RESEARCH ARTICLE

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Construction of Functionalized *ortho*-Naphthoquinone Methides via Site-Selective Ring Opening of 1-Siloxy-1,4-epoxy-1,4-dihydronaphthalenes

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Abstract. 1-Siloxy-4-(benzyloxy)methyl-1,4-epoxy-1,4-dihydronaphthalenes, generated from benzynes and furans, underwent automatic site-selective ring opening because of the synergetic effect of the steric strain of the 1,4-epoxy moiety and the electron-donating ability of the siloxy group on the acetal structure to afford the precursors of *ortho*-naphthoquinone methides (*o*-NQMs). Subsequent Lewis acid-facilitated *o*-NQM formation and annulation with olefins afforded multi-fused heterocycles. Notably, the consecutive hexacyclic skeleton of rubioncolin B was constructed via solvent-dependent regioselective annulation of naphthofuran derivatives.

Keywords: *ortho*-naphthoquinone methides; Lewis acid catalyst; heterocycles; natural products

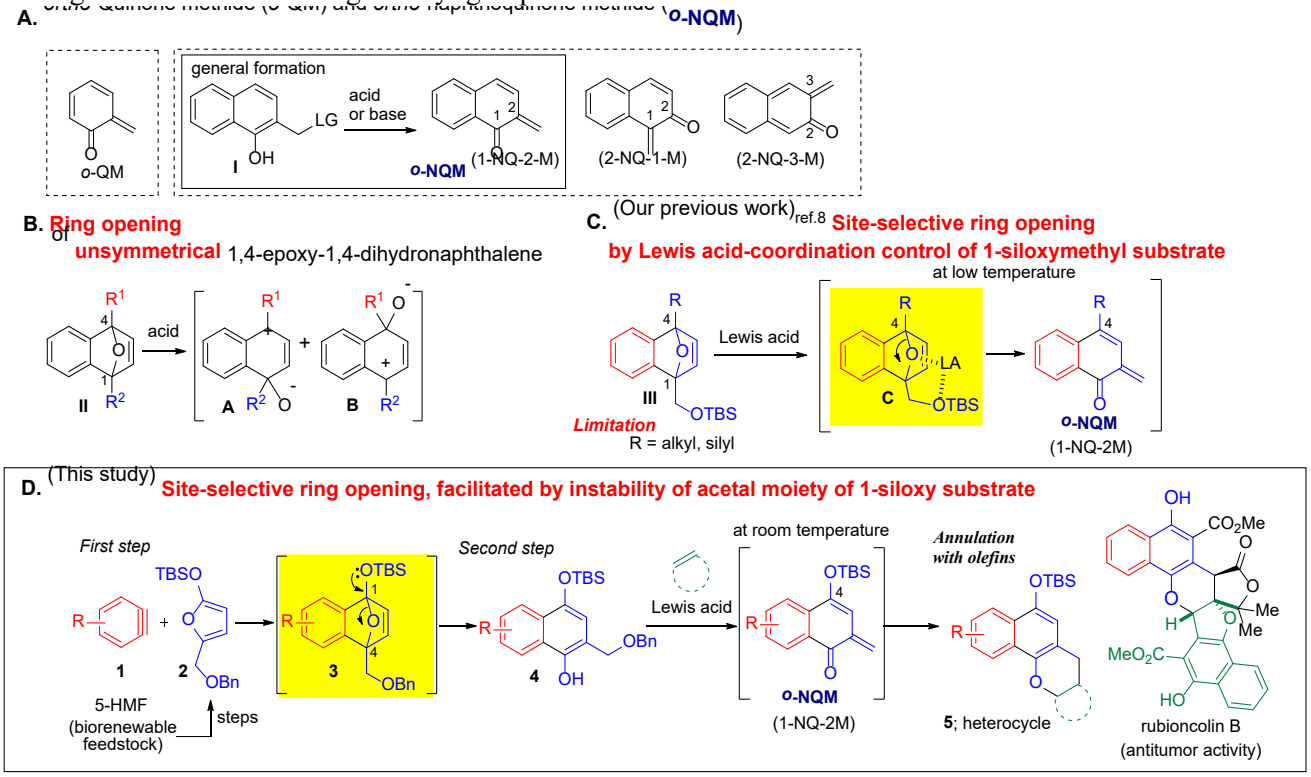
Introduction

Efficient construction of functionalized reactive intermediates and control of site-selective transformations are frequently demanded to synthesize the complicated target molecules including natural products. *Ortho*-naphthoquinone methides (*o*-NQMs) are utilized as highly reactive intermediates to construct naphthalene-based compounds via annulation and 1,4-addition of α,β-unsaturated carbonyl moieties (Scheme 1-A).[1] *o*-NQMs (1-NQ-2-M,[2] 2-NQ-1-M,[3] and 2-NQ-3-M[4]) are categorized according to the substituent positions of the carbonyl and exo-methylene groups. Although various preparation methods for *o*-quinone methides (*o*-QMs; *o*-NQMs without the benzene ring),[1,5] have been widely developed, only a few reports are available on the preparation and further transformation of *o*-NQMs.[2–4] For example, 1-NQ-2-M is generally prepared from 1-naphthol (**I**), which possesses a functionalized benzylic carbon at the *ortho*-position of the hydroxy group, via acid- or base-catalyzed elimination of the leaving group. However, the less preparation method of functionalized derivatives of **I** may hinder the development of *o*-NQM chemistry.

