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Biomimetic Asymmetric Total Syntheses of Spirooliganones A and B

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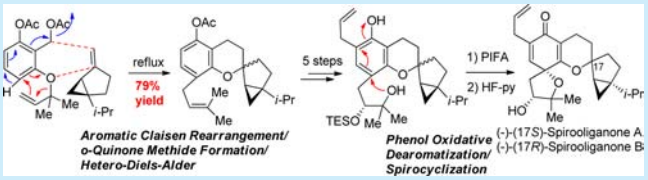
Supporting Information

ABSTRACT: Biomimetic total syntheses of potent antiviral spirooliganones A and B were achieved with 3% and 2% yield, respectively, in 12 steps from commercially available materials. The synthetic strategy was inspired primarily by the biogenetic hypothesis and was enabled by two independent cascade events: (i) an unprecedented reaction involving aromatic Claisen rearrangement/*o*-quinone methide formation/hetero-Diels–Alder cycloaddition to construct the tetracyclic framework and (ii) phenol oxidative dearomatization/spirocyclization to build the spiro-fused cyclohexadienone/tetrahydrofuran moiety.



Influenza virus infections continue to threaten human life as evident by a recent influenza pandemic in 2009 (H1N1/09, >17,700 deaths).[1] Mutations of influenza viruses would make the current antiviral drugs/vaccines ineffective, and the deadly mutated viruses would spread rapidly and pose a pandemic threat. In addition to the slow vaccine development,[2] antiviral agents would provide a first line of defense and a powerful weapon against these deadly influenza viruses.[3] In the search for new antiviral natural products, Yu[4] and co-workers reported in 2013 the two structurally novel antiviral spirooliganones A and B (Figure 1) isolated from the roots of *Illicium oligandrum*, which has demonstrated a variety of antiviral activities and has been widely used in Chinese folk medicine for treatment of rheumatoid arthritis. In contrast to other natural products from this species displaying no antiviral activity, spirooliganones A and B were found to exhibit potent activity against Coxsackie virus B3 and influenza virus A/Hanfeng/395/95 (H3N2) with IC_{50}'s ranging from 3.7 to 33.3 μM, which with comparable selectivity index (TC_{50}/IC_{50}) are stronger than that of the clinically used ribavirin. Noticeably, although its selectivity index value was less than that of the positive control oseltamivir (Tamiflu), spirooliganone B showed comparable activity against influenza A with an IC_{50} of 5.05 μM. Therefore, spirooliganones with skeletons distinct from those of all known antiviral agents (cf., oseltamivir and zanamivir) hold great potential as promising antiviral drugs/leads. In addition, spirooliganones A and B displayed moderate cytotoxicity against Vero and MDCK cells.

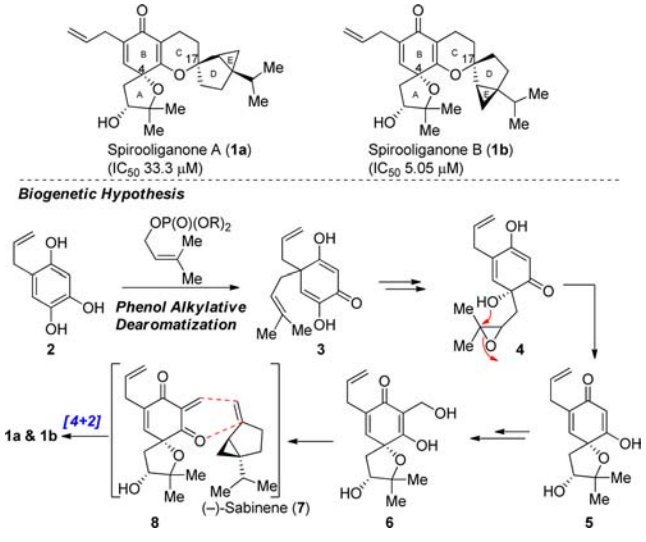


Figure 1. Spirooliganones A and B and their biogenetic hypothesis.

