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Total Synthesis and Structural Revision of (+)-Yaoshanenolide B

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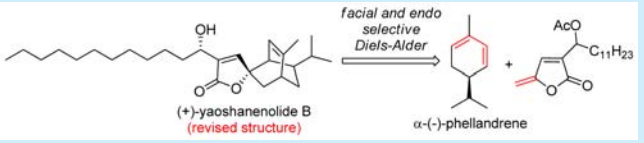
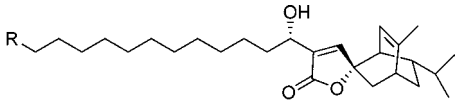
Supporting Information

ABSTRACT: (+)-Yaoshanenolide B was synthesized employing as a key step an endo- and face-selective Diels–Alder reaction between natural *R*-(−)-α-phellandrene and the exocyclic double bond of a 5-methylene-2(5*H*)-furanone. The dienophile furanone was prepared by photooxygenation of a suitably substituted 2-thiophenylfuran followed by dehydration of the resulting γ-hydroxybutenolide. Through this synthesis, the initially proposed structure for (+)-yaoshanenolide B has been revised to the 1*R*,2*S*,4*R*,7*R*,1″*S* diastereomer.



(+)-Yaoshanenolides A and B (Figure 1) are tricyclic spirolactones with an unprecedented 5′*H*-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one skeleton. They were isolated[1] from the bark of *Machilus yaoshansis* and differ by two carbon atoms in their linear alkyl side chain. Their relative configuration was elucidated from 2D NMR experiments, while the absolute configuration of the secondary alcohol was assigned as *S* using the bulkiness rule for the $Rh_2(OCOCF_3)_4$-induced circular dichroism data. Yaoshanenolides A and B have been found to exhibit nonselective cytotoxic activity against some human cancer cell lines. The unusual tricyclic spirolactone system of the yaoshanenolides presents a unique synthetic challenge. The construction of such a core skeleton was recently achieved[2] via a multistep sequence featuring oxidation of *o*-hydroxymethylphenol, cycloaddition of the resulting labile spiroepoxycyclohexa-2,4-dienone with a reactive dienophile, a stereoselective Grignard reaction, an alkylation, and finally, a ring-closing metathesis reaction.

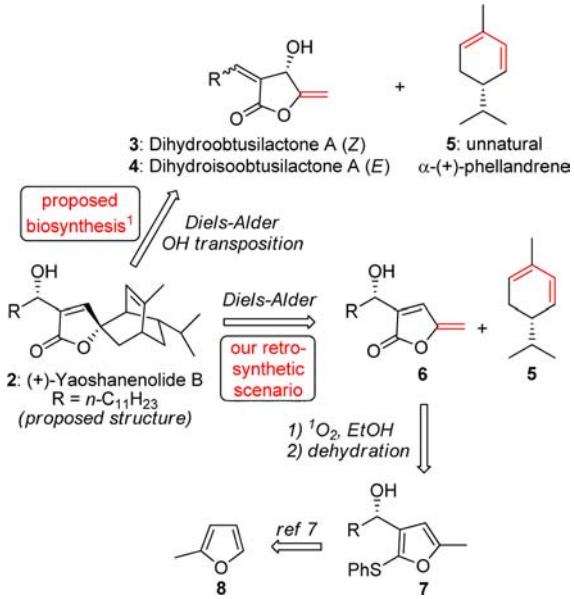


1: (+)-Yaoshanenolide A (R = Et)
2: (+)-Yaoshanenolide B (R = H)
(proposed structures)

Figure 1. Assigned structures of (+)-yaoshanenolides A and B.[1]