1,4-Epoxy-1,4-dihydronaphthalenes (**II**), directly prepared by the Diels–Alder reaction between benzynes and furans, have been also employed to construct naphthalene-based compounds via ring opening of the 1,4-epoxy moiety (Scheme 1-B).[6] Although the 1,4-epoxy moiety of **II** can be comparatively easily cleaved because of its steric strain, this process generally requires acidic conditions. Moreover, unsymmetrical substrates with different substituents (R^1 and R^2) at the bridgehead positions of **II** can be transformed into two carbocation intermediates (**A** and **B**) via ring opening at different cleavage positions. Therefore, accurate control to achieve perfect site-selectivity of ring opening position is required to efficiently synthesize target molecules.[7]

We have recently reported the Lewis acid-catalyzed site-selective ring opening of 4-alkyl/silyl-1-siloxymethyl-1,4-epoxy-1,4-dihydronaphthalenes (**III**) and subsequent tandem reactions to produce *o*-NQM (Scheme 1-C).[8] The cleavage path of the 1,4-epoxy moiety of **III** could be controlled by Lewis acid coordination (**C**) between the two oxygen atoms at 1,4-epoxy and siloxy moieties. However, this process, including the subsequent functionalization of *o*-NQM, requires the strict control of the reaction temperature (-40 °C, which is then gradually increased up to rt). Additionally, the substituents at the 4-position of **III** are limited to alkyl or silyl groups, which is disadvantage in application to synthesis of natural and bioactive compounds.

Herein, we demonstrate a new concept for realizing the automatic site-selective ring opening of 1-siloxy-4-(benzyloxy)methyl-1,4-epoxy-1,4-dihydronaphthalenes (**3**) for the construction of functionalized 1-naphthols (**4**) as *o*-NQM precursors (Scheme 1-D). Here, **3** was prepared by the Diels–Alder reaction of the corresponding benzynes (**1**) and furan derivative (**2**), derived from 5-(hydroxymethyl)furfural (5-HMF) as biorenewable feedstock.[9] The site-selective ring opening of **3** is automatically triggered by the steric strain of the 1,4-epoxy moiety and the unstable acetal structure possessing the electron-donating siloxy group.[10] The subsequent Lewis acid-catalyzed formation of *o*-NQM and annulation with olefins efficiently proceed at room temperature to produce various pharmaceutically useful complicated heterocyclic skeletons (**5**) in a two-step manner from **1** and **2**.[11] The present reaction could be applied to construct the consecutive hexacyclic skeleton of rubioncolin B (antitumor active compound).[12,13]



