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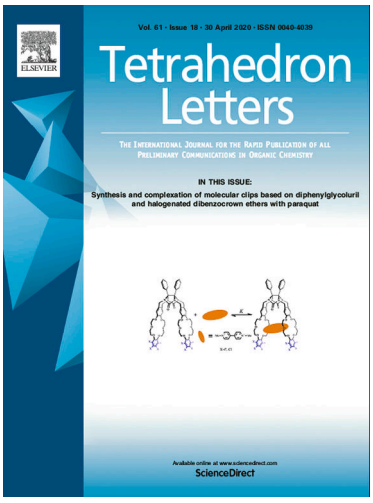

Synthesis of botryolide E, ophiocerins A, B and C from D-glucono-δ-lactone

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PII: S0040-4039(20)30403-2
DOI: https://doi.org/10.1016/j.tetlet.2020.151960
Reference: TETL 151960

To appear in: *Tetrahedron Letters*

Received Date: 18 March 2020
Revised Date: 15 April 2020
Accepted Date: 19 April 2020

Please cite this article as: Zhou, F., Liu, X., Jia, Y., Hu, Y., Luo, G., Chen, X., Synthesis of botryolide E, ophiocerins A, B and C from D-glucono-δ-lactone, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.151960

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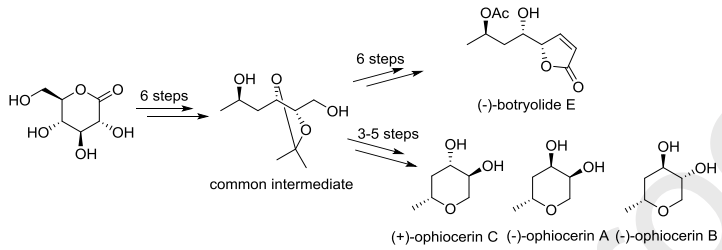

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Botryolide E
Ophiocerin
γ-Lactone
Tetrahydropyran

ABSTRACT

A concise synthesis of a chiral hexane-tetraol intermediate is achieved from D-glucono-δ-lactone in 6 steps featuring the successively selective deoxygenation. The versatile intermediate can be easily converted into the γ-lactone compound botryolide E and tetrahydropyran derivative ophiocerins A-C respectively. In addition, the direct transformation of ophiocerin C to ophiocerins A and B by Mitsunobu reaction was studied for the first time.

1. Introduction

Tetrahydropyrans [1] and γ-lactones [2] both are important subunits occurring in a variety of biologically active natural products. (-)-Botryolide E (**1**; Fig. 1), an unsaturated γ-lactone, was isolated from cultures of the *fungicolous Botryotrichum sp.* (NRRL 38180) by Gloer and coworkers in 2008 [3], and it exhibited promising antibacterial activity against *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96) and *Escherichia coli* (MTCC 443), as well as antifungal activity against *Aspergillus niger* (MTCC 1344) and *Saccharomyces cerevisiae* (MTCC 171) [4]. Another class of natural products, ophiocerins A–C (**2**-**4**), which represent a new type of tetrahydropyran derivatives with two hydroxyl groups, were isolated from cultures of the aquatic fungus *Ophioceras venezuelense* [5].

Due to the promise of biological activities associated with natural product containing γ-lactone or tetrahydropyran moiety, botryolide E and ophiocerins A–C attracted considerable interest from synthetic chemists. Venkateswarlu group reported their first [4] and second generation [6] synthesis of (-)-botryolide-E featuring Jacobsen's hydrolytic kinetic resolution of propylene oxide and Sharpless asymmetric dihydroxylation. A chiral-pool synthesis of (-)-**1** starting from (+)-diethyl (L)-tartrate was achieved by Madabhushi et al [7]. Das and coworkers developed another approach to (-)-**1** via allyl boration, Sharpless asymmetric dihydroxylation and ring-closing metathesis reaction [8]. Likewise, several syntheses of ophiocerins A–C using chiral-pool sources and asymmetric reactions also have been reported. Yadav and coworkers accomplish the synthesis of ophiocerins B and C from a chiral epoxide [9] and the synthesis of ophiocerin C from L-(+)-tartaric acid [10] successively. Kang et al. synthesized ophiocerins A–C starting from methyl α-D-glucopyranoside [11] and (R)-(-)-4-penten-2-ol [12] respectively. Moreover, the Kumar [13], Damera [14] and Das groups [15] developed other synthetic routes to compounds **2**–**4** from (R)-propylene oxide or L-malic acid, independently. Up to now, only two divergent routes that led to botryolide E and ophiocerins via a common intermediate were developed in view of the similar triol moiety of the two type of compounds. Yadav group employed a chiral homoallylic alcohol to prepare a key polyhydroxy intermediate in 8 steps, which could be converted separately to botryolide E and ophiocerin C in 5 steps [16].

