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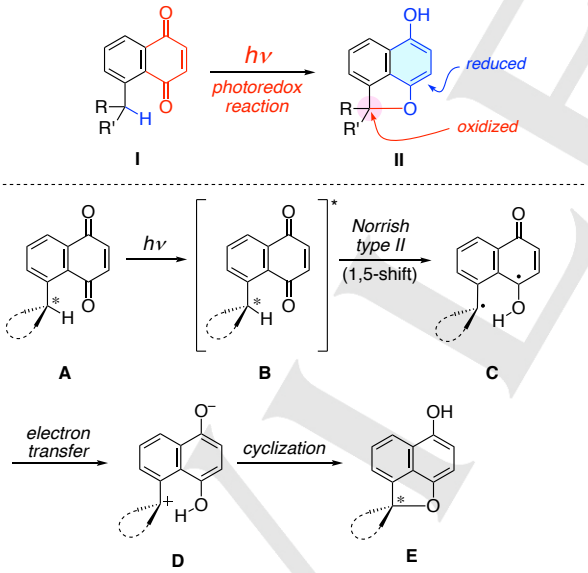
Stereospecificity in Intramolecular Photoredox Reactions of Naphthoquinones: Enantioselective Total Synthesis of (–)-Spiroxin C

Yoshio Ando, Atsuko Hanaki, Ryota Sasaki, Ken Ohmori, and Keisuke Suzuki*

In memory of Takao Ikariya

Abstract: Intramolecular photoredox reactions of naphthoquinone derivatives were shown to proceed in a stereospecific manner, by which the first enantioselective total synthesis of (–)-spiroxin C has been achieved.

Previously we reported a photoredox reaction of naphthoquinone derivatives (Scheme 1).[1] Upon ambient light irradiation, naphthoquinones **I** undergo an intramolecular photoredox reaction to give oxacycle **II**, where the benzylic oxidation level is increased and the quinone is reduced. The mechanism was assumed to follow Norrish-type II intramolecular 1,5-hydrogen shift to form diradical **C** and subsequent electron transfer to zwitterion **D** that undergoes oxycyclization to form product **E**.[1] Aside from some reports on the biosynthetic implications,[2] such a photoredox process of quinones has been overlooked and never been exploited in organic synthesis. However, we recognized a great potential of the process, particularly if the following stereochemical question were positively answered.



Scheme 1. Photoredox reaction and a stereochemical question.

Is the reaction stereospecific? – which could be addressed by using substrates **A** with a stereogenic center at the benzylic position (asterisked). We investigated this question in the context of the total synthesis of spiroxin C (**1**), one of the members of a class of marine antibiotics (Figure 1).[3] It could be regarded as a naphthoquinone dimer, and the twenty carbon-atom framework with dense oxygen functionalities constitutes a complex hexacyclic structure with six stereogenic centers, posing intriguing challenges for chemical synthesis. Although such unusual structural features as well as potential bioactivity attracted attention of the synthetic community,[4,5] Imanishi's work on *rac*-**1** is the only example of the completed synthesis.[4] Critical to our synthetic planning was the stereochemical course of the photoredox reaction of naphthoquinone **III,** which would hopefully proceed in a stereospecific manner. If viable, spiro-ether **IV** would be available in a stereo-defined form, bearing the C-4' quaternary center in **1**.

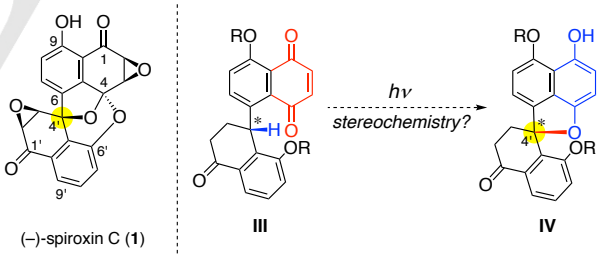


Figure 1. (–)-Spiroxin C and the stereochemical question.

In this communication, we wish to describe an affirmative answer to this scenario, achieving the first enantioselective total synthesis of (–)-spiroxin C (**1**).

