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Total Synthesis of (±)-Spiroxin C

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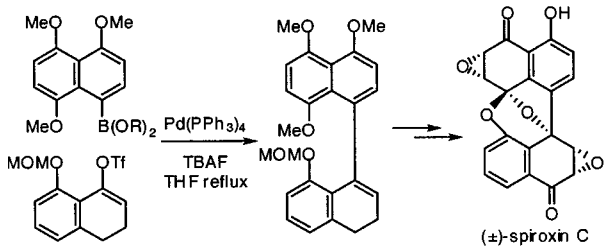
ABSTRACT



The first total synthesis of a marine-derived potent antitumor antibiotic, (±)-spiroxin C, was achieved via a TBAF-activated Suzuki–Miyaura cross-coupling reaction as a key step, which was also shown to be useful for the synthesis of sterically hindered binaphthyl derivatives.

Recently, natural products bearing a bisnaphthospiroketal structure have been attracting much attention because of their unique structures and biological activities. For instance, preussomerins were reported to show antibacterial, antifungal, and also ras farnesyl-protein transferase inhibitory activities.[1] Spiroxins A−E (**1a**−**e**), isolated from a marine-derived fungal strain LL-37H248, are another type of such compounds, in which, differently from preussomerins, two naphthoquinone moieties are directly connected by a C−C bond in place of one ether linkage, forming a unique bisnaphthospiroketal octacyclic ring system. Spiroxin A (**1a**), which is the major component produced in culture, was also reported to show antibacterial activity against Gram-positive bacteria and antitumor activity against ovarian carcinoma in nude mice, the mechanism of which was suggested to be due to its single-stranded DNA cleavage activity.[2] However, details of the DNA cleavage mechanism are not clear. A number of total syntheses of the preussomerins and related natural products have been reported.[3] However, synthesis of spiroxins requires an additional C−C bond formation to achieve the formation of the unique basic skeleton, and in fact, there is no report dealing with synthesis of spiroxins. In this paper, we describe the first total synthesis of racemic spiroxin C (**1c**).

Our retrosynthetic analysis of spiroxin C (**1c**) is shown in Figure 2. The two epoxide moieties were expected to be stereospecifically introduced from a sterically less hindered side after construction of the basic skeleton. As regards the basic bisnaphthospiroketal skeleton, the spiroketal structure was planned to be constructed after formation of a binaphthyl structure. The binaphthyl derivative was expected to be

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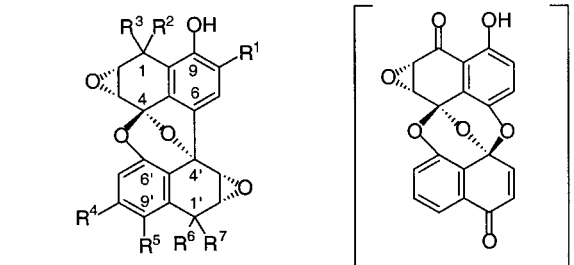


	R^1	R^2	R^3	R^4	R^5	R^6	R^7
A	Cl	–O–		H	OH	–O–	
B	Cl	–O–		Cl	OH	–O–	
C	H	–O–		H	H	–O–	
D	H	OH	H	H	H	–O–	
E	Cl	–O–		Cl	OH	OH	H

Figure 1. Structures of spiroxins A−E (**1a**−**e**) and preussomerin G.

obtained by coupling of two naphthalene units that were derived from known compounds.

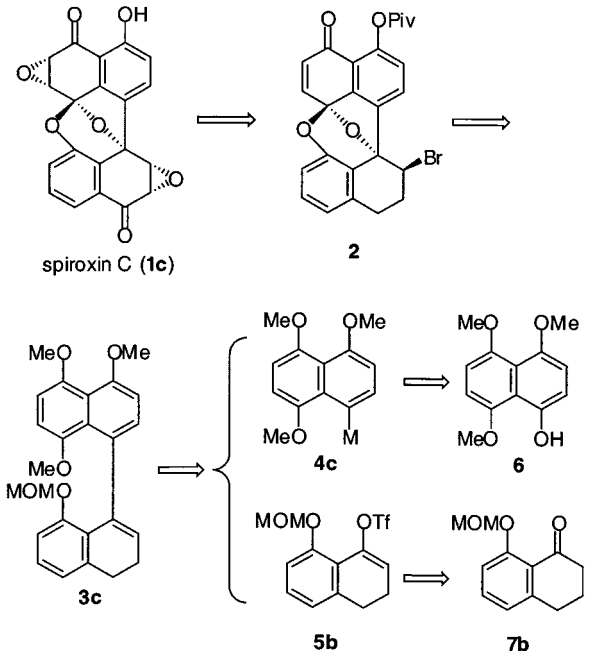
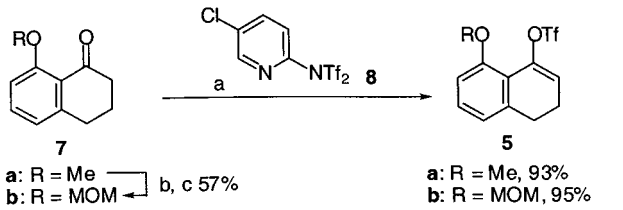


