

# CHEMISTRY OF ANTI-HIV ACTIVE TRIMERIC PYRANONAPHTHO-QUINONE CONOCURVONE: SYNTHETIC STUDIES TOWARDS MONOMERIC TERETIFOLIONE B AND RELATED COMPOUNDS

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**Abstract** – Pyranonaphthoquinone natural products are widely distributed in plants and microorganisms and have diverse biological activities. Angular benzochromenes are a small class of natural products isolated from *Conospermum* and *Pentas* plants. Of these, conocurvone was isolated from *Conospermum* as a trimeric pyranonaphthoquinone that has potent anti-HIV activity. We have focused on the total synthesis of compounds that exhibit biological activity or whose activity is enhanced upon oligomerization. This review describes the discovery and biological activities of the trimeric pyranonaphthoquinone conocurvone and related compounds, as well as our and other researchers' synthetic studies toward monomeric pyranonaphthoquinones.

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## 1. INTRODUCTION

Pyranonaphthoquinone (also called chromenoquinone) natural products have been isolated from various plants and bacteria and exhibit characteristic biological activities.<sup>1,2</sup> Busseihydroquinones B-D (**1-3**) and pyranonaphthalene **4** were isolated from *Pentas bussei* as antiplasmodial compounds.<sup>3</sup> Monomeric teretifolione B (**5**)<sup>4</sup> and its trimeric conocurvone (**6**) were isolated from *Conospermum* plants. Compound **6** exhibits anti-HIV-1 activity (Figure 1). The first part of this review provides background information regarding the isolation and studies on the biological activities of conocurvone (**6**) and related monomeric and oligomeric pyranonaphthoquinones. The second part of this review discusses synthetic studies by our laboratory and others on monomeric pyranonaphthoquinones, including teretifolione B (**5**).

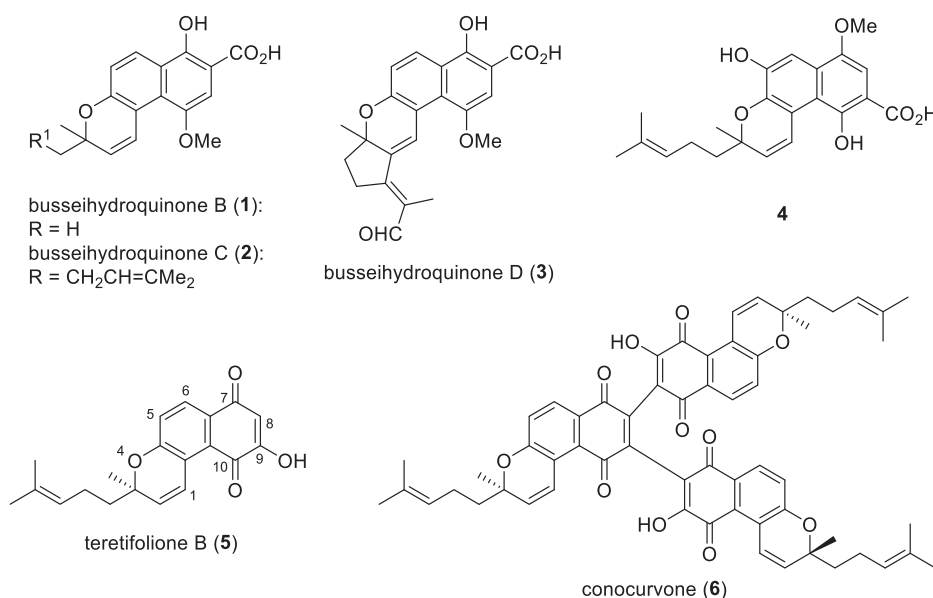


Figure 1. Natural pyranonaphthoquinones isolated from *Conospermum* and *Pentas* plants

## 2. ISOLATION AND STRUCTURAL DETERMINATION OF CONOCURVONE AND RELATED COMPOUNDS

In 1975, Cannon *et al.*<sup>5</sup> reported the isolation of ten quinones from *Conospermum teretifolium* (Proteaceae) roots, including the five new pyranonaphthoquinones **5** and **7-10** and the three

naphthoquinones **11-13**. Of these compounds, teretifolione B (**5**) and the C8-methylated derivative **9** were isolated as angular pyranonaphthoquinones with one quaternary chiral center (Figure 2).

Biological assays conducted at the U. S. National Cancer Institute showed that an extract of *Conospermum* plants exhibited inhibitory activity towards the cytopathic effects of HIV-1 infection. Boyd *et al.*<sup>6</sup> explored the chemical constituents of this extract using bioassay-guided separation and isolated conocurvone, a compound with anti-HIV activity. <sup>1</sup>H-NMR structural analysis provided a very complex spectrum with many highly overlapping resonances. For example, several components were observed whose abundance ratios depended on the solvent used and the temperature, suggesting a dynamic intramolecular process observable on the NMR time scale. The observation of multiple peaks upon HPLC analysis of conocurvone supported this result. High-resolution fast-atom bombardment mass spectrometry analysis showed the molecular formula of conocurvone to be C<sub>60</sub>H<sub>56</sub>O<sub>11</sub>. Negative-ion fast-atom bombardment mass spectrometry of deuterated conocurvone disclosed the presence of two exchangeable H atoms. Observation of the product ions derived from species with molecular weights one-third and two-thirds that of conocurvone indicated that **6** is the trimeric structure of monomeric pyranonaphthoquinone, which corresponds with monomeric teretifolione B (**5**). The complexity of the <sup>1</sup>H-NMR spectrum of conocurvone (**6**) was attributed to the slow tautomerization of the hydroquinone part and the existence of rotational isomers of the pyranonaphthoquinone unit. Acetylation of conocurvone (**6**) under reductive conditions using Zn dust in Ac<sub>2</sub>O gave the octaacetate whose <sup>1</sup>H-NMR spectrum indicated a single entity without tautomerization or slow rotation on the NMR time scale. Mass spectrometry analysis showed that the compound corresponds to structure **14** (Scheme 1a).

The structure of conocurvone (**6**) was elucidated by its semisynthesis from teretifolione B (**5**). First, the absolute configuration of teretifolione B (**5**) was determined as (*R*) by X-ray crystallographic analysis of the corresponding *p*-bromobenzoate **15**. The reaction of **15** with thiophenol, followed by treatment of the resulting bis(thiophenol) derivative **16** with Raney Ni, gave deoxyteretifolione B (**17**). Coupling of **17** and 2 equivalents of natural teretifolione B (**4**) in pyridine gave conocurvone (**6**), presumably via 1,4-addition of **4** to **17**, simultaneous oxidation of resultant hydroquinone to quinone in aerobic condition, second addition of **4** to the quinone followed by re-oxidation. The semisynthetic **6** was identical with naturally occurring conocurvone (**6**) in the terms of spectroscopic data and anti-HIV activity profiles (EC<sub>50</sub> 0.02 μM) (Scheme 1b). The anti-HIV activity of conocurvone (**6**) was demonstrated by its inhibition of both HIV-1 activity towards killing of human CEM-SS target cells and HIV-1 replication. The reaction of **5** and naphthoquinone **18** in AcOH gave semisynthetic dimer **19** and trimer **20** (Scheme 1c). The trimer **20** showed similar anti-HIV activity to **6**, however, semisynthetic dimer **18** showed no anti-HIV activity. Armstrong and coworkers<sup>4</sup> examined the constituents of *Conospermum brachyphyllum* and reported the isolation of brachyphyllone (**21**), conocurvone (**6**), and teretifolione B (**5**) and its methylated derivative

(9). They also reported the direct semisynthesis of conocurvone (6) from teretifolione B (5), in which a mixture of teretifolione B (5) and *p*-TsCl in pyridine was heated under a dry air atmosphere to give conocurvone (6) in 10% yield (Scheme 2).

