Polyaromatic Compounds

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Ring Selectivity: Successive Ring Expansion of Two Benzocyclobutenes for Divergent Access to Angular and Linear Benzanthraquinones**

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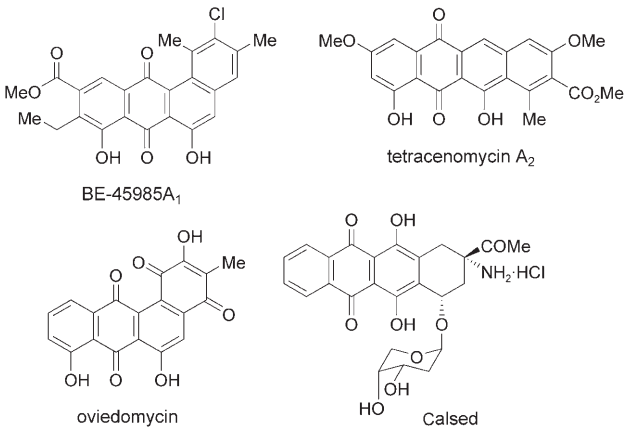
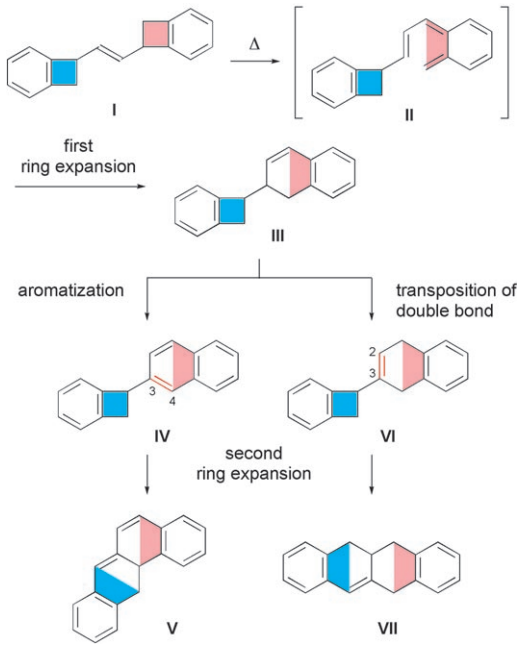
Highly oxygenated tetracycles constitute a structural motif shared by many biologically active natural products and pharmaceuticals.[1,2] The array of four rings is classified as angular, such as in BE-45985A$_1$[3a] and oviedomycin,[3b] or



linear, as found in tetracenomycin A$_2$ [3c,d] and Calsed,[3e] the first fully synthetic anthracycline carcinostatic agent.

As a potentially versatile method for the rapid, general assembly of such angular and linear tetracycles, we envisioned the successive ring expansion of two benzocyclobutenes connected by an ethenyl group (Scheme 1). If the more reactive four-membered ring (pink) were to undergo selective four-electron electrocyclic ring opening to generate the quinodimethane **II**, subsequent six-electron ring closure would give the key intermediate **III** with a 6,4,6,6 ring system.[4,5] The aromatization of **III** would lead to naphthalene **IV**, which could undergo a second ring expansion, this time of the four-membered ring in blue. This sequential process with recyclization at the more reactive 4-position

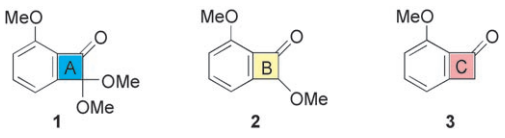


Scheme 1. Divergent access to angular and linear tetracycles.

would lead to the angular tetracycle **V**. On the other hand, if the double bond at the 1,2-position in **III** were transposed to the 2,3-position, the second ring expansion from the dihydronaphthalene **VI** would lead to the linear tetracycle **VII**.

For this strategy to be successful, two fundamental issues must be addressed: 1) The "ring selectivity", that is, the relative susceptibilities of the two four-membered rings toward ring expansion, must be established, and 2) it is essential for the second ring expansion that site selectivity is possible with respect to the key double bond (shown in red). Herein, we provide solutions for these two key challenges.