Structurally, spirooliganones A and B were reported as spiro-isomers at C17. The 5/6/6/5/3 pentacyclic skeleton (ABCDE rings) of spirooliganones, confirmed by the single-crystal X-ray diffraction analysis of their benzoate derivatives, was unprecedented in natural products. Particularly, the fashion of ring conjunction as dioxa-spiro (AB and CD) was very unique, which might pose significant synthetic challenges. The combination of the potent antiviral activity and the structural novelty prompted us to undertake synthetic studies of spirooliganones A and B. Herein, we report a biomimetic total synthesis of spirooliganones A and B, which were enabled by two independent cascade reactions: (i) aromatic Claisen rearrangement/*o*-quinone methide formation/hetero-Diels–Alder cycloaddition and (ii) phenol oxidative dearomatization/spirocyclization. It was noted that Xie and co-workers reported the first total synthesis of spirooliganones A and B employing a similar oxidative dearomatization/cyclization.[5]

Biogenetically (Figure 1), diastereomeric spirooliganones A and B were proposed to be derived from the 5-allylbenzene-1,2,4-triol (**2**) via a number of key steps including the phenol alkylative dearomatization (prenylation, **2** → **3**), 1,3-σ migration[6]/epoxidation (**3** → **4**), 5-*endo*-*tet* cyclization via epoxide opening[7] (**4** → **5**) and hetero-Diels–Alder reaction[8] of *o*-quinone methide (**8**) and (−)-sabinene (**7**) (**6** → **1a** and **1b**).

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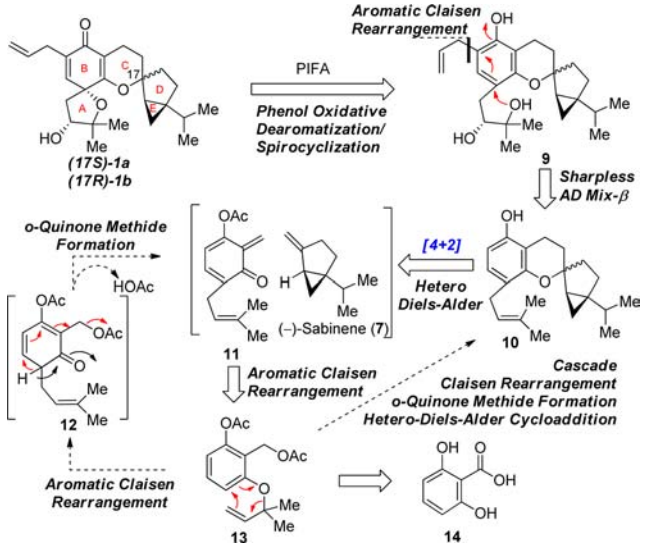
It is noteworthy that the regioselective hetero-Diels–Alder reaction of *o*-quinone methides,[9] consistent with the natural production of spiroisomeric spirooliganones A and B, has been proposed in many biosyntheses of other natural products and successfully exploited as a key synthetic strategy for biomimetic total synthesis.[10]

Inspired by this biosynthetic hypothesis and previous insights on hetero-Diels–Alder reaction of *o*-quinone methides,[10] we proposed a biomimetic synthetic strategy[11] for spirooliganones A and B (**1a** and **1b**) as depicted in Scheme 1. We envisioned

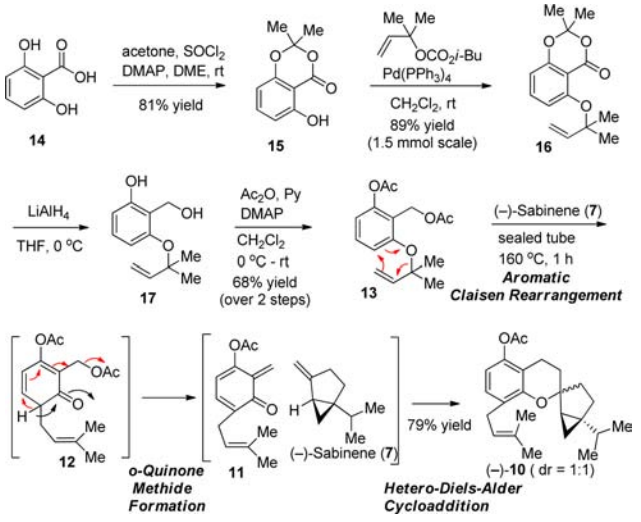
Scheme 1. Synthetic Plan for Spirooliganones A and B



