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A facile Garratt–Braverman cyclization route to intercalative DNA-binding bis-quinones

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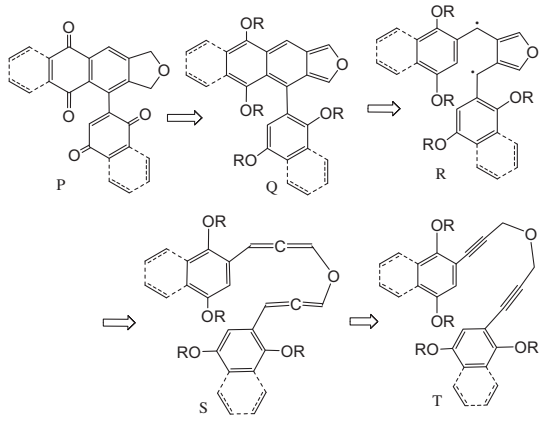
ABSTRACT

Bispropargyl ethers (both symmetrical and non-symmetrical) equipped with 1,4-dimethoxyaryl groups were synthesized. Under strongly basic conditions (KOBu^t/toluene/reflux), these ethers underwent Garratt–Braverman type cyclization to the tetramethoxy bi-aryl systems in high yields presumably via the bisallenes. The products could be successfully converted to the bis-quinones via CAN-mediated demethylation cum oxidation. This two-step protocol offers a simple route to bis-quinones, connected by C1–C2′ bonds, in good yields. Fluorescence based EB-displacement assay, CD spectroscopy and viscosity measurements confirmed the DNA-binding ability of the synthesized quinones via intercalation.

Organic reactions involving formation of two carbon–carbon bonds in high yields, either concerted or stepwise are extremely attractive in synthesis.[1,2] Diels–Alder and related cycloadditions are by far the best examples of concerted formation of two C–C bonds with extensive applications.[3] The logical targets using such reactions are cyclic compounds that include alicyclic, aromatic, or heterocyclic derivatives which are all important for various reasons. Garratt–Braverman cyclization[4] involving diradical as the intermediate[5] and discovered about 30 years ago forms two C–C bonds at the same time. But its synthetic potential is yet to be fully explored. It is only recently[6] that applications of GB cyclization have started to appear. In an effort to expand the synthetic scope further, we have selected a synthetic target the bis-quinone core with C1–C2′ connectivity between the two quinonoid moieties as it can be found[7] in several natural products like **1–3** (Fig. 1) as a synthetic target. Herein we describe our results.



Scheme 1. Retro synthetic analysis using GB cyclization.

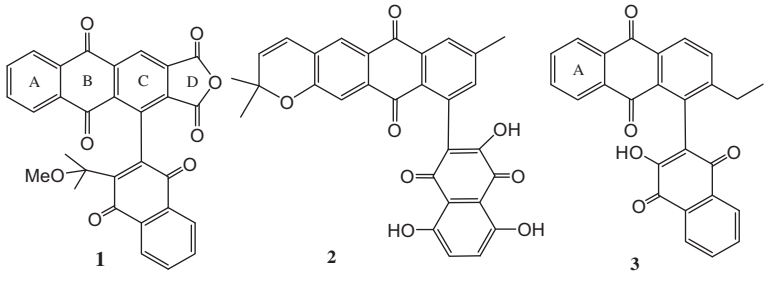


Figure 1. The naturally occurring bis-quinones.

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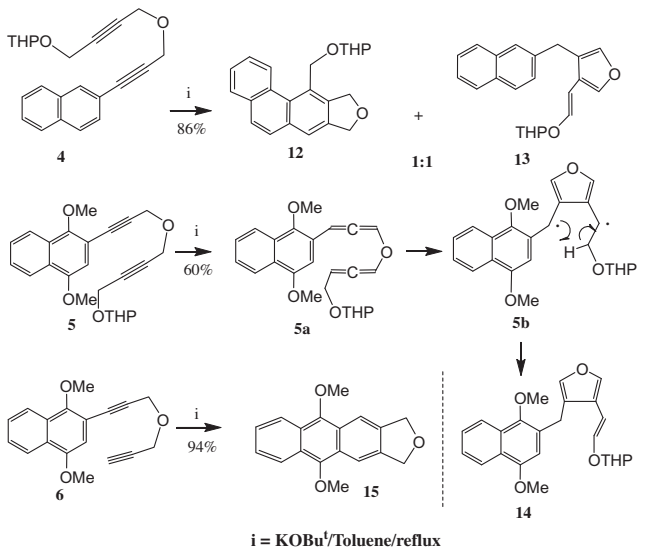


Scheme 2. Importance of double bond character.

