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Convergence in [2+2+2] synthesis of β-phenylnaphthalene motif in polyaromatic natural products

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Abstract—Two optional routes to β-phenylnaphthalene structure are developed by introducing α- and β-styryl groups onto different positions in the benzocyclobutene ring followed by ring enlargement.

β-*Phenylnaphthalene* is a structure commonly found in various polyketide-derived polyaromatic natural products (Fig. 1).[1] We previously reported an approach to this motif by assembling three two-carbon units, benzyne **I**, olefin **II**, and a styryl group **IV** (Scheme 1), by which the above structure is accessible as its dihydro form.[2,3] Thanks to the inherent selectivities of the reactions and also by proper choice of reaction partners, one could not only *divergently* construct various related structures, but also devise optional routes *convergent* to a single skeleton, albeit with subtle differences in substitution or oxidation patterns.

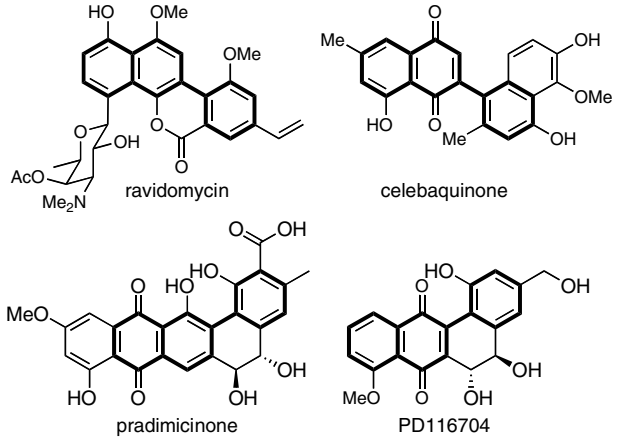
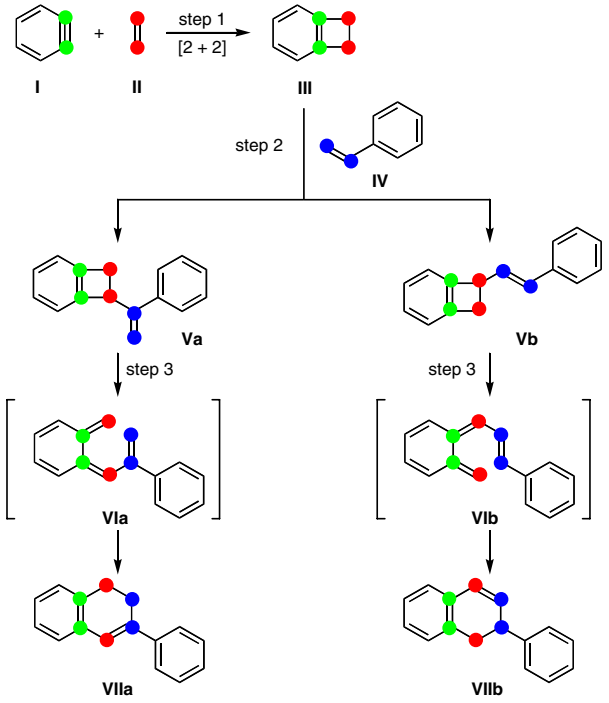


Figure 1.

This letter focuses the latter aspect of the approach; introduction of α- and β-styryl groups onto different positions in the benzocyclobutene ring leads, after ring expansion stage, to the same skeleton, **VIIa** and **VIIb**.



Scheme 1. Convergence in [2+2+2] approach.

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To address such scenario, we examined two optional synthetic routes to a model tetracyclic lactone **1**, reminiscent of the gilvocarcin–ravidomycin class antibiotics.[4] The routes differ in the initial connectivity of the benzocyclobutenedione unit **A** and the styryl unit **B** as shown by two arrows, *a* and *b* (Fig. 2).

For the selective bond connection at the two carbonyls in unit **A**, we used a set of mono-protected benzocyclobutenediones, $\mathbf{A}_1$ and $\mathbf{A}_2$, available via the regioselective [2+2] cycloaddition of α-alkoxybenzynes and ketene silyl acetals.[5] Thus, the question was centered at their partners, that is, the styryl anion equivalents $\mathbf{B}_1$ and $\mathbf{B}_2$, suitable for coupling with $\mathbf{A}_1$ and $\mathbf{A}_2$, for the projected ring enlargement to phenylnaphthalenes $\mathbf{A}_1\mathbf{B}_1$ and $\mathbf{A}_2\mathbf{B}_2$ (Scheme 2). Note that two routes, if viable, lead to the same skeleton, but with different protection patterns for phenols (R, R′).