that the spiro-fused AB rings of spirooliganones might arise from the phenol oxidative dearomatization[12] and simultaneous, favorable 5-*exo*-*trig* spirocyclization[13] (**9** → **1**, Scheme 1) at the final stage of synthesis. This orchestration as compared with the corresponding transformations in the biogenetic hypothesis would minimize the manipulations of the inherently unstable cyclohexadienone moiety[14] and avoid the involvement of a chemically unfavorable 5-*endo*-*tet* cyclization via epoxide opening (**4** → **5**, Figure 1) according to Baldwin's rule.[15] In fact, a similar phenol oxidative dearomatization/cyclization has been proposed as a potential biosynthetic pathway for many natural products (cf., aculeatins and amonols) and elegantly exploited for biomimetic total synthesis.[16] In light of these facts, we speculated that spirooliganones might be biogenetically produced via this type of processes. The structure of type **9** could be prepared in a straightforward manner from **10** in three steps: Sharpless asymmetric dihydroxylation, phenol *ortho*-allylation, and aromatic Claisen rearrangement.[17] The construction of the key tetracyclic framework (BCDE rings, **10**) could be achieved in a biomimetic fashion by a hetero-Diels–Alder cycloaddition of (−)-sabinene (**7**) and *o*-quinone methide **11**. Given the fact that *o*-quinone methides were unstable and commonly generated *in situ* by elimination of a neutral small molecule such as H_2O, HOAc, or $RNMe_2$,[10] we proposed that the *o*-quinone methide **11** could arise from a thermal aromatic Claisen rearrangement of **13** followed by elimination of acetic acid, although such method was unprecedented in the literature. Due to the same thermal reaction conditions for hetero-Diels–Alder cycloaddition and aromatic Claisen rearrangement/*o*-quinone methide formation, we imagined that these two processes could be performed in a single pot sequentially, which would become a highly concise cascade reaction (**13** → **12** → **11** → **10**, Scheme 1). The easy preparation of **13** from the commercially available **14** via several known transformations encouraged us to explore this sequence first. If successful, such cascade reaction would generate two carbon–carbon bonds and one carbon–oxygen bond, leading to the tetracyclic core system of spirooliganones. In addition, both spirooliganones A and B might be produced from the hetero-Diels–Alder cycloaddition reaction in support of their biogenetic hypothesis.

Our synthesis (Scheme 2) began with preparation of acetonide **15** from commercially avialable 2,6-dihydroxybenzoic

Scheme 2. Synthesis of Tetracyclic Framework of Spirooliganones A and B



acid (**14**) by using the protocol developed by Jennings.[18] Palladium-catalyzed etherification[19] of **15** with isobutyl-2-methyl-3-buten-2-yl carbonate provided the ether **16** in 89% yield as a single regioisomer. It was noted that the reaction yield on large scale (3–10 mmol) dropped significantly to 20–55%. Consequently, the reaction on a 1.5 mmol scale was repeated several times to supply sufficient amount of **16** for further elaboration. Reduction of ester **16** with $LiAlH_4$, followed by acylation with acetic anhydride in the presence of pyridine and 4-dimethylaminopyridine, gave the desired substrate **13** in 68% yield over two steps. Thus, we arrived at the first key cascade reaction. When a solution of **13** in (−)-sabinene (used as the solvent) was heated to reflux (∼160 °C) under nitrogen atmosphere in a sealed tube, to our delight, it cleanly produced a 1:1 diastereomeric mixture of the desired tetracyclic core system (**10**) in a remarkable 79% yield with an exclusive regioselectivity.[9,10] It was noteworthy that the tethered trisubstituted alkene of *o*-quinone methide **11** did not compete with the 1,1-disubstituted alkene of sabinene for hetero-Diels–Alder cycloaddition in either intra- or intermolecular manner, which was a main concern in our design phase. Mechanistically, this novel cascade reaction was proposed to start with aromatic Claisen rearrangement[20] of **13** upon heating to provide the hypothetic intermediate **12**, followed by 1,6- or 1,4-elimination of acetic acid[21] to give *o*-quinone methide **11**, which underwent regioselective hetero-Diels–Alder cycloaddition with sabinene. To the best of our knowledge, this is a new cascade reaction and the first example recording *in situ* formation of *o*-quinone methide from aromatic Claisen rearrangement. In addition, the

