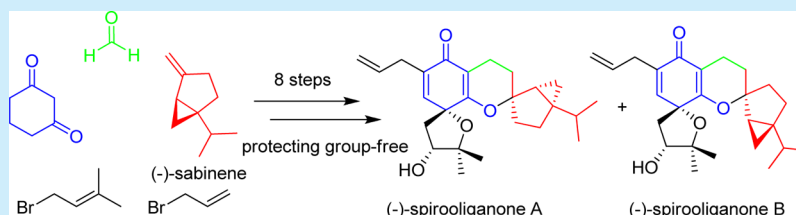# Total Syntheses of (−)-Spirooliganones A and B

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S *Supporting Information*

ABSTRACT: The enantioselective syntheses of (−)-spirooliganones A and B have been accomplished in eight steps from commercially available starting materials. Noteworthy transformations include a three-component hetero-Diels−Alder cycloaddition to construct the tetracyclic core of spirooliganones, a Sharpless asymmetric dihydroxylation, and a tandem oxidative dearomatization/cyclization to build the oxa-spiro cyclohexadienone skeleton. The straightforward syntheses were performed without protecting groups.

Illicium oligandrum has been used in Chinese folk medicine for the treatment of rheumatoid arthritis for centuries. In 2013, Yu and co-workers reported the isolation of a pair of spiro carbon epimers, spirooliganones A and B (Figure 1), from the roots of
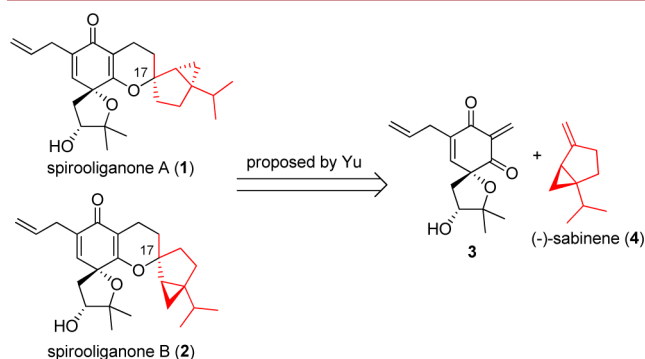

Figure 1. Proposed biogenetic pathway by Yu for spirooliganones A and B.

I. oligandrum.[1] The two compounds possess a unique pentacyclic skeleton that contains a rare dioxa-spiro system and a cyclohexadienone moiety. Their structures were established by X-ray diffraction analysis of their *p*-bromobenzoyl derivatives, with the absolute configuration being determined by Mosher's method, suggesting that they differ only in the absolute configuration of the spiro carbon (C17). Moreover, they exhibit potent activity against coxsackie virus B3 and influenza virus A (H3N2) (IC_{50} 3.70−33.33 μM) and were the first natural products isolated from *I. oligandrum* that show antiviral activity. The unprecedented molecular structure of spirooliganones along with the potent antiviral activity stimulated our interest in their total syntheses. Herein, we

present the first enantioselective total syntheses of (−)-spirooliganones A and B.