Herein, we report the realization of both of these routes, and their comparison within the synthesis of model lactone **1**.

Scheme 3 shows divergent preparation of styryl bromide **5** and acetylene **6**, which were used as precursors of anions $\mathbf{B}_1$ and $\mathbf{B}_2$ (as its equivalent, vide infra) for introducing a styryl group at the internal or the terminal position, respectively. Phenol **2**[6] was converted to the corresponding triflate, which was subjected to Sonogashira reaction[7] with $Me_3SiC{\equiv}CH$ to give acetylene **3**, which served as the divergent point to **5** and **6**. Thus,

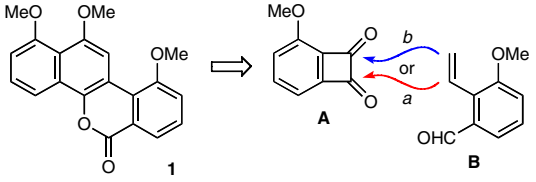
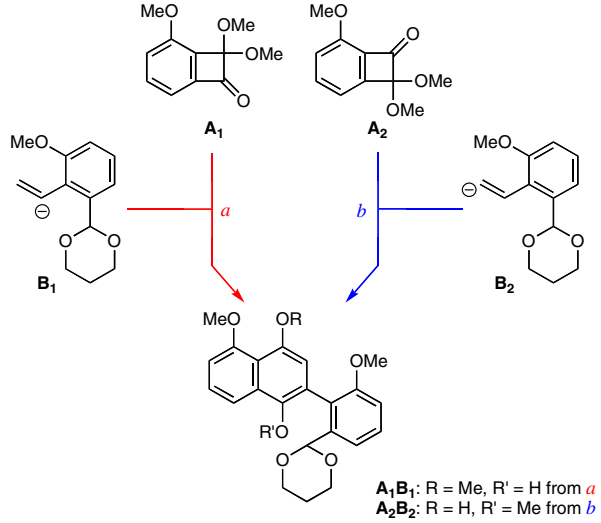
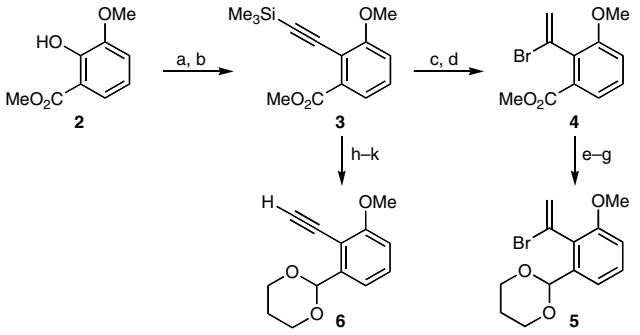


Figure 2.



Scheme 2.

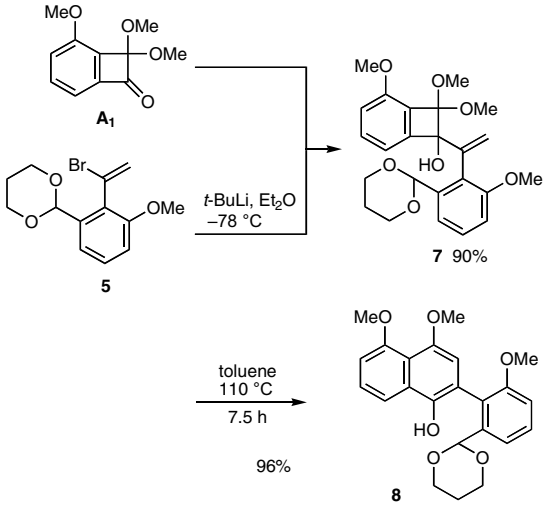


Scheme 3. Reagents and conditions: (a) Tf_2O, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, −78 °C (97%); (b) $Me_3SiC{\equiv}CH$, cat. $(Ph_3P)_2PdCl_2$, DMF, 90 °C (85%); (c) K_2CO_3, MeOH (quant.); (d) $Et_4N^+(HBr_2)^-$, CH_2Cl_2 (95%); (e) $LiAlH_4$, THF, −78 → 0 °C (98%); (f) MnO_2, $CHCl_3$, reflux (94%); (g) 1,3-propanediol, cat. TsOH, toluene, reflux (89%); (h) $LiAlH_4$, THF, −78 → −20 °C (97%); (i) MnO_2, $CHCl_3$, reflux (86%); (j) K_2CO_3, MeOH (98%); (k) 1,3-propanediol, cat. TsOH, toluene, reflux (98%).

after desilylation of **3**, selective addition of hydrogen bromide to the triple bond was achieved by using $Et_4N^+(HBr_2)^-$,[8] giving vinyl bromide **4** in excellent yield. Conversion of **4** to styryl bromide **5** was effected by reduction with $LiAlH_4$, oxidation of the resulting benzyl alcohol followed by acetalization.