As initial model compounds, we prepared a diastereomeric pair of naphthoquinones **2** and **4** (*cis* and *trans*,[6] racemate),[7] which were subjected to the photoredox reaction (Scheme 2). We were pleased to find that, upon exposure to fluorescent light (CH_3CN, RT, 8 h), the *cis*-isomer **2** was converted to spiroether **3** in excellent stereoisomeric purity (**3**:**5** = 98:2).[8] Under the same conditions, the *trans*-isomer **4** was converted to the isomeric spiroether **5** (**3**:**5** = 3:97).[8] Thus, these photoreactions proceeded in almost complete stereospecificity. The structures of **3** and **5** were assigned by NOE correlations,[7] proving that the photochemical reaction occurred in a *retentive* manner: the

[*] Dr. Y. Ando, A. Hanaki, R. Sasaki, Prof. Dr. K. Ohmori, Prof. Dr. K. Suzuki
Department of Chemistry, Tokyo Institute of Technology
2-12-1 O-okayama, Meguro, Tokyo 152-8551 (Japan)
E-mail: ksuzuki@chem.titech.ac.jp

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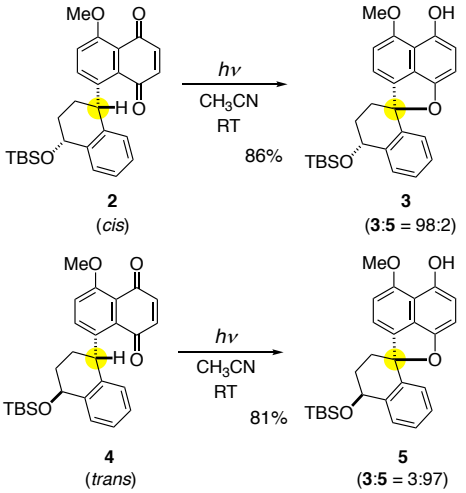
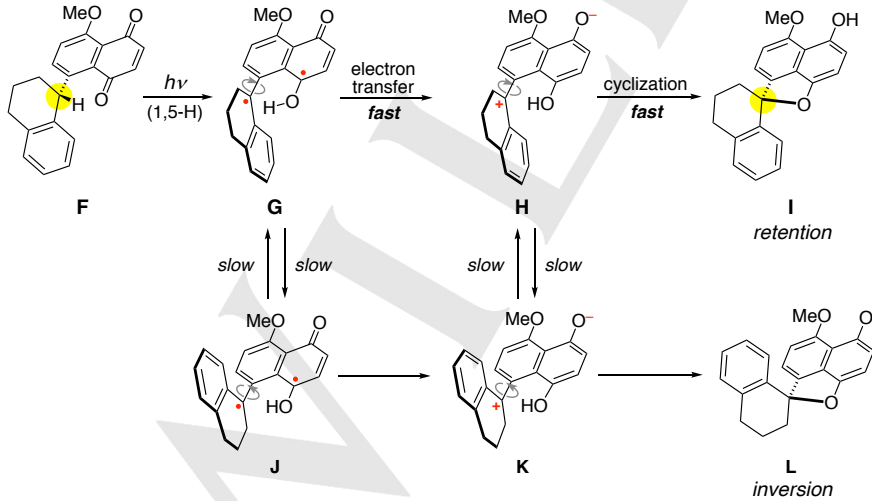
benzylic C–H bonds in **2** and **4** were replaced by a C–O bond with retention of the configuration, respectively.



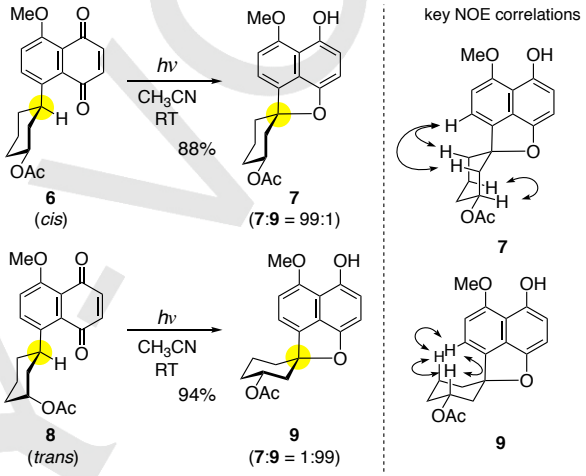
Scheme 2. Stereospecific photoredox reactions-1.

