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Enantioselective Total Synthesis of (–)-Spiroxins A, C and D

Xin Shu,[†] Chong-Chong Chen,[†] Tao Yu, Jiayi Yang, and Xiangdong Hu*

Abstract: Spiroxins A, C and D are metabolites that have been identified in marine fungal strain LL-37H248. Their unique polycyclic structures and intriguing biological activities make them attractive targets for the synthetic community. Based on a scalable enantioselective epoxidation of 5-substituted naphthoquinone, an oxidation/spiroketalization cascade, *ortho*-selective chlorination of the phenol unit, and oxime ester-directed acetoxylation, an enantioselective total synthesis of (–)-spiroxins A and C and the first total synthesis of (–)-spiroxin D have been achieved.

Marine fungi have been established as a rich source of metabolites with diverse molecular architectures and intriguing biological features.[1] In 1999, McDonald and coworkers reported the discovery of spiroxins A–E from fungal strain LL-37H248, a marine-derived fungus collected from a soft orange coral found in Dixon Bay, Vancouver Island, Canada.[2] Notably, spiroxin A displayed antitumor activity toward human ovarian carcinoma in a mouse xenograft model and antibacterial activity against Gram-positive bacteria. The mechanism of action that led to these valuable features may come from a particular property of cleavage of single-stranded DNA. Structurally, spiroxins A–E share an unusual polycyclic skeleton **I**, formed from a combination of two naphthoquinone epoxide moieties through a carbon–carbon bond and a spiroketal unit (Figure 1).[3] Furthermore, six or seven stereocenters were forged in a distorted cage-like frame.

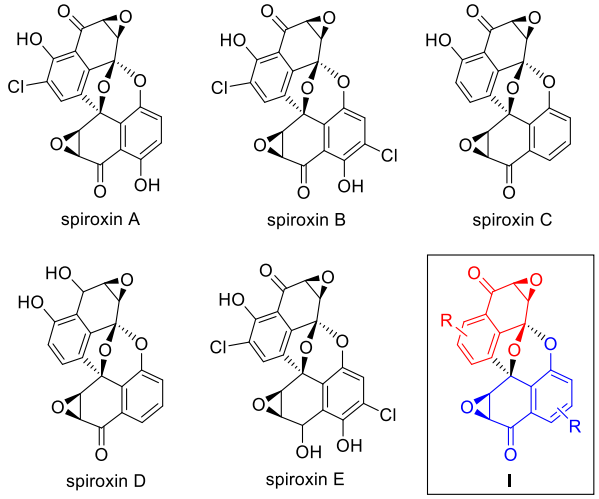

Figure 1. Structures of spiroxins A–E.

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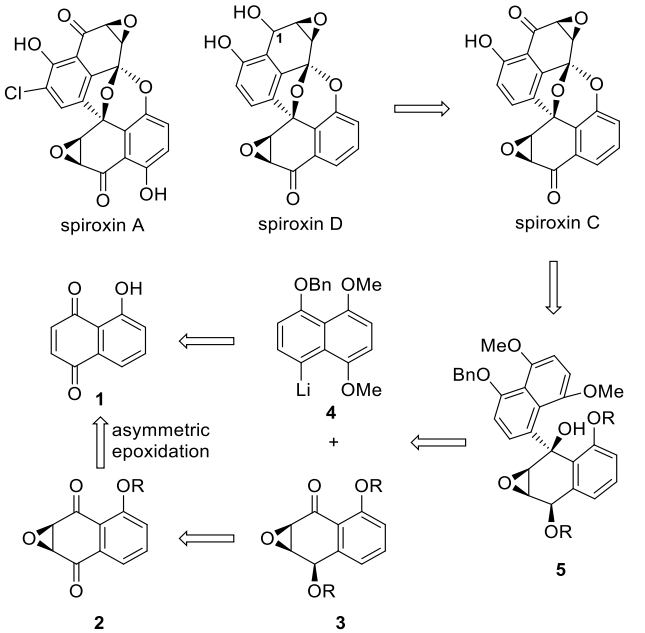
Structural differences are primarily manifested in the varied oxidation states and degrees of chlorination. The promising biological activities and challenging polycyclic architecture made these natural compounds attractive to organic synthetic chemists.[4] As the pioneering contribution, Imanishi and coworkers achieved the gentle total synthesis of (±)-spiroxin C through a TBAF-activated Suzuki–Miyaura cross-coupling reaction.[5] In 2017, based on the development of a stereospecific intramolecular photoredox reaction of naphthoquinone derivatives, Suzuki and coworkers achieved the first enantioselective total synthesis of (–)-spiroxin C.[6] Later, the same group reported two competing cascade processes involving an intramolecular redox reaction under photoirradiation and acid/base conditions, which enabled the retention and inversion of the absolute configuration of identical intermediates, respectively. Thus, the ingenious first total synthesis of both enantiomers of spiroxin A was accomplished.[7]

