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A SIMPLE DESYMMETRIZATION APPROACH TO THE SPIROXIN FRAMEWORK

Kazuyuki Nabatame,[1] Masahiro Hirama,[1] and Masayuki Inoue[2,]*

[1]Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan, and [2]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Tokyo, Japan. inoue@mol.f.u-tokyo.ac.jp

Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

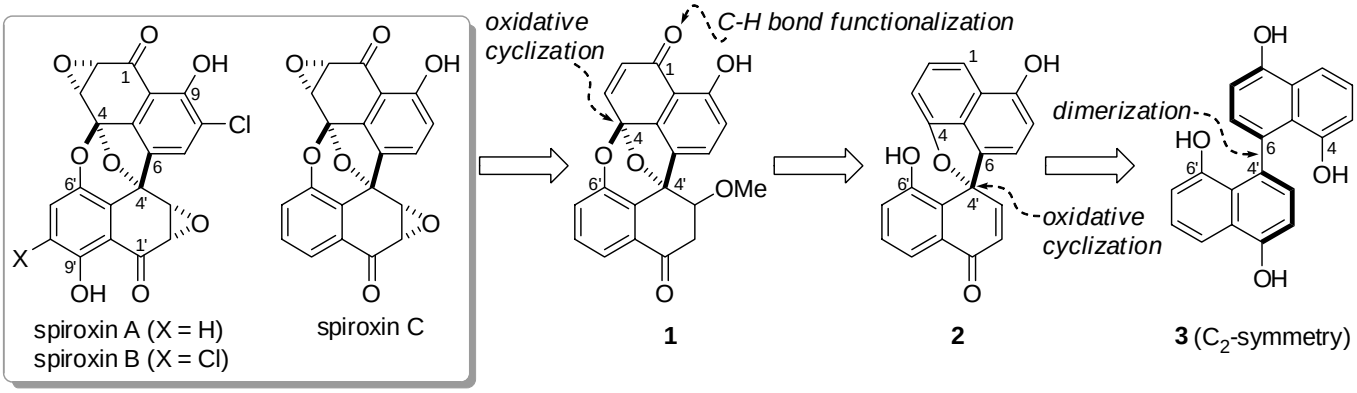
Abstract – The highly strained hexacyclic framework of spiroxins, a family of 1,8-dihydroxynaphthalene-derived natural products, was efficiently constructed in ten steps from commercially available naphthalene-1,5-diol using a symmetry-based strategy. Key reactions in this synthesis are biaryl homocoupling, oxidative desymmetrization of a C_2-symmetric intermediate, selective oxidation of the naphthalene portion, and oxidative cyclization.

In 1999, spiroxins A-C were isolated by McDonald and co-workers from fungal strain LL-37H248, which was found in a soft orange coral collected from the waters of Vancouver Island, Canada (Scheme 1).[1] Their unique structures were elucidated by NMR spectroscopy and the absolute configuration of spiroxin A was determined by exiton-coupled CD. Spiroxin A showed modest activity against Gram-positive bacteria, potent cytotoxicity against a panel of 25 diverse cell lines, and antitumor activity against ovarian carcinoma in nude mice. Although the single-strand DNA cleavage by spiroxin A was demonstrated, the detailed mechanism of action has not yet been elucidated.

Structurally, the two partially saturated naphthalene rings of the spiroxins are joined together by the C6-C4' bond and the C4-spiroketal linkage, and are further elaborated by two epoxides.[2] This highly oxygenated and strained hexacyclic fused-ring system with six stereogenic centers is a daunting challenge for chemical construction. In this communication, we report the concise synthesis of the entire spiroxin framework (**1**) by utilizing a newly developed desymmetrization strategy.[3]

To establish a general route to spiroxins A-C, we focused our attention on the common hexacyclic skeleton **1**. Further functional group manipulation has the potential to lead to all spiroxins (Scheme 1).