Scheme 3 shows a rationale for these pleasing results. Regardless of the preferred ground state conformation, the initial hydrogen abstraction in the excited state must occur within a conformation similar to **F**, where the benzylic hydrogen is allocated near the excited quinone carbonyl. The retentive nature of the process is explained by assuming rapid following events, i.e., (1) the electron transfer from biradical **G** to generate zwitterion **H**, and (2) the cyclization of **H** to give oxacycle **I**. In other words, although the central chirality is lost after the hydrogen abstraction, the chiral information is preserved as an axial chirality[9] in the intermediary radical **G** and the cation **H**, thanks to scaffold a reminiscent of biaryl compounds.[10]



Scheme 3. Rationale for the stereospecificity.

In the case of systems with less steric hindrance, the C–C bond rotation would become easier, and corrosion of the sterechemical integrity may begin. Thus, we prepared seemingly more challenging model substrates, a set of naphthoquinones **6** and **8** possessing a 1,3-disubstituted cyclohexane ring with *cis* and *trans* substituents[6] (Scheme 4). Pleasingly, the photoredox reactions of **6** and **8** (fluorescent light, CH_3CN, RT, 8 h) again proceeded smoothly, giving spiroethers **7** and **9** with virtually complete retention of the stereochemistry (d.r. = 99:1), respectively.[8] The stereochemical assignments of **7** and **9** were based on the NOE correlations, respectively. Note that the cyclohexyl ring in **9** was flipped as shown.



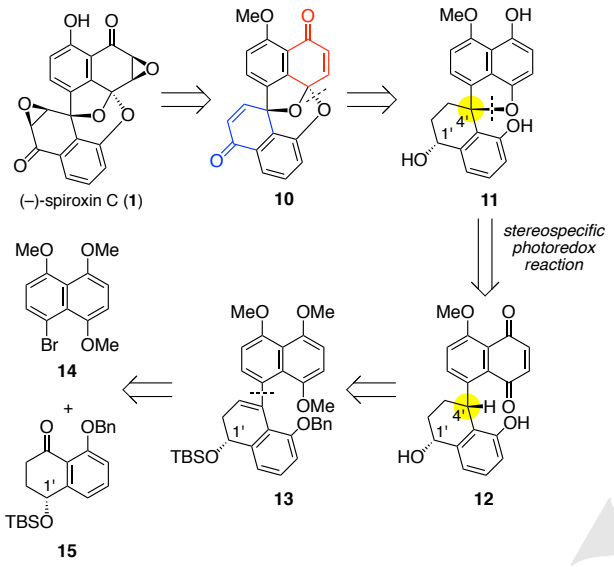
Scheme 4. Stereospecific photoredox reactions-2.

With these promising results in hand, we proceeded to plan the total synthesis of **1**. Our retrosynthetic analysis is shown in Scheme 5. Two oxirane rings in **1** could be derived from bis-enone **10** by two-fold epoxidation, for which we could expect good stereoselectivities, learning from the synthesis.[4] As the precursor for bis-enone **10**, spiroether **11** was envisaged, assuming that one of the enones (highlighted in red) would be constructed by an oxidative spiro-acetal formation, while the other (highlighted in blue) was retrosynthetically reduced to a saturated alcohol. The key was use of the C-1' stereogenic center as the basis for the absolute stereocontrol as will be discussed later.

Assuming the retentive nature of the key photoredox reaction, oxacycle **11** could be traced back to naphthoquinone **12** with the (*R*)-stereogenic center at C-4', which could be induced by the hydrogenation of alkene **13**. The hope was a high diastereofacial discrimination during the hydrogenation by the influence of the stereogenic center at C-1'. Final dissection suggested a set of starting materials, bromonaphthalene **14**[1] and enantio-enriched tetralone **15**. The C-1' stereogenic center in **15** could be

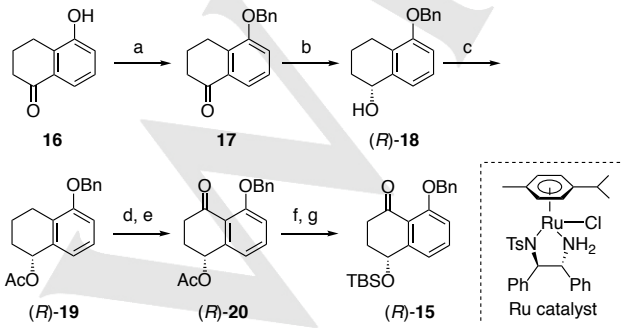
established by the enantioselective reduction of the corresponding carbonyl compound.