Stimulated by the interest in these marine-derived fungal metabolites, we commenced a synthetic study with the plan shown in Scheme 1. Compared with spiroxin C, the only difference from spiroxin D is the hydroxyl group on C1, the relative configuration of which was unknown. Spiroxin A contains one more hydroxy group and a chlorine substituent. Therefore, we anticipated that spiroxin C could be a common intermediate for spiroxins A and D. With respect to the construction of the core polycyclic skeleton, we anticipated that oxidation of **5** and subsequent spiroketalization could be achieved in one step. For the synthesis of **5**, the diastereoselective addition of lithium reagent **4** to chiral α,β-epoxyketone **3** would be applied. Both **3** and **4** can be prepared from commercially available juglone **1**, and



Scheme 1. Our synthetic plan to spiroxins A, C and D

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an enantioselective epoxidation was to be employed for the introduction of initial chiral stereogenic centers in **2**, which would enable the syntheses of spiroxins A, C and D in an enantioselective manner.

The first challenge we faced was to synthesize **3** with high enantioselectivity. For this purpose, the enantioselective epoxidation of 5-substituted naphthoquinone **6**, which was readily prepared from commercially available juglone **1**, was carried out under various asymmetric phase-transfer catalysis conditions (Table 1). Attempts with Murphy's tetracyclic C2-symmetric guanidinium salt (**C-1**)[8] led to formation of the expected product **2** in good yield. However, the enantioselectivity was inferior. Maruoka's N-spiro-C2-symmetric chiral quaternary ammonium bromides (**C-2** to **C-4**)[9] were also checked, whereupon the yield for **2** was slightly improved. Unfortunately, the enantioselectivity remained very low. During our tests on cinchona-based catalysts (**C-5** to **C-10**),[10] increases in the enantioselectivity were observed. To our delight, the use of **C-11**, which was developed independently by Lygo et al.[11] and Corey et al.[12] led to the production of **2** at 10 gram scale, in 96% yield with 80 % ee (>99% ee after recrystallization). Protection of the hydroxyl group in **C-11** (**C-12**, **C-13**)[13] resulted in reverse enantioselectivity. Notably, the protecting group in **2** had a significant impact on the enantioselectivity.[14]

With chiral **2** in hand, we focused our attention on the synthesis of (–)-spiroxin C (Scheme 2). Reduction of **2** was checked under a range of conditions, including $NaBH_4$, DIBAL-H and L-selectride; however, excellent regioselectivity and diastereoselectivity were only observed with the application of $(CH_3)_4NBH(OAc)_3$, which led to the formation of **3** as a single product after hydroxyl protection.