Retrosynthetically, **1** would be prepared from pentacyclic compound **2** through C-H bond functionalization at C1, followed by oxidative cyclization of C6'-OH to C4. Compound **2** would in turn be generated from oxidative desymmetrization of C_2-symmetric binaphthyltetraol **3**.[4] It was anticipated that both the C4'- and C4-asymmetric stereocenters of **1** could be controlled by the intrinsic conformational bias of the precursors upon the two oxidative reactions. The rotationally fixed C6-C4' bond[5] of **3** would only allow attachment of C4-OH on C4' from the α-face, and the resulting rigid five-membered ether (see **2**) would force the addition of C6'-OH to C4 from the β-face. Importantly, the key symmetric intermediate **3** was to be simply prepared by dimerization of the naphthalene substructure. In order to prove the feasibility of this symmetry-based procedure, we first synthesized **1** as a racemate.

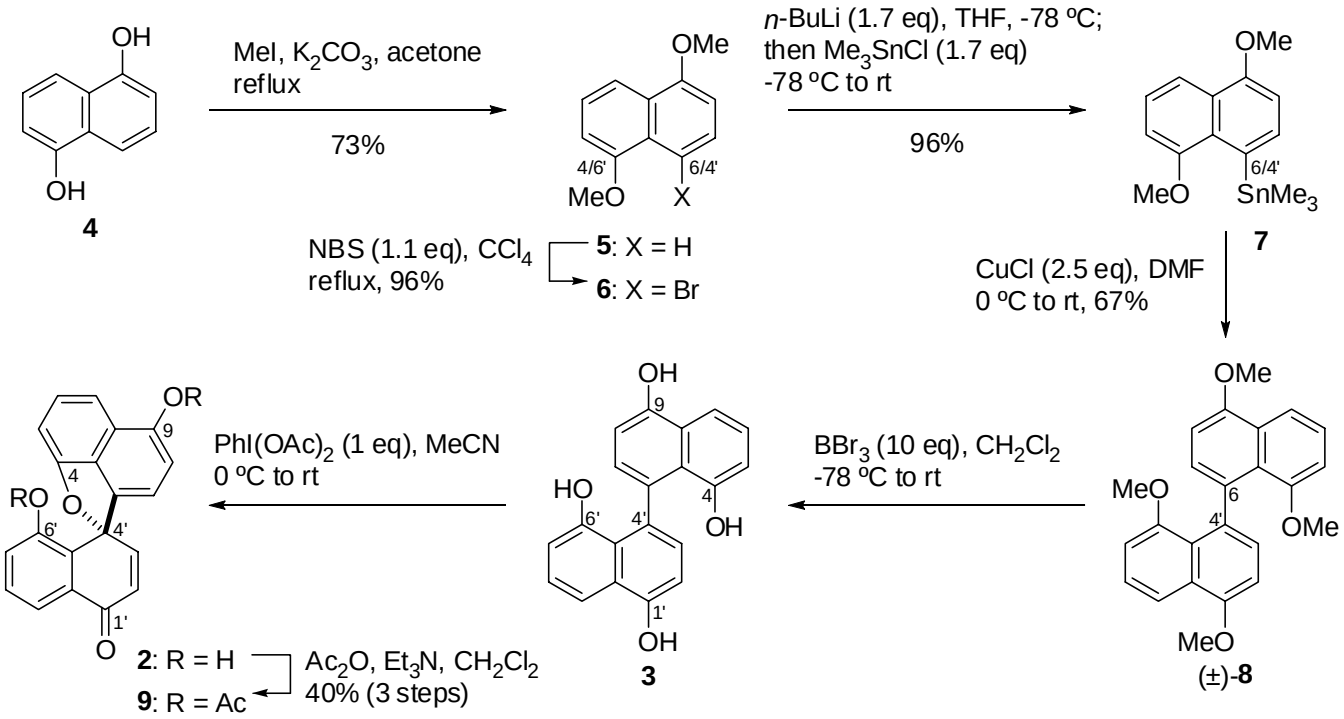


Scheme 1. Retrosynthesis of spiroxins

The five-step preparation of racemic **3** was realized from commercially available naphthalene-1,5-diol (Scheme 2). Diol **4** was first converted to methyl ether **5**, which was selectively mono-brominated with 1.1 equivalent of *N*-bromosuccinimide, providing **6**.[6] A number of attempts for homocoupling of **6** (e.g., using the Ullmann reaction[7]) were unsuccessful, likely due to the steric shield of the reacting C6/C4' by the C4/C6'-methoxy group. Thus, the bromide of **6** was converted into the more reactive trimethyltin. Namely, lithium-bromine exchange of **6** with *n*-butyllithium, followed by addition of Me_3SnCl, furnished arylstannane **7**. According to the general method of Piers,[8] treatment of **7** in dry DMF with copper (I) chloride resulted in clean formation of the coupling adduct **8** in 67% yield. This experimentally simple, yet powerful, procedure enabled the routine preparation of **8** on a gram scale. Demethylation of **8** using BBr_3 smoothly afforded tetraol **3** in high yield, whereas treatment of **8** with iodotrimethylsilane[9] led to decomposition.

Direct oxidative conversion from tetraol **3** to diol **2** was realized with no protecting groups. After careful tuning of the reaction conditions, it was found that one equivalent of diacetoxyiodobenzene in

acetonitrile effected the cyclization to yield the desymmetrized pentacycle **2**.[10,11,12] Finally, the two phenolic groups of **2** were acetylated to afford **9** in 40% yield over three steps.

