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Asymmetric Total Syntheses of *ent*-Ascospiroketals A and B

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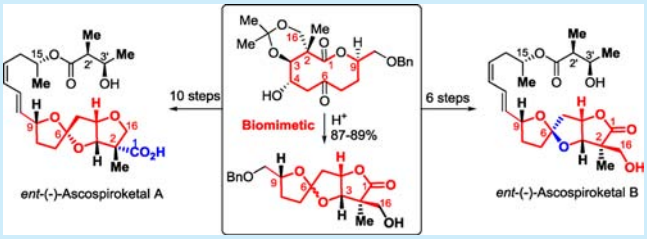
Supporting Information

ABSTRACT: A new hypothetic biosynthesis of the tricyclic spiroketal core of ascospiroketals A and B is proposed, which guided the development of a novel synthetic strategy for the asymmetric total synthesis of *ent*-ascospiroketals A and B. The synthesis features an efficient ring contraction rearrangement of the 10-membered lactone to the tricyclic spiroketal *cis*-fused γ-lactone core, which served as the common intermediate for the synthesis of both *ent*-ascospiroketals A and B through the Stille coupling reaction at the final step. In addition, seven diastereomers were prepared to conclusively confirm the structure of *ent*-ascospiroketal B.



Ascospiroketals A and B (Figure 1a) were reported in 2007 by König[1] and co-workers as an unprecedented structural

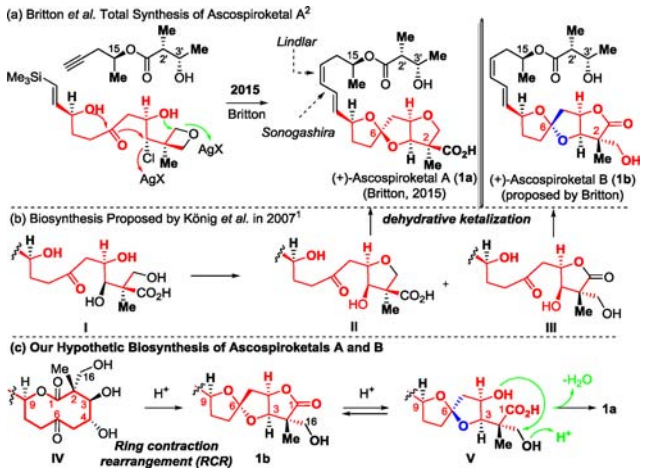


Figure 1. (a) Synthetic strategy of Britton et al.[2] to ascospiroketal A, the revised structure of ascospiroketal B; (b) possible biosyntheses of the tricyclic core of ascospiroketals A and B proposed by König et al.;[1] (c) our hypothetic biosynthesis.

type, but with no stereochemical information about the side chain or relative configuration relationship between the tricyclic core and the side chain after unsuccessful attempts using degradation and J-based approaches. In 2015, Britton[2] et al. reported an elegant Ag-promoted cyclization cascade syntheses of four candidate stereostructures for (+)-ascospiroketal A (**1a**) and established its relative and absolute stereochemistry by meticulous comparison of their NMR spectra and sign of the specific rotations (Figure 1a). Ascospiroketal B was thought to have the same relative and absolute stereochemistry as **1b** (Figure 1a), even though the tricyclic core is obviously different from the corresponding sector of ascospiroketal A. Such structural revision of ascospiroketal B calls for confirmation by total synthesis, which has not been reported to date and promoted our interest in undertaking this challenge with additional consideration of the unprecedented substitution[3] of the tricyclic 5,5-spiroacetal *cis*-fused γ-lactone (SAFL)[4] with a methyl and a hydroxymethylene group at the C2 position.

In addition, we were particularly attracted by the biosynthetic hypothesis of ascospiroketals A and B by König,[1] who, on the basis of Oltra's biosynthetic hypothesis of cephalosporolides E and F from bassianolone,[5] proposed that the tricyclic core might be formed by dehydrative ketalization of **II** and **III** that were derived from the ring closure of the common linear precursor **I**, respectively (Figure 1b). However, we disclosed in 2014 that the structure for bassianolone was wrong.[6] Therefore, we speculated that the biosynthesis of the tricyclic spiroketal core of ascospiroketals should be similar to our revised hypothetic biosynthesis of cephalosporolides.[7]