Scheme 1. Site-selective ring opening of unsymmetrical 1,4-epoxy-1,4-dihydronaphthalene and formation of reactive and functionalized *ortho*-naphthoquinone methide (*o*-NQM). (LG; leaving group, 5-HMF; 5-(hydroxymethyl)furfural, LA; Lewis acid)

Results and Discussion

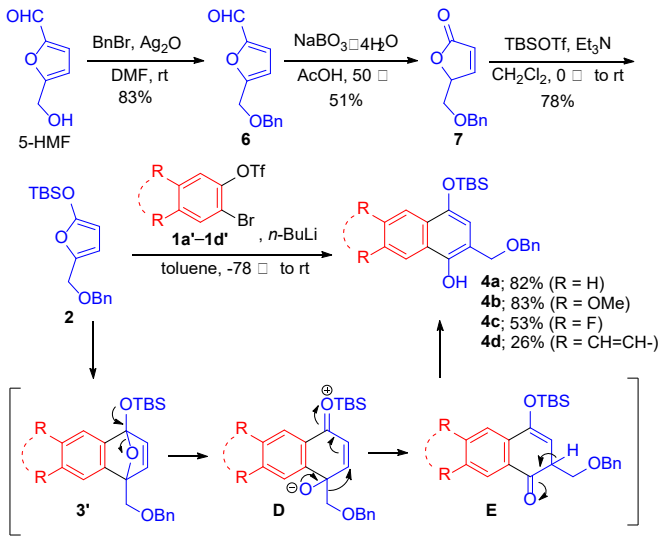
1-Siloxy-4-(benzyloxymethyl)furan (**2**) was prepared from 5-HMF via benzylation of the hydroxy group and oxidation of the furfural moiety by $NaBO_3 \cdot 4H_2O$[14] to butenolide (**7**), followed by silylation with TBSOTf and Et_3N (Scheme 2-A). The Diels–Alder reaction between **2** and benzynes (**1a**–**1d**) generated from precursors **1a'**–**1d'** with *n*-BuLi provided 1-siloxy-4-(benzyloxy)methyl-1,4-epoxy-1,4-dihydronaphthalene derivatives (**3'**), which smoothly underwent the site-selective ring opening of the acetal moiety, 1,2-shift of the (benzyloxy)methyl group on **D**, and aromatization of **E** to afford *o*-NQM precursors (**4a**–**4d**). It was not ruled out that the side-products, generated during the formation of benzyne from **1a'**–**1d'** and *n*-BuLi, facilitated the ring-opening reaction of **3'**.

Formation of *o*-NQM from **4a** and subsequent annulation using indene effectively proceeded in the presence of catalytic amounts of $FeCl_3$ in toluene at room temperature to produce the pentacyclic product (**5a**) in 79% isolated yield (Scheme 2-B, entry 1). Next, the effect of the solvent was examined. The reaction in $CHCl_3$ and CH_2Cl_2 instead of toluene also provided the desired product **5a** in good yields (entries 2 and 3), whereas the use of THF decreased the yield (entry 4). In contrast, DMF is ineffective (entry 5). Although $Fe(OTf)_3$, an iron (III) salt, can be used in toluene, similar to $FeCl_3$ (entries 1 *vs.* 6), the use of $FeCl_2$ did not produce **5a** and afforded 85% recovery of **4a** (entry 7). $AlCl_3$ was also an effective catalyst to produce **5a** in 83% isolated yield (entry 8). Other traditional Lewis acids such as $ZnCl_2$, $MgCl_2$, and AgOTf led to lower yields or no reaction (see