Three synthetic challenges en route to **1** were, (1) enantioselective synthesis of naphthoquinone **12** as the substrate for the key photoreaction, (2) viability and stereospecificity of the photoreaction to such functionalized substrate **12**, and (3) construction of the highly oxygenated polycyclic structure.



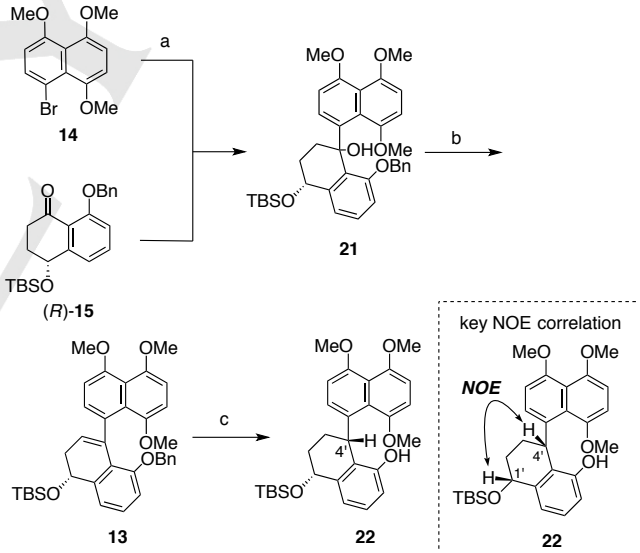
Scheme 5. Retrosynthesis.

Scheme 6 shows the preparation of chiral, non-racemic tetralone **15** via Noyori–Ikariya asymmetric hydrogenation.[11] Commercially available tetralone **16** was benzylated (BnBr, K_2CO_3, DMF, RT, 2.5 h) to give ketone **17**, which was subjected to the hydrogenation in the presence of chiral Ru catalyst, RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN], (formic acid, triethylamine, RT, 42 h),[11] giving (*R*)-alcohol **18**[12] in 89% yield with virtually perfect enantioselectivity (>99% *ee*).[7,13] Acetylation of alcohol (*R*)-**18** followed by the benzylic oxidation[14] [(1) cerium(IV) ammonium nitrate (CAN), CH_3CN, H_2O, 0 °C, 1.5 h; (2) TPAP, NMO, MS4A, CH_2Cl_2, RT, 3 h], and a conventional protection/deprotection sequence gave tetralone (*R*)-**15** in 65% yield over 5 steps from (*R*)-**18**.



Scheme 6. Synthesis of tetralone (*R*)-**15**. a) BnBr, K_2CO_3, DMF, RT, 2.5 h; b) RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (1 mol%), formic acid, triethylamine, RT, 42 h, 89%, >99% *ee* (2 steps); c) acetic anhydride, pyridine, 4-DMAP, CH_2Cl_2, 2.5 h; d) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O, 0 °C, 1.5 h; e) TPAP, 4-methylmorpholine *N*-oxide, molecular sieves 4A, CH_2Cl_2, RT, 3 h; f) LiOH·H_2O, THF, H_2O, 50 °C, 10 h; g) TBSCl, imidazole, DMF, 18 h, 65% (5 steps). Bn = benzyl, (*R*,*R*)-Ts-DPEN = (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine, 4-DMAP = *N*,*N*-dimethyl-4-aminopyridine, TPAP = tetrapropylammonium perruthenate, TBS = *tert*-butyldimethylsilyl.

Two building blocks **14**[1] and (*R*)-**15** were combined (Scheme 7). A solution of tetralone (*R*)-**15** and $LaCl_3$·2LiCl[15] in a mixed solvent (THF, Et_2O, v/v = 2/1) was added to a solution of the aryllithium derived from **14** (*s*BuLi, THF, Et_2O, 0 °C, 15 min). The crude adduct **21** was treated with silica gel[16] in dichloromethane (RT, 19 h), where dehydration occurred to give styrene **13** in 85% yield in two steps. It should be noted that styrene **13** was labile under acidic conditions (e.g. a trace acid in $CDCl_3$), easily aromatized to give the corresponding bis-naphthalene. Catalytic hydrogenation of **13** (H_2, 10% Pd/C, THF, MeOH, 12 h) saturated the C=C bond and also cleaved the benzyl protection to give a quantitative yield of phenol **22** as an inseparable mixture of diastereomers (ratio 14:1, ^{1}H NMR assay).[7] The relative stereochemistry of the major isomer was determined as *cis* by the NOE correlation between the 1'- and 4'-hydrogens.[8]



Scheme 7. Synthesis of **22**. a) *s*BuLi, THF, Et_2O, 0 °C, 15 min, then (*R*)-**15**, $LaCl_3$·2LiCl, THF, Et_2O, 0 °C, 15 min; b) SiO_2, CH_2Cl_2, RT, 19 h 85% (2 steps); c) H_2, 10% Pd/C, THF, MeOH, RT, 12 h, quant. (d.r. = 14:1).