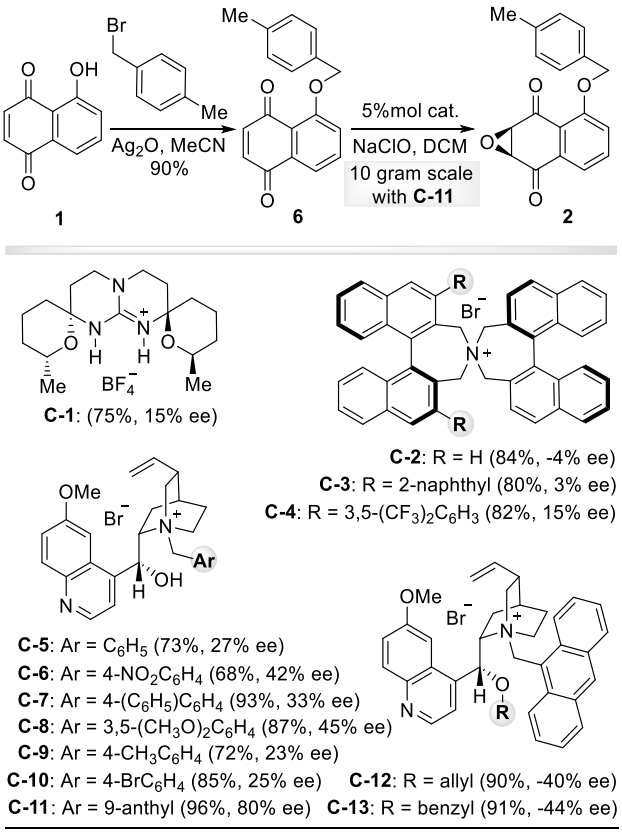

Table 1. Enantioselective epoxidation of 5-substituted naphthoquinone **6**

Based on an unambiguous X-ray crystallographic analysis,[15] the absolute configuration of the epoxide unit of **3** was found to be identical to those of (–)-spiroxins A and C. Furthermore, compound **1** was subjected to benzyl protection, quinone reduction–dimethylation and bromination, affording the known bromide **7**[6a] in three steps. Connection of **3** with the lithium reagent prepared from **7**, proceeded through the expected diastereoselectivity, which secured the formation of **5** after the removal of benzyl and 4-methylbenzyl groups. Our next task was to assemble the core polycyclic skeleton through introduction of a spiroketal unit. Various oxidants, for instance cerium (IV) ammonium nitrate, PIDA and PIFA, were checked. The test with PIFA enabled the generation of spiroketal **8** but in only 29% yield. To our delight, the system of silver (II) oxide and phosphoric acid, which was initially developed by Syper,[16] delivered **8** in a much better yield. The presence of phosphoric acid was essential for this oxidation/spiroketalization cascade.[17]As a result, construction of the core polycyclic skeleton was achieved in only one step from **5**. Furthermore, the total synthesis of (–)-spiroxin C was readily completed through removal of the TBS group, oxidation of the hydroxyl moiety and subsequent epoxidation operations. The physical data of our synthetic sample found good agreement with those of the natural isolate.[2] Following our synthetic plan (Scheme 1), we then started the synthesis of (–)-spiroxin D, which bears an unknown relative configuration at C1. Pleasingly, use of DIBAL-H allowed the synthesis of spiroxin D to be accomplished through reduction of the C1 carbonyl group in spiroxin C with excellent regioselectivity and diastereoselectivity. The previously unknown relative configuration of (–)-spiroxin D was unambiguously determined through X-ray crystallographic analysis.[18] The synthetic sample displayed identical spectral properties to those of the natural isolate of spiroxin D. The sign and magnitude of the optical rotation of synthetic spiroxin D were measured (synthetic: $([\alpha]_D^{19}$=–670 (*c* = 0.16, $CHCl_3$); natural: not reported).

To achieve the synthesis of (–)-spiroxin A, the *ortho*-selective chlorination of the phenol unit of (–)-spiroxin C was carried out. The DMSO/NCS system, which was developed by Jiao and coworkers,[19] was not effective in this case. Baran's reagent, Palau'Chlor,[20] enabled the expected *ortho*-selective chlorination but in inferior yield. The best result was recorded when 1,3-dichloro-5,5-dimethylhydantoin (DCDMH)[21] was used; the system enabled the formation of chloride **9** in 73% yield. As a note, Yeung's conditions, DCDMH/$(i\text{-}Pr)_2NH{\cdot}HCl$,[22] did not increase the efficiency for the generation of **9**. At this point, we reached the final challenge: regioselective introduction of the hydroxyl on the bottom aromatic ring. Our expectation was that the oxime ester-directed acetoxylation developed by Sanford and coworkers[23] could be a feasible solution. Therefore, oxime ester **10** was prepared and submitted to acetoxylation. Unfortunately, consumption of **10** was not observed under the standard condition ($Pd(OAc)_2$, PIDA, $AcOH/Ac_2O$). We then investigated different oxidants. Application of PIFA led to the successful formation of the expected product **11** but in quite low yield. Selectfluor and oxone both led to decomposition of **10**. To our delight, employment of $K_2S_2O_8$ afforded **11**, which was isolated in an acceptable yield. After the removal of all acetyl and oxime ester groups, the synthesis of (–)-spiroxin A was finally accomplished. Physical data matched very well with those of the natural sample[2] and of the synthetic report.[7]