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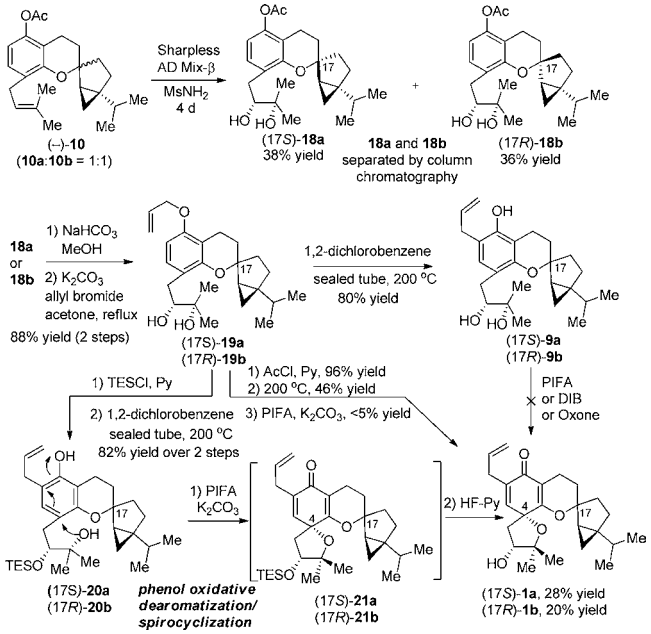
successful implementation of hetero-Diels–Alder cycloaddition of *o*-quinone methide and sabinene provided compelling chemical evidence in support of the hetero-Diels–Alder cycloaddition process in the biogenetic hypothesis of spirooliganones.

With the key tetracyclic core (**10**) in hand, we directed our attention to explore the phenol oxidative dearomatization/spirocyclization as proposed in our synthetic plan (Scheme 1). To this end, (−)-**10** (a mixture of **10a** and **10b**) required to be further elaborated to phenol **9** (Scheme 3).

Scheme 3. Completion of Total Syntheses of Spirooliganones A and B via Phenol Oxidative Dearomatization/Spirocyclization



First, Sharpless asymmetric dihydroxylation of the diastereomeric mixture of (−)-**10** (**10a** and **10b**) with AD mix-β at 0–8 °C for 4 days provided two separable diastereomers, **18a** (38% yield) and **18b** (36% yield), in excellent combined yield. The individual diastereomer (**18a** or **18b**) was employed in the subsequent transformations. After removal of the acetyl protecting group of **18a** and **18b**, the resulting crude phenol was alkylated with allyl bromide in the presence of K_2CO_3 to give **19a** and **19b**, respectively, in excellent yield. Aromatic Claisen rearrangement of **19a** and **19b** at 200 °C in a sealed tube cleanly produced the desired phenol **9a** and phenol **9b**, respectively, which unfortunately decomposed in the course of phenol oxidative dearomatization with various oxidants and solvents.[22] Careful analysis of the ^{1}H NMR spectra of the crude products led us to discover that a characteristic aldehyde signal was present, which might be attributed to an oxidative cleavage of the vicinal diol. Therefore, the secondary alcohol of individual **19a** and **19b** was selectively protected as triethylsilyl ether derivative, which was used directly for aromatic Claisen rearrangement at 200 °C to provide the desired phenol **20a** and phenol **20b**, respectively, for the final phenol oxidative dearomatization/spirocyclization. To our delight, after screening a variety of oxidants and solvents, we found that treatment of **20a** (or **20b**) with PIFA in the presence of K_2CO_3 promoted smoothly the phenol oxidative dearomatization/spirocyclization in an exclusive 5-*exo*-*trig* cyclization manner to furnish the spirooliganones A and B, respectively, as the major isolable products in moderate yields after desilylation with HF-pyridine. It was noted that the acetyl derivative of **19a** (or **19b**) led to a lower yield, and the resulting aromatic Claisen rearrangement adduct produced only trace amount of **1a** or **1b**. Nonetheless, the successful implementation of the phenol oxidative dearomatization/spirocyclization implied that **1a** and **1b** might arise from a similar biological cyclization process in the roots of *Illicium oligandrum*. All spectroscopic data of our synthetic **1a** and **1b** were in well agreement with those reported for the natural **1a** and **1b**.[23]

In conclusion, we have achieved biomimetic total syntheses of potent antiviral spirooliganones A and B with 3% and 2% yield, respectively, in 12 steps from commercially available matereials. Our synthesis featured an unprecedented cascade reaction involving aromatic Claisen rearrangement/*o*-quinone methide formation/hetero-Diels–Alder cycloaddition and phenol oxidative dearomatization/spirocyclization. In addition, the successful implementation of hetero-Diels–Alder cycloaddition of *o*-quinone methide provided compelling chemical evidence for the biogenetic hypothesis of spirooliganones A and B.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterizations, and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(23) See Supporting Information.