To address the question of ring selectivity, we prepared three benzocyclobutenones, **1**–**3**, with different levels of oxygenation of the four-membered ring through the regioselective [2+2] cycloaddition of α-methoxybenzyne with ketene silyl acetals.[6] The interconnection of pairs of these benzocyclobutenones with an ethenyl bridge led to the three model bis(benzocyclobutene)s **6**–**8** (Scheme 2). The preparation of **6**



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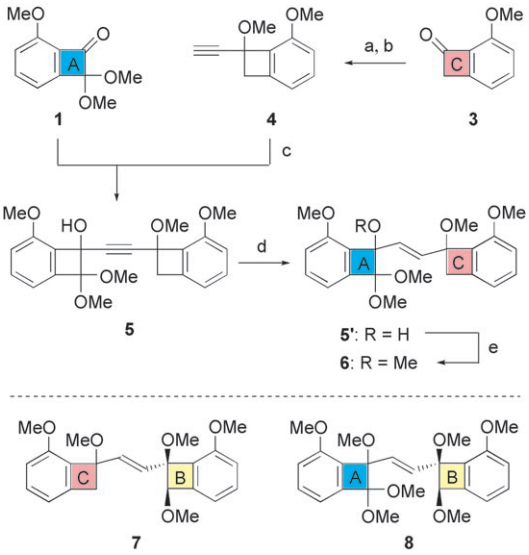
is representative: The benzocyclobutenone **3** was treated with lithium trimethylsilylacetylide, and the resulting alkoxide was trapped in situ with methyl triflate. Desilylation then gave acetylene **4** in 69% overall yield. The lithium salt of **4** was



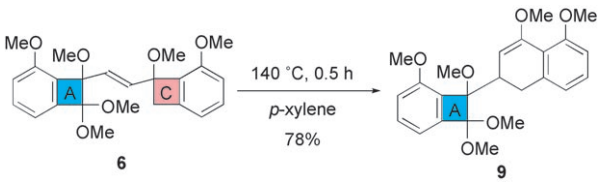
Scheme 2. Synthesis of the bis(benzocyclobutene)s **6**–**8**: a) LiC≡CTMS, Et_2O, −78→−40 °C, then MeOTf, Et_2O, −78→10 °C; b) K_2CO_3, MeOH, 20 min, 69% (2 steps); c) *n*BuLi, then **1**, THF, −78→−20 °C, 98%; d) $LiAlH_4$, THF, 0→10 °C, 6 h, 91%; e) *n*BuLi, then MeOTf, Et_2O, −78→10 °C, 90%. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

combined with ketone **1** to give the adduct **5** in 98% yield.[7,8] Partial reduction of the triple bond in **5** with $LiAlH_4$ gave the bis(benzocyclobutene) **5′** (91%),[9] which was methylated to afford the model compound **6** in 90% yield.

The combination of **4** and ketone **2** afforded the bis(benzocyclobutene) **7**, in which the two methoxy groups on the B ring have a *cis* relationship.[10] Similarly, the model compound **8** with A and B rings was obtained by forming an acetylide connection first to ketone **1** and subsequently to ketone **2** by following the procedure described in Scheme 2. The two methoxy groups on the B ring in **8** again have a *cis* relationship.[10]

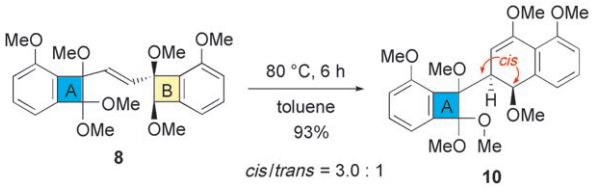
The bis(benzocyclobutene)s **6**–**8** were used to examine the relative propensity of rings A–C to undergo thermal ring expansion. The three compounds were used as obtained, as mixtures of almost equal amounts of two diastereomers. When **6** was heated in xylene at 140 °C for 0.5 h, the C ring underwent expansion exclusively to give the enol ether **9** as a single product in 78% yield [Eq. (1)].[11] Two factors may explain this impressive selectivity for the expansion of the C ring over that of the A ring: 1) the relative ease of quinodimethane generation from the C ring for electronic reasons, and 2) the facile nature, from a steric point of view, of the six-electron ring closure of the hexatriene intermediate derived from the C ring.[12]