Yu proposed a biogenetic pathway of spirooliganones A and B: they were derived from a hetero-Diels−Alder reaction between monoterpene (−)-sabinene (**4**) and **3**, which could be generated from 5-allylbenzene-1,2,4-triol.[1] Considering that the cycloaddition would confront the problematic regioselectivity and possible dimerization of **3**, we envisioned that an early-stage hetero-Diels−Alder cycloaddition of (−)-sabinene (**4**) and symmetrical 2-methylenecyclohexane-1,3-dione **6**[2a−c] could solve this problem (Scheme 1).
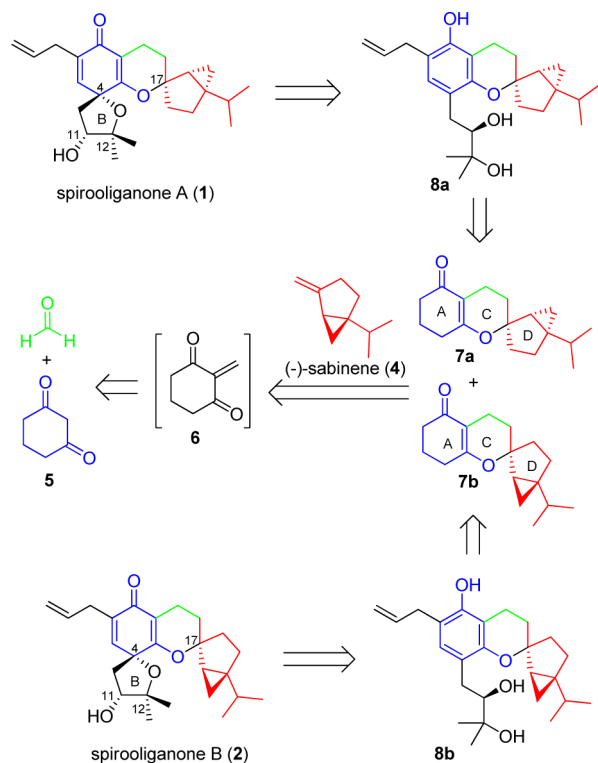
Scheme 1 outlines our retrosynthetic analysis of spirooliganones. We envisioned that the oxa-spiro cyclohexadienone skeleton of **1** and **2** could be constructed from diol **8a** and **8b** via a tandem oxidative dearomatization/cyclization.[3] The dihydroxy at C11 and C12 could be introduced via an asymmetric dihydroxylation[4] of the corresponding prenyl chain. Aromatization[5] of the tetracyclic adducts **7a** and **7b** would give the corresponding phenol, from which the prenyl and allylic side chains could be assembled via twice *O*-alkylation/Claisen rearrangement sequence. The two stereoisomers, **7a** and **7b**, could be provided via a one-pot Knoevenagel/hetero-Diels−Alder reaction[2] from commercially available 1.3-cyclohexanedione, formalin, and (−)-sabinene.

As shown in Scheme 2, the synthesis was begun to prepare the tetracyclic intermediate **7a** and **7b**. Under Hoffmann conditions,[2] 1, 3-cyclohexanedione was added slowly to the formalin and (−)-sabinene solution in CH_3CN, and the hetero-Diels−Alder reaction proceeded uneventfully in one pot to afford a 1:1.2 mixture of epimeric tetracyclic adducts in 79%
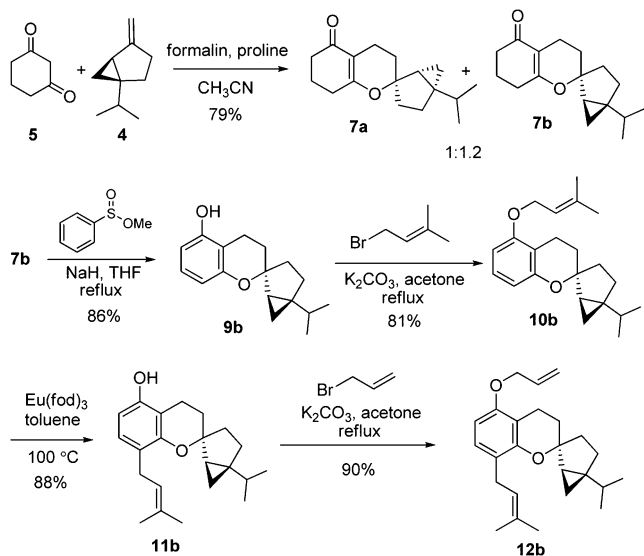
Scheme 1. Retrosynthetic Analysis of Spirooliganones

spirooliganone A (**1**)   **8a**

5   +   (-)-sabinene (**4**)   **6**   **7a**   +   **7b**

spirooliganone B (**2**)   **8b**

Scheme 2. Synthesis of Allyl Ether 12b

5 + **4** → formalin, proline, CH$_3$CN, 79% → **7a** + **7b** (1:1.2)

7b → NaH, THF, reflux, 86% → **9b** → Br (prenyl), K$_2$CO$_3$, acetone, reflux, 81% → **10b**