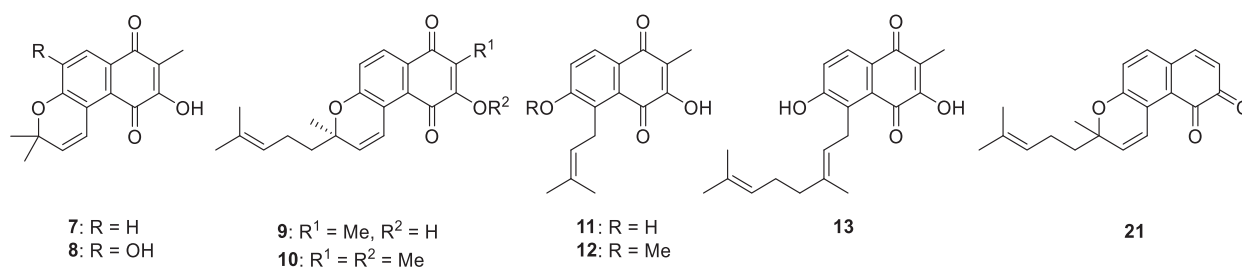
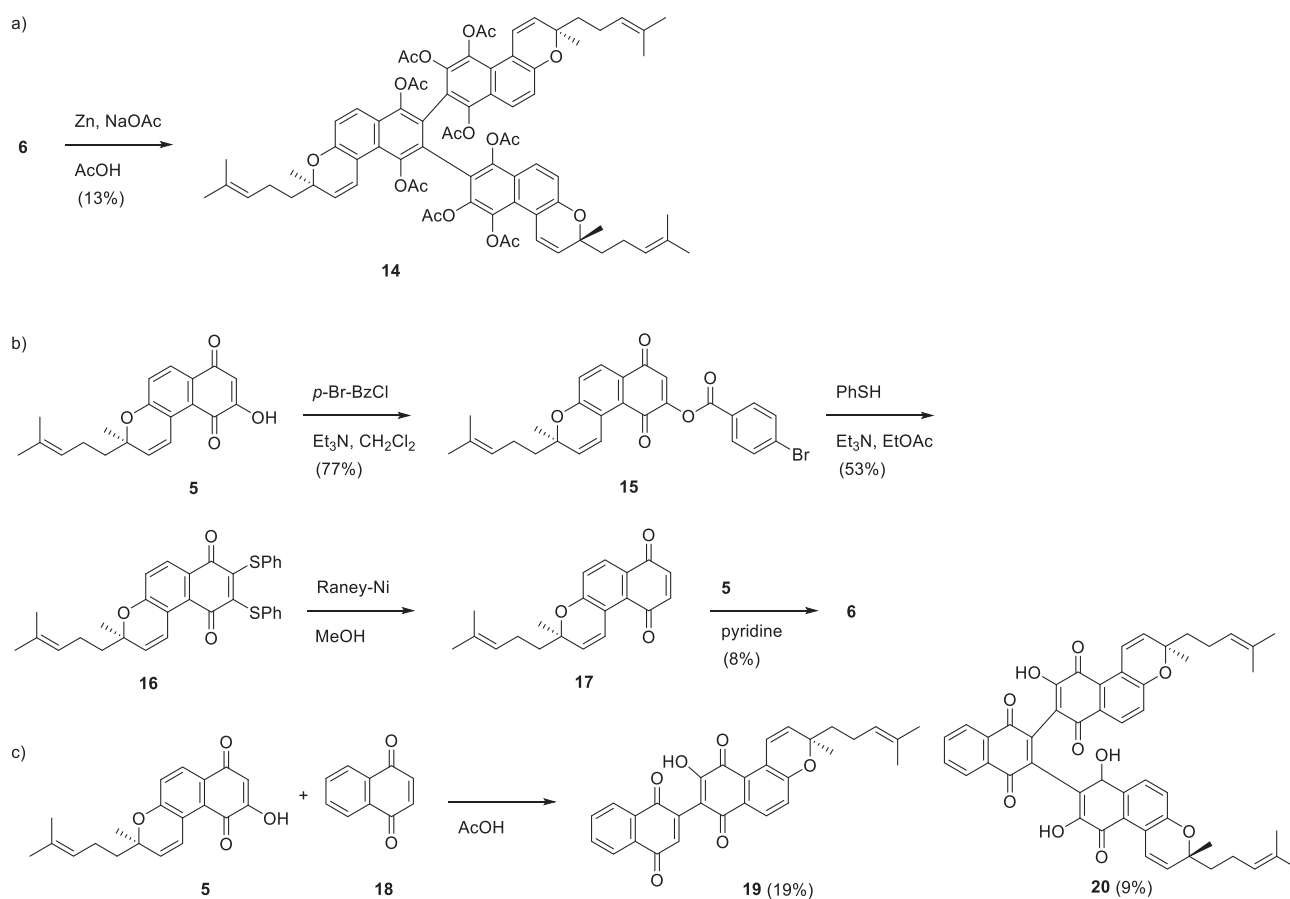
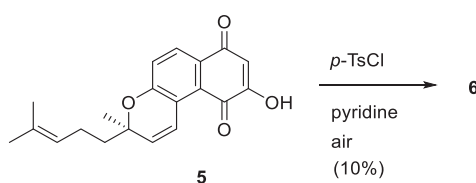


Figure 2. Representative naphthoquinones isolated from *Conospermum* sp. by Cannon *et al.*



Scheme 1. Derivatization of conocurvone (6) and teretifolione B (5)

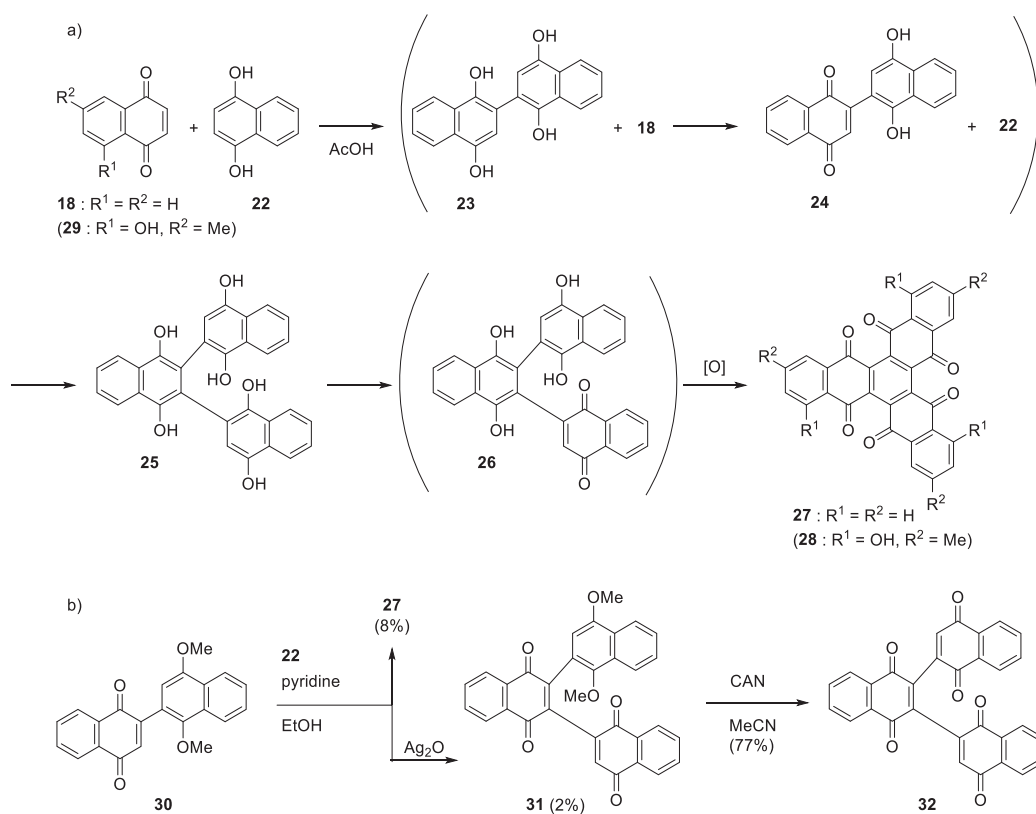


Scheme 2. Direct semisynthesis of conocurvone (6) from teretifolione B (5)