Figure 2. Retrosynthetic analysis of spiroxin C.

As the binaphthyl derivative **3** has two oxygen substituents at both *peri*-positions, synthesis of compound **3** by a coupling reaction was expected to be difficult due to steric repulsion. In fact, synthesis of 1,1′-binaphthyls having two *peri*-substituents by a homocoupling reaction has been reported,[4] but to the best of our knowledge, synthesis by a cross-coupling reaction has not been reported. As binaphthyl derivatives having two *peri*-substituents are important not only as a key intermediate for the synthesis of spiroxins but also as a chiral auxiliary,[5] we decided to undertake the synthesis of binaphthyls having two *peri*-substituents using the Pd(0)-catalyzed cross-coupling reaction as the first step.

Enol triflates **5** were easily obtained from the corresponding tetralones **7** under conventional conditions,[6] while attempts to prepare organotin or organoboronic acid from bromide **9a** via lithiation resulted in failure, probably due to steric interaction with the hydrogen at the *peri*-position. However, the Pd(0)-catalyzed coupling reaction of **9a** with diborane **10** successfully proceeded to give oraganoboronate **4a** under the conditions reported by Miyaura's group.[7] Boronates, **4b** and **4c**, bearing a methoxy group at the *peri*-position were also successfully prepared under the same conditions from bromide **9b** and triflate **11**, respectively.

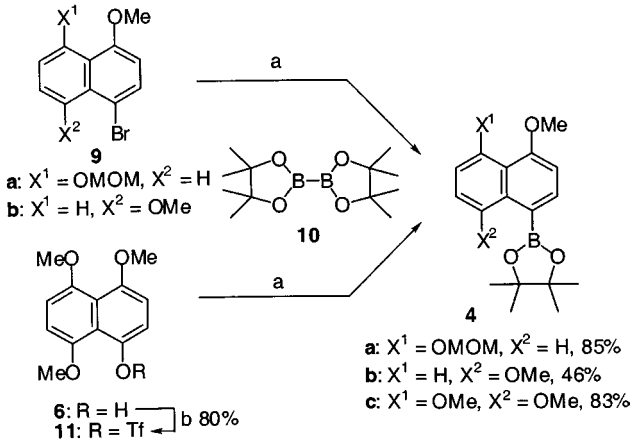
Scheme 1[a]



[a] MOM = methoxymethyl, Tf = trifluoromethanesulfonyl, NaHMDS = sodium hexamethyldisilazide. Reagents and conditions: (a) NaHMDS, **8**, THF, −78 °C; (b) BCl_3, CH_2Cl_2, −78 °C; (c) MOMCl, NaH, DMF, 0 °C.

At first, we examined a coupling reaction between **4a** and **5a** (Table 1). However, the desired coupling product **3a** was not obtained at all under the usual conditions,[8] and the product obtained was **12**, which is a homocoupling product of **5a** (Run 1). This result suggested that boronate **4a** was not so active that transmetalation between **4a** and an organopalladium species did not proceed.[9] We therefore tried

Scheme 2[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, **10**, KOAc, DMF, 80−90 °C; (b) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, 0 °C.