10b → Eu(fod)$_3$, toluene, 100 °C, 88% → **11b** → Br (allyl), K$_2$CO$_3$, acetone, reflux, 90% → **12b**

the reaction time and changed the amount of DDQ. We reasoned that phenol **9b** might be sensitive to oxidizing agents, due to the electron-rich nature of resorcinol monoether moiety.[2b] Therefore, **7b** was transformed into the corresponding β-keto sulfoxide by use of methylbenzenesulfinate,[5c,6] which was easily converted to the phenol **9b** in 86% yield via elimination of the sulfoxide group in one pot. With phenol **9b** in hand, the stage was now set for introduction of the prenyl and allylic side chains of the phenol ring. A general alkylation/ Claisen rearrangement sequence was adopted. Treatment of phenol **9b** with prenyl bromide and K$_2$CO$_3$ in refluxing acetone efficiently delivered prenyl ether **10b**, which was heated in toluene in the presence of a catalytic amount of Eu(fod)$_3$[7] to afford *p*-prenylated phenol **11b** in 88% yield with high regioselectivity. To our delight, the acid-sensitive propane ring was retained. Direct Sharpless asymmetric dihydroxylation[4] (AD-mix-β) of *p*-prenylated phenol **11b** gave a messy mixture, presumably due to the easily oxidized nature of phenol. Therefore, allyl ether **12b** was afforded from *p*-prenylated phenol **11b** in 90% yield and the newly installed allyl group would also act as a protecting group.

Under Sharpless' conditions (0.02 equiv K$_2$OsO$_2$(OH)$_4$, 0.1 equiv (DHQD)$_2$PHAL), diol **13b** was obtained in 57% (78% based on recovered starting material) yield, with high regio- and diastereoselectivity (dr determined by ^{1}H NMR) (Scheme 3).

Scheme 3. Total Synthesis of (−)-Spirooliganone B

12b → 0.02 equiv K$_2$OsO$_2$(OH)$_4$, 0.1 equiv (DHQD)$_2$PHAL, 3.0 equiv K$_3$Fe(CN)$_6$, 3.0 equiv K$_2$CO$_3$, 2.0 equiv MeSO$_2$NH$_2$, t-BuOH/H$_2$O (1:1), 57%, dr 14.5:1 → **13b**

13b → 230 °C, N,N-dimethylaniline, 91% → **8b**

8b → PIDA, HFIP, K$_2$CO$_3$, 0 °C → (-)-C4-*epi*-spirooliganone B (**14**), 19% + (-)-spirooliganone B (**2**), 45%
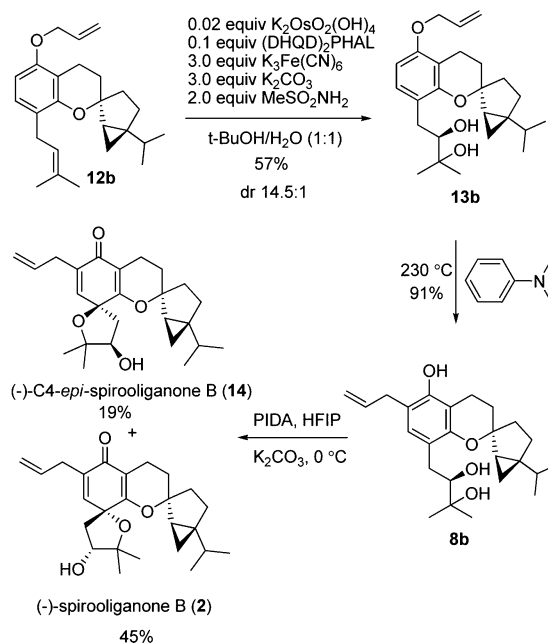
yield. The poor diastereoselectivity could be attributed to the slight steric difference between α and β face of sabinene. We could just take advantage of this to access both diastereomeric spirooligaones from **7a** and **7b**. After preliminary separation by silica gel chromatography, **7b** was successfully isolated as a white solid by recrystallization from ethyl acetate/petroleum ether to leave **7a** in the filtrate containing ∼30% of **7b**. Thus, we commenced the syntheses of spirooliganones from **7b**.

