tsuda, Takagi, and Irie research group reported the first total synthesis of racemic zephyranthine.[4a,b] Enantioselective synthesis of (+)-trianthine, an enantiomer of (–)-zephyranthine, was reported from the Oppolzer's laboratory in 1994.[4c] In 2017, the Sun group disclosed the asymmetric syntheses of (–)-zephyranthine, (–)-α-lycorane, and (+)-clivonine from the common intermediate derived by a Pd-catalyzed cinnamylation of and *N-tert*-butanesulfinyl imine.[4d] Our group has been engaged in the synthesis of highly functionalized natural products utilizing sequential [3,3] sigmatropic rearrangements of enantiopure allylic polyols, which are derived from easily available natural chiral pool.[6,7] The salient feature of this chiral pool/sigmatropic rearrangement methodology is the highest level of the chirality transfer of hydroxy groups in the starting allylic polyols, enabling the stereoselective formation of C-C and/or C-N bonds. In this communication, we report the chiral total synthesis of (–)-zephyranthine **1** based on the chiral pool/sigmatropic rearrangement methodology starting from D-arabinose.

Our synthetic plan (Figure 1) suggested that **1** would be obtained by the dihydroxylation of the alkene followed by reduction of the lactam carbonyl in pentacycle **2**. Compound **2** was planned to be constructed from diene **3** by the ring-closing metathesis (RCM) and Pictet-Spengler reactions. Acyclic amide-ester **4** having the suitable functionalities and stereocenters would be a precursor of diene **3**. For the construction of the three contiguous chiral centers (C-10b, 4a, and 4, zephyranthine numbering) in **4**, three consecutive sigmatropic rearrangements of allylic polyol **5** (1st: Claisen, 2nd: Overman, and 3rd: Claisen rearrangements) were envisioned as the key transformations. For the second and third rearrangements, we planned to apply the sequential Overman/Claisen rearrangement in a one-pot process via a cyclic orthoamide derivative.[6d,e] Acyclic polyol **5**, possessing an alkene moiety and proper array of hydroxy groups, would be easily obtained by Wittig reaction of D-arabinose.

Wittig reaction of the known acetonide **6**, prepared from D-arabinose in one step,[8] with ylide generated from **7**[9] afforded *Z*-alkene **8** and its *E*-isomer in 60 and 19% yields, respectively (Scheme 1).[10] Reaction of 1,4-diol **8** with $MeC(OMe)_2NMe_2$ in *o*-xylene at 160 °C gave a product of Claisen rearrangement **9** in 81% yield as a single isomer.[11] The structure of **9** was fully confirmed by the single X-ray crystal analysis.[12] The amide function in **9** was reduced to give diol **10**, of which hydroxy groups were protected as benzyloxymethyl (BOM) ethers to provide **11** (94% for 2 steps). Mild acid hydrolysis of **11** cleanly removed an acetonide group to give allylic diol **12** in 92% yield. With allylic vicinal diol **12** in hand, the sequential Overman/Claisen rearrangement in a one-pot process[6d,e] was examined. Thus, treatment of **12** with Cl_3CCN, DBU, and a catalytic amount of $ZnCl_2$ at 0 °C afforded cyclic orthoamide **13** as a single diastereomer in 90% yield.[6d,e] Heating of **13** in *t*-BuPh in the presence of water (2.4 equiv)