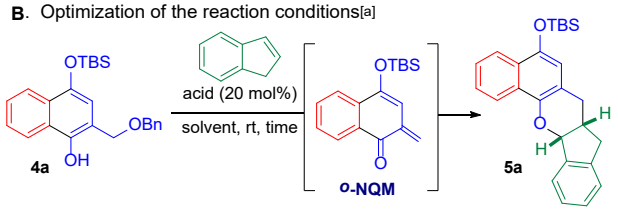
Supporting Information). When trifluoroacetic acid (TFA) was used as a Brønsted acid, **5a** was obtained in moderate yields (entry 9). When (+)-camphorsulfonic acid (CSA) was used as a chiral Brønsted acid, racemic **5a** was obtained in 29% yield (entry 10).

Encouraged by the achievement of the desired reaction shown in Scheme 2, we next evaluated the substrate scope under the optimal conditions using $AlCl_3$ or $FeCl_3$ in toluene (Table 1).[15] The olefin moiety of styrene and isobutene successfully underwent annulation with *o*-NQM to generate dihydronaphthopyran derivatives **5b** and **5c** in moderate to good yields, respectively. Benzofuran and benzothiophene were also applicable to provide pentacyclic compounds **5d** and **5e** with excellent regioselectivities. These regioselectivities can be explained by the general nucleophilic positions of benzofuran and benzothiophene. Nuclephilic attack of benzofuran proceeds at its C2 position,[16] while nuclephilic attack of benzothiophene proceeds at its C3 position.[17] Dihydronaphthopyran derivatives (**5f**–**5h**) were obtained from the non-substituted *o*-NQM precursor (**4a**) and dimethoxy-*o*-NQM precursor (**4b**) in good yields when allyl silanes were used as olefins. **4c**, containing strong electron-withdrawing fluorine atoms, and **4d**, bearing an anthracene skeleton, can be used to achieve annulation with an allyl silane derivative to produce **5i** and **5j**, respectively. Furthermore, *o*-NQMs were effectively transformed into biarylmethanes (**8**) via 1,4-addition of the α,β-unsaturated carbonyl moiety of *o*-NQMs with arene nucleophiles.[18] 1,3-Dimethoxybenzene and 1,3,5-trimethoxybenzene were successfully reacted with non-substituted, di-substituted, and benzene-fused *o*-NQM (**4a**–**4d**) to produce **8a**–**8e** in good to excellent yields. 1-Methoxynaphthalene and *N*-phenyl-indole were also applicable to afford **8f** and **8g**, respectively. The reaction using indole derivative gave the biarylmethane (**8f**), while the annulated products (**5d** and **5e**) were obtained uisng benzofuran and benzothiophene. The reasons are unclear at this stage, however the similar tendency was observed in the reported literature.[8]