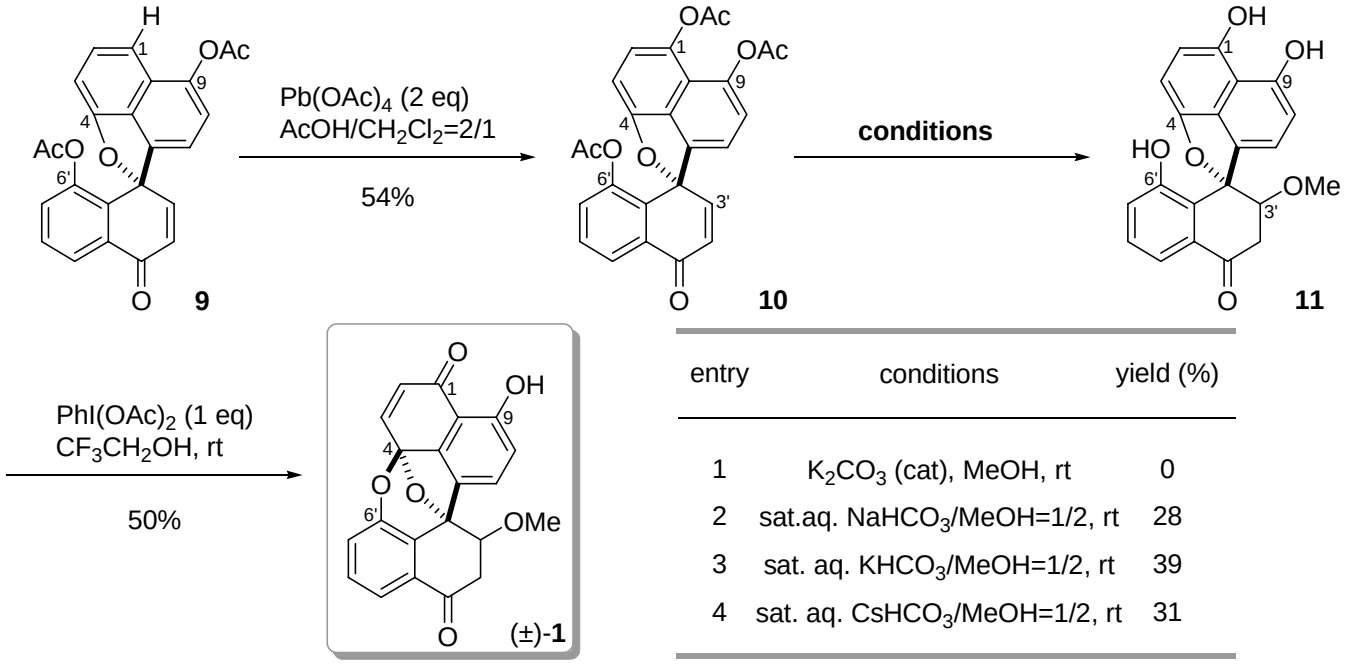


Scheme 2. Oxidative desymmetrization of C_2-symmetric intermediate

Having realized desymmetrization of the two naphthalene moieties, the next task was to raise the oxidation level of both C1 and C4 (Scheme 3). Interestingly, lead (IV) tetraacetate[13] selectively functionalized C1 of the more electron-rich upper naphthalene ring in the presence of numerous other potentially reactive sites, resulting in the formation of **10** in 54% yield. Deacetylation of tris-acetoxy compound **10**, however, was no easy task, because of the chemical instability of the phenol product. Triol **11** was prone to oxidation under basic conditions. For instance, when **10** was subjected to potassium carbonate in methanol (entry 1), only decomposition of the substrate was observed. Less basic conditions using bicarbonate salt were found to be effective for this particular reaction (entries 2-4), with potassium bicarbonate giving the highest yield. Treatment of **10** with the 1:2 mixture of saturated aqueous $KHCO_3$ and methanol at room temperature afforded **11** with the concomitant 1,4-addition of methanol at C3' (39% yield, entry 3). Finally, oxidative cyclization of triol **11** to phenol **1** was achieved using one equivalent of diacetoxyiodobenzene in trifluoroethanol,[11] delivering the highly strained skeleton **1** of the spiroxins in 50% yield.