In the isolation paper,[1] the authors proposed a possible biosynthesis for yaoshanenolides involving [4 + 2] cycloaddition of unnatural α-phellandrene (**5**) (mistakenly assigned therein as β-phellandrene) with dihydroobtusilactone A (**3**) and/or dihydroisoobtusilactone (**4**)[3] followed by 1,3-transposition of the allylic hydroxyl (Scheme 1). We envisioned a more direct retrosynthetic scenario based on the [4 + 2] cycloaddition[4,5] between α-phellandrene and 5-alkylidenebutenolide **6**, as shown in Scheme 1. Lactones **3** and **4** possess an exocyclic double bond that is not sufficiently electron-deficient to be considered a reactive dienophile. Instead, the double bond conjugated to the carbonyl in these molecules is expected to be the reactive site in any hypothetical Diels–Alder reaction. On the other hand, 5-methylene-2(5*H*)-furanones, such as the one proposed in our retrosynthetic scenario (**6**), are known to undergo Diels–Alder cycloadditions with dienes exclusively at the desired exocyclic double bond.[6] 5-Methylenebutenolide **6** is a constitutional isomer of **3** and **4**. On the basis of a methodology recently developed by our group for the synthesis of γ-hydroxybutenolides,[7] **6** might be synthesized via photooxygenation of a suitably substituted 2-thiophenylfuran such as **7** in ethanol with subsequent dehydration (Scheme 1). Furan **7**

Scheme 1. Our Retrosynthetic Scenario for (+)-Yaoshanenolide B and the Biosynthesis Proposed in the Isolation Paper



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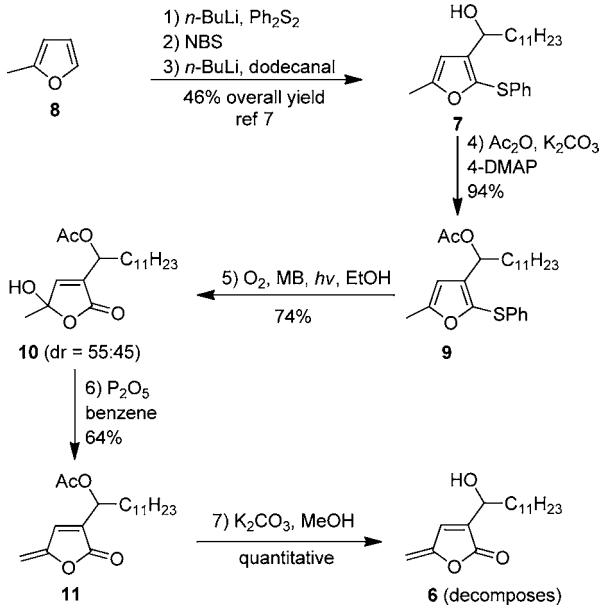
might in turn be readily obtained from 2-methylfuran (**8**) in 3 steps.[7,8]

To put this plan into action, the first task was to attempt the synthesis of the requisite dienophile, 5-methylene-2(5*H*)-furanone **6** (Scheme 2). Following steps elaborated earlier by

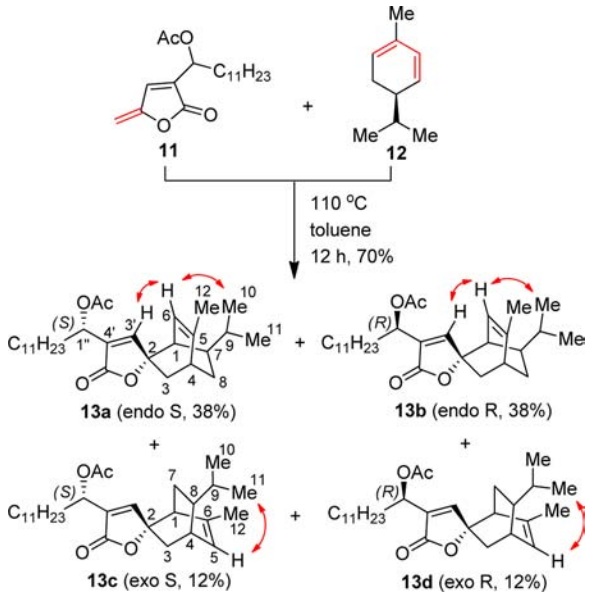
Scheme 2. Synthesis of Dienophile 5-Methylene-2(5*H*)-furanone 11