Naphthalene **22** was oxidized with CAN, and the acidic reaction medium led to cleavage of the TBS group, affording naphthoquinone **12**, ready for the key photoredox reaction (Scheme 8). We were pleased to find that irradiation of naphthoquinone **12** with a xenon lamp (>380 nm, 300 W, CH_3CN, RT, 1 h) nicely gave the corresponding photoredox product.[17] At this stage, the crude material was purified by medium-pressure liquid chromatography to give the desired spiroether **11** in 65% yield over two steps and a small amount of

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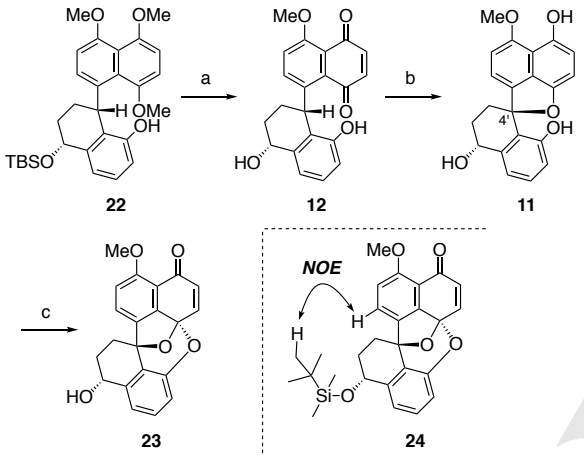
the C-4' epimer **11'** (not shown) in 5% yield,[7] which arose from the minor isomer of **22**.[18] Thus, the photoredox reaction proved applicable without problems to such a highly functionalized naphthoquinone **12**, bearing a free alkanol and a phenol. The relative stereochemistry of **11** was determined as in the following. The oxidative spirocyclization of **11** was realized by using $PhI(OCOCF_3)_2$, giving spiroacetal **23** in 86% yield. Among the derivatizations for structural assignment, the TBS ether **24** derived from **23** (TBSCl, imidazole, DMF, RT, 2.5 h, 54%)[7] gave a key evidence for the relative stereochemistry by NOE correlation,[19] establishing that the key photoredox reaction on **12**→**11** proceeded in a retentive manner.

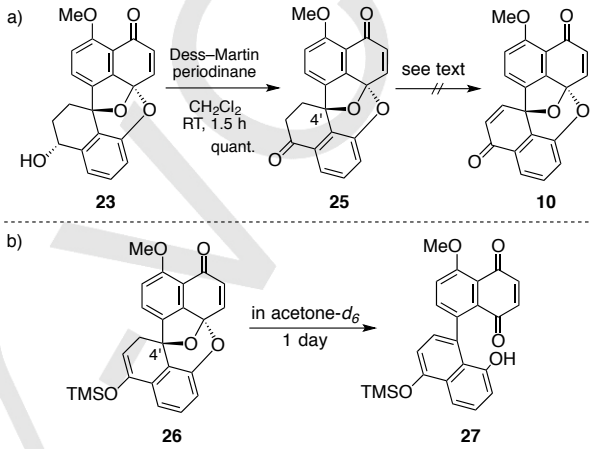


Scheme 8. Photoredox reaction and oxidative cyclization. a) $Ce(NH_4)_2(NO_3)_6$, H_2O, CH_3CN, 0 °C, 1.5 h; b) xenon lamp (300 W), CH_3CN, RT, 1 h, 65% for **11**, 5% for **11'** (2 steps); c) $PhI(OCOCF_3)_2$, EtOAc, 0 °C, 5 min, 86%.