The aromatization step was tried with a number of methods[5] (Pd/C, LDA/TMSCl) but failed completely. DDQ in dioxane solvent alone gave the trace desired product, and when excess BSA[2a] was added, phenol **9b** was afforded in 20% yield. The yield could not be improved, no matter how much we extended

It is noteworthy that decreasing the amount of K$_2$OsO$_2$(OH)$_4$ led to low conversion, and increasing it gave more over-oxidation byproduct. The stereochemistry of the formed diol was assigned according to the Sharpless model[4a] and eventually verified by the late-stage cyclization of the oxa-spiro B ring. N,N-Dimethylaniline[8] was found to be the optimal solvent (230 °C) in Claisen rearrangement of **13b** to cleanly furnish O-allyl phenol **8b** in 91% yield, while 4-isopropyltoluene gave a complex mixture.

The last challenge was cyclization of the oxa-spiro B ring using a tandem oxidative dearomatization/cyclization sequence. Initial treatment of O-allyl phenol **8b** with phenyliodine

bistrifluoroacetate (PIFA) in CH_3NO_2[3b] afforded trace spirooliganone B (**2**). After examining a number of oxidative dearomatization conditions, HFIP[3e] was found to be the optimal solvent, and phenyliodine diacetate (PIDA) was much better than PIFA. The addition of $NaHCO_3$ as an additive improved the yield, but the main product was (−)-C4-*epi*-spirooliganone B (**14**) (47%, dr ~2:1). After exploring many bases, this problem was solved by using K_2CO_3 to deliver a 45% yield of (−)-spirooliganone B (**2**) and a 19% yield of (−)-C4-*epi*-spirooliganone B (**14**). The spectral data of synthetically obtained **2** (¹H NMR, ¹³C NMR, and HRMS) were in full agreement with those of the natural (−)-spirooliganone B. Thus, the stereostructure of **7a** and **7b** were distributed, and undergoing an identical route, **7a** would lead to (−)-spirooliganone A (**1**).

Aromatization of **7a** (containing ~30% of **7b**), followed by *O*-prenylation, afforded pure **10a** in 56% overall yield (Scheme 4). Claisen rearrangement of **10a** and sequent *O*-allylation gave

Scheme 4. Total Synthesis of (−)-Spirooliganone A
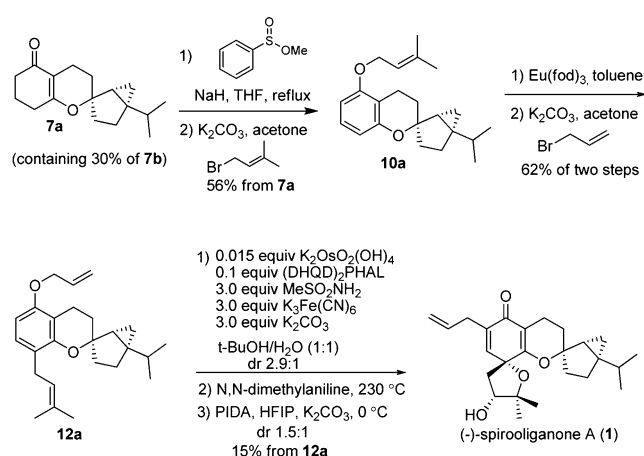
a 62% overall yield of **12a**, which was subjected to Sharpless asymmetric dihydroxylation, Claisen rearrangement, and dearomatizaiton sequence to deliver (−)-spirooliganone A (**1**) and C4-epimer in 15% and 10% overall yield from **12a**, respectively. The relatively low diastereoselectivity of dihydroxylation and dearomatization/cyclization, compared to those in the synthesis of spirooliganone B, could be caused by the different configuration at C17. The spectral data of synthetic **1** were in accord with those reported for the natural (−)-spirooliganone A.