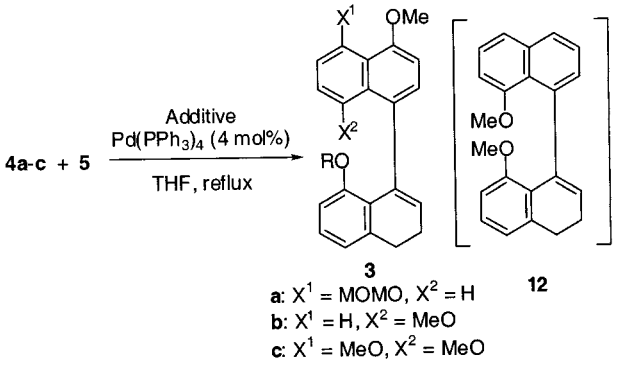


Table 1. Pd(0)-Catalyzed Cross-Coupling Reaction of **4** and **5**

run	boronate **4**		triflate **5**		time,	yield,
no.	X^1	X^2	R	additive	h	%
1[a]	**a**, MOMO	H	**a**, Me	K_3PO_4 (1.5 equiv)	19	0[b]
2	**a**, MOMO	H	**a**, Me	CsF (1.0 equiv)	24	28
3	**a**, MOMO	H	**a**, Me	TBAF (1.0 equiv)	21	50
4	**a**, MOMO	H	**a**, Me	TBAF (2.0 equiv)	14	78
5	**b**, H	MeO	**a**, Me	TBAF (3.0 equiv)	0.75	67
6	**c**, MeO	MeO	**b**, MOM	TBAF (3.0 equiv)	1.5	82

[a] The reaction was carried out in dioxane at 83 °C. [b] Compound **12** was obtained in 34% yield. TBAF = tetra-*n*-butylammonium fluoride.

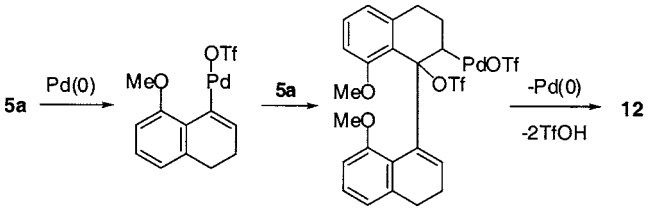
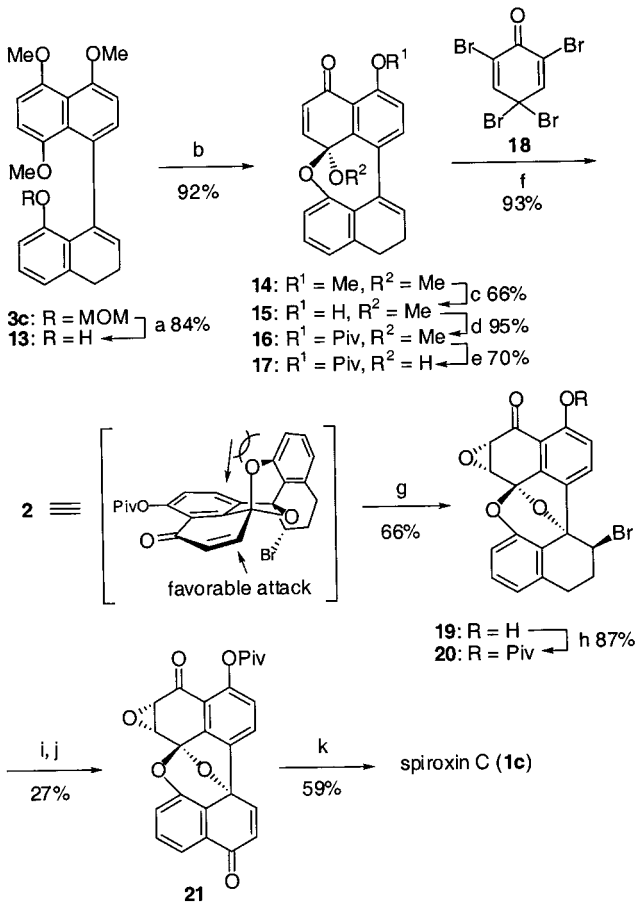


Figure 3. Possible mechanism for the formation of **12**.

to activate boronate **4a** to complete the transmetalation procedure. Desurmont and co-workers reported that CsF can work as an activator of pinacol-boronate,[10] under the conditions by which **3a** was obtained, but the yield was low (Run 2). After several attempts, the addition of TBAF was found to be the most effective (Run 3). Increasing the amount of TBAF afforded a better result (Run 4). The coupling reaction between **4b** and **5a**, both of which have a methoxy group at the *peri*-position, also successfully proceeded under these conditions to give **3b** (Run 5). Binaphthyl **3c** having *O*-substituents at the suitable positions for the synthesis of spiroxin C (**1c**) was also obtained in good yield (Run 6).