us,[7] 2-thiophenyl-substituted furanyl alcohol **7** was synthesized. The hydroxyl group of **7** was then protected as the corresponding acetate (compound **9**) because it was our intention to dehydrate a hydroxybutenolide later on in the sequence, and the possible concomitant dehydration of the *sec*-hydroalkyl moiety, which would then be present at the allylic position, needed to be avoided. Photooxygenation of **9** in ethanol[7] cleanly afforded γ-hydroxybutenolide **10** in good yield as a mixture of two diastereomers in a relative ratio of ∼55/45. Dehydration of **10** with P_2O_5 in benzene[9] led to 5-methylene-2(5*H*)-furanone **11** in 64% isolated yield. Although the basic hydrolysis of acetate **11** proceeded smoothly, the hydroxylfuranone **6** produced proved to be labile under the reaction conditions and decomposed rapidly. Thus, it was decided that we should proceed with the hydroxyl moiety of the projected dienophile still protected as an acetate (compound **11**). The lability of a structurally similar hydroxyl-substituted 5-methylene-2(5*H*)-furanone had been previously noted by our group during the synthesis of (*Z*)-ascladiol and isopatulin.[10] In that case, the problem was overcome by performing an enzyme (lipase)-catalyzed hydrolysis. In the current example, however, substrate **11** is exceedingly lipophilic, and an analogous enzyme-catalyzed hydrolysis conducted as required in pure water failed.

The biosynthetic scenario proposed by the isolation team required unnatural (*S*)-α-(+)-phellandrene. In our exploration of the key step, the Diels–Alder reaction that it was hoped would lead to the anticipated fused tricyclic 5′*H*-spiro-[bicyclo[2.2.2]oct[2]ene-7,2′-furan]-5′-one skeleton, we commenced by reacting natural (*R*)-α-(−)-phellandrene (**12**), which is readily available from commercial sources, with racemic dienophile **11**. The optimum conditions for achieving a quantitative reaction between **11** and (*R*)-α-phellandrene were found to be use of a dienophile/diene relative molar ratio of ∼1/3–4, a concentration of 0.6 mmol/mL for the dienophile in toluene, and heating to 110 °C for 12 h. There were four cycloaddition products: the two endo adducts **13a** and **13b** in equal amounts (combined ∼75% relative ratio) and the two exo adducts **13c** and **13d**, also present in equal amounts and in a ∼25% combined relative ratio (Scheme 3). The outcome of the

Scheme 3. Diels–Alder Reaction between Racemic 5-Methylene-2(5*H*)-furanone 11 and Natural (*R*)-α-Phellandrene



Diels–Alder reaction is impressive given that dienophile **11** was used as a racemate and each antipode has two diastereotopic faces. Furthermore, the diene used is unsymmetrically substituted and has two diastereotopic faces of approach for the dienophile[11] in exo and endo modes; thus, there were a total of 16 possible diastereomeric products. The origins of this reaction's stereoselectivity will be analyzed below. After very careful column chromatography purification, all four isomers were separated. The two slightly less polar major adducts **13a** and **13b** have an identical carbon skeleton in their bicyclic part, as judged by 2D NMR and NOE experiments, and thus differ only in the relative stereochemistry in the stereogenic center bearing the acetate group. This result is not surprising given that **11** was a racemate. These two isomers were assigned as being endo products on the basis of typical NOEs enhancements observed between the olefinic hydrogen atom on the butenolide ring H3′ and olefinic hydrogen H6 as well as the vinyl methyl (H12) on the bridge of the phellandrene-derived bicyclic moiety. The relative position/stereochemistry of the isopropyl group on the bicyclic moiety was established beyond doubt (as shown), given the NOE enhancements for both isomers **13a** and **13b** between the olefinic hydrogen atom H6 and the methyls of the isopropyl (C10 and C11).[12] The spiro system is connected as appears on C2 (and not on C3) because the tertiary allylic hydrogen atom H1 presents as a clean doublet of doublets as a result of its coupling with olefinic H6 and homoallylic H7, in contrast to the analogous tertiary allylic H4, which appears as a broad multiplet. In addition, an HBMC correlation between H6 and the spiro carbon C2 clearly