In conclusion, we developed a facile and efficient route to accomplish the first enantioselective total syntheses of (−)-spirooliganones A and B in 8 steps from commercially available 1, 3-cyclohexanedione, formalin, (−)-sabinene, prenyl bromide, and allyl bromide. The key steps in the syntheses procedure include a Knoevenagel/hetero-Diels–Alder reaction to establish the tetracyclic core and a tandem oxidative dearomatization/cyclization to construct the oxa-spiro B ring. Furthermore, suitable introduction of the necessary allylic chain and sequent excellent regioselective Sharpless asymmetric dihydroxylation avoided the cumbersome procedures for protection and deprotection.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ¹H and ¹³C NMR (Dept 135) spectra for all 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.

■ REFERENCES

(1) Ma, S.-G.; Gao, R.-M.; Li, Y.-H.; Jiang, J.-D.; Gong, N.-B.; Li, L.; Lü, Y.; Tang, W.-Z.; Liu, Y.-B.; Qu, J.; Lü, H.-N.; Li, Y.; Yu, S.-S. *Org. Lett.* **2013**, *15*, 4450−4453.

(2) (a) Koser, S.; Hoffman, H. M. R. *J. Org. Chem.* **1993**, *58*, 6163−6165. (b) Krause, M.; Hoffman, H. M. R. *Tetrahedron Lett.* **1990**, *31*, 6629−6632. (c) Koser, S.; Hoffman, H. M. R. *Heterocycles* **1994**, *37*, 661−666. (d) Kim, I.; Kim, S. G.; Choi, J.; Lee, G. H. *Tetrahedron* **2008**, *64*, 664−671. (e) Lee, Y. R.; Hung, T. V. *Tetrahedron* **2008**, *59*, 7338−7346. (f) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.

(3) (a) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394−5397. (b) Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun.* **2009**, 662−664. (c) Flyer, A. N.; Si, C.; Myers, A. G. *Nat. Chem.* **2010**, *2*, 886−892. (d) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650−6653. (e) Fujioka, H.; Komatsu, H.; Nakamura, T.; Miyoshi, A.; Hata, K.; Ganesh, J.; Murai, K.; Kita, Y. *Chem. Commun.* **2010**, *46*, 4133−4135. (f) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942−3945. (g) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820−2823. (h) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 16905−16918.

(4) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345−1376. (c) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570−7571. (d) Li, Y.; Hu, Y.; Xie, Z.; Chen, X. *Tetrahedron: Asymmetry* **2003**, *14*, 2355−2360. (e) Duan, Z.-Y.; Zhang, J.-Y.; Xu, X.-X. *Acta Chim. Sin.* **2004**, *62*, 811−817.

(5) (a) Shono, T.; Matsumura, Y.; Kashimura, S. *J. Org. Chem.* **1981**, *46*, 3719−3721. (b) Chen, K.; Liu, C.; Deng, L.; Xu, G. *Steroids* **2010**, *75*, 513−516. (c) Aso, M.; Ojida, A.; Yang, G.; Cha, O.-J.; Osawa, E.; Kanematsu, K. *J. Org. Chem.* **1993**, *58*, 3960−3968.

(6) (a) Monteiro, H. J.; De Souza, J. P. *Tetrahedron Lett.* **1975**, *16*, 921−924. (b) Resek, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 7051−7054.

(7) (a) Minassi, A.; Giana, A.; Ech-Chahad, A.; Appendino, G. *Org. Lett.* **2008**, *10*, 2267−2270. (b) Al-Maharik, N.; Botting, N. P. *Tetrahedron* **2003**, *59*, 4177−4181. (c) Gester, S.; Metz, P.; Zierau, O.; Vollmer, G. *Tetrahedron* **2001**, *57*, 1015−1018.

(8) (a) Daskiewicz, J.-B.; Bayet, C.; Barron, D. *Tetrahedron* **2002**, *58*, 3589−3595. (b) Jin, Y. L.; Kim, S.; Kim, Y. S.; Kim, S.-A.; Kim, H. S. *Tetrahedron Lett.* **2008**, *49*, 6835−6837.