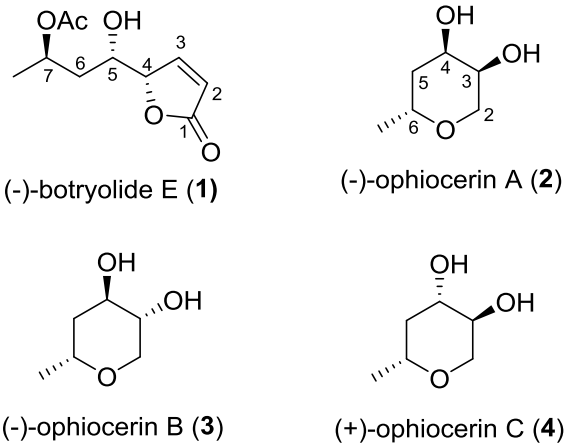

Fig. 1. (-)-Botryolide E and ophiocerins A–C.

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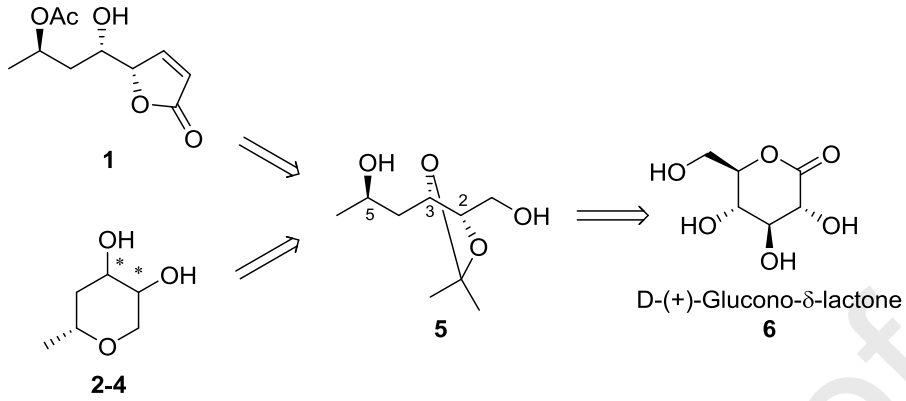
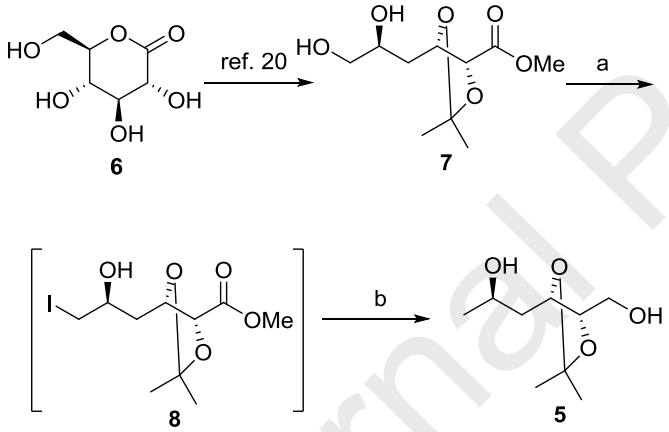
Ku the glyceraldehyde acetonide in 16 to 19 steps via a common tetraol intermediate [17].



Scheme 1. Our retrosynthetic analysis of **1**-**4**.

Recently the first synthesis of (+)-botryolide E and its C-7 epimer was achieved from D-glucono-δ-lactone in our laboratory [18]. In continuation of our interest in the synthesis of bioactive natural products and their enantiomers using commercial carbohydrates [9,19], herein we reported a new approach to (-)-botryolide E and ophiocerins A–C by way of a common building block derived from D-glucono-δ-lactone.



