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Synthetic Study on Naphthospironone A: Construction of Benzobicyclo[3.2.1]octene Skeleton with Oxaspirocycle

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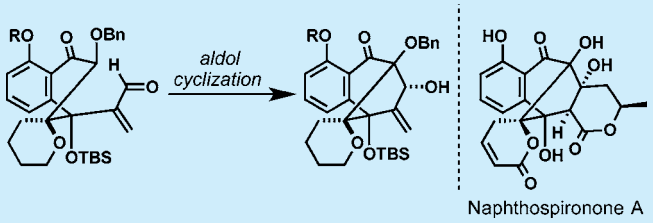
Supporting Information

ABSTRACT: In connection with the total synthesis of naphthospironone A, a model study has revealed a promising approach to construct a benzobicyclo[3.2.1]octene skeleton possessing an oxaspirocycle by employing an intramolecular aldol cyclization.



Naphthospironone A (**1**) is an antibiotic recently isolated from *Nocardiopsis* sp. that exhibits cytotoxicity against several cancer cell lines and antimicrobial activity against various bacteria.[1] The structure features a skeletal complexity associated with the unique bridged skeleton that is attached to two lactones, one fused and the other one spiro. Other characteristics include the dense oxygen functionalities and the stereochemical complexity. Intrigued by the potential biological activities as well as the unusual complex molecular architecture, we embarked on a synthetic study of **1**. This paper describes a viable approach to construct the benzobicyclo[3.2.1]octene structure, providing a promising platform to achieve the total synthesis of **1**.

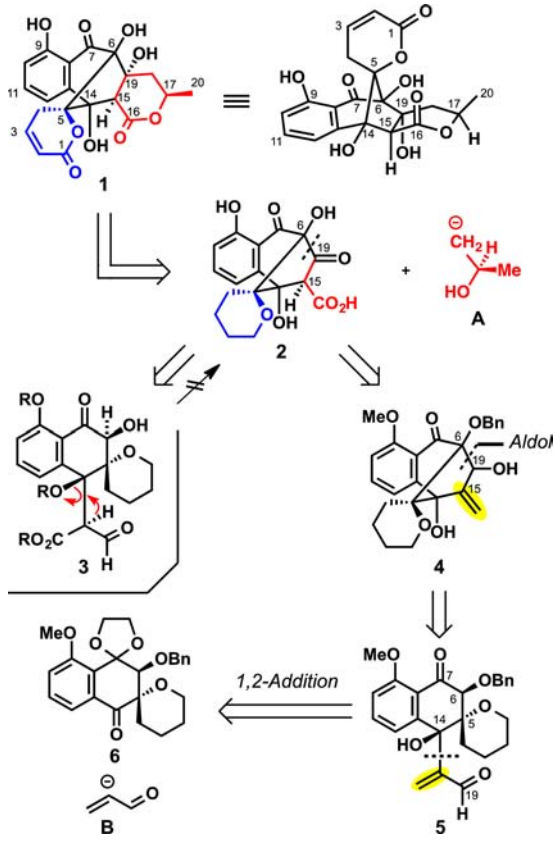
Scheme 1 outlines a retrosynthetic analysis in which two lactone moieties are simplified: The spirolactone (blue) in **1** is replaced by a simple tetrahydropyran, while the fused lactone (red) is disconnected into spirobicyclic intermediate **2** and three-carbon donor synthon **A**. For further disconnection of the bicyclo[3.2.1]octene skeleton, we focused on the C6−C19 bond.

However, this particular bond formation needs to address several issues: (1) the seven-membered ring formation that is often unfavorable, (2) molecular strain of the bridged ring system and also steric hindrance around the reaction site, and (3) the potential β-elimination reaction of the precursor **3**, which may occur under acidic or basic conditions.

At this juncture, we envisaged an *exo*-methylene group as a surrogate to the carboxy group at C15 as in **4**, hoping that the corresponding aldol progenitor **5** would have less steric demand and be free from the β-elimination issue. The intermediate **5** could finally be dissected into ketone **6** and a three-carbon donor synthon **B**.