### 3. SYNTHESIS OF OLIGOMERIC NAPHTHOQUINONES AND THEIR BIOLOGICAL ACTIVITIES

#### 3-1. Formation of cyclic and acyclic trimeric naphthoquinones

Pummerer *et al.*<sup>7</sup> reported the oligomerization of monomeric naphthoquinones under both acidic (in AcOH) and basic (in pyridine) conditions. Brockmann<sup>8</sup> explained that this oligomerization starts with the Michael reaction of **18** and a small amount of contaminated hydroquinone **22** to afford hydroquinone dimer **23**. Bishydroquinone **23** reacts with quinone **18** and is converted to hydroquinone-quinone adduct **24** and hydroquinone **22** via an auto-redox process. Further conjugate addition of **22** to **24** affords acyclic trimer **25**, which cyclizes simultaneously under air to give cyclic trimer **27** via the assumed acyclic trimeric intermediate **26**.<sup>8</sup> This method was applied to the synthesis of natural cyclic trimer xylospyrin (**28**) via the trimerization of 7-methyljuglone (**29**) under similar reaction conditions (Scheme 3a).



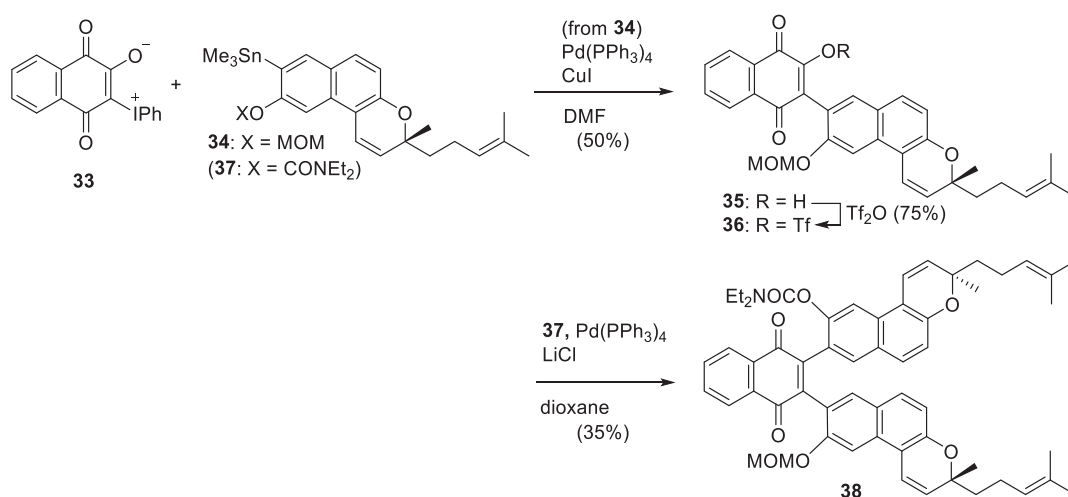
Scheme 3. Formation of cyclic **27** and **28**, and acyclic **32** quinone trimers, by the cyclotrimerization of naphthoquinones

Laatsch<sup>9</sup> reported the formation of cyclic trimer **27** in the reaction of quinone-methylated hydroquinone adduct **30** and hydroquinone **22** in the presence of pyridine. The filtrate obtained after the removal of precipitated **27** was treated with  $\text{Ag}_2\text{O}$  to afford a small amount of acyclic trimer **31** that could be converted to acyclic quinone trimer **32** via CAN oxidation (Scheme 3b).<sup>9</sup> Thus, trimerization of the

simple naphthoquinones **22** gave mainly cyclic trimers. Prevention of the assumed cyclotrimerization of teretifolione B (**5**) to afford conocurvone (**6**) (*vide infra*) has been attributed to the hydroxy groups at position 8 in **5**.<sup>10</sup>

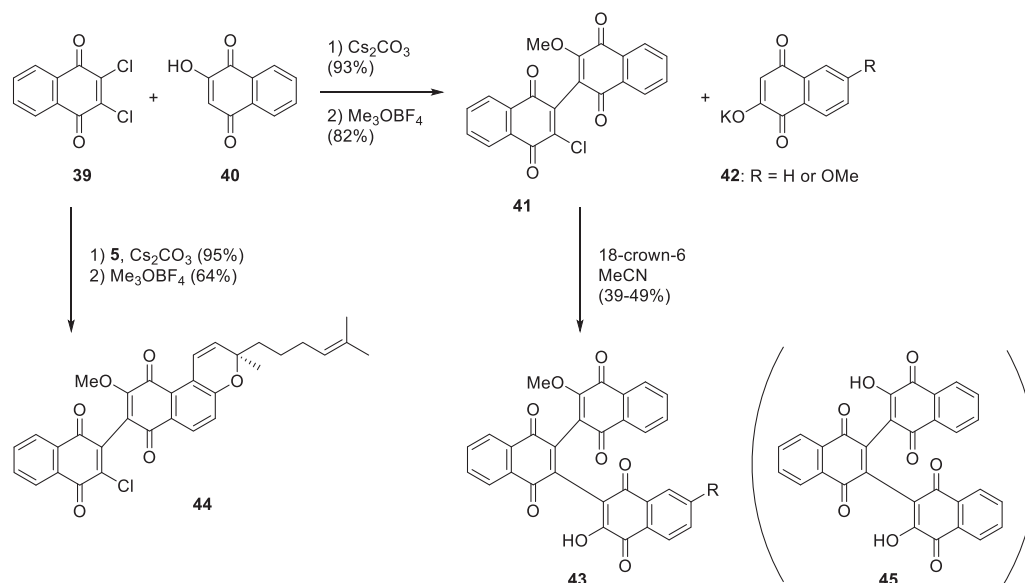
### 3-2. Synthesis of acyclic trimeric naphthoquinones using halogenated monomers

Stagliano *et al.* examined the application of quinone iodonium salt **33** as a quinone 1,4-dipole for the synthesis of acyclic trimeric naphthalenes.<sup>11</sup> A series of iodonium salts can be prepared by the reaction of 2-hydroxynaphthoquinones and  $\text{PhI}(\text{OAc})_2$ .<sup>12</sup> Stille coupling of the iodonium salt **33** and stannylbenzopyrane **34** in the presence of palladium catalysts gave dimer **35**. After conversion of the hydroxy group in **35** to triflate **36**, Stille coupling of **36** and stannane **37** gave 2,3-bis(pyranonaphthyl)-1,4-naphthoquinone **38** (Scheme 4).