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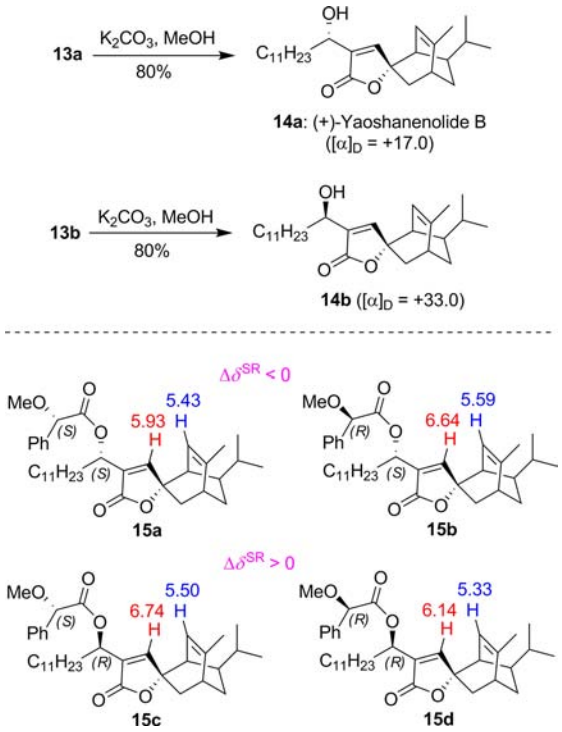
supports this structural assignment. Analogous NOE signal enhancements between the two olefinic hydrogen atoms H3′ and H5 are clearly absent in the minor isomers **13c** and **13d**. The carbon framework for these isomers (connection of the spiro system on C2 and not on C3) was established by the fact that there is no HBMC correlation between the olefinic H5 and the spiro carbon C2. As a result, isomers **13c** and **13d** were assigned as the exo products (Scheme 3), which are not related to the yaoshanenolide B framework and thus were not considered further. The relative position of the isopropyl groups in these minor diastereoisomers was assigned on the basis of the NOE signal enhancement observed between the olefinic hydrogen atom on the bridge of the bicycle (H5) and the isopropyl methyl groups.

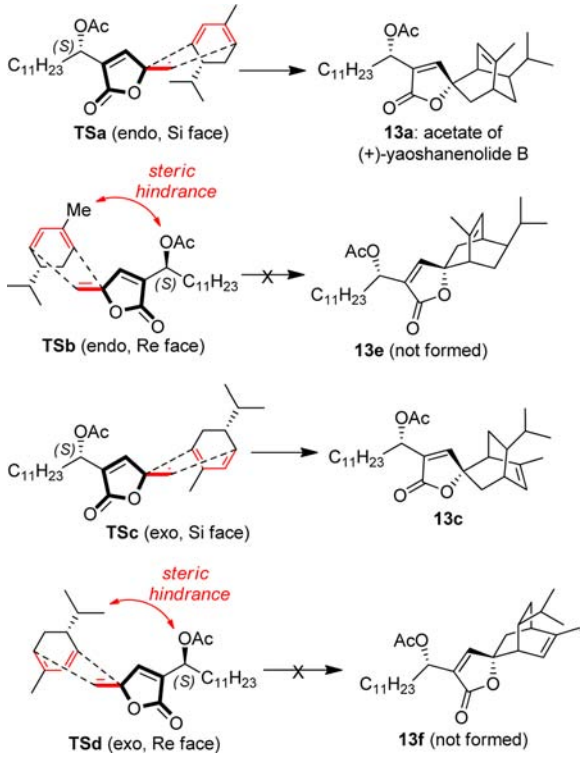
Scheme 4. Deprotection of the Endo Adducts 13a and 13b and Proof of the Structure of (+)-Yaoshanenolide B Assigned as Compound 14a



The next steps were deprotection of the acetate group of the major isomers **13a** and **13b** and a subsequent check to see whether any of the corresponding alcohols matched yaoshanenolide B. Thus, treatment with K_2CO_3 in MeOH yielded **14a** and **14b**, respectively (Scheme 4). To our delight, the ^1H[13] and, more importantly, the ^{13}C NMR data of **14a** match perfectly those of the natural product, while the specific rotation of **14a** ($[\alpha]_D$ = +17.0, c = 0.6 in $CHCl_3$) is very close to that reported for the natural product in the isolation paper ($[\alpha]_D$ = +19.6, c = 0.48 in $CHCl_3$). On the other hand, the NMR data of **14b** are quite close to the natural product's but are not identical, and the specific rotation of $[\alpha]_D$ = +33.0 (c = 0.6 in $CHCl_3$) is not in agreement with the reported one. In regard to the correct structure of the natural product, the first conclusion was that if unnatural (*S*)-α-phellandrene had been used, the optical rotation of both synthetic diastereomers **14a** and **14b** should not have had a positive sign.