Scheme 2 illustrates the preparation of ketone **6**, starting from 5-methoxy-1-naphthol (**7**).[2] For installing the 4-hydroxybutyl group corresponding to the latent five-atom unit of the spiro-tetrahydropyran ring, we adopted the O → C rearrangement used in aryl *C*-glycoside synthesis:[3] Treatment of **7** with dihydrofuran in the presence of catalytic pyridinium

Scheme 1. Structure and Retrosynthesis of 1



p-toluenesulfonate[4] gave THF ether **8** in excellent yield, which rearranged to *C*-furanyl naphthol **9** in 97% yield by the action of $BF_3{\cdot}OEt_2$. Hydrogenolytic cleavage of the tetrahydrofuran

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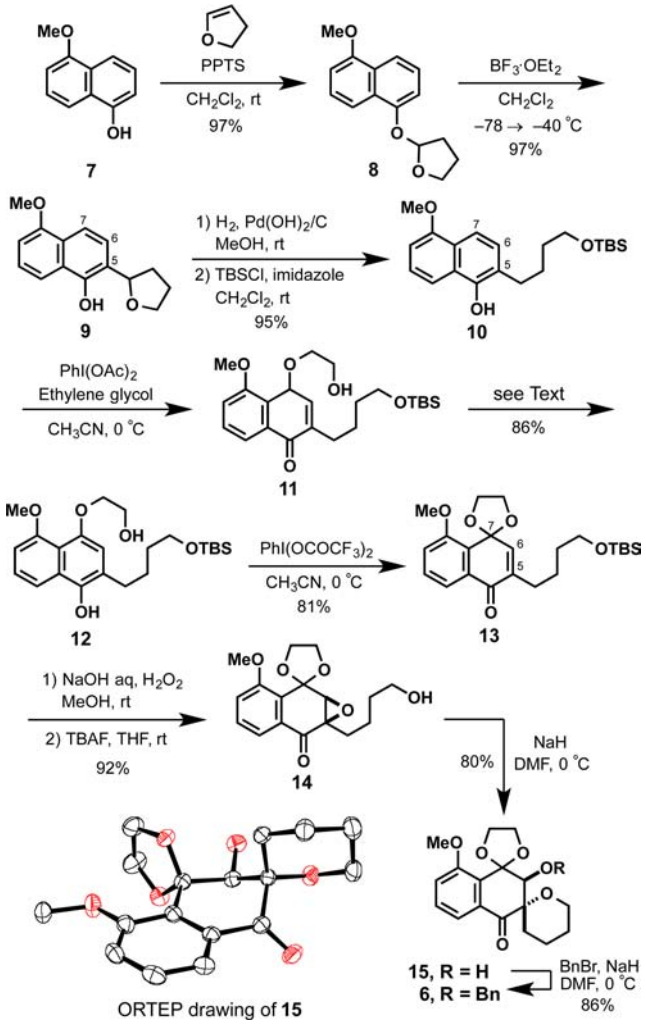
Scheme 2. Synthesis of Ketone 6



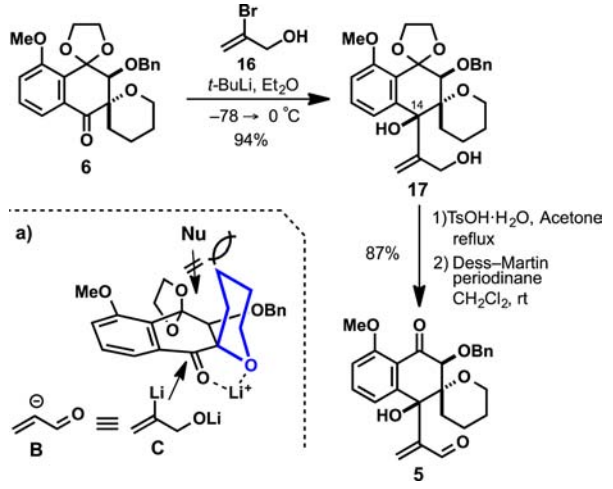
ring in **9** generated a 4-hydroxybutyl side chain, and selective protection of the resulting *prim*-alcohol gave naphthol **10**.