This assumption directed us to propose a similar ring contraction rearrangement of the 10-membered lactone **IV** to the tricyclic SAFL, corresponding to ascospiroketal B **1b** (Figure 1c). Under the acidic conditions, the tricyclic SAFL might isomerize at the spiroketal center with simultaneous lactone opening to produce the intermediate **V**, which subsequently underwent an intramolecular etherification to generate the tricyclic 5,5-spiroacetal *cis*-fused tetrahydrofuran (SAFT) core of ascospiroketal A **1a**. If our hypothesis is correct, the possible biosynthesis of all SAFL-bearing natural products[4] including their direct congeners (e.g., ascospiroketal A) could be understood by a uniform process involving a ring contraction rearrangement of the 10-membered lactones. Herein, we describe our synthetic efforts on this hypothetic ring contraction rearrangement of the 10-membered lactone to the tricyclic SAFL core, culminating in the first, asymmetric total synthesis of *ent*-ascospiroketals A and B, confirming the stereochemical assignments by Britton. Notably, unprecedented chemical conversion

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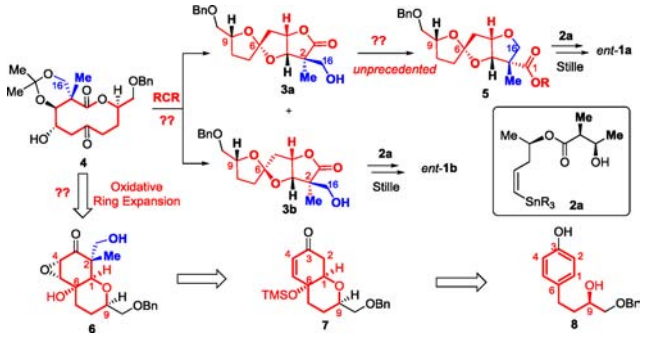
of the key tricyclic SAFL core to ascospiroketal A, mimicking our hypothesis (**1b** → **V** → **1a**) in Figure 1c, was achieved efficiently.

At the outset of our synthetic plan, we chose to prepare the enantiomers of the natural ascospiroketals A and B and expected to further corroborate the absolute configuration established by Britton et al.,[2] who reported the significantly low specific rotation value of the synthetic **1a**. Our synthetic strategy toward ascospiroketals was built on our biosynthetic hypothesis: ring contraction rearrangement of the 10-membered lactone **4** to the tricyclic SAFLs **3a** and **3b**, which would be elaborated individually to *ent*-ascospiroketals A and B, respectively, through Stille cross-coupling reactions with vinylstannane **2a** as the key step at the late stage (Scheme 1). The key 10-membered lactone

Scheme 1. Retrosynthetic Analysis Based on Our Revised Biosynthetic Hypothesis

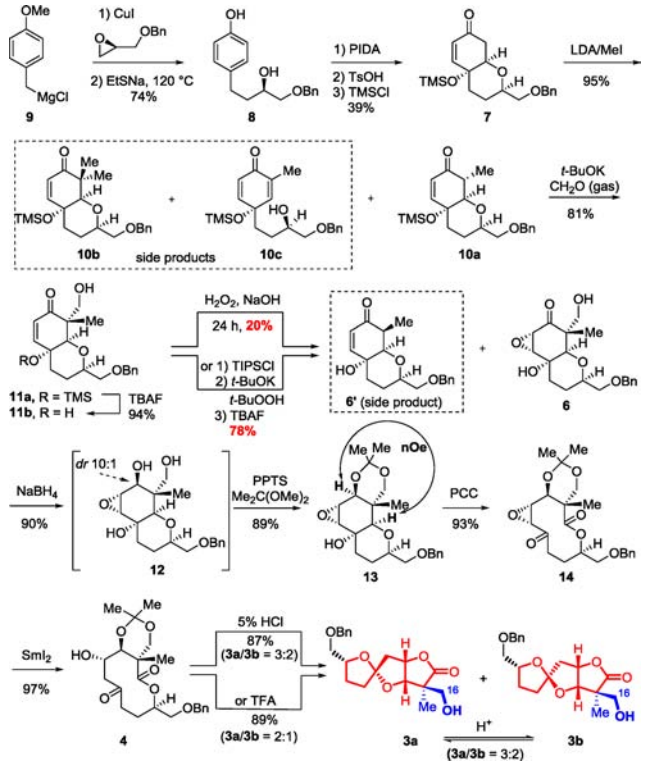


4 could be derived from phenol **8** through phenol oxidative dearomatization[8]/oxa-Michael cyclization (**8** → **7**),[9] methylation followed by aldol reaction with formaldehyde (**7** → **6**), and PCC-mediated oxidative ring expansion.[10] Notable in this route to SAFLs **3a** and **3b** were that the stereochemistry at C2, C3, C4, and C9 of the ascospiroketals could be derived from the absolute stereochemical information at C9 of the phenol **8** and that the 10-carbon skeleton of the tricyclic SAFLs featured in ascospiroketals originates from the 10 carbons of the phenol **8** including six aromatic carbons. However, the obvious challenges of this route included (1) the unknown C2 disubstitution effect on the two key reactions: PCC-mediated oxidative ring-expansion and acid-promoted ring-contraction rearrangement, (2) stereoselective construction of the C2 all-carbon quaternary center, and (3) the unprecedented rearrangement of the SAFL **3a** to the SAFT **5**.