An experiment to determine the selectivity for ring expansion in **8**, which contains an A ring and a B ring, revealed two interesting features: 1) complete ring selectivity,



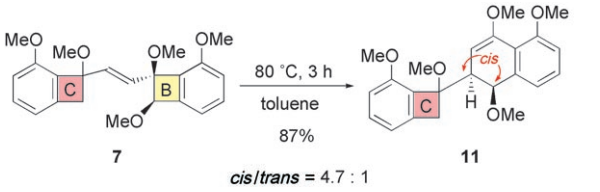
(1)

and 2) anomalous stereoselectivity [Eq. (2)]. When **8** was heated in toluene at 80 °C for 6 h, the less-substituted B ring underwent ring expansion exclusively to afford the dihydronaphthalene **10** in 93% yield.[13] The configuration of the product was anomalous in that *cis*-**10** was obtained as the major product, whereas orbital considerations predict the formation of *trans*-**10**.



(2)

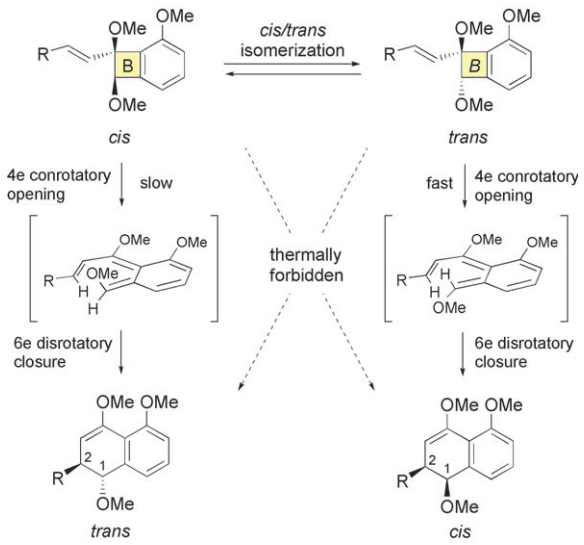
Furthermore, the reactivity of the B ring proved to exceed that of the C ring [Eq. (3)]. Heating of the bis(benzocyclobutene) **7** (toluene, 80 °C, 3 h) resulted in the exclusive ring expansion of the B ring to afford **11** in 87% yield. Again the stereochemical course of the reaction contradicted expectations based on orbital considerations: The major product was *cis*-**11**, as evidenced by X-ray crystal-structure analysis.[14]



(3)

The origin of the high reactivity of the B ring can be correlated to the unusual stereoselectivity. The two substituents at the sp^3 centers of the dihydronaphthalene in **10** and **11** have a 1,2-*cis* relationship, whereas orbital considerations point to the respective *trans* product of a conrotatory ring opening followed by a disrotatory six-electron ring closure. On the basis of previous reports by Roth et al.,[15a] Sustmann and co-workers,[15b] and us,[15c–e] this stereochemical anomaly could be attributed to a biradical-mediated *cis*/*trans* isomerization of the starting benzocyclobutene prior to the ring expansion (Scheme 3). The *trans* isomer generated in situ would be highly reactive toward ring expansion, as the two oxy groups facilitate the ring opening cooperatively by outward conrotation (torquoselectivity).[16]

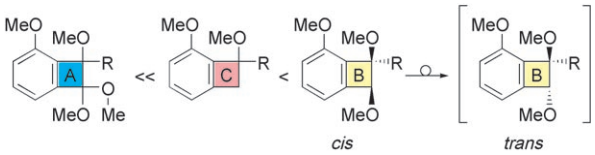
Indeed, *cis*/*trans* isomerization of *cis*-**8** to *trans*-**8** was observed upon gentle warming in toluene at 40 °C. After 24 h, the *cis*/*trans* ratio of the recovered material **8** (43%) was



Scheme 3. Origin of the high reactivity of the B ring.

1.3:1, as determined by ^{1}H NMR spectroscopy. The conversion of **8** into the ring-enlarged product **10** (34%) proceeded even under these mild conditions, whereby **10** was further enriched with the *cis* isomer (*cis*/*trans* = 5.2:1). The latter aspect is consistent with the isomerization mechanism described above. Furthermore, to our surprise, this stereomutation was found to occur even at 0°C, at which temperature the *cis*/*trans* ratio of **8** reached 2.7:1 in 50 days.