For installation of an oxygen function onto the C7 position of **10** to form naphthoquinone derivative **13**, a stepwise oxidation protocol was adopted.[5,6] Upon treatment of naphthol **10** with $PhI(OAc)_2$, γ-alkoxy enone **11** was identified as the major product in the crude mixture (^{1}H NMR), which however, underwent decomposition during the attempted silica gel column chromatography. Fortunately, the issue was solved by adding 1% of Et_3N to the eluent of the chromatography,[7] which allowed not only the purification but also facilitated the aromatization of **11**, giving naphthol **12** in 86% yield. Naphthol **12**, thus obtained, was treated with $PhI(OCOCF_3)_2$, giving quinone monoacetal **13** in 81% yield.

Enone **13** was treated with 30% H_2O_2 (6 M NaOH, MeOH, room temperature) and the silyl group removed, giving epoxide **14** in 92% yield in two steps. Upon treatment of epoxy alcohol **14** with NaH (DMF, 0 °C), an intramolecular attack of the alkoxide to the oxirane ring in **14** occurred regioselectively at the α-position to the carbonyl group, giving 80% yield of spirocycle **15** as a single stereoisomer, which was assigned by single-crystal X-ray diffraction analysis.[8] Protection of the *sec*-hydroxy group in **15** by a benzyl group gave ether **6** in 86% yield.

With the ketone **6** in hand, we focused our attention on introducing the nucleophilic acrolein unit **B** (Scheme 3). As a

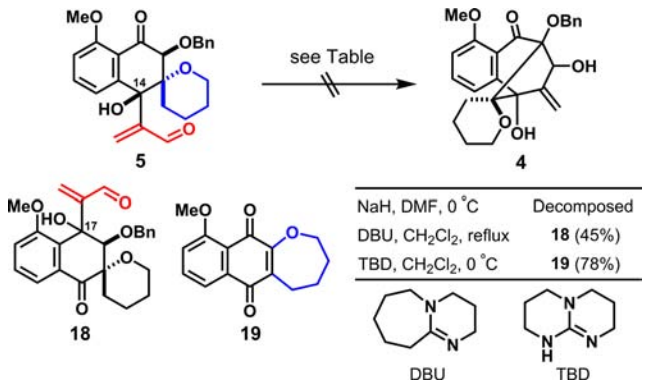
Scheme 3. Synthesis of Ketoaldehyde 5



synthetic equivalent to **B**, we employed the *O*- and *C*-dilithio species **C** [see (a) in Scheme 3].[9] Treatment of bromo alcohol **16** (3.4 equiv) with *t*-BuLi (10 equiv, Et_2O, − 78 → 0 °C) followed by the addition of ketone **6** gave adduct **17** as a sole product in 94% yield. The β stereochemistry of the C14 alcohol was proven at the stage of **21** (vide infra). The stereoselectivity is explained by the chelation control, where the nucleophile attacked from the α face, avoiding steric interaction with the spiroether moiety [see (a) in Scheme 3]. Exposure of adduct **17** to acid (TsOH·H_2O, acetone, reflux) and Dess−Martin oxidation gave ketoaldehyde **5**, ready for the key aldol cyclization.

However, attempts at the projected reaction of **5** were unfruitful (Scheme 4). Treatment of **5** with NaH (DMF, 0 °C)

Scheme 4. Side Reactions of 5



caused only decomposition. Surprisingly, use of DBU gave ketoaldehyde **18** (45%),[10] formally derived from the 1,4-transposition of the enal unit. By contrast, use of 1,5,7-triazabicylo[4.4.0]-dec-5-ene (TBD) led to a good yield of a different product, i.e., naphthoquinone **19** with a tetrahydro oxepin.