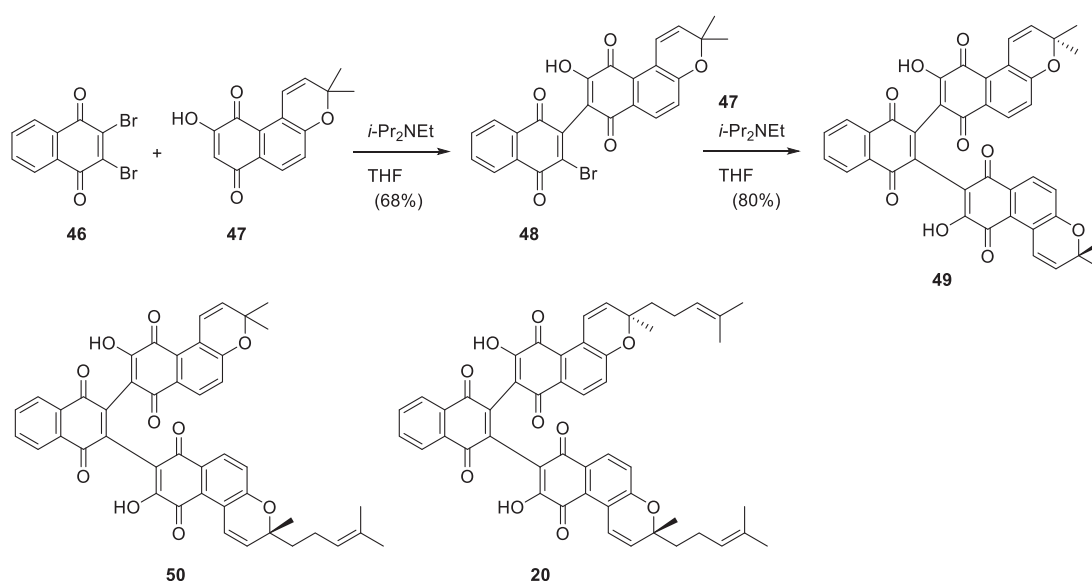
Scheme 4. Synthesis of 2,3-bisnaphthyl naphthoquinone **38** by double Stille coupling

Stagliano *et al.*<sup>13</sup> also reported the synthesis of oligomeric hydroxynaphthoquinones by a Michael addition-elimination sequence using 2,3-dichloronaphthoquinone **39** and 2-hydroxynaphthoquinone **40**. The reaction of **39** and 1 mol equivalent of **40** in the presence of  $\text{Cs}_2\text{CO}_3$  as a base gave dimer **41** after methylation of the hydroxy group using Meerwein reagent. The dimeric quinone **41** was further treated with hydroquinone potassium salts **42** in the presence of 18-crown-6 to give the trimeric naphthoquinones **43**. Condensation of **39** and 1 mol equivalent of teretifolione B (**5**) was examined under similar conditions to afford methylated unsymmetrical dimeric quinone **44**. Several trimeric quinones prepared by this method were assayed for anti-HIV activity. Compound **45** showed weaker activity than did conocurvone (**6**) (Scheme 5).<sup>14</sup>



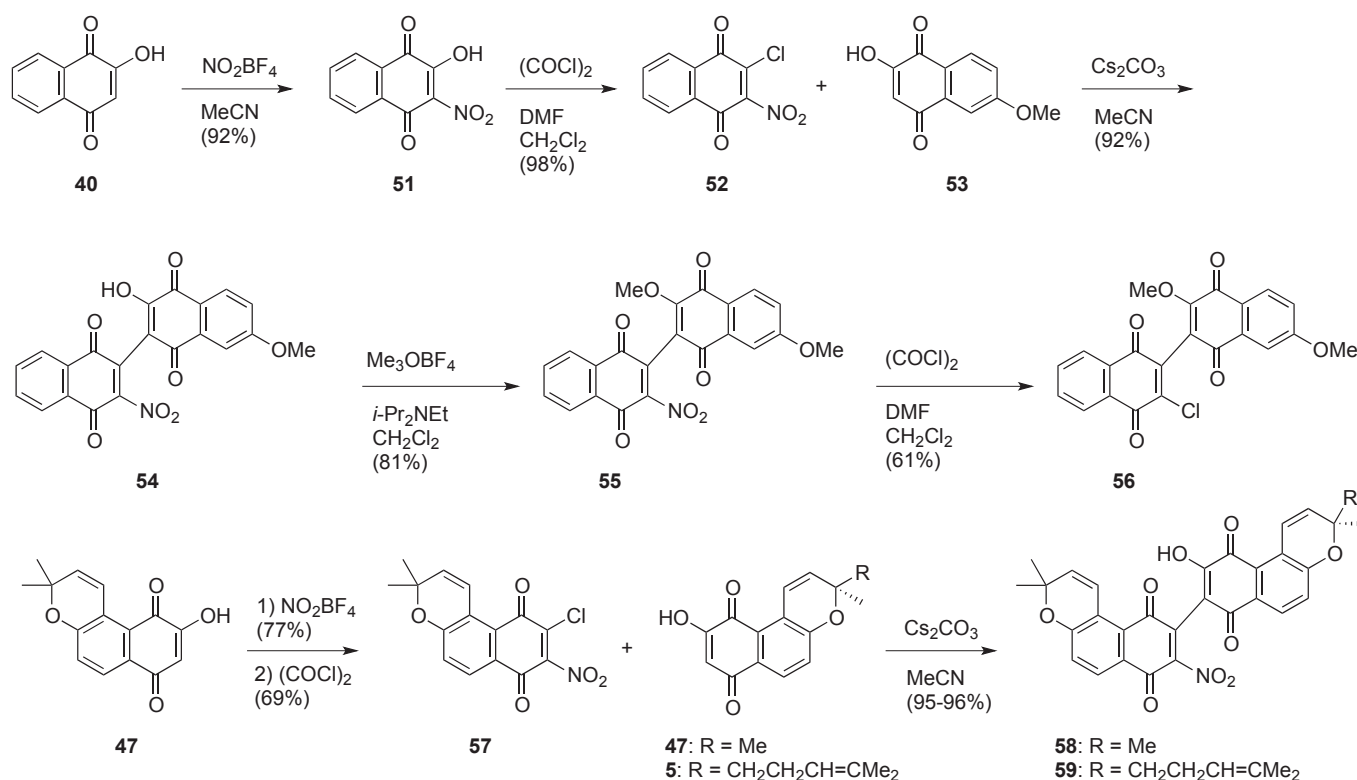
Scheme 5. Synthesis of the partially methylated oligomeric naphthoquinones **43-45**

The synthesis of trimeric quinones by a similar method and their biological activities were examined by Crosby *et al.*<sup>15</sup> The reaction of 2,3-dibromonaphthoquinone (**46**) and hydroxyquinone **47** in the presence of tertiary amine gave dimeric quinone **48**, which was further treated with **47** under the same conditions to give trimeric quinone **49**. A similar stepwise procedure provided asymmetric **50** and symmetric trimeric naphthoquinones **20** (Scheme 6). Screening the cytopathic effects of trimers **49**, **50**, and **20** towards HIV-infected cells showed inhibitory activities comparable with conocurvone (**6**) but with lower selective indices.