In summary, we accomplished construction of the entire hexacyclic spiroxin framework in only ten steps from naphthalene-1,5-diol. The key reactions in this synthesis were (1) the copper (I) chloride-mediated oxidative biaryl coupling (**7** → **8**), (2) the oxidative desymmetrization of the C_2-symmetric intermediate

(**3** → **2**), (3) the site-selective acetoxylation (**9** → **10**), and (4) the oxidative cyclization to the highly strained hexacycle (**11** → **1**).



entry	conditions	yield (%)
1	K_2CO_3 (cat), MeOH, rt	0
2	sat.aq. $NaHCO_3$/MeOH=1/2, rt	28
3	sat. aq. $KHCO_3$/MeOH=1/2, rt	39
4	sat. aq. $CsHCO_3$/MeOH=1/2, rt	31

Scheme 3. Synthesis of the spiroxin framework

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14. Physical data of (±)-**1**: FT-IR (film) ν 3342, 2932, 1693, 1663, 1581, 1478, 1276, 1174, 1088, 1007, 953, 800, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (1H, d, *J*=10.5 Hz, H2), 7.45 (1H, d, *J*=7.5 Hz, H9'), 7.39 (1H, t, *J*=7.5 Hz, H8'), 6.97 (1H, d, *J*=9.5 Hz, H7), 6.96 (1H, d, *J*=7.5 Hz, H7'), 6.94

(1H, d, *J*=9.5 Hz, H8), 6.60 (1H, d, *J*=10.5 Hz, H3), 4.62 (1H, dd, *J*=3.0, 2.5 Hz, H3'), 3.91 (3H, s, Me), 3.39 (1H, dd, *J*=18.5, 3.0 Hz, H2'), 3.01 (1H, dd, *J*=18.5, 2.5 Hz, H2'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 184.1, 158.2, 155.6, 147.9, 135.7, 135.6, 132.7, 131.4, 130.6, 125.2, 124.3, 120.0, 118.0, 116.5, 115.7, 84.6, 76.0, 75.5, 56.7, 40.1; HRMS (EI) calcd for $C_{21}H_{14}O_6$ (M^+) 362.0790, found 362.0788.