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4-*endo*-Hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one as a useful building block in the formal total syntheses of furofurandione natural products

Yung-Son Hon* and Hsien-Fan Chen

Department of Chemistry and Biochemistry, National Chung Cheng University, Chia-Yi, Taiwan 62102, Taiwan, ROC

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This Letter is dedicated to Professor Tze-Lok Ho for his inspiration and friendship

Abstract— 4-*endo*-Hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one (**9**) is a useful building block in the formal total syntheses of both Types **A** and **B** furofurandione natural products. The success of Pd-catalyzed epimerization of the γ-alkenyl substituent of the bislactones makes this methodology useful and versatile.

The furofurandione metabolites avenaciolide (**1**),[1] *epi*-ethisolide (**2**),[2] isoavenaciolide (**3**),[3] ethisolide (**4**)[3] and discosiolide (**5**)[2] constitute a class of ecologically significant substances. These fungal products inhibit the growth of other fungi to enable the host species compete successfully. Two structural subtypes of the compounds are **A**/**B** and **C** that differ in bond connectivities, whereas in all these compounds the two rings are cis-fused. The **A** and **B** groups represent diastereomers due to orientation of the alkyl side chain (Fig. 1). Naturally, both their bioactivities and chemical structures have attracted interests from synthetic organic chemists, and as a result, elaboration of one[4,5] or two[6] classes of these compounds has been reported. Many syntheses were claimed on arriving at the bislactones because α-methylenations had been established in earlier works.[5a,7] Most of them could only synthesize one type of these natural products. Only few reports make efforts to prepare both of Types **A** and **B** compounds.[6] Among them, diastereoselective synthetic routes involving common intermediates are those described by Martin,[6d] Burke,[6e] and Suzuki,[6f] respectively. Liu[6g] utilized an intramolecular alkoxycarbonylation of tungsten–π-allyl complexes in the key steps from different starting materials.

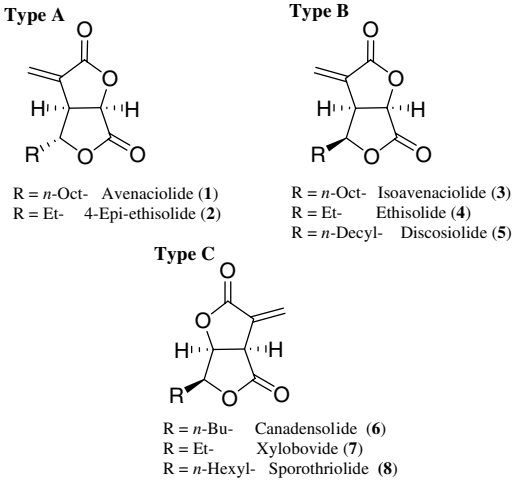

Figure 1. Some natural products with α-methylenefurofurandione moiety.

In our previous research in this area a general and diastereoselective methodology to prepare Type **C** furofurandione natural product.[8] The key step is to introduce the α-methylene group by the ozonolysis of mono-substituted alkenes followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH.[9] Unfortunately, the method failed to deliver the products of Types **A** and **B**. Now we wish to describe an alternative approach to address this deficiency. By using hydroxy lactone **9**,

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* Corresponding author. Tel.: +886 5 2720411x66412; fax: +886 5 2721040; e-mail: cheysh@ccu.edu.tw

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which is available from the reaction of cyclopentadiene with glyoxylic acid, as the starting material,[10] we have been able to synthesize compounds of two series.

The retrosynthetic analysis of compounds **A** and **B** (Fig. 2) indicate that, if the full side chain except for one residual carbon atom of such a target molecule is temporarily deleted, recombination of this residue with the 'distal' lactone carbonyl would result in a cyclopentene unit. That **9** is an ideal intermediate is apparent because once the double bond is cleaved to a dialdehyde, lactolization should be readily achieved and the free aldehyde group is epimerizable. Thus, depending on reaction conditions either the **A**- or **B**-series of compounds can be reached. Note that in the **A** series the *exo* orientation of the side chain is thermodynamically favored.