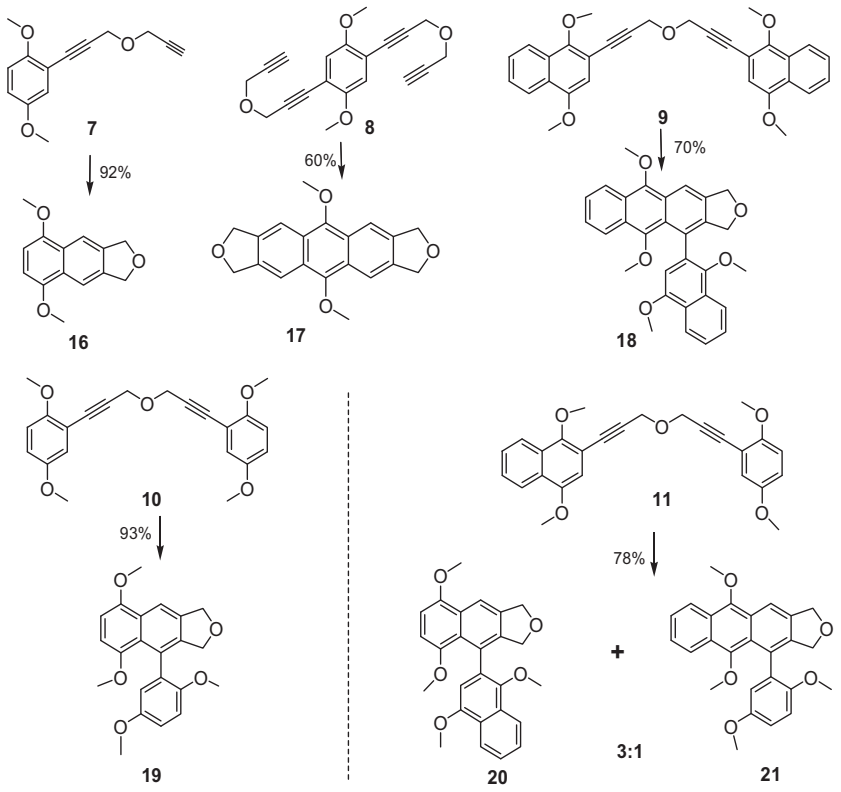
The retro synthesis of the target bis-quinone core is shown in Scheme 1. The bispropargylic ether moiety was needed to do the isomerization to the bisallene and subsequent GB cyclization to construct the critical C–C bonds. The product of GB cyclization, namely the cyclic ether, can also be further functionalized, for example, to lactone[6] or anhydride.

To our knowledge although a large plethora of bis-quinones, both natural and unnatural are known, most of them have a different connectivity between the two quinones. Several elegant methods do exist for the synthesis of their core structure. However, to our knowledge, there is no report yet on the synthetic approaches to structures **1–3**. It may be mentioned that bis-quinones are constantly drawing interest because of their biological profile[8] which includes anticancer, antimalarial, and anti-HIV activities. They also have a variety of other applications, for example as probe[9] for studying the biochemical processes and materials for data recording, storage, and reproduction.[10]