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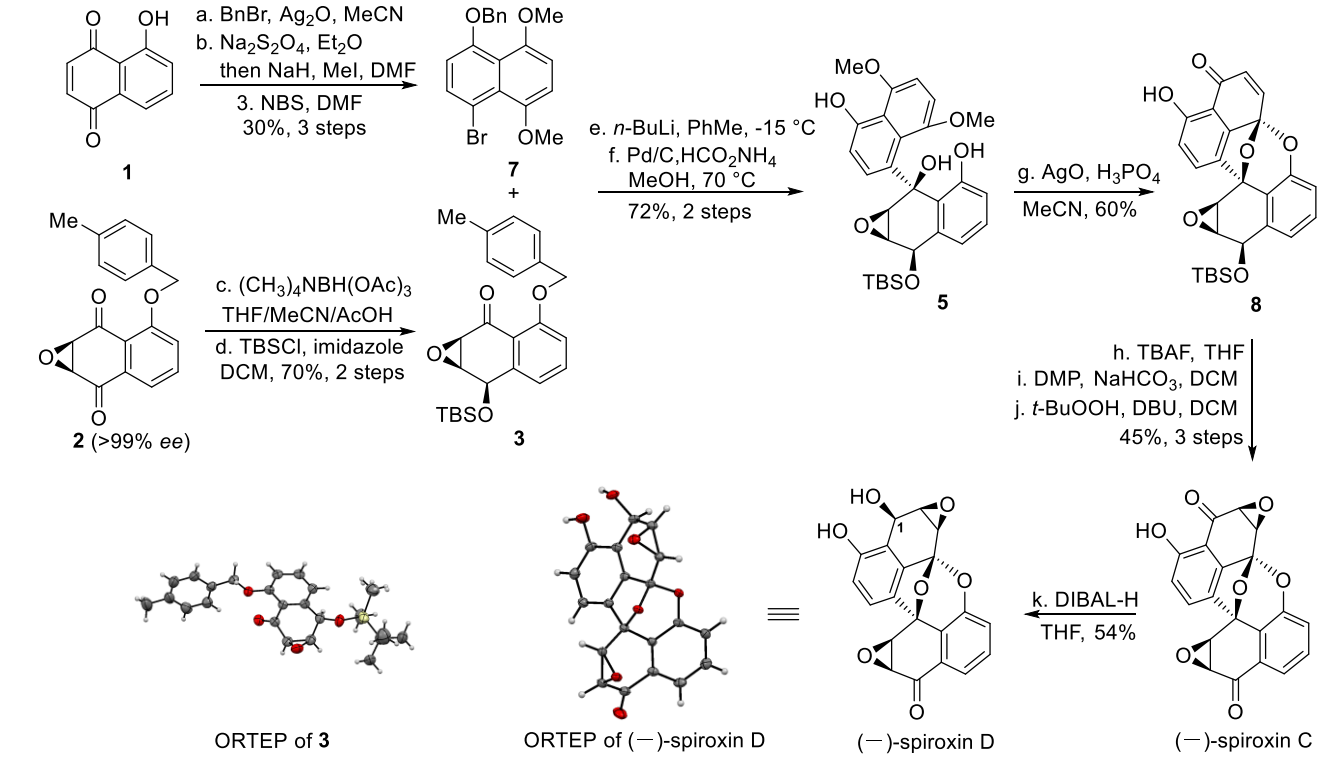

Step g

Conditions	Yield of **8**
DDQ, DCM	N.R.
CAN, MeCN/H_2O	Decomposition
PIFA, MeCN/THF/H_2O	29%
PIDA, MeCN/THF/H_2O	N.R.
AgO, H_3PO_4, MeCN	60%
AgO, MeCN	N.R.