Accordingly, ozonolysis of the *endo*-hydroxylactone **9** in CH_2Cl_2 at −78 °C followed by treatment with Me_2S gave tricyclic hemiacetal **10** in 63% yield as a 10:1 mixture of two diastereomers. The axial anomer is the major isomer confirmed by its 2D-NOSEY spectrum. The C-4 side chain is elongated by Wittig reaction. We found that the semistable ylides are good for this purpose. Hemiacetal **10** reacted with (*E*)-Ph_3 P=CHCH=CHBu-*n* (1.1 mol equiv) in THF at −78 °C to give the mono-Wittig reaction product **11**, which was oxidized by pyridinium chlorochromate (PCC) to give bislactone **12** in 76% yield. The ratio of (*ZE*) and (*EE*) isomers is approximately 4.4:1 based on the integration of their ^{1}H NMR spectra. Catalytic hydrogenation of diene **12** yielded the bislactone **15** in 89% yield (Scheme 1). Interestingly, when compound**12** was treated with a catalytic amount of $Pd(OAc)_2$ in the presence of Ph_3P in THF at room temperature, the *exo*-epimer **13** was obtained in 62% yield as a sole product. Presumably, the initially formed π-allyl palladium intermediate underwent isomerization to a more stable form, which was followed by recyclization. During this process, the diene moiety was also isomerized to the more stable *EE*-form. The catalytic hydrogenation of diene **13** yielded the corresponding saturated product **14** in 89% yield. α-Methylenation of compounds **14** and **15** was reported to convert to avenaciolide (**1**) and isoavenaciolide (**3**), respectively, by using the procedure of Parker and Johnson[7a,b] (Scheme 1).

Hemiacetal **10** reacted with Ph_3P=CHBr (1.1 mol equiv) to afford vinyl bromide **16**. Since this product was rather difficult to separate from Ph_3PO due to their similar polarity, the crude mixture was used directly for the further oxidation to give bislactone **17** in 56% yield for two steps. Only *Z*-vinyl bromide **17** was isolated and its structure was determined by its coupling constant ($J = 6.8$ Hz). The, catalytic hydrogenation of **17** furnished compound **18** in 89% yield (Scheme 2). Vinyl bromide **17** also underwent Pd-catalyzed epimerization to give the *exo*, *E*-isomer **19** in 87% yield. The catalytic hydrogenation of compound **19** afforded compound **20**