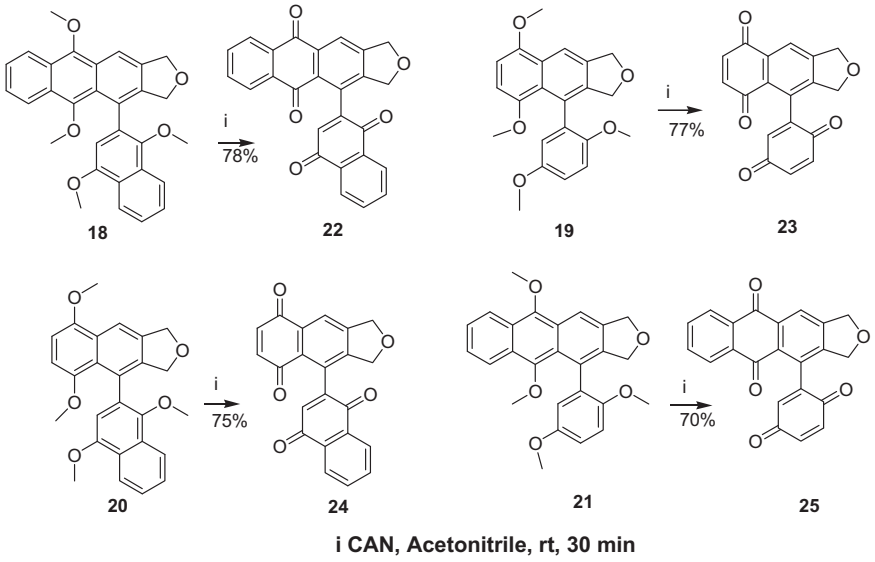
One aspect that did bother us initially was concerning with the lower double bond character of the C2–C3 bond in a naphthalene system. This might prevent self quenching of the intermediate diradical **R** (Scheme 1) involving the C2–C3 bond. In order to clarify this point, we first subjected the unsymmetrical bispropargyl ethers **4–6** to GB cyclization conditions (K *tert*-butoxide, toluene, reflux). Interestingly, the compound **4** smoothly cyclized to the product involving the C1–C2 bond with greater double bond character. In addition, another product via an intramolecular 1,5-H-shift, often observed in GB cyclization, was also isolated. But no normal GB product involving the C2–C3 bond could be isolated from the reaction. When the participation of the C1–C2 double bond was blocked by incorporating a substituent at C-1 as shown in **5**, the reaction followed only the intramolecular 1,5-H-shift pathway. It is only when the H required for such 1,5-shift was missing like in **6** that the standard GB-product **15**, formed via the C2–C3 double bond was isolated in 94% yield (Scheme 2).

As a follow-up of this result and with an aim to prepare the biaryl skeleton, we carried out the GB cyclization of various bispropargyl ethers[11] having 1,4-dialkoxy naphthalene/benzene moiety with no possibility of 1,5-shift. Gratifyingly, all the ethers produced only the GB products in good yields (Scheme 3). In those cases where mixture of products was obtained, the individual isomers were separated by silica gel column chromatography and carried to the next step.

The products of GB cyclization, namely the dimethoxy compounds, underwent smooth demethylation followed by in situ oxidation with CAN[12] to produce the bis-quinones in 70–78% yield



Scheme 3. Result of GB cyclization.



Scheme 4. Result of oxidative demethylation for the synthesis of bis-quinones (CAN/acetonitrile/rt/30 min).

(Scheme 4).[13] Considering the complexity of the bis-quinones, our method offers a simple and efficient strategy to synthesize such targets.

The structures of the GB products **16**–**21** were confirmed by NMR and mass spectroscopy.[14] Thus in the ^{1}H NMR, the peri H at C-1 appeared as a singlet in the characteristic region of δ 8–8.5. The formation of bis-quinone core was reflected by the absence of methyl signals in $^{1}H/^{13}C$ spectra as well as appearance of four carbonyl signals in the region of δ 180–190. Final confirmation of the structure came from the X-ray structure of one of the bis-quinone **22** (Fig. 2).

The well known intercalation properties of quinones, especially the anthraquinones,[15] prompted us to study the DNA-binding activities of the synthesized compounds using the established techniques of fluorescence,[16] CD,[17–20] and viscosity measurements.[21] Upon titration of the ethidium bromide-DNA complex with the bis-quinones, considerable decrease in the fluorescence intensity was observed, which is characteristic of the intercalative mode of binding (Fig. 3). The highest decrease was observed for the compound **25** followed by compounds **23**, **22**, and **24**. Circular dichroism studies furthermore substantiate the mode of interaction of the compounds with the asymmetric environment of the DNA helix. CD spectra were collected for ct-DNA starting from 200 to 350 nm. Gradual addition of the synthesized ligands to the solution of the ct-DNA led to perturbations of both the positive and the negative bands at 277 and 245 nm, respectively. Here again, the increase in ellipticity at 277 nm, primarily associated with reduced DNA winding angle,[22,23] was maximum for the analog **25** and **23** with pendant benzoquinone moiety.