These side reactions could be rationalized by invoking enolate **I** generated by the conjugate addition of the base (DBU or TBD) to the C=C bond of enal **5** (Scheme 5).[11] If the enolate moiety in **I** attacked the C17 carbonyl group, a

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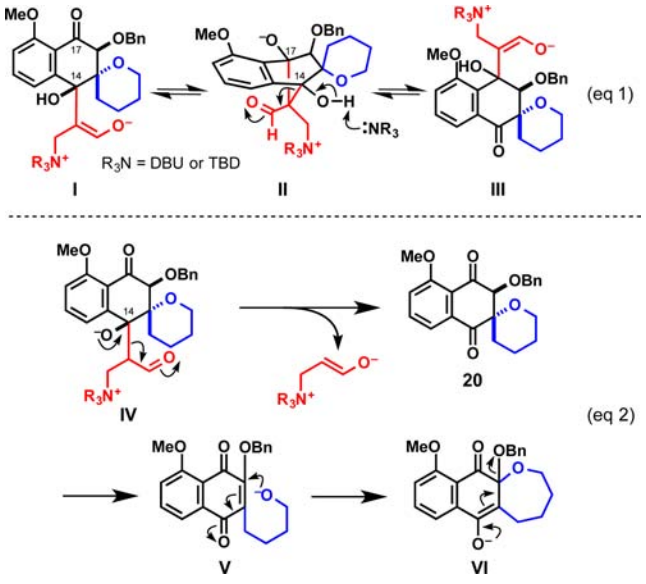
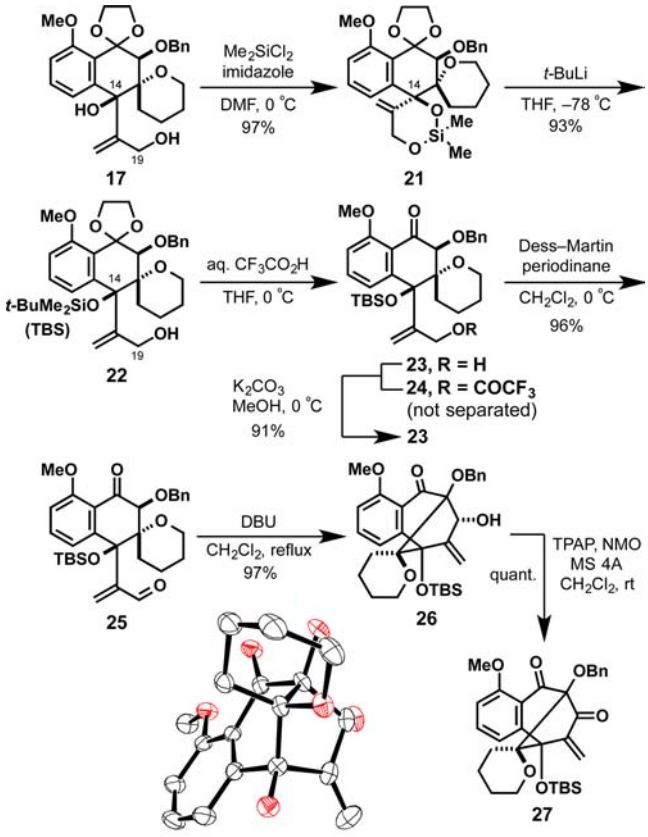
Scheme 5. Rationale for the Side Reactions



Scheme 6. Construction of the Bicyclic Skeleton



pseudosymmetric intermediate **II** would be formed (Scheme 5, eq 1). Base-induced cleavage of the C−C bond (**II** → **III**) was followed by the retro-1,4-addition account for the formation of **18**.

In contrast, if a retro-aldol reaction occurred from **I** via **IV**, diketone **20** was generated (Scheme 5, eq 2), which further underwent base-promoted elimination to cleave the spiro-ether ring (**20** → **V**), and the resulting alkoxide underwent addition/elimination to replace the benzyloxy group (**V** → **VI**), giving naphthoquinone **19**. Indeed, treatment of **20**, prepared by the acid hydrolysis of ketone **6**,[12] with TBD (CH_2Cl_2, 0 °C) gave **19** in 88% yield.