Scheme 4 summarizes the ring selectivity for the expansion of the three benzocyclobutene rings A–C. The dioxygenated B ring is the most reactive as a result of in situ

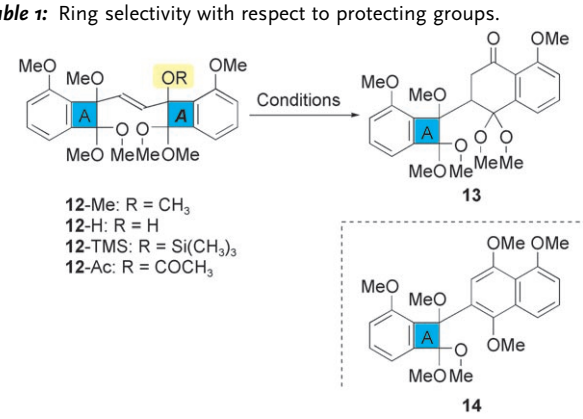


Scheme 4. Relative reactivity of benzocyclobutenes.

isomerization, the C ring showed the next highest reactivity, and the fully oxygenated A ring appeared to be unreactive. However, we found that the A ring also undergoes ring expansion at higher temperatures. The symmetrical substrate **12**-Me with two identical A rings underwent ring expansion upon prolonged heating (3 h) at 140°C. During the long reaction period, the initial product underwent aromatization to give the naphthalene **14** in moderate yield (Table 1, entry 1).

The use of a different alcohol protecting group R greatly facilitated the expansion of the A ring. Substrates **12**-H, **12**-TMS, and **12**-Ac each have two A rings which differ in the way they are protected. Upon thermolysis at 140°C, the A ring with the protecting group R (R = H, TMS, Ac) underwent ring expansion exclusively to give **13** in excellent yield (Table 1, entries 2–4).[17]

Table 1: Ring selectivity with respect to protecting groups.



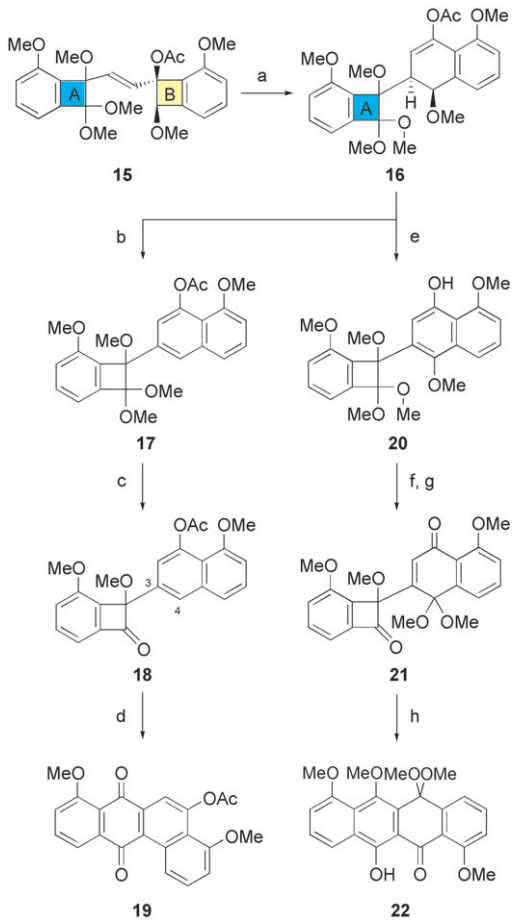
Entry	Substrate	Conditions	Yield of **13** [%]
1	**12**-Me	*p*-xylene, 140°C, 3 h	58[a]
2	**12**-H	*p*-xylene, 140°C, 1 h	85
3	**12**-TMS	*p*-xylene, 140°C, 20 min, then TBAF, THF	87
4	**12**-Ac	*p*-xylene, 140°C, 1 h, then K_2CO_3, MeOH	81

[a] Yield of the aromatized product **14**. TBAF = tetra-*n*-butylammonium fluoride.