Step l

Conditions	Yield of **9**
NCS, DMSO, $CHCl_3$	N.R.
TCICA, DCM	trace
Palau'chlor, $CHCl_3$	12%
t-BuOCl, THF	40%
DCDMH, $CHCl_3$	73%
DCDMH, $(i\text{-Pr})_2NH$•HCl, toluene	66%

Step n

Conditions	Yield of **11**
$Pd(OAc)_2$, PIDA, $AcOH/Ac_2O$	N.R.
$Pd(OAc)_2$, PIFA, $AcOH/Ac_2O$	24%
$Pd(OAc)_2$, selectfluor, $AcOH/Ac_2O$	Decomposition
$Pd(OAc)_2$, Oxone, $AcOH/Ac_2O$	Decomposition
$Pd(OAc)_2$, PIFA, MeOH	N.R.
$Pd(OAc)_2$, $K_2S_2O_8$, $AcOH/Ac_2O$	62%

Scheme 2. Total synthesis of (–)-spiroxins A, C and D**.** CAN = cerium (IV) ammonium nitrate, DBU = 1,8-diazabicyclo [5.4.0] undec-7-ene, DCDMH = 1,3-dichloro-5,5-dimethylhydantoin, DDQ = 2,3-dicyano-5,6-dichlorobenzoquinone, DMF = *N*, *N*-dimethylformamide, DMP = Dess-Martin Periodinane, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, PIDA = (diacetoxyiodo)benzene, PIFA = [bis(trifluoroacetoxy)iodo]benzene, TBAF = tetrabutyl ammonium fluoride, TBSCl = *t*-butyl dimethylsilyl chloride, TCICA = trichloroisocyanuric acid.

In conclusion, a divergent synthetic route to (–)-spiroxin C, (–)-spiroxin D and (–)-spiroxin A has been successfully developed. Major features of the synthetic strategy include: 1) a scalable enantioselective epoxidation of 5-substituted naphthoquinone, which paved the way for the enantioselective synthesis of these metabolites; 2) the oxidation/spiroketalization cascade as a concise pathway to the core polycyclic skeleton; 3) the *ortho*-selective chlorination of the phenol unit enabled by DCDMH; and 4) the oxime ester-directed acetoxylation, which secured the synthesis of (–)-spiroxin A. Benefiting from the synthetic route developed, the synthesis of (–)-spiroxin C, (–)-spiroxin D and (–)-spiroxin A was accomplished in 10, 11 and 14 steps, respectively, for the longest linear sequence. Additionally, X-ray crystallographic analysis allowed the unknown relative

configuration of spiroxin D to be unambiguously determined. Follow-up studies on the valuable bioactivities of these metabolites, explorations on antitumor activity and antibacterial activity of (–)-spiroxins A, C and D and their synthetic intermediates are ongoing.

Acknowledgements

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Keywords: core skeleton • enantioselective epoxidation • natural product • total synthesis

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[14] For details on enantioselective epoxidation with varied protecting groups in **2**, other optimization attempts and substrates scope please see Supporting Information file.

[15] CCDC 2079854 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[18] CCDC 2079853 ((–)-spiroxin D) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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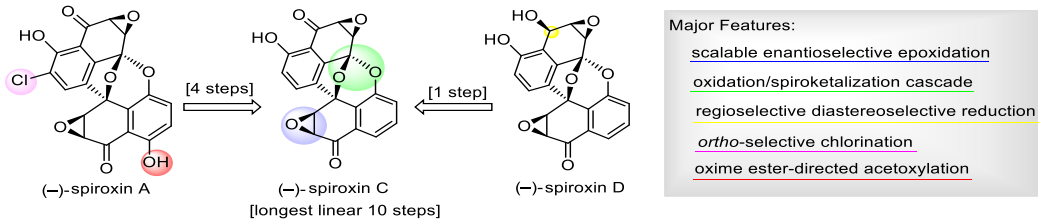

Spiroxins A, C and D are metabolites with unique polycyclic structures and intriguing biological activities. Based on a scalable enantioselective epoxidation of 5-substituted naphthoquinone, an oxidation/spiroketalization cascade, *ortho*-selective chlorination of phenol unit and oxime ester-directed acetoxylation, a divergent and enantioselective synthetic route to (–)-spiroxins A and C and the first total synthesis of (–)-spiroxin D have been achieved. The synthetic compounds provide a good foundation for the investigation of antitumor activity and antibacterial activity of the natural products and their synthetic intermediates.