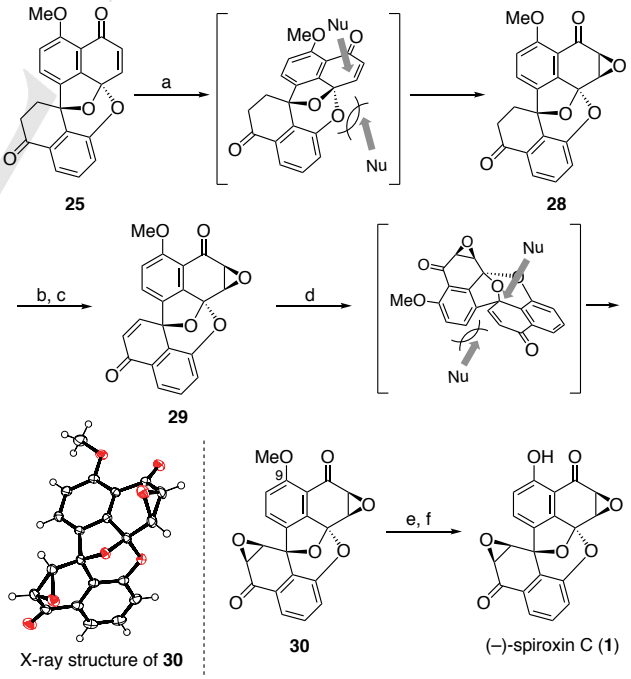
With key spirocycle **23** in hand, the next task was the conversion into bis-enone **10**, the planned intermediate for a single step installation of the two epoxides (Scheme 9a). Along these lines, alcohol **23** was quantitatively converted to ketone **25** by Dess–Martin oxidation.[20] However, attempts at the dehydrogenation of **25** into bis-enone **10** were all fruitless –either by IBX,[21] $Ph_2Se_2O_3$,[22] or the Mukaiyama oxidation.[23] The Ito–Saegusa protocol[24] via the corresponding enol silyl ether gave only trace amounts of bis-enone **10**. The origin of the issue seemed the high lability of the spiro acetal moiety, where facile elimination of the C-4' oxygen gave the corresponding naphthoquinone derivatives. Such a tendency was already presaged by acid lability of the foregoing spiro compounds **11** and **23**, and the chemical instability was particularly serious on **25** and its derived enol silyl ether **26**, which spontaneously aromatized to naphthoquinone **27** even under neutral conditions (Scheme 9b). Thus, we judged that bis-enone **10** is not a viable intermediate.

To circumvent this issue, we decided to transform the quinone acetal **25** into epoxy ketone **28**, in hope for improved chemical stability (Scheme 10). Indeed, nucleophilic epoxidation of **25** (*t*BuOOH, TBD, CH_2Cl_2, RT, 3.5 h)[25] gave epoxy ketone **28** as a single diastereomer, whose stereochemistry was assigned at a later stage. Importantly, in contrast to ketone **25**, epoxy ketone **28** showed an improved chemical stability, and furthermore good reactivity to undergo the Ito–Saegusa oxidation method,[24] giving enone **29** in 63% yield, ready for the second epoxidation.

We were pleased to find that treatment of **29** with *t*BuOOH (TBD, CH_2Cl_2, 0 °C, 10 min) gave bis-epoxide **30** as a single product, whose stereochemistry was determined by single crystal X-ray diffraction analysis.[26] Thus, both of the two nucleophilic epoxidations (**25**→**28** and **29**→**30**) proceeded with the desired stereoselectivities, which could be rationalized by the convex–concave analysis.



Scheme 9. Bis-enone formation from ketone **25**.



Scheme 10. Endgame. a) *t*BuOOH, TBD, CH_2Cl_2, RT, 3.5 h, 96%; b) TMSOTf, NEt_3, CH_2Cl_2, RT, 30 min; c) $Pd(OAc)_2$, $CaCO_3$, CH_3CN, 15 °C, 26 h, 63% (2 steps); d) *t*BuOOH, TBD, CH_2Cl_2, 0 °C, 10 min, 95%; e) BBr_3, CH_2Cl_2, –78 °C, 20 min; f) K_2CO_3, MeOH, RT, 30 min, 55% (2 steps). TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

For the final cleavage of the C-9 methyl ether, we had a prior concern that the strong Lewis acidic conditions may deteriorate the labile oxirane and acetal moieties. However, Heathcock's report nicely cleared this hurdle.[27,28] Brief exposure of bisepoxide **30** to BBr_3 (CH_2Cl_2, –78 °C, 20 min) effected demethylation and also the oxirane-ring openings to form the corresponding bromohydrins.[7] By treatment of the crude products with K_2CO_3 in MeOH, the oxirane rings were reconstructed, giving (–)-spiroxin C (**1**) in 55% yield over two steps. The synthetic material **1** exhibited physical data indistinguishable from the reported data in all respects (^{1}H-, ^{13}C NMR, IR, UV, HRMS).[7]