On the other hand, acetylene **6** was also prepared from **3** in high yield by desilylation and conversion of the ester moiety into acetal in a similar manner as above.

Scheme 4 shows *route a* by the $\mathbf{A}_1$–$\mathbf{B}_1$ combination. Halogen–lithium exchange of styryl bromide **5** (*t*-BuLi, Et_2O, −78 °C, 10 min) followed by addition of ketone $\mathbf{A}_1$ (−78 °C, 5 min) gave adduct **7** in 90% yield. Upon heating (toluene, reflux, 7.5 h), benzocyclobutenol **7** underwent clean ring expansion, giving naphthol **8** in 96% yield. Thus, the expected sequential ring opening of the benzocyclobutene ring and the 6π-electrocyclization occurred smoothly, which was followed by in situ-elimination of an equivalent of methanol to complete



Scheme 4. Combination of units $\mathbf{A}_1$–$\mathbf{B}_1$.

the aromatization. It should be noted that full aromatization at the final stage is the long-term reflection of high oxidation state of the starting material $\mathbf{A}_1$.

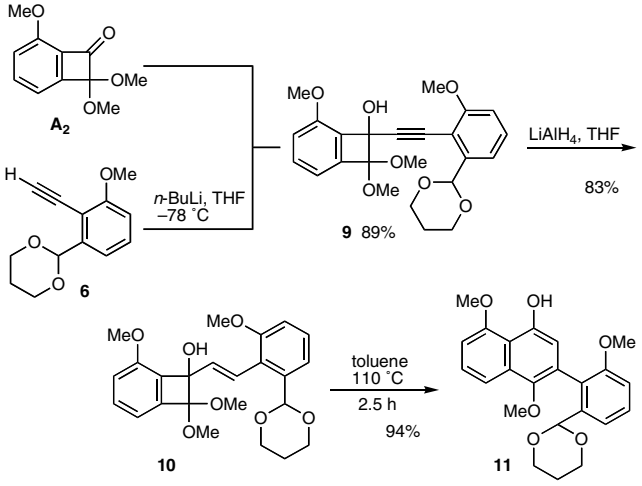
Scheme 5 shows *another unit combination*, $\mathbf{A}_2$–$\mathbf{B}_2$. Introduction of the styryl unit at its terminal position was effected in an indirect way by using an acetylide addition followed by hydroalumination. Thus, lithiation of acetylene **6** (*n*-BuLi, THF, −78 °C, 5 min) followed by treatment with ketone $\mathbf{A}_2$ (−78 → 0 °C, 75 min) cleanly gave propargyl alcohol **9** in 89% yield. Hydroalumination of **9** ($LiAlH_4$, THF, −78 → 0 °C, 4 h) gave benzocyclobutenol **10** with an (*E*)-styryl group,[9] ready for the key ring expansion reaction. Again, upon heating compound **10** in toluene for 2.5 h, the ring enlargement smoothly proceeded, which was accompanied by in situ-elimination of methanol to give arylnaphthalene **11** in 94% yield.

Both approaches proved to work fine, giving a pair of isomeric phenylnaphthalenes **8** and **11** in high yields. The *semi-convergence* should be noted in the fact that isomeric starting materials converged to two arylnaphthalenes **8** and **11**, which *share the same oxygenation pattern, but with different protection pattern*.

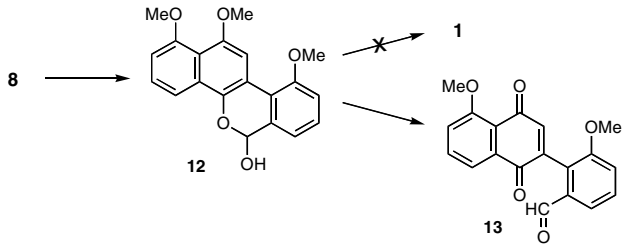
Our attention was turned to test their conversion to the model target **1**. Upon simple comparison of the protection pattern of **8** and **11**, it seemed that **8** would be more easily convertible to **1**, as only two steps would be formally necessary: the acetal hydrolysis and oxidation, which turned out to be not the case.