To complete the characterization, the stereochemistry of the secondary alcohol was established through the formation of MPA esters (using both enantiomers of α-methoxyphenylacetic acid) and comparison[14] of the ^1H NMR data for each pair of diastereomeric esters formed (Scheme 4). The differences $\Delta\delta^{SR}$ in the chemical shifts of the two olefinic resonances (right hemisphere of molecules as depicted) for the (*S*)- and the (*R*)-MPA esters **15a** and **15b** derived from **14a** are negative ($\Delta\delta^{SR}$ = −0.71 ppm for the olefinic H3′ on the butenolide, and $\Delta\delta^{SR}$ = −0.16 ppm for the olefinic H6 on the bicycle), while for the corresponding (*S*)- and (*R*)-MPA esters **15c** and **15d** derived from **14b** the differences are positive ($\Delta\delta^{SR}$ = +0.60 ppm for the olefinic H3′, and $\Delta\delta^{SR}$ = +0.17 ppm for the olefinic H6). These results establish the absolute configuration at C1″ as *S* in **14a** (in agreement with the proposed configuration in the isolation paper) and as *R* in **14b**.

Scheme 5. Possible Transition States in the Reaction between (*S*)-11 and the Less Hindered Face of (*R*)-α-Phellandrene



The origins of the selectivity in the Diels−Alder reaction between **11** and (*R*)-α-phellandrene (**12**) are shown in Scheme 5. For clarity, we consider only the *S* enantiomer of the dienophile. In the [4 + 2] reaction between (*S*)-**11** and **12**, eight possible transition states can be drawn: two endo and two exo transition states arising from the approach of the *Si* and *Re* faces of (*S*)-**11** toward the less hindered face of the diene and an additional two endo and two exo transition states arising through reaction with the more hindered face of the diene. In transition state **TSa** that forms **13a**, the acetate of the natural product (+)-yaoshanenolide B, there is a remarkable facial selectivity with regard to the exocyclic double bond of the dienophile. The less hindered face of (*R*)-α-phellandrene approaches the *Si* face of the double bond of the dienophile in an endo fashion. Analysis of simple models reveals that in

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any other endo approach between any face of the diene and either the *Si* or *Re* face of the exocyclic double bond of the dienophile, steric interactions develop between the vinylic methyl or the isopropyl group of α-phellandrene and the acetoxyalkyl side chain of the butenolide or the butenolide itself. For instance, the endo transition state **TSb**, which occurs when the less hindered face of the diene approaches the *Re* face of the dienophile (Scheme 5), is unfavorable, and the product **13e** is not formed. The same steric factors control the outcome of all possible exo approaches, giving rise to the formation of **13c** (transition state **TSc**) as a minor product. In **TSc** there is an exo approach of the less hindered face of the diene to the *Si* face of the dienophile. It should be noted that analogous approaches of (*R*)-α-phellandrene to the *Si* face of the *R* enantiomer of **11** lead to **13b** (endo) and **13d** (exo), respectively. Exo approach from the *Re* face should form **13f**, which is excluded on the basis of the lack of an HBMC correlation between olefinic H5 and C2 (see the Supporting Information). Therefore, the presence of a stereogenic center on dienophile **11** has nothing to do with the facial selectivity seen at its double bond.

In conclusion, we have achieved the first total synthesis of (+)-yaoshanenolide B and revised its structure. The natural product was found to be a diastereomer of the initially proposed structure at C7. The key step in this short synthesis (five steps from a known compound and eight steps total) is a stereoselective Diels–Alder reaction between (*R*)-α-phellandrene and the exocyclic double bond of a 5-methylene-2(5*H*)-furanone. The dienophile was synthesized using as the key step photooxygenation of a furan,[15] adding a new example of singlet oxygen's utility in natural product syntheses.[16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02446.

Experimental section, product spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra of all reaction products (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Although NOESY data were not provided for yaoshanenolide B, in the NOESY spectrum of the structurally similar yaoshanenolide A, an NOE correlation appears between olefinic H6 and the isopropyl group (see the Supporting Information of ref 1), in agreement with our structural assignment.
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