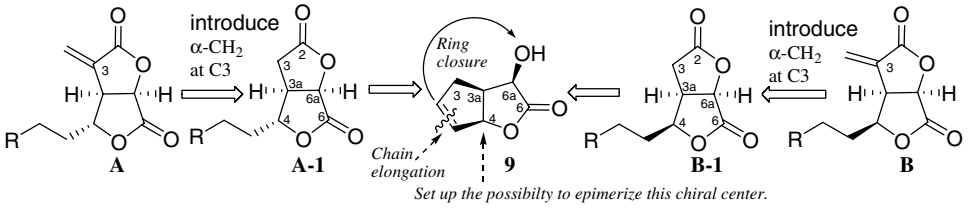
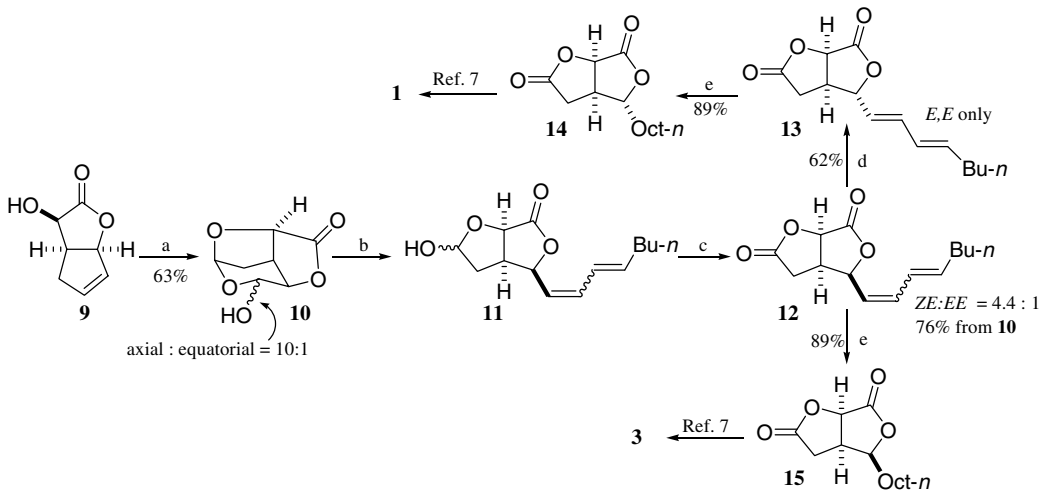
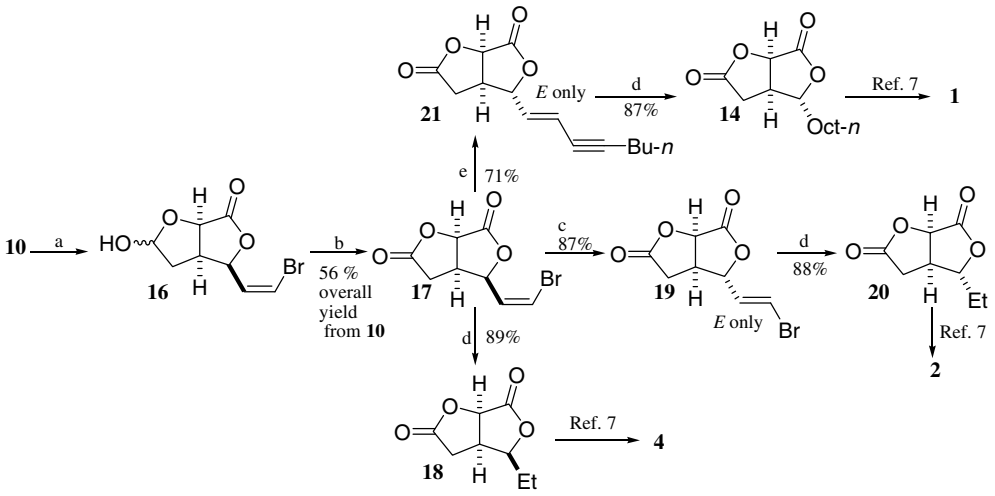


Figure 2. Retrosynthetic analysis of Types **A** and **B** natural product via a common starting material **9**.



Scheme 1. Reagents and conditions: (a) (i) O_3, CH_2Cl_2, −78 °C; (ii) Me_2S, CH_2Cl_2, 0 °C, 6 h; (b) 1.1 equiv (*E*)-Ph_3P=CHCH=CHBu-*n*, THF, −78 °C to rt, 13 h; (c) 1 equiv PCC, CH_2Cl_2, 0 °C to rt; (d) cat. $Pd(OAc)_2$, PPh_3, THF, rt, 3 h; (e) H_2/Pd/C, EtOAc, 4 h.



Scheme 2. Reagents and conditions: (a) 1.1 equiv $Ph_3P{=}CHBr$, THF, −78 °C to rt, 13 h; (b) Jones' reagent, acetone, 0 °C, 2 h; (c) cat. $Pd(OAc)_2$, PPh_3, THF, rt, 24 h; (d) H_2/Pd/C, NaOAc, EtOAc, 12 h; (e) cat. $PdCl_2(PPh_3)_2$, cat. CuI, Et_3N, 1-hexyne, THF, 60 °C, 5 h.

in 88% yield. α-Methylenation of **18** and **20** is reported to convert to ethisolide (**4**) and 4-*epi*-ethisolide (**2**), respectively[5d,7] (Scheme 2). Interestingly, under Sonogashira coupling reaction condition,[11] 1-hexyne reacted with vinyl bromide **17** to give crossed coupling product **21** in 71% yield. The crossed coupling, epimerization at C-4 chiral centre and the isomerization of the vinyl bromide double bond occur in the same flask. The catalytic hydrogenation of compound **21** yielded the corresponding saturated product **14** in good yield (Scheme 2).

In summary, our work represents a new stereocontrolled route for access to two types of furofurandione fungal metabolites from the readily available *endo*-hydroxyl-actone **9**. A Pd-catalyzed reaction of **12** and **17** proved highly effective in epimerizing C(4). Since optical resolution of **9** by lipase is known,[10a] our method should be applicable to an enantioselective synthesis of these natural products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.036.

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