As depicted in Scheme 2, our synthesis began with the preparation of enantiomerically pure phenol **8** by epoxide opening with in situ generated Grignard **9** and subsequent demethylation with EtSNa.[11] Phenol oxidative dearomatization of **8** proceeded smoothly, and subsequent oxa-Michael cyclization was effectively promoted by *p*-TsOH at room temperature to provide the bicyclic ether **7** after protection of the tertiary alcohol as the trimethylsilyl ether. Monomethylation of **7** was highly susceptible to the reaction conditions such as the base, solvent, temperature, and the time of deprotonation.[12]

Nevertheless, the well-optimized condition still delivered 95% yield of **10a** as the single diastereomer with very small amounts of side products **10b** (double methylation) and **10c** (*retro*-oxa-Michael addition). The aldol reaction[13] of **10a** with gaseous formaldehyde in situ generated by pyrolysis of paraformaldehyde was effected best by *t*-BuOK to provide a mixture of **11a** and **11b** in 81% combined yield and the retro-oxa-Michael product **10c** in 5−10% yield, while other attempted bases including LDA,[12,13]

Scheme 2. Synthesis of Tricyclic SAFL 3a and 3b



KHMDS, NaHMDS, and LiHMDS resulted in formation of a significant amount of **10c** (>20% yield). Epoxidation of **11a** or **11b** with the classical $NaOH/H_2O_2$ in methanol was found to be sluggish (about 20% conversion over 24 h), while extended reaction time (2−4 days) led to significant retro-aldol reaction of **11a**, **11b**, and **6**. Since most relative epoxidation conditions[14] (K_2CO_3/H_2O_2/MeOH, *t*-BuOOH/NaH/THF, *t*-BuOOH/DBU/CH_2Cl_2, *t*-BuOOH/Amberlyst21/THF, and DMDO/CH_2Cl_2) failed, we decided to temporarily protect the troublesome alcohol as its triisopropylsilyl (TIPS) ether. Gratifyingly, the TIPS ether was resistant to desilylation and suppressed the undesired retro-aldol reaction under the epoxidation conditions (*t*-BuOK/ *t*-BuOOH/THF), which produced **6** in 78% overall yield after desilylation with TBAF. Alcohol-directed $NaBH_4$ reduction[15] of the ketone **6** occurred with excellent diastereoselectivity (dr 10:1) to provide the triol **12**, for which relative stereochemistry was confirmed by NOE experiments of its acetonide derivative **13**. PCC-mediated oxidative ring expansion[10] proceeded smoothly to provide the 10-membered lactone **14**, which underwent rapid and effective reductive epoxide ring opening with SmI_2[16] to provide the substrate **4** for the key ring-contraction rearrangement. To our delight, using our optimized conditions, the ring-contraction rearrangement of 10-membered lactone **4** with either 5% HCl/MeOH or TFA/THF/H_2O produced a separable mixture of the tricyclic SAFLs **3a** and **3b** (3:2 to 2:1) in a remarkable 87−89% combined yield. It was found that under mild acidic conditions (5% HCl in MeOH) the spiroisomeric **3a** and **3b** equilibrated readily at the constant ratio 3/2 at room temperature within 3 h. The assignments of the spiroepimeric structures to the corresponding (6*S*)-**3a** and (6*R*)-**3b** were made on the basis of their distinct ^1H NMR coupling patterns (H4: triplet versus doublet of doublet of doublets) similar to those SAFLs reported by Brimble.[17]