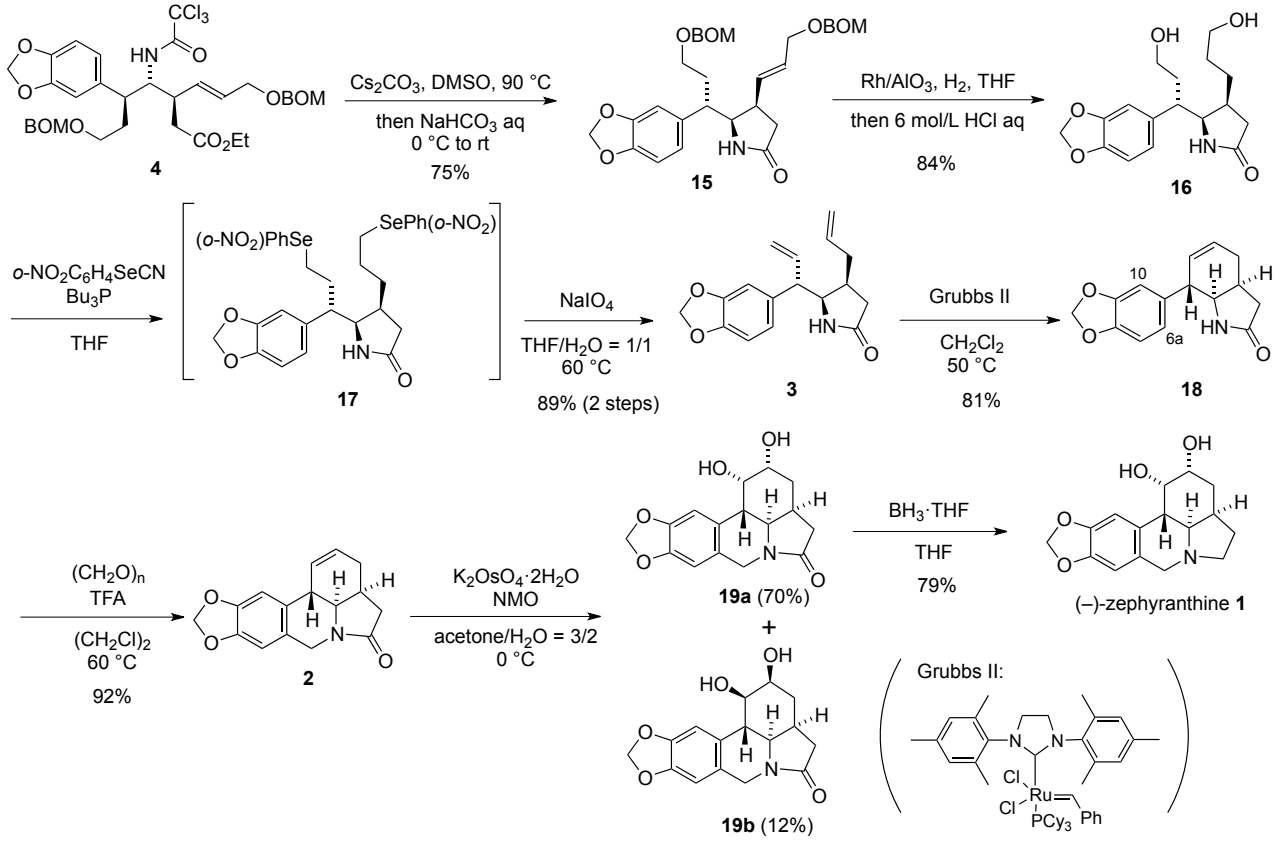


Scheme 1. Construction of three contiguous chiral centers by the sequential sigmatropic rearrangements BOM = -CH_2OCH_2Ph

in a sealed tube at 180 °C gave Overman rearrangement product **14** through equilibrium with imidate **13'**.[13] After the consumption of **13** was confirmed by TLC analysis, triethyl orthoacetate and 2-nitrophenol were added to the resulting **14**. Further heating of the reaction mixture at 140 °C successfully afforded the sequential Overman/Claisen rearrangement product **4** as a single isomer in 57% yield in a one-pot operation.

As the three contiguous chiral centers (C-10b, 4a, and 4) in zephyranthine have been successfully generated in a stereoselective manner by the sequential sigmatropic rearrangements, we then turned our attention to the construction of the ABCD-ring system (Scheme 2). First, the D-ring was formed as a γ-lactam under Isobe's conditions.[14] Reaction of **4** with Cs_2CO_3 in DMSO transformed the trichloroacetamide moiety in **4** to an isocyanate, which was then treated with aqueous base to give γ-lactam **15** in 75% yield. Hydrogenation of **15**, followed by acid hydrolysis afforded saturated diol **16** in one-pot process with 84% yield. Diol **16** was then converted to diene **3** by the double Nishizawa-Grieco dehydration.[15] Thus, treatment of **16** with excess amount of Bu_3P and *o*-nitrophenyl selenocyanate afforded di-selenide **17**, which, without isolation, was oxidized by $NaIO_4$ to provide diene **3** in 89% from **16**. RCM reaction of **3** with Grubbs II catalyst smoothly constructed the C-ring, and ACD-ring **18** was obtained in 81% yield.[16] The Pictet-Spengler reaction of **18** with paraformaldehyde and trifluoroacetic acid generated the B-ring to afford ABCD-ring **2** in 92% yield.[17] Dihydroxylation of

2 with K_2OsO_4•$2H_2O$ in the presence of NMO proceeded in a stereoselective manner to give the desired α-diol **19a** and its isomeric β-diol **19b** in 70 and 12% yields, respectively.[18] Finally, reduction of the lactam carbonyl in **19a** by the action of BH_3•THF[5,19] furnished (–)-zephyranthine **1** in 79% yield. The spectral data and $[\alpha]_D$ value of synthetic **1** were in good accordance with those reported by Sun.[4d]



Scheme 2. Total synthesis of (–)-zephyranthine **1**

In conclusion, we have accomplished the chiral total synthesis of (–)-zephyranthine **1** in 16 steps from D-arabinose. This synthesis fully revealed that the chiral pool approach from carbohydrates utilizing the sigmatropic rearrangements is a powerful method for the stereoselective synthesis of natural products in optically pure forms. Especially, the highest level of the chirality transfer in the sigmatropic rearrangements of acyclic secondary alcohols originated from the starting sugar would be useful and reliable for the stereoselective generation of C-C and C-N bonds. Further study on the synthesis of structurally complex natural products based on the chiral pool/sigmatropic rearrangement strategy is underway.

ACKNOWLEDGEMENTS

This research was partially supported by a Grant-in-Aid for Scientific Research (B) from MEXT (26288018).

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17. The formation of regioisomer of **2** in which the methano-bridge formed between ortho position of catechol (C-10) and nitrogen was not detected. The similar regioselective construction of a 6-memberd ring by the Pictet-Spengler reaction of the catechol system has been reported in the synthesis of an *Amaryllidaceae* alkaloid, crinine (vittatine), see: a) S. F. Martin and C. L. Campbell, *Tetrahedron Lett*., 1987, **28**, 503; b) S. F. Martin and C. L. Campbell, *J. Org. Chem*., 1988, **53**, 3184; c) M. Bohno, H. Imase, and N. Chida, *Chem. Commun*., 2004, 1086; d) M. Bohno, K. Sugie, H. Imase, Y. B. Yusof, T. Oishi, and N. Chida, *Tetrahedron*, 2007, **63**, 6977.
18. The ABCD-ring structure in **2** was important for the stereoselective dihydroxylation. Under the same reaction conditions, compound **18** possessing the ACD-ring with a rotatable catechol ring showed low stereoselectivity (α-diol : β-diol = 1.5 : 1). The dihydroxylation of **2** would proceed from the less hindered convex face of the rigid ABCD-ring framework.
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