Concerning the stereochemical integrity, assessment on the samples of **30** and **1** by HPLC on chiral stationary phase proved the enantiomeric purity (>99% *ee*).[29] The sign and magnitude of the optical rotation of the synthetic material **1** matched those reported for the natural product {synthetic $[\alpha]_D^{22}$ –692 (c 0.650, MeOH), *lit.* $[\alpha]_D^{25}$ –706 (c 0.256, MeOH)}.[3a] The absolute structures of the spiroxins relied on the exciton-coupled CD study on a congener, (–)-spiroxin A,[3b] and the present study has provided an independent validation.

In summary, the first enantioselective total synthesis of (–)-spiroxin C (**1**) has been accomplished, featuring a stereospecific photoredox reaction for construction of the key spiroether structure. The synthetic route should be widely applicable to other natural/unnatural congeners with potential biological activities. Further work along these lines is in progress.

Acknowledgments

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Keywords: naphthoquinone • photoreaction • redox reaction • spiroxin C •stereospecificity

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[6] The term *cis*/*trans* refers to the mutual relation of the oxy substituent and the naphthoquinone moiety within the six-membered ring.

[7] For the experimental procedures and the structure identification, see Supporting Information.

[8] The ratio of diastereomers was determined by HPLC analysis of the crude materials, respectively. For detail, see Supporting Information.

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[16] Silica gel 60N (spherical neutral, particle size 40–50 μm) from Kanto Chemical was used.

[17] The preparative-scale reaction of naphthoquinone **12** was slow with ambient light.

[18] Part of the C4' epimer **11'** may also arise from the minor photoredox reaction pathway of the major isomer **22** (invertive), which, however, should be minimal, judging from the results of model study.

[19] Since the stereochemical assignment of **11** itself was difficult, the silyl ether **24** was prepared for the NOE experiment.

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[26] CCDC 1550962 (**7**), 1550961 (**29**), and 1550960 (**30**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.ac.uk/data_request/cif

[27] S. Chi, C. H. Heathcock, *Org. Lett.* **1999**, *1*, 3–5.

[28] Other reagents, such as $MgI_2{\cdot}OEt_2$, $CeCl_3{\cdot}7H_2O$ and NaI, or $AlCl_3$, were also tested in a model study. Notably, the iodide-containing reagents were ineffective, because the resulting α-iodoketone underwent further reductive removal of the α-iodine, giving the corresponding "non-iodo" β-hydroxy ketone, losing the opportunity to recover the desired epoxy ketone structure.

[29] In our exploratory study, we prepared also the racemic samples of **30** and **1**, which were used for these HPLC analyses. For HPLC analysis on chiral stationary phase: DAICEL column (0.46 cm ϕ 25 cm, flow rate 1.0 mL/min, λ = 254 nm, 25 °C): **30**; CHIRALPAK® IF, hexane/EtOAc =

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75/25, t_R = 12.8 min for the synthetic material, 14.8 min for the enantiomer. **1**; CHIRALPAK® IB, hexane/EtOAc = 85/15, t_R = 19.2 min for the (+)-spiroxin C, 21.9 min for the (–)-spiroxin C.

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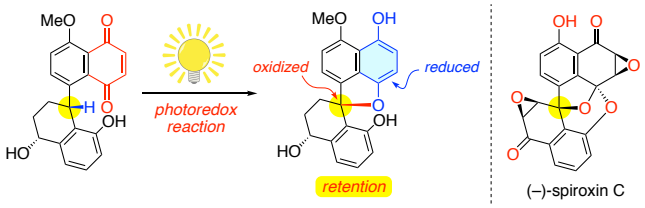

The stereospecific conversion of naphthoquinone derivatives into the corresponding spiroethers via intramolecular photoredox reaction has been developed. Based on this method, the enantioselective total synthesis of (–)-spiroxin C, a highly oxygenated dimeric naphthoquinone, has been achieved.

*Y. Ando, A. Hanaki, R. Sasaki, K. Ohmori, K. Suzuki**

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