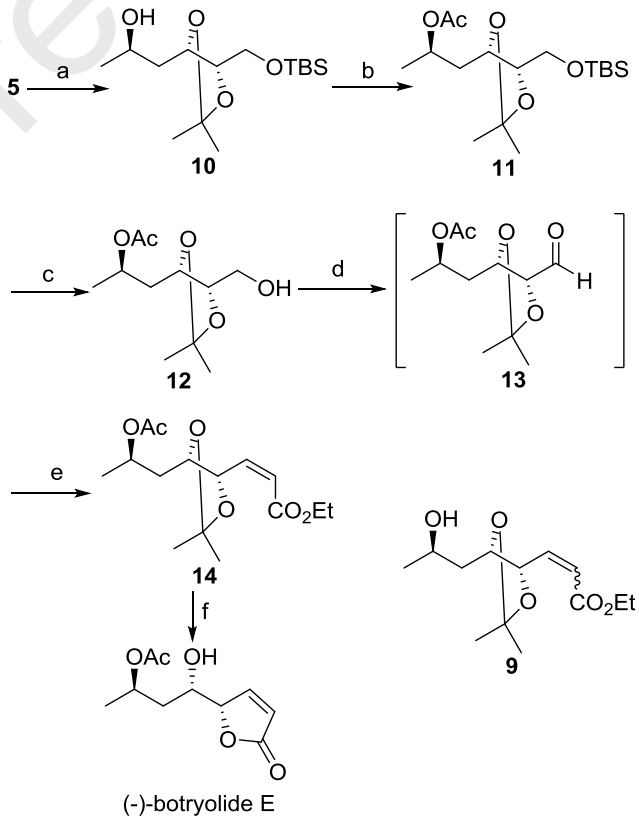
Scheme 2. Reagents and conditions: (a) I_2, PPh_3, imidazole, THF, rt; (b) $LiAlH_4$, THF, 0°C, 62% over two steps

2. Results and discussion

Our approach to the synthesis of **1**-**4** was shown in Scheme 1. It is envisaged that the target molecules **1** and **2**-**4** could be prepared from the common intermediate **5** via lactonization or S_N2 cyclization, respectively. (2*S*,3*S*,5*R*)-hexane-1,2,3,5-tetraol **5** was proposed to be derived from D-glucono-δ-lactone (**6**) by the successively selective deoxygenation.

Our synthesis began with the preparation of the known ester **7** from **6** (Scheme 2). Following to the literature procedure [20], **6** was converted into the hydroxyl ester **7** in a four-step sequence involving protection as isopropylidene derivative, Barton-McCombie deoxygenation [21] and selective hydrolysis of terminal acetonide. Under the Appel reaction conditions [22], the primary alcohol group in diol **7** was selectively iodinated leading to the corresponding iodide **8**, in which the simultaneous reduction of the ester and the iodo functional groups with excessive $LiAlH_4$ to afford the target common intermediate **5** in 62% overall yield for two steps.

With the key intermediate **5** in hand, we first aimed the synthesis of (-)-botryolide E (Scheme 3). The attempts on direct selective oxidation of the primary hydroxy group in diol **5** alcohol **12**. Oxidation of alcohol **12** with Dess-Martin periodinane afforded the corresponding aldehyde **13**, without further purification, which underwent Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane to generate *Z*-conjugated ester **14** with good geometric selectivity. Finally, **14** underwent one-pot acetonide deprotection and lactonization in 80% AcOH affording (-)-botryolide-E [23].



Scheme 3. Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2, 0°C, 92%; b) Ac_2O, Et_3N, DMAP, rt, 92%; c) TBAF, THF, 0°C, 96%; d) Dess−Martin periodinane, CH_2Cl_2, rt; e) $Ph_3P{=}CHCO_2Et$, MeOH, 0°C, 72% over two steps; f) 80% aq. AcOH, rt, 91%.

Next, advancing the intermediate **5** toward synthesis of ophiocerins A–C was set out. Following to Kumar's strategy [13,17], **5** was smoothly converted (+)-ophiocerin C (**4**) via sequential tosylation of the primary alcohol, base-induced cyclization and deprotection of acetonide. In Kumar's work [17], ophiocerins A–C were synthesized from their common intermediate by employing three different approaches