A. Preparation of the *o*-NQM precursors



B. Optimization of the reaction conditions[a]

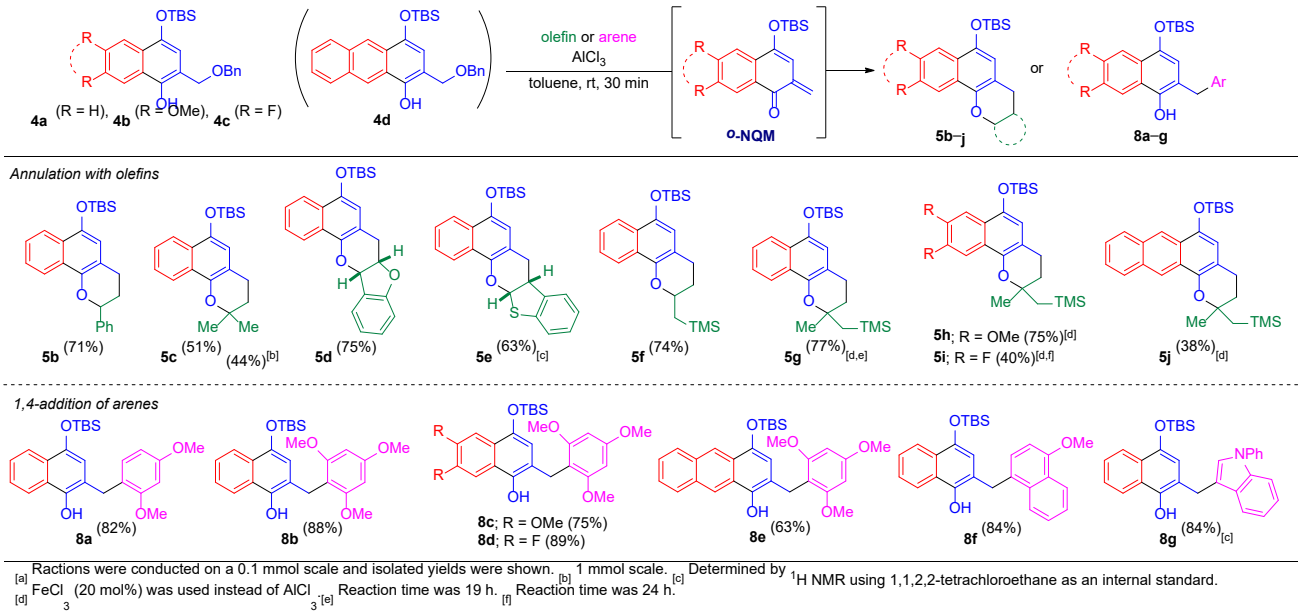


entry	acid	solvent	time (h)	yield (%)[b]
1	$FeCl_3$	toluene	0.5	80 (79)[c]
2	$FeCl_3$	$CHCl_3$	1	77
3	$FeCl_3$	CH_2Cl_2	0.5	75
4	$FeCl_3$	THF	24	41
5	$FeCl_3$	DMF	24	0
6	$Fe(OTf)_3$	toluene	0.5	72
7	$FeCl_2$	toluene	24	0
8	$AlCl_3$	toluene	0.5	85 (83)[c]
9	TFA (100 mol%)	toluene	8	65
10	(+)-CSA (100 mol%)	toluene	24	29[d]

[a] Reactions are conducted on a 0.1 mmol scale. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] 0% ee.

Scheme 2. (A) Preparation of *o*-NQM precursors **4a**–**4d** and (B) Optimization of reaction conditions using indene.

Table 1. Scope of substrates[a]