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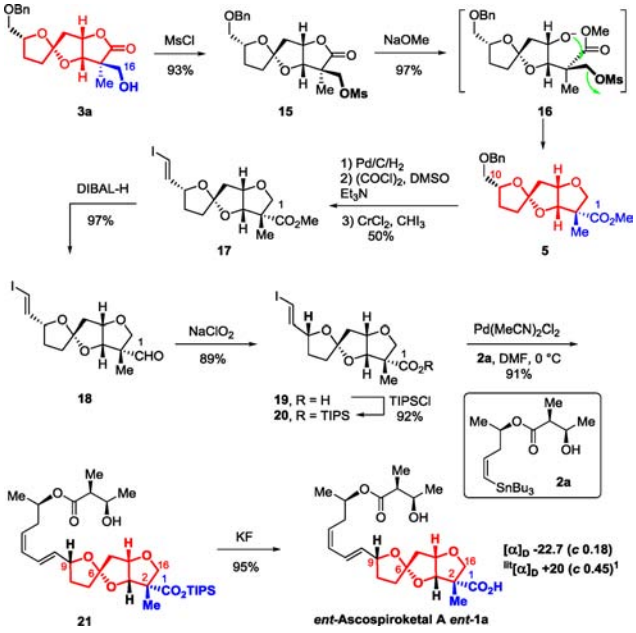
With the key tricyclic SAFLs (**3a** and **3b**) in hand, we set out to prepare *ent*-ascospiroketal A (*ent*-**1a**) through the planned rearrangement of the tricyclic SAFL **3a** to the tricyclic spiroacetal-*cis*-fused-tetrahydrofuran SAFT **5** (Scheme 3). To

Scheme 3. Total Synthesis of *ent*-Ascospiroketal A *ent*-1a

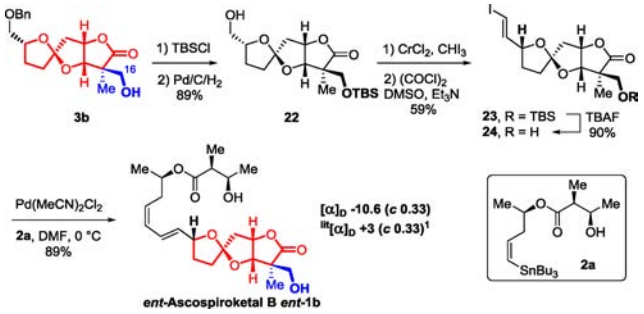


this end, the C16 alcohol of **3a** was converted into a leaving group mesylate **15**, which upon treatment of NaOMe in MeOH at 40 °C for 12 h produced the SAFT **5** in a remarkable 97% yield. To the best of our knowledge, this rearrangement of the tricyclic SAFL (**3a**/**15**) to the SAFT (**5**) was unprecedented,[18] but the ease of this process might reveal the biogenetic relationship of these two ring systems of ascospiroketal A and B.

Further elaboration of the SAFT **5** to *ent*-**1a** entailed functional group transformations of C10 benzyl ether to vinyl iodide for Stille coupling with vinylstannane **2a** (for preparation, see Scheme 5). The alcohol at C10 was unmasked quantitatively by palladium-catalyzed hydrogenation and then oxidized by Swern oxidation.[19] Fourther Takai olefination[20] of the resulting aldehyde in dioxane/THF (5:1) gave vinyl iodide **17** as a 5:1 *E*/*Z* mixture in 70% yield while using THF as the only solvent decreased the *E*/*Z* selectivity to 2:1 *E*/*Z* ratio.[21] Sequential DIBAL-H reduction and Pinnick oxidation[22] delivered acid **19** in 86% yield. Unfortunatly, Stille coupling reaction of vinyl iodide **19** with vinylstannane **2a** upon treatment of catalytic Pd(MeCN)$_2$Cl$_2$ (or Pd(PPh$_3$)$_4$[23]) in DMF at 0 °C led to extensive homocoupling byproduct, which showed the carboxylic acid was not suitable in the Stille coupling reaction. This issue had to be solved via an alternative route: TIPS protection and desilylation. Nevertheless, this route provided a reliable entry to *ent*-(−)-ascospiroketal A (*ent*-**1a**, SSL, 25 steps with 3.47% overall yield). The NMR spectra of our synthetic *ent*-**1a** was consistent with those reported for the natural product except for the opposite sign of the specific rotation [[α]$_D$ −22.7 (*c* 0.18 in MeOH) (lit.[24] [α]$_D$ +20 (*c* 0.45 in MeOH))].