The results obtained for viscosity measurements of DNA which showed an increase in viscosity with increasing amounts of the synthesized ligands (bis-quinones) also supported the intercalative mode of binding. The analog **25** is intercalated into the ct-DNA maximally followed by **23**, **22**, and **24**, a trend observed earlier in fluorescence and CD studies.[24]

In conclusion, we have developed a high yielding GB route to bis-quinones (a hybrid of anthra/naphtha/benzo quinone) with a C1–C2′ connectivity. Fluorescence based EB-displacement assay,

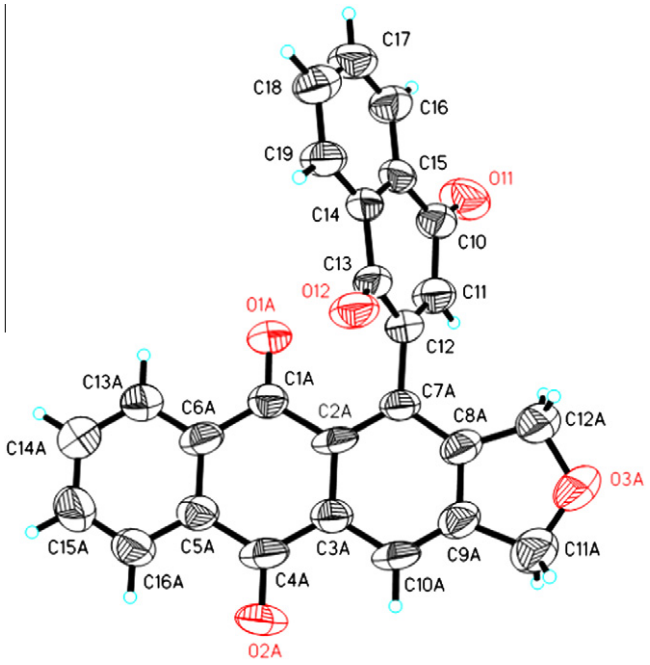


Figure 2. X-ray structure of bis-quinone **22**.

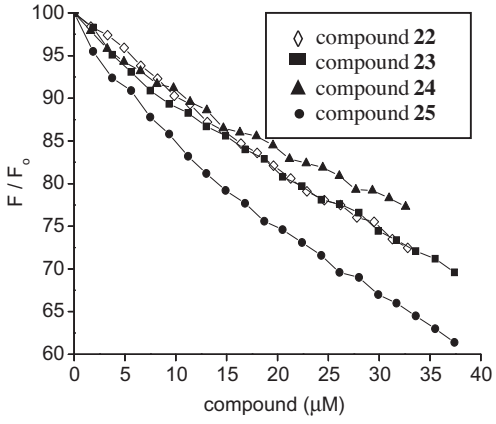


Figure 3. Relative fluorescence intensity decrease of EB (2.26 μM) induced by the competitive binding of the synthesized compounds to ct DNA (20 μM).

CD spectroscopy, and viscosity measurements confirmed the DNA-binding ability of the synthesized quinines. The mode of binding was also shown to be intercalative.

Acknowledgments

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Supplementary data

Supplementary data (Spectral data.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.030.