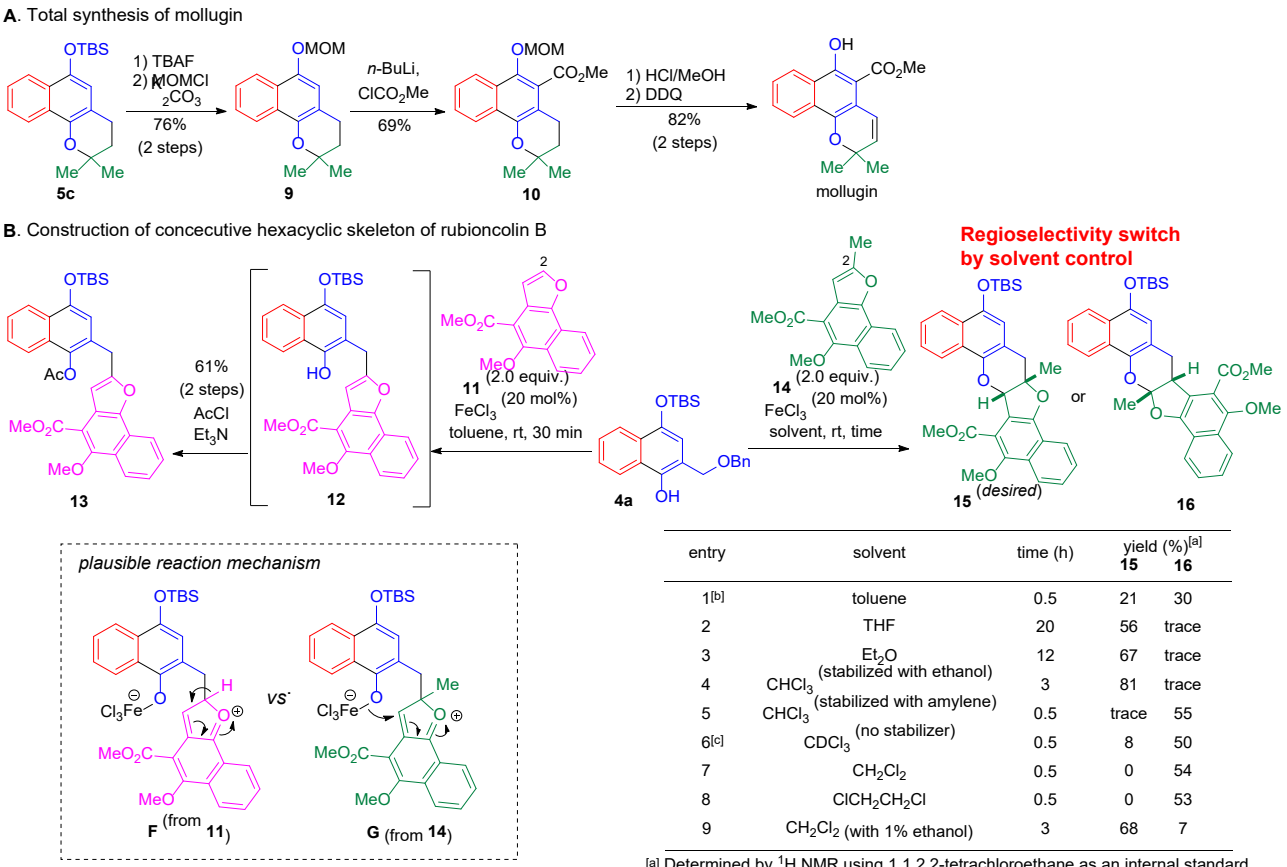


[a] Ractions were conducted on a 0.1 mmol scale and isolated yields were shown. [b] 1 mmol scale. [c] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [d] $FeCl_3$ (20 mol%) was used instead of $AlCl_3$. [e] Reaction time was 19 h. [f] Reaction time was 24 h.

The present methodology was applied to the synthetic studies on natural products, mollugin[19] and rubioncolin B[12,13] (Scheme 3). Mollugin was synthesized from **5c**, obtained in Table 1 (Scheme 3-A). The *tert*-butyldimethylsilyl (TBS) group of **5c** was transformed into a methoxymethyl (MOM) group to obtain **9** in 76% yield (2 steps). MOM-directed *ortho*-lithiation and subsequent nucleophilic addition to methyl chloroformate afforded **10** in 69% yield. Deprotection of the MOM group using HCl/MeOH followed by dehydrogenation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) afforded mollugin in 82% yield in 2 steps.

Next, the construction of the consecutive hexacyclic skeleton of rubioncolin B was attempted (Scheme 3-B). Unfortunately, the 2-non-substituted naphthofuran derivative (**11**)[13,20] did not undergo annulation with the *o*-NQM, derived from **4a**. Instead, 1,4-addition product **12** was generated in the presence of $FeCl_3$[15] in toluene. Because **12** was unstable, acetylation was performed to afford biarylmethane **13** in 61% yield (2 steps). In contrast, the use of a 2-methyl-naphthofuran derivative (**14**)[20] facilitated the desired annulation with *o*-NQM to afford a hexacyclic product (**15**) in 21% yield, accompanied by the formation of its regioisomer (**16**) in 30% yield (Scheme 3-B, entry 1). Note that **15** corresponds to the main backbone of rubioncolin B. Intermediate **F**, generated by the 1,4-addition of the 2-non-substituted naphthofuran derivative (**11**), easily undergoes deprotonative aromatization to produce biarylmethane (**12**). Meanwhile, the substitution of a methyl group at the C2 position of the naphthofuran derivative inhibited the aromatization of **G**, which promoted the desired cyclization by attack of phenoxide ion to arenium moiety. Both concerted ([4+2]-cycloaddition) and stepwise reaction mechanisms for annulation between *o*-NQM and the olefin moiety were conceivable. At this stage, the actual reaction pathway could not be determined.[21]