Synthesis of spiroxin C (**1c**) from binaphthyl **3c** was achieved as follows. The methoxymethyl group of **3c** was removed by acidic treatment to give **13**, oxidation of which with $PhI(OCOCF_3)_2$ yielded naphthoquinone monoacetal **14**. After demethylation of the phenolic methoxy group of **14**, the resultant phenolic hydoxyl group of **15** was protected with a pivaloyl group to afford **16**.[11] Acetal **16** was hydrolyzed by acidic treatment, yielding hemiacetal **17**. After

Scheme 3[a]



[a] Piv = pivaloyl, TBHP = *tert*-butyl hydroperoxide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NBS = *N*-bromosuccinimide, AIBN = 2,2′-azobisisobutyronitrile. Reagents and conditions: (a) conc HCl−MeOH−THF (1:4:4), 0 °C to rt; (b) $PhI(OCOCF_3)_2$, MeCN−THF−H_2O (2:2:1), 0 °C; (c) LiBr, DMF, 130 °C; (d) NaH, THF then PivCl, 0 °C; (e) 1.2 M H_2SO_4−MeCN−THF (4:3:1), 0 °C to rt; (f) **18**, CH_2Cl_2, 0 °C; (g) TBHP, DBU, CH_2Cl_2, 0 °C to rt; (h) NaH, THF then PivCl, 0 °C; (i) NBS, AIBN, benzene, reflux; (j) $NaHCO_3$, DMSO, rt; (k) TBHP, DBU, CH_2Cl_2, 0 °C to rt.

several attempts to construct the basic spiroketal skeleton, it was found that treatment with 2,4,4,6-tetrabromocyclohexadienone (**18**) was effective to obtain **2**. Although enone **2** was epoxidized stereospecifically, the pivaloyl group was also removed simultaneously under these conditions to afford monoepoxide **19** as the sole product.[12] From a molecular model of **2**, it was found that a conformation of **2** was highly restricted as shown in Scheme 3 because of the spiro-ketal structure. The stereochemistry of the epoxide was assigned to be as shown from consideration of the fact that the peroxy anion approached from the sterically less hindered side, which is the other side of the axial C−O bond as shown. After reprotection of the hydroxyl group, the benzylic position of **20** was brominated with NBS, then treated with DMSO to produce enone **21**. Under the previous conditions, epoxidation and deprotection of **21** also took place stereospe-

cifically to produce spiroxin C (**1c**) as the sole product, the spectral properties (IR, ^{1}H NMR, and ^{13}C NMR) of which were identical with those of an authentic sample. The stereochemical outcome of the last epoxidation procedure would be also explained similarly to that of the previous epoxidation.

In conclusion, we have achieved the first total synthesis of spiroxin C (**1c**) (15 steps and 1.3% overall yield from **7a**) involving a Suzuki−Miyaura cross-coupling reaction as a key reaction. The present Suzuki−Miyaura cross-coupling reaction activated by TBAF would be of great use for the synthesis of sterically hindered binaphthyls. Some issues, such as the reprotection of the C-9 hydroxyl group of **19** and the low yield of the benzylic oxidation at the C-1′ position of **20**, remain to be solved. Further improvement of the present synthetic route and synthetic study of the optically active spiroxins are now in progress, and the results will be reported in due course.

Acknowledgment. We gratefully acknowledge Dr. Leonard A. McDonald of Wyeth-Ayerst Research for the kind gift of spectral data of spiroxin C.

Supporting Information Available: Experimental conditions and ^{1}H NMR spectra for natural and synthetic spiroxin C. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(9) A possible mechanism for the formation of **12** is proposed; see Figure 3.

(10) Desurmont, G.; Dalton, S.; Giolando, D. M.; Srebnik, M. *J. Org. Chem.* **1996**, *61*, 7943−7946.

(11) At first, we selected a methyl group as a protecting group of the C-9 hydroxyl group. However, every attempt for demethylation after construction of the spiro-ketal structure resulted in failure.

(12) At first, we tried to introduce the two epoxide moieties simultaneously after derivatization to a bis-enone derivative, which, however, was so unstable that we were unable to employ it for epoxidation. In contrast, the monoepoxide **2** was stable enough to handle.