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11. These were prepared by O-alkylation of the substituted propargyl alcohols with the bromides of the other arm of the ether in presence of NaH in THF.
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13. Controlled oxidation can give rise to monoquinone. This aspect is currently under investigation.
14. Selected spectral data: For 4-(1,4-Dimethoxy-naphthalen-2-yl)-5,10-dimethoxy-1,3-dihydro-anthra[2,3-c]furan (**18**): State: Yellow gummy mass; Yield 67%; δ_H (200 MHz, $CDCl_3$): 8.39–8.36 (2H, m), 8.29 (1H, s), 8.22–8.16 (2H, m), 7.67–7.46 (4H, m), 6.85 (1H, s), 5.40 (2H, s), 5.06 (1H, d, J = 14 Hz), 4.91 (1H, d, J = 14 Hz), 4.21 (3H, s), 3.54 (3H, s), 3.40 (3H, s); δ_C (50 MHz, $CDCl_3$): 150.9, 150.0, 148.5, 145.9, 139.5, 137.5, 129.4, 128.7, 127.5, 126.6, 126.2, 125.9, 125.6, 125.4, 125.2, 124.9, 123.7, 123.5, 122.5, 122.3, 113.5, 105.9, 94.7, 73.5, 63.2, 61.2, 55.9; MS: m/z 467 [MH^+]; HRMS: Calcd for $C_{30}H_{26}O_5$+H^+ 467.1859, found 467.1863.
For 4-(2,5-Dimethoxy-phenyl)-5,8-dimethoxy-1,3-dihydro naphtha [2,3-c]furan (**19**): State: White gummy mass; yield 93%; δ_H (400 MHz, $CDCl_3$): 8.15 (1H, s), 7.28 (1H, s), 6.89–6.84 (3H, m), 6.75–6.68 (3H, m), 5.32 (2H, s), 4.96 (1H, d, J = 13 Hz), 4.84 (1H, d, J = 13 Hz), 3.99 (3H, s), 4.78 (3H, s), 3.65 (3H, s), 3.43 (3H, s); δ_C (100 MHz, $CDCl_3$): 153.0, 151.4, 150.6, 149.9, 138.7, 137.0, 132.6, 127.4, 114.9, 114.6, 113.2, 112.2, 111.3, 106.3, 103.3, 73.8, 73.4, 56.4, 56.3, 55.8, 55.7; MS: m/z 367 [MH^+]; HRMS: Calcd for $C_{22}H_{22}O_5$+H^+ 367.1546, found 367.1548.
For 4-(1,4-Dioxo-1,4-dihydro-naphthalen-2-yl)-1,3-dihydro-anthra[2,3-c]furan-5,10-dione (**22**): State: Golden yellow crystal; mp: 215 °C; Yield 78%; δ_H (400 MHz, $CDCl_3$): 8.37 (1H, s), 8.34 (1H, d, J = 1.6 Hz), 8.29 (1H, d, J = 1.6 Hz), 8.19–8.17 (1H, m), 8.12 (1H, dd, J = 7.6 Hz, 1.2 Hz), 7.89–7.74 (4H, m), 6.86 (1H, s), 5.31 (2H, s), 5.27 (1H, d, J = 14 Hz), 5.04 (1H, d, J = 14 Hz); δ_C (100 MHz, $CDCl_3$): 184.5, 183.1, 182.9, 182.5, 150.6, 146.0, 145.2, 134.7, 134.4, 134.0, 133.9, 133.3, 132.6, 132.5, 132.4, 32.0, 131.6, 129.0, 127.5, 127.2, 127.1, 126.8, 126.4, 121.2, 74.1, 72.8; MS: m/z 407 [MH^+]; HRMS: Calcd for $C_{26}H_{14}O_5$+H^+ 407.0920, found 407.0922.
For 4-(3,6-Dioxa-cyclohexa-1,4-dienyl)-1,3-dihydro-naptho[2,3-c]furan-5,8-dione (**23**): State: Light yellow gummy mass; Yield 77%; δ_H (400 MHz, $CDCl_3$): 8.09 (1H, s), 7.01–6.91 (3H, m), 6.86 (1H, d, J = 10.4 Hz), 6.62 (1H, s), 5.28 (2H, bs), 5.19 (1H, d, J = 13.6 Hz), 4.96 (1H, d, J = 13.6 Hz); δ_C (100 MHz, $CDCl_3$): 186.6, 184.9, 184.6, 184.2, 147.7, 145.9, 144.9, 138.9, 137.9, 137.2, 132.9, 130.4, 129.8, 127.5, 120.6, 74.0, 72.6; MS: m/z 307 [MH^+]; HRMS: Calcd for $C_{18}H_{10}O_5$+H^+ 307.0606, found 307.0607.
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24. The CD spectra and the viscosity trends are included in the Supplementary data.