Scheme 6. Synthesis of trimeric naphthoquinones **49**, **50**, and **20**

An approach for the synthesis of dimeric nitronaphthoquinones was examined by Stagliano *et al.* using 2-hydroxy-3-nitronaphthoquinones.<sup>16</sup> Mild conditions for the nitration of 2-hydroxynaphthoquinone **40** to nitroquinone **51** using nitronium tetrafluoroborate ( $\text{NO}_2\text{BF}_4$ ) as a nitration reagent prevented decomposition of the benzopyrane moiety (*i.e.*, **47**) that occurs under highly acidic conditions. This reaction step gave a better yield than did the conventional method (e.g., aq.  $\text{HNO}_3$ ,  $\text{CHCl}_3$ ). After the conversion of **51** to cholide **52** using  $(\text{COCl})_2$ , regiospecific substitution of **52** with hydroxyquinone **53** in the presence of  $\text{Cs}_2\text{CO}_3$  gave dimeric nitrobisnaphthoquinone **54**. The methylation of **54** was followed by further substitution of the nitro group in **55** to chlorine to afford chloromethoxybiquinone **56**. This method was applied to the synthesis of 3-hydroxy-3'-nitrobispyranonaphthoquinones **59** and **60**, which can be converted to trimers using the reported procedure (Scheme 7).<sup>16</sup>



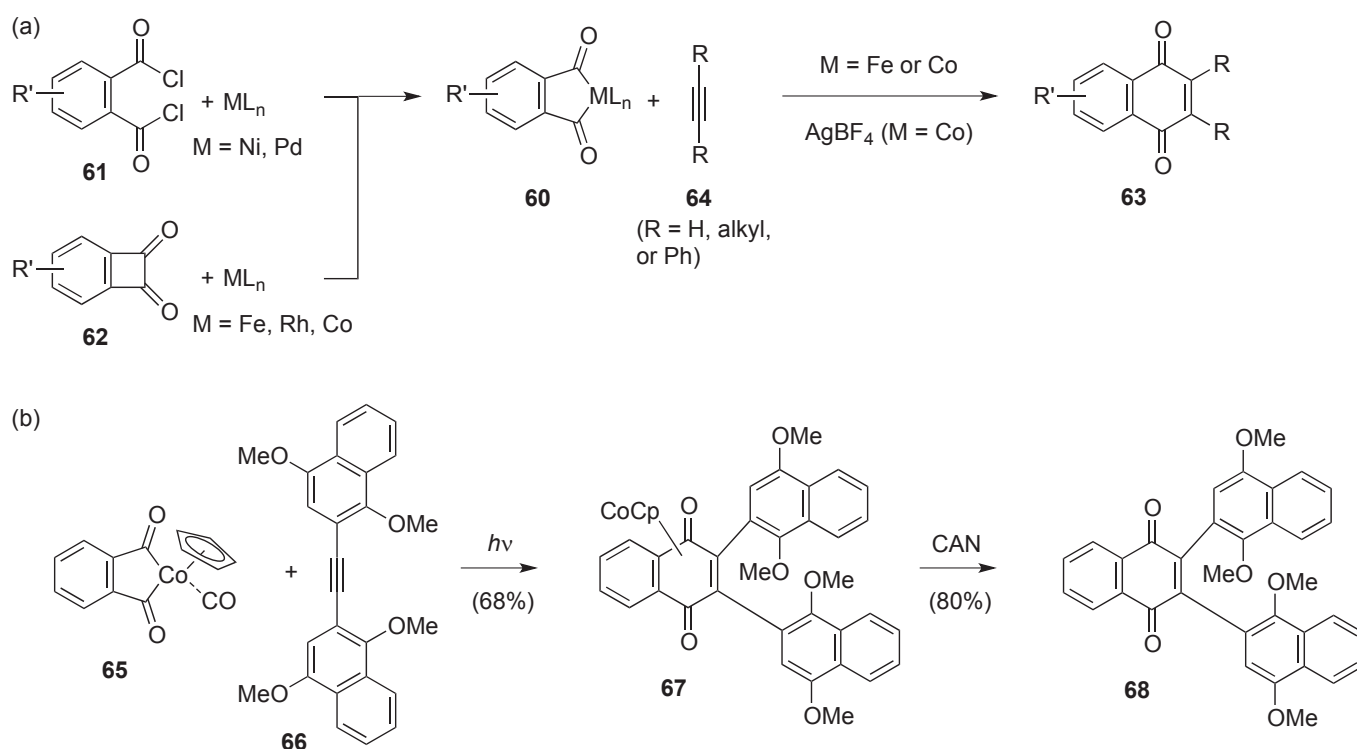
Scheme 7. Synthesis of the dimeric naphthoquinones **56**, **57** and **59** via the nitronaphthoquinones **52** and **57**

### 3-3. Synthesis of acyclic trimeric naphthoquinones from phthaloyl-metal complexes

Liebeskind *et al.*<sup>17</sup> reported the synthesis of acyclic trimeric naphthoquinones by an insertion reaction of phthaloyl-metal complexes and bisnaphthylalkynes. The phthaloyl-metal complexes **60** were prepared by the reaction of phthaloxyl chlorides **61** or benzocyclobutane-1,2-diones **62** and various metal reagents.



Formation of naphthoquinones **63** was observed when the phthaloyl-Fe and Co complexes of **60** were used in the insertion reaction with disubstituted alkynes **64**. The addition of  $\text{AgBF}_4$  was necessary for reaction of the Co complex.<sup>17</sup> This methodology was applied to the synthesis of trisnaphthoquinones. Examination of insertion reactions of the phthaloyl-metal complexes to bisnaphthoalkynes showed that the reaction of phthaloyl-Co complex with Cp ligand **65** and alkyne **66** under photoirradiation condition gives the desired trisquinone **67** as a Co complex. Treating the quinone-Co complex **67** with CAN gave the demetallated trisquinone **68** in high yield (Scheme 8).<sup>18</sup>