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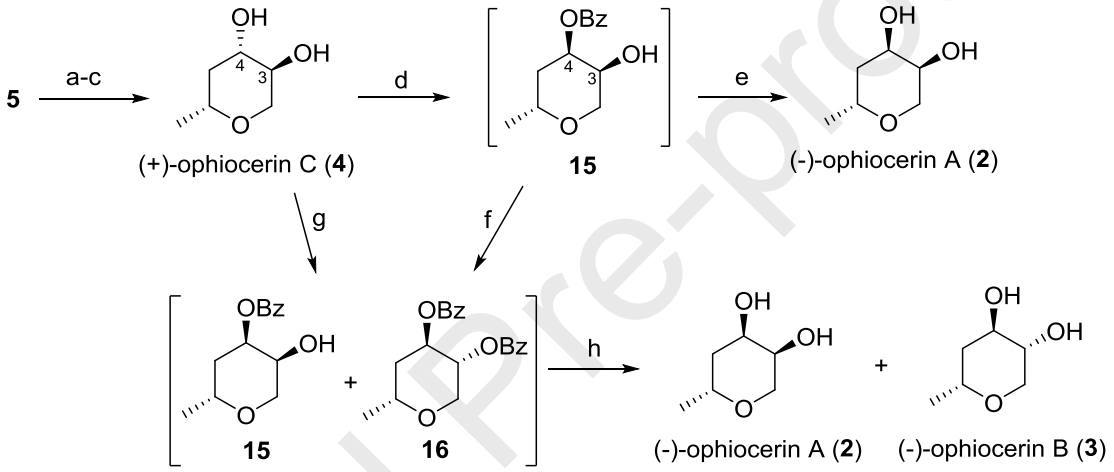
2 and **3** for the first time. (+)-Ophiocerin C was subjected to Mitsunobu reaction procedure [24] (1.6eq. DIAD, Ph_3P and BzOH) at room temperature to yield a single monobenzoate **15**. Unfortunately, the Mitsunobu product **15** is difficult to purify due to the presence of the inseparable impurities derived from DIAD and Ph_3P. However, the impure benzoate **15** was hydrolyzed to furnish (-)-ophiocerin A in 78% overall yield for two steps after chromatography purification. It is assumed that the phosphonium intermediate preferentially binds to the C-4 alcohol oxygen in **4** so that the carboxylate approaches the alkoxy phosphonium salt from the side opposite to the C-6 methyl group to generate thermodynamically more stable product **15**. Subsequent inversion of the C-3 hydroxyl configuration in **15** via the second Mitsunobu reaction was examined. The reaction of the crude **15** with 2.0 eq. DIAD, Ph_3P and BzOH proceeded sluggishly at 50°C, and considerable **15** was remained after a long span. The resulting mixture containing **15** and **16** was treated with K_2CO_3 in methanol to afford **2** (45% for 3 steps) and **3** (22% for 3 steps),

This work was supported by grants from the National Natural Science Foundation of China (No. 21172153), the Sichuan Science and Technology Program (2019YJ0032) and "the Fundamental Research Funds for the Central Universities". We thank the Comprehensive Training Platform of Specialized Laboratory, College of Chemistry, Sichuan University, for spectral data measurement.

Supplementary Material

Supplementary data (experimental procedures and characterization data for compounds, and copies of ^1H and ^{13}C NMR spectra for compounds **5**, **10**, **11**, **12**, **14**, (-)-**1**, (-)-**2**, (-)-**3**, (+)-**4** associated with this article can be found, in the online version, at



Scheme 4. Reagents and conditions: (a) TsCl, NaH, THF, 0°C; (b) *t*BuOK, Et_2O, 0°C; (c) *p*TsOH, MeOH, rt, 80% over three steps; (d) DIAD, Ph_3P, BzOH, THF, rt; (e) K_2CO_3, MeOH, rt, 78% over 2 steps; (f) DIAD, Ph_3P, BzOH, THF, 50°C; (g) DIAD, Ph_3P, BzOH, toluene, 110°C; (h) K_2CO_3, MeOH, rt, 45% for **2** and 22% for **3** over three steps (d, f, h), 33% for **2** and 41% for **3** over two steps (g, h).

which was readily separated on column chromatography. In order to optimize the process and yield in the preparation of **3**, the one-pot double Mitsunobu reactions of **4** performed in refluxing toluene or THF in the presence of excessive reagents (4.0 eq.) were attempted. Under these conditions the ratio of **3** to **2** was improved indeed, and after hydrolysis of the reaction mixture (-)-ophiocerin B was obtained in 41% yield over two steps, together with 33% yield of (-)-ophiocerin A. All spectroscopic and spectrometric data (NMR, IR, MS and $[\alpha]^D$) for the synthesized products **2**-**4** [25] are in good accord with the data reported for natural examples, respectively.

3. Conclusion

In conclusion, we developed a concise approach to an useful tetraol intermediate **5** from the known ester **7** via chemoselective Appel reaction and reduction. The synthetic utility of the chiral intermediate **5** was demonstrated by its transformation into the γ-lactone compound (-)-botryolide E and tetrahydropyran derivative ophiocerins A-C in 3 to 6 steps. Moreover, the conversion of ophiocerin C to ophiocerins A and B via Mitsunobu reaction was investigated for the first time. We think that this strategy should be employable for more related unsaturated lactone and hydroxylated pyran derivatives.