Next, we focused our attention to the synthesis of *ent*-ascospiroketal B from the tricyclic SAFL **3b** (Scheme 4). The primary alcohol at C16 of **3b** was protected as its TBS ether and the alcohol at C10 was unmasked quantitatively by palladium-catalyzed hydrogenation to provide **22**, which underwent the

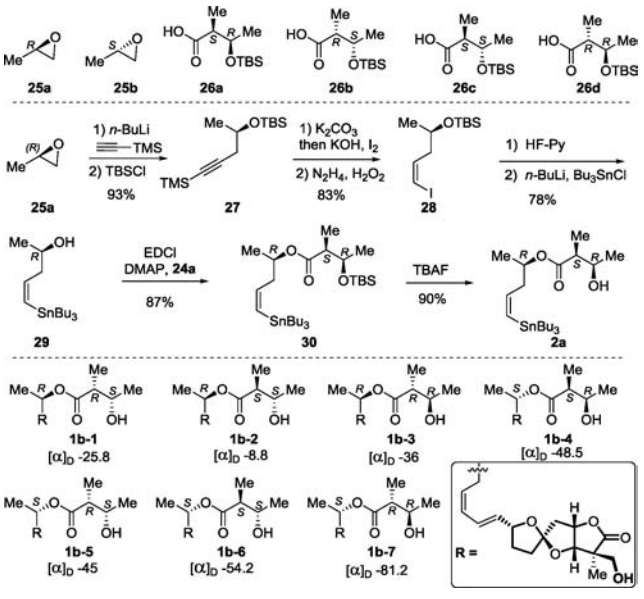
Scheme 4. Total Synthesis of *ent*-Ascospiroketal B *ent*-1b



Swern oxidation and Takai olefination to provide vinyl iodide **23** in 60% yield. Desilylation of **23** with TBAF provided the key vinyl iodide **24**, which was efficiently coupled with vinylstannane **2a** upon treatment of catalytic Pd(MeCN)$_2$Cl$_2$ in DMF at 0 °C, furnishing *ent*-(−)-ascospiroketal B (*ent*-**1b**) in 89% yield. All spectroscopic data matched perfectly those of the natural material ($\Delta\delta$(^{1}H) ≤ 0.01 ppm, $\Delta\delta$ (^{13}C) ≤ 0.1 ppm) except for the opposite sign of their specific rotation [[α]$_D$ −10.6; (lit.[25] [α]$_D$ +3)]. This constitutes the first total synthesis of *ent*-ascospiroektal B (LLS 21 steps with 5.19% overall yield).

Finally, we investigated the relative configuration relationship between the side chain and the tricyclic core of ascospiroketal B since the remote stereocenters might result in identical NMR spectra for diastereomers, which is not rare in the literature.[26] The high convergency of our synthetic route (e.g., the side chain was coupled with the tricyclic core at the last step, Scheme 2) offerred us a great opportunity to examine this issue. As depicted in Scheme 3, the preparation of eight diastereomeric vinylstannanes **2a**−**h** was readily achieved in a parallel fashion in eight steps from two enantiomerically pure propene oxides (**25a**,**b**) and four chiral nonracemic TBS-protected 3-hydroxy-2-methylbutyric acids (**26a**−**d**).[27] Not surprisingly, the other seven diastereomers (**1b-1** to **1b-7**) of *ent*-**1b** were obtained with similar or identical yields (87−91%) in the final Stille coupling reactions (Scheme 5). Comprehensive analysis (see the

Scheme 5. Synthesis of Vinylstannane 2a and Its Diastereomers and Seven Diastereomers of *ent*-1b



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Supporting Information) of the NMR spectra derived from all synthetic samples and the authentic ascospiroketal B was performed and revealed that these eight diastereomers had different ^{1}H and ^{13}C NMR spectra.[25] In particular, the specific rotation derived from these eight synthetic materials (*ent*-**1b** and **1b-1**−**1b-7**) was negative irrespective of their stereochemistry at the side chain, suggesting that the tricyclic SAFL core is responsible for the dextrorotary/levorotary rotation direction of the plane-polarized light.[28] These findings conclusively substantiated *ent*-**1b** to be the enantiomer of the natural ascospiroketal B.

In summary, a new biosynthetic pathway for the tricyclic core of ascospiroketals A and B was proposed and guided us to develop a novel synthetic strategy that lead to convergent asymmetric total syntheses of *ent*-ascospiroketals A and B. Seven additional diastereomers of *ent*-ascospiroketal B were prepared, which upon comprehensive spectral analysis allowed us to conclusively substantiate our synthetic *ent*-**1b** to be the enantiomer of the ascospiroketal B. Our synthesis was enabled by a ring contraction rearrangement of the 10-membered lactones to the structurally unique tricyclic 5,5-spiroacetal-*cis*-fused-γ-lactone (SAFL) framework and Stille coupling at the final stage of the synthesis. The synthetic studies not only greatly extended our biomimetic strategy developed for total synthesis of cephalosporolides but also provided solid chemical evidence supporting plausibly similar biosynthesis of ascospiroketals and cephalosporolides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00796.

Detailed experimental procedures, comprehensive NMR spectra (data) comparison, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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