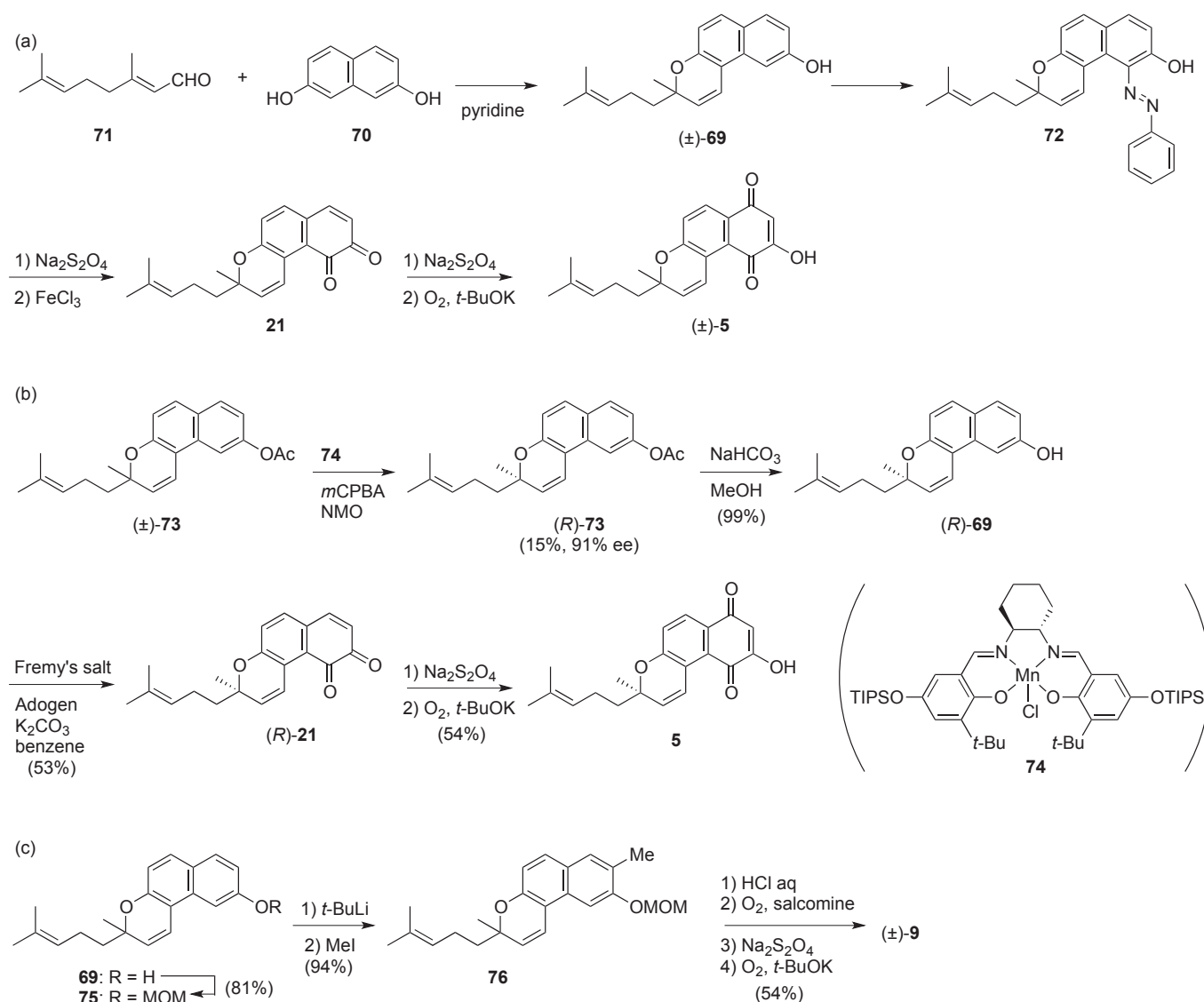


Scheme 8. Synthesis of monomeric **63** and trimeric naphthoquinones **68** via the insertion reaction of phthaloyl-metal complexes **60** and **65** to alkynes **64** and **66**.

#### 4. PREVIOUS EXAMPLES OF SYNTHETIC STUDIES OF TERETIFOLIONES

Several groups previously reported the total synthesis of teretifolione B (**5**) and related compounds. In the total synthesis of racemic teretifolione B [(±)-**5**] by Cannon *et al.*,<sup>5</sup> chromene substrate (±)-**69** was obtained by the condensation reaction of naphthalene-2,7-diol (**70**) and enal **71** in the presence of pyridine. Chromene (±)-**69** was converted to azo compound **72**, and dithionite reduction followed by oxidation with  $\text{FeCl}_3$  yielded *o*-quinone **21**. After further dithionite reduction of **21**, the hydroquinone was subjected to autooxidation conditions under an oxygen atmosphere in the presence of *t*-BuOK to give the desired racemic teretifolione B [(±)-**5**] (Scheme 9a). The asymmetric synthesis of teretifolione B (**5**) was achieved

by Vander Velde and Jacobsen<sup>19</sup> through the kinetic resolution of racemic acetoxychromene **73** by epoxidation using the optically active salen-Mn complex **74**, and *m*CPBA and NMO as co-oxidant and additive, respectively. The (*S*)-isomer of **73** was preferentially consumed to afford (*R*)-**73** in 15% yield and 91% *ee*. Deprotection of the acetyl group in (*R*)-**73** followed by a modified oxidation sequence for phenol (*R*)-**69** and quinone (*R*)-**21** yielded teretifolione B (**5**) with the same absolute configuration as the natural product (Scheme 9b).<sup>19</sup> Stagliano and Malinakova<sup>20</sup> reported the total synthesis of racemic methylteretifolione B [(±)-**9**]. Hydroxychromene **70** was protected by a MOM group, and the MOM ether **75** was subjected to MOM-directed regioselective ortho lithiation and methylation to give **76**. Deprotection and oxygenation of **76** afforded methylteretifolione B [(±)-**9**] (Scheme 9c).<sup>20</sup>

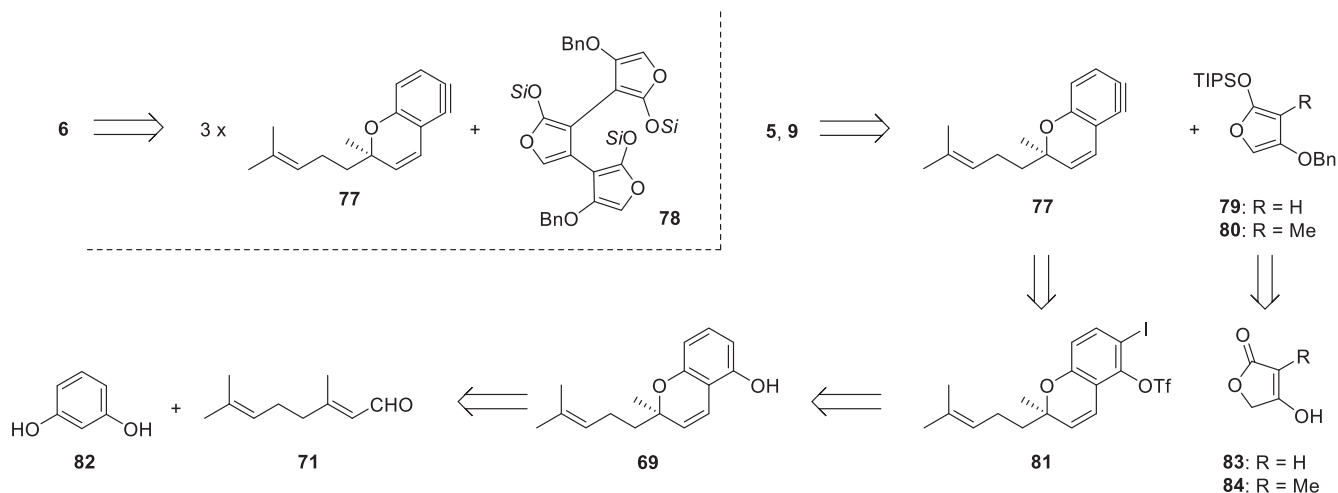


Scheme 9. Reported total synthesis of teretifolione B (**5**) and methylteretifolione B [(±)-**9**]

## 5. SYNTHESIS OF PYRANONAPHTHOQUINONES VIA THE DIELS-ALDER APPROACH

### 5-1. Retrosynthesis

Our synthetic study towards conocurvone (**6**) is based on the construction of the trimeric angular pyranonaphthoquinone framework by Diels-Alder reaction (DAR) of optically active pyranobenzene **77** and trimeric oxygenated furan **78**. Natural monomeric teretifolione B **5** and methylated **9** would be accessed via DAR of **77** and monomeric furans **79** and **80**. Benzene **77** would be generated from iodo-triflate **81**, which would be converted from optically active hydroxychromene **69**. **69** would be synthesized by condensation of resorcinol (**82**) and citral (**71**) followed by optical resolution of ( $\pm$ )-**69**. Siloxyfurans **79** and **80** would be converted from tetronic acids **83** and **84**. In our first trial, we focused on DAR using methylated furan **79** for the synthesis of **9** because no asymmetric total synthesis of **9** has been reported to date (Scheme 10).



Scheme 10. Retrosynthesis of conocurvone (**6**) and teretifoliones **5** and **9** via DAR of benzene **77** and furans **79** and **80**. *Si* = silyl protecting group.