Notably, changes of solvent were found to switch the regioselectivity of the annulation of *o*-NQM with **14** (Scheme 3-B; Table). Reactions in THF, Et_2O, and $CHCl_3$ containing EtOH as a stabilizer afforded **15** as the main product (entries 2–4). Meanwhile, **16** was mainly produced when using $CHCl_3$ containing amylene as a stabilizer, $CDCl_3$ (no stabilizer), CH_2Cl_2, and $ClCH_2CH_2Cl$ (entries 5–8). The reaction in CH_2Cl_2 with 1% EtOH provided **15** as the main product (entry 9). Remarkably, the use of CH_2Cl_2 without or with 1% EtOH switched the regioselectivity (entries 7 *vs.* 9). From these results, Lewis basicity of the oxygen atoms of EtOH, Et_2O, and THF is presumed to play a key role in the regioselectivity. When 2-methylbenzofuran was used in place of 2-methylnaphthofuran derivative **14**, a mixture of regioisomers was obtained in low yields. Their regioselectivities could not be controlled by changing the solvent. When using **11** in CH_2Cl_2 instead of toluene, **12** was generated as sole product. The reasons for this remain unclear.



entry	solvent	time (h)	yield (%)[a] 15	16
1[b]	toluene	0.5	21	30
2	THF	20	56	trace
3	Et_2O	12	67	trace
4	$CHCl_3$ (stabilized with ethanol)	3	81	trace
5	$CHCl_3$ (stabilized with amylene)	0.5	trace	55
6[c]	$CDCl_3$ (no stabilizer)	0.5	8	50
7	CH_2Cl_2	0.5	0	54
8	$ClCH_2CH_2Cl$	0.5	0	53
9	CH_2Cl_2 (with 1% ethanol)	3	68	7

[a] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] 1.5 equiv. of **14** was used. [c] $CDCl_3$ was used after treatment with basic Al_2O_3.

Scheme 3. Application to synthetic studies on natural products.

Conclusion

In conclusion, we established a synthetic method for functionalized *o*-NQM precursors via the site-selective ring opening of 1-siloxy-4-benzyloxymethyl-1,4-epoxy-1,4-dihydronaphthalene, followed by a 1,2-shift of the (benzyloxy)methyl group and aromatization. Reactive *o*-NQM intermediates were prepared in the presence of a catalytic Lewis acid at room temperature. Successive annulation of olefin substrates or 1,4-addition of arene nucleophiles provided heterocycles or biarylmethanes, respectively. Furthermore, the present method was applied to synthetic studies on natural products. The consecutive hexacyclic skeleton of rubioncolin B was regioselectively constructed using a solvent control.

Experimental Section

General procedure for annulation with olefins and 1,4-addition of arenes

Lewis acid (0.020 mmol) was added to a solution of **4a**–**4d** (0.100 mmol) and olefin/arene (0.400 mmol) in toluene (1.0 mL) at room temperature. After being stirred for adequate time, water was added to the mixture. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to afford fused heterocyclic arenes **5a**–**5j** or biarylmethanes **8a**–**8g**.

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Construction of Functionalized *ortho*-Naphthoquinone Methides via Site-Selective Ring Opening of 1-Siloxy-1,4-epoxy-1,4-dihydronaphthalenes

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