Noting that these undesired processes both involve deprotonation of the C14 alcohol (see **II** and **IV**), we reasoned that protection of this alcohol would solve the issues. For this purpose, selective protection of the C14 *tert*-alcohol was necessary, leaving the C19 *prim*-alcohol free, which was nicely realized by the Mukaiyama strategy.[13] Diol **17** was converted to dimethylsilylene acetal **21**,[8] which was treated with *t*-BuLi to give the selectively protected silyl ether **22** (Scheme 6). Exposure of **22** to acid (80% aq CF_3CO_2H, THF, 0 °C) gave a mixture of the desired ketone **23** and its trifluoroacetate **24**, which converged into ketone **23** by treatment with K_2CO_3 in MeOH (91% yield in two steps). Dess−Martin oxidation of **23** gave ketoaldehyde **25**, ready for the retrial of the key aldol cyclization.

We were pleased to find that treatment of **25** with DBU (CH_2Cl_2, reflux, 9 h) cleanly furnished spirobicycle **26** in 97% yield as the sole product, whose structure was verified by single-crystal X-ray diffraction analysis.[8] In contrast, use of NaH or TBD led to quite low yields of **26**. The positive outcome by protecting the C14 alcohol is ascribable to the expected avoidance of the alkoxide formation but may as well be due to the steric bulk of the silyl group, shielding the enal C=C bond from the conjugate addition of the base.

Finally, TPAP oxidation[14] of **26** afforded diketone **27** in quantitative yield, which is equivalent to the planned key intermediate **2** (cf. Scheme 1). The remaining problems for achieving the total synthesis of **1** include the construction of the fused and the spirolactones in a stereoselective manner. The conversion of **25** to **27** was also viable by a one-pot procedure, where Dess−Martin periodinane was used as the oxidant.[12]

In conclusion, a promising approach has been developed for constructing the core carbon framework of naphthospironone A, which will contribute to the projected total synthesis. Further work is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01732.

X-ray crystallographic data for **21** (CIF)
X-ray crystallographic data for **15** (CIF)
X-ray crystallographic data for **26** (CIF)
Full experimental procedure and characterization data (PDF)
^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Masaaki Miyashita.

■ REFERENCES

(1) Ding, Z. G.; Li, M. G.; Zhao, J. Y.; Ren, J.; Huang, R.; Xie, M. J.; Cui, X. L.; Zhu, H. J.; Wen, M. L. *Chem. - Eur. J.* **2010**, *16*, 3902−3905.
(2) Naphthol **7** was prepared from commercially available 1,5-dihydroxynaphthalene via dimethylation and mono-demethylation. For the dimethylation step, see: Tyson, D. S.; Fabrizio, E. F.; Panzner, M. J.; Kinder, J. D.; Buisson, J. P.; Christensen, J. B.; Meador, M. A. *J. Photochem. Photobiol., A* **2005**, *172*, 97−107.
(3) (a) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935−6938. (b) Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, *1988*, 1005−1007.
(4) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772−3774.
(5) Attempted direct oxidative acetalization of **10** gave naphthoquinone monoacetal **13** in low yield.
(6) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927−3930.
(7) Hexane/AcOEt = 4:1. For details, see the Supporting Information.
(8) CCDC 1403885 (**15**), 1403883 (**21**), and 1403886 (**26**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(9) Cuomo, J. *J. Agric. Food Chem.* **1985**, *33*, 717−719.
(10) Obtained as a single isomer, although the C17 stereochemistry was unassigned.
(11) DBU is known to be effective for promoting the Morita−Baylis−Hillman reactions; see: Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311−2312.
(12) For the details, see the Supporting Information.
(13) Mukaiyama, T.; Shiina, I.; Kimura, K.; Akiyama, Y.; Iwadare, H. *Chem. Lett.* **1995**, *24*, 229−230. See also: Tanino, K.; Shimizu, T.; Kuwahara, M.; Kuwajima, I. *J. Org. Chem.* **1998**, *63*, 2422−2423.
(14) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.

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