### 5-2. Naphthoquinone synthesis by Diels-Alder reaction of benzyne and substituted furans

We examined the *O*-benzylation of methyltetronic acid (**84**) as a first step in the preparation of oxygen-substituted furans. Alkylation under basic conditions using a relatively less reactive alkyl halide such as EtI gave the corresponding *O*-alkylated product selectively, whereas use of the more reactive benzyl bromide gave a mixture of *C*- and *O*-alkylated products.<sup>21</sup> Benzylation of **84** using benzyl bromide in the presence of K<sub>2</sub>CO<sub>3</sub> gave the desired *O*-benzylated **85** in low yield (Table 1, run 1). In contrast, the use of CsF as a base provided *C*-benzylated furanone **86** as a major product (run 2). Application of BnOTs<sup>22</sup> improved the ratio of *O*-/*C*-benzylation to 3:1 (run 3), and the desired **85** was afforded as the sole product when K<sub>2</sub>CO<sub>3</sub> was used as a base (run 4). The corresponding *O*-benzylated products were

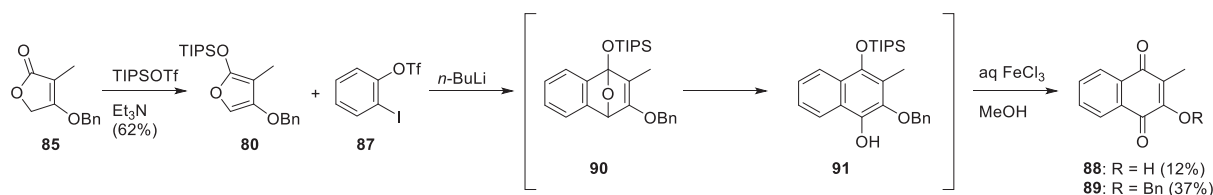
obtained in the reaction of other  $\beta$ -carbonyl compounds such as tetronic acid (**84**) and cyclopentane-1,3-dione using this method.

Siloxyfuran **80** was prepared by the treatment of furanone **85** with TIPSOTf<sup>23</sup> and subjected to DAR with benzyne *in situ* prepared by the reaction of iodophenyl triflate **87** and *n*-BuLi. The desired natural hydroxynaphthoquinone **88** and the benzyl ether **89** were obtained via formation of epoxynaphthalene **90** and the FeCl<sub>3</sub> oxidation of naphthol **94** (Scheme 11).<sup>24</sup>

Table 1. Trials for *O*-selective benzylation of **84**

run	BnX (1 eq)	base (2 eq)	ratio ( <b>85</b> : <b>86</b> )	<b>85</b> (%)
1	BnBr	K <sub>2</sub> CO <sub>3</sub>	-	22
2	BnBr	CsF	1 : 2	-
3	BnOTs	CsF	3 : 1	48
4 <sup>a</sup>	BnOTs	K <sub>2</sub> CO <sub>3</sub>	1 : 0	86

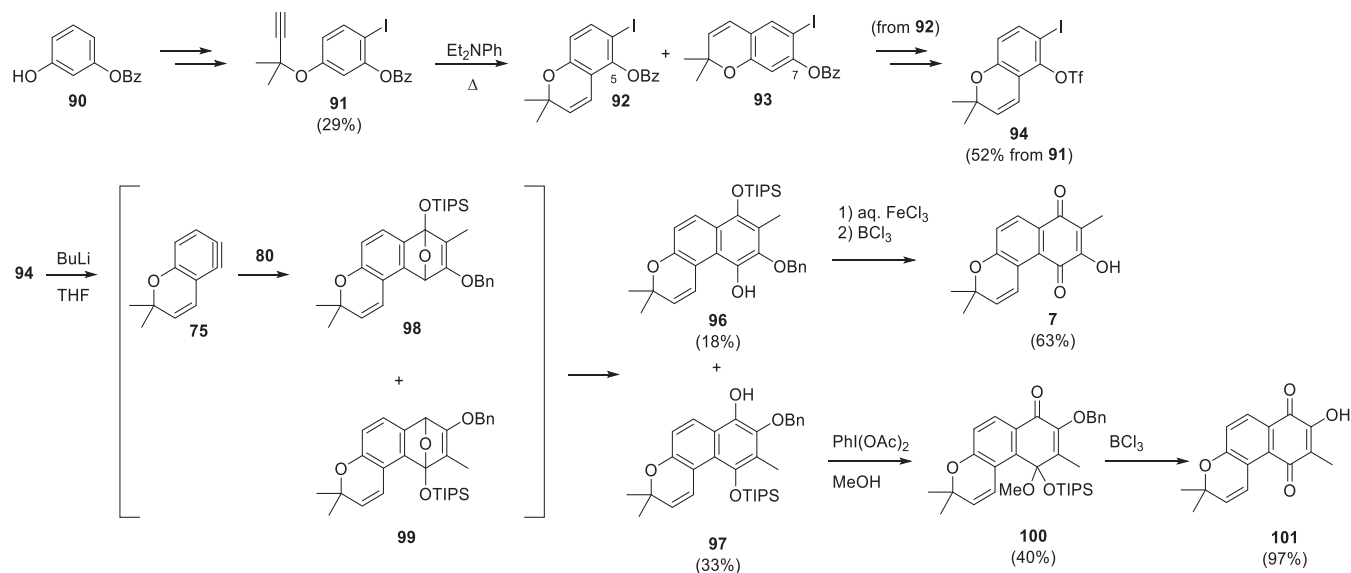
<sup>a</sup> BnOTs (1.5 eq) and K<sub>2</sub>CO<sub>3</sub> (3 eq) were applied.



Scheme 11. Synthesis of naphthoquinones **88** and **89**  
via DAR of iodophenyl triflate **87** and furan **88**

Scheme 12 illustrates the DAR approach to constructing the angular pyranonaphthoquinone core using pyranobenzyne. Iodination and introduction of a propargyl group to resorcinol benzoate (**90**) furnished propargyl ether **91**, which was subjected to thermal Claisen rearrangement to give a mixture of the desired 5-benzyloxy **92** and 7-benzyloxychromones **93** in the ratio 2:1. The benzoate **92** was converted to the corresponding triflate **94** as a benzyne precursor. DAR of the pyranobenzyne **95**, derived from **94**, and furan **80** gave a 1:2 isomeric mixture of the desired hydroxypyranonaphthoquinone **96** and the undesired regioisomer **97** via epoxynaphthalenes **98** and **99**, respectively. Oxidation of hydroquinone **96** followed by deprotection of the benzyl group using BCl<sub>3</sub> gave natural pyranonaphthoquinone **7**. Trials for the oxidation of regioisomer **97** in the same manner gave complex mixtures, perhaps because the higher reactivity of **97** due to its 2,6-dihydroxynaphthalene moiety can result in oxidation to 2,6-naphthoquinone-type compounds. The application of (diacetoxyiodo)benzene (PIDA)-oxidation in