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[23] Spectral data for (-)-**1**: $[\alpha]_D^{16.0}$ = –42.6 (*c* = 0.50, $CHCl_3$). IR (neat) ν_{max}: 3450, 2982, 2930, 1740, 1376, 1247, 1036, 827cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.8, 2.0 Hz, 1H), 6.17 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.13 (m, 1H), 5.01 (dt, *J* = 4.0, 1.6 Hz, 1H), 3.86 (dt, *J* = 8.3, 4.4 Hz, 1H), 2.83 (s, 1H), 2.05 (s, 3H), 1.76 – 1.59 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.8, 153.8, 122.8, 85.5, 67.7, 67.3, 39.2, 21.3, 20.7. HRMS (ESI-TOF): m/z $[M+Na]^+$ $C_{10}H_{14}NaO_5^+$: 237.0733, found: 237.0736.
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[25] Spectral data for **2**-**4**: (+)-**4**: mp 81-83 °C; $[\alpha]_D^{25}$= +43.2 (*c* = 0.8, CH_2Cl_2); IR (neat) ν_{max}: 3280, 1451, 1378, 1240, 1147, 1091, 1073, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 2H), 3.90 (dd, *J* = 11.2, 5.0 Hz, 1H), 3.55 – 3.45 (m, 2H), 3.42(ddd, *J* = 10.0, 9.0, 5.2 Hz, 1H), 3.10 (dd, *J* = 11.0, 10.2 Hz, 1H), 1.94 (ddd, *J* = 13.2, 4.8, 1.6 Hz, 1H), 1.30 (m,1H), 1.18 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.0, 72.8, 72.0, 69.7, 40.6, 21.2. HRMS (ESI-TOF): m/z $[M+Na]^+$ calcd for $C_6H_{12}NaO_3^+$ 155.0679; found 155.0685.
(-)-**2**: mp 62-64 °C; $[\alpha]_D^{25}$ = –25.7 (*c* =1.0, CH_2Cl_2); IR (neat) ν_{max} = 3390, 1381, 1095, 1054, 1011 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (m, 1H), 3.80 (ddq, *J* = 12.6, 6.3, 2.1 Hz, 1H), 3.74 – 3.63 (m, 2H), 3.54 (m, 1H), 2.78 (s, 2H), 1.91 – 1.81 (ddd, *J* = 14.3, 3.6, 2.3 Hz, 1H), 1.51 (ddd, *J* = 14.0, 11.2, 2.6 Hz, 1H), 1.14 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.3, 67.2, 67.0, 65.9, 39.0, 20.8 ppm. HRMS (ESI-TOF): m/z $[M+Na]^+$ calcd for $C_6H_{12}NaO_3^+$ 155.0679; found 155.0683.
(-)-**3**: $[\alpha]_D^{25}$ = –35.7 (c = 0.3, CH_2Cl_2); IR (neat) ν_{max} = 3388, 1452, 1380, 1266, 1079, 1004 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 1.6, 12.3, Hz, 1H), 3.95(m, 1H), 3.85 (m, 1H), 3.71 (m, 1H), 3.48 (m, 1H), 2.53 (s, 1H), 2.01 (s, 1H), 1.80 (ddd, *J* = 14.1, 10.8, 3.1 Hz, 1H), 1.60 (dt, *J* = 14.3, 3.0 Hz 1H), 1.18 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.4, 68.3, 67.5, 67.3, 36.0, 21.2. HRMS (ESI-TOF): m/z $[M+Na]^+$ calcd for $C_6H_{12}NaO_3^+$ 155.0679; found 155.0678.

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Synthesis of botryolide E, ophiocerins A, B and C from D-glucono-δ-lactone

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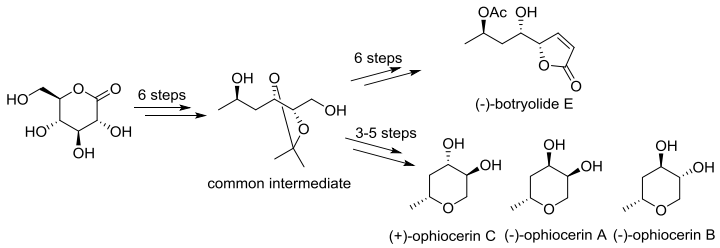
Faling Zhou, Xiaojing Liu, Yuanliang Jia, Yue Hu, Guiyin Luo and Xiaochuan Chen*



Highlights

- The first employment of D-glucono-δ-lactone to synthesize (-)-Botryolide E and ophiocerins A–C
- Concise and versatile synthetic route
- The first transformation of ophiocerin C to ophiocerins A and B via Mitsunobu reaction