Although acetal **8** was hydrolyzed (3 M aq HCl, THF, 77% yield) without event, the resulting lactol **12** failed to be oxidized under various conditions. For example, treatment of **12** with PCC (CH_2Cl_2, 8 h) gave none of lactone **1**, but instead gave quinone **13** in quantitative yield (Scheme 6).

This detour was solved as in Scheme 7. Acetylation of phenol **8** and hydrolysis of the acetal gave aldehyde **14**. Oxidation of **14** was effected by $NaClO_2$, and esterification of the resulting carboxylic acid with TMS–diazomethane gave methyl ester **15** in high overall yield. Finally, removal of the acetyl group in basic methanol followed by acidification gave lactone **1** in 80% yield.

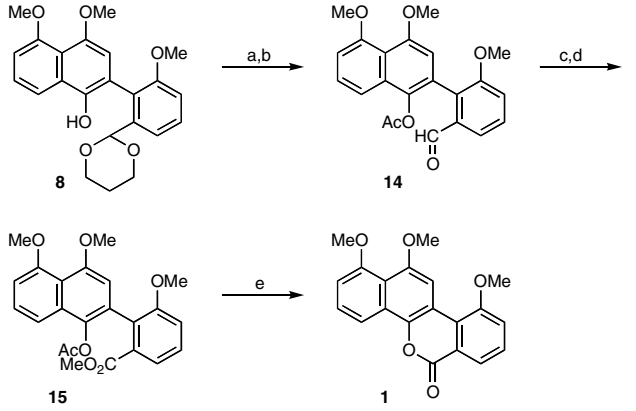


Scheme 5. Combination of units $\mathbf{A}_2$–$\mathbf{B}_2$.

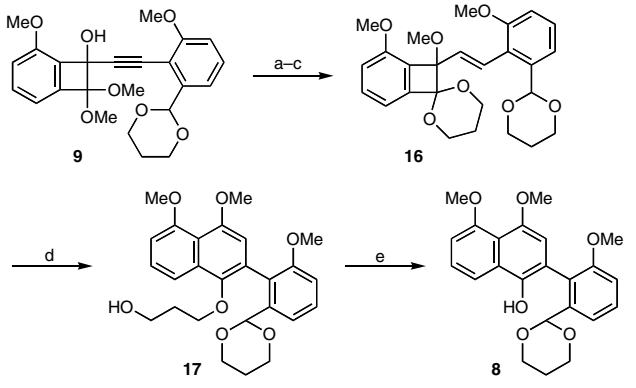


Scheme 6.

By contrast, the conversion of the isomeric arylnaphthalene **11** (see Scheme 5) into lactone **1** appeared to be less straightforward in view of its protection pattern. One can, nevertheless, devise an effective route by using a 'trick' prior to the ring expansion: replacement of the dimethyl acetal in **9** by a 1,3-dioxane acetal (Scheme 8).



Scheme 7. Reagents and conditions: (a) Ac_2O, 4-DMAP, pyridine (97%); (b) 80% aq AcOH (97%); (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O, acetone; (d) Me_3SiCHN_2, MeOH, benzene (89%, two steps); (e) K_2CO_3, MeOH, reflux; then 2 M aq HCl, 0 °C (80%).



Scheme 8. Reagents and conditions: (a) 1,3-propanediol, cat. CSA, THF, 50 °C (87%); (b) $LiAlH_4$, THF, −78 °C → rt (95%); (c) *n*-BuLi, Et_2O, −78 °C; then MeOTf, −78 °C → rt (90%); (d) toluene, 110 °C, 2.5 h (97%); (e) SO_3·pyridine, Et_3N, DMSO, rt, 8 h (64%).

Hydroalumination and methylation gave *the modified substrate* **16** in high yield. Thermal reaction of **16** (toluene reflux, 2.5 h) proceeded smoothly to give naphthalene **17** in 97% yield. Treatment of alcohol **17** with SO_3·pyridine (Et_3N, DMSO) effected oxidation of the γ-(aryloxy)propanol moiety and the β-elimination to provide **8**, which was identical with the sample shown in Scheme 4, convertible by the same sequence of reactions (Scheme 7) into the model lactone **1**.

In conclusion, two viable, complementary routes have been described for the synthetic approach to the β-phenylnaphthalene structure motifs embedded in various polyaromatic natural products.

Acknowledgement

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