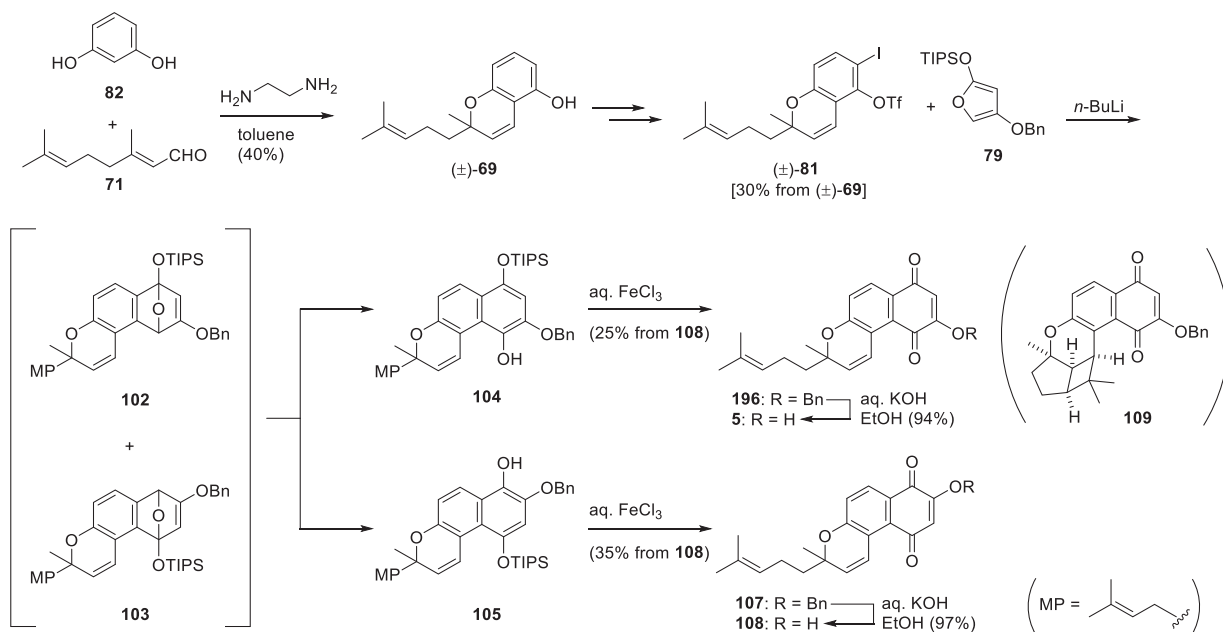
methanol gave quinone monoacetal **100**. Subsequent debenzoylation and deacetalization using  $\text{BCl}_3$  gave **101**, the corresponding regioisomer of **7** (Scheme 12).<sup>25</sup>



Scheme 12. Synthesis of pyranonaphthoquinones **7** and **101**

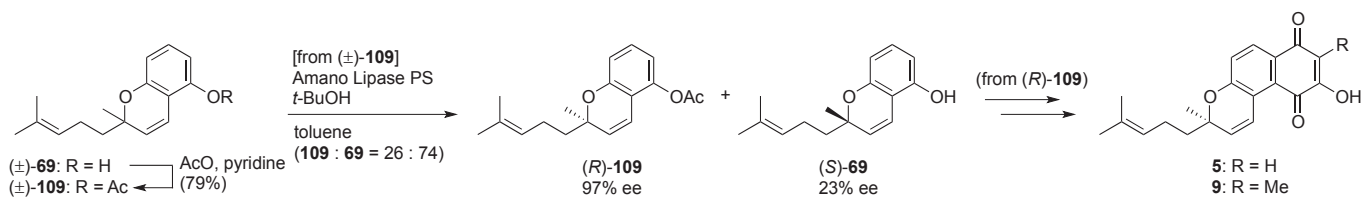
### 5-3. Total synthesis of teretifoliones

The strategy described above was applied to the total synthesis of teretifolione B (**5**). Racemic chromene ( $\pm$ )-**69** was prepared by the condensation reaction of resorcinol (**82**) and citral (**71**) using ethylenediamine as a catalyst, then was converted to the corresponding triflate ( $\pm$ )-**81** as a benzyne precursor. Treatment of ( $\pm$ )-**81** with  $n$ -BuLi in the presence of siloxyfuran **79** gave a regioisomeric mixture of epoxynaphthalenes **102** and **103**, which spontaneously isomerized to hydroquinones **104** and **105**, respectively. After separation, **104** and **105** were subjected to  $\text{FeCl}_3$  oxidation to give benzyl-protected naphthoquinones **106** and **107**, which were hydrolyzed in basic conditions to give racemic teretifolione B [ $(\pm)$ ]-**5** and its regioisomer **108**. During the purification of **106**, cyclized product **109** formed, presumably by the photo-irradiated [2+2] cycloaddition of **106**. The application of ODS column chromatography under dark conditions suppressed this side reaction (Scheme 13).



Scheme 13. Synthesis of racemic teretifolione B [(±)-5] and its regioisomer **108**

Based on a report by Zammattio *et al.*,<sup>26</sup> optically active chromene **69** was prepared by lipase-catalyzed kinetic resolution of racemic acetate (±)-**109** under hydrolytic conditions. When (±)-**109** was treated with Amano Lipase PS in H<sub>2</sub>O-saturated *i*Pr<sub>2</sub>O, the hydrolyzed phenol **69** was obtained in 35% yield and 18% *ee*. We also examined transesterification conditions<sup>27</sup> by conducting reactions using various enzymes and alcohols. The reaction of **109** using *tert*-butyl alcohol and Amano Lipase PS in toluene gave optically active acetate **109** in 97% *ee*. Reaction in TBME and acetonitrile proceeded faster than in toluene and with similar enantioselectivity, whereas the application of hexanoyl or chloroacetyl ester decreased selectivity. The racemization of **69** (23% *ee*) under thermal conditions results in the recovery of (±)-**69**. The optically active acetate **109** was hydrolyzed to (*R*)-**69**, which was subjected to the same synthetic pathway described above to furnish teretifolione B (**5**) and its methyl derivative **9**. Comparison of the optical rotations of natural and synthetic **5** and **9** revealed that both teretifolione B (**5**) and its methyl derivative **9** possess the (*R*) absolute configuration (Scheme 14).<sup>28,29</sup>



Scheme 14. Enzymatic resolution of (±)-**109** and the asymmetric total synthesis of teretifoliones **5** and **9**

## 6. CONCLUSION

This review provided an overview of the chemistry of anti-HIV active trimeric pyranonaphthoquinone conocurvone and its monomeric teretifolione. Conocurvone was isolated from *Conospermum* plants as an anti-HIV-1 active compound. The structural determination of conocurvone was challenging due to the complexity of its spectral data arising from an assumed dynamic intramolecular process. Its structure was finally assigned as a trimeric pyranonaphthoquinone based on the derivatization of conocurvone and its semisynthesis from monomeric teretifolione B.

Independent studies examined the trimerization of naphtho(hydro)quinones. The reaction of simple naphthoquinone furnished a cyclic trimer via conjugate addition of hydroquinone, a redox process, and oxidative cyclization. This approach succeeded in the synthesis of acyclic naphthoquinones using halogenated naphthoquinones to provide the conocurvone derivative, and several anti-HIV-active compounds with a trimeric quinone framework were identified. The methodology for the synthesis of trimeric naphthoquinones via the cycloaddition of phthaloyl-metal complexes and bisnaphthylalkynes is also noteworthy.

Based on the background described above, we developed the total synthesis of monomeric teretifoliones by DAR of pyranobenzyne and oxygenated furans as a key step. Optically active pyranobenzyne precursor was prepared via enzymatic resolution of the racemic chromenes. The desired pyranonaphthoquinone framework was constructed by DAR of the corresponding furan and pyranobenzyne, and the total synthesis of teretifolione B and its methyl derivative was achieved. In future we anticipate reporting the total synthesis of conocurvone through the effective construction of optically active chromenes, improvement in the regioselectivity of DAR, and the synthesis of trimeric furans using DAR approaches.

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