This established ring selectivity provided us with a firm basis for the successive activation of bis(benzocyclobutene)s for divergent access to angular and linear tetracycles. As an example of divergent access to angular and linear benzanthraquinones, we investigated the transformation of the bis(benzocyclobutene) **15**, which contains A and B rings (Scheme 5). The thermolysis of **15** at 80°C for 4 h in toluene gave the enol acetate **16** in 91% yield. Thus, the B ring with an acetyl protecting group underwent cleanly selective ring expansion.[18] Upon exposure to mild acidic conditions (PPTS, MeOH, 40°C, 6 h), **16** underwent smooth elimination of a mole of methanol to give the naphthalene **17**, the substrate for the next ring expansion.

Initial attempts to trigger the ring expansion of **17**, however, met with no success. For example, even under forcing conditions (mesitylene, 166°C, 5 h), **17** remained intact and was recovered in 63% yield. After considerable experimentation, we found that the removal of the acetal in **17** provided a substrate of sufficient reactivity for the desired ring expansion. Ketone **18**, available from acetal **17** by hydrolysis ($TsOH\cdot H_2O$, acetone, H_2O, 25°C, 25 h, 93%) or directly from **16** ($TsOH\cdot H_2O$, acetone, 40°C, 1 h, 74%), was heated in mesitylene at reflux to effect the second ring expansion via a dienylketene intermediate followed by a 6π cyclization.[4c–e] The reactive 3,4-π bond of the naphthalene core participated selectively in the reaction to afford the angular benzanthraquinone **19** as a red powder in 69% yield.

This approach also provided access to the corresponding linear tetracycle. The branching point in the synthesis was the transposition of the double bond in **16**. Thus, **16** was converted into the dihydrobenzoquinone **20** by treatment with MeLi (THF, 0°C) followed by direct oxidation with the reagent *N*-*tert*-butylbenzenesulfinimidoyl chloride described by Matsuo, Mukaiyama, and co-workers.[19] Hydrolysis of the acetal in **20**



Scheme 5. Divergent construction of benzanthraquinones: a) toluene, 80 °C, 4 h, 91 %; b) PPTS, MeOH, 40 °C, 6 h, 91 %; c) $TsOH \cdot H_2O$, acetone, H_2O, 25 °C, 25 h, 93 %; d) mesitylene, reflux, 4 h, 69 %; e) MeLi; then *N*-*tert*-butylbenzenesulfinimidoyl chloride, THF, −78→25 °C, 58 %; f) 46 % aqueous HF, CH_3CN, −15→0 °C, 1.5 h, 60 %; g) $PhI(OAc)_2$, MeOH, 0 °C, 10 min, 80 %; h) *p*-xylene, 120 °C, 7 h, 73 %. PPTS = pyridinium *p*-toluenesulfonate.

followed by oxidation in methanol furnished the quinone monoacetal **21**, which was heated in *p*-xylene at 120 °C to afford the linear tetracenone **22** as a yellow solid in 73 % yield.

In conclusion, the present approach should allow flexible access to various important classes of densely oxygenated polycyclic natural and non-natural compounds. Further studies are in progress toward the synthesis of complex molecules.

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Keywords: pericyclic reactions · polyaromatic compounds · ring expansion · ring selectivity · strained molecules

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[7] All new compounds were characterized fully by spectroscopy and combustion analysis.

[8] Compound **5** was obtained as a mixture of two diastereomers, which was used without separation; see the Supporting Information.

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[10] The relative configuration of the carbon centers bonded to the two methoxy groups was determined by NOE studies.

[11] Product **9** was obtained as a mixture of diastereomers in a 1:1 ratio. The diastereomers were separated by recycling preparative HPLC for structure assignment; see the Supporting Information.

[12] a) K. N. Houk, D. C. Spellmeyer, C. W. Jefford, C. G. Rimbault, Y. Wang, R. D. Miller, *J. Org. Chem.* **1988**, *53*, 2125–2127; b) J. D. Evanseck, B. E. Thomas IV, D. C. Spellmeyer, K. N. Houk, *J. Org. Chem.* **1995**, *60*, 7134–7141.

[13] Products *cis*-**10** and *trans*-**10** were obtained as mixtures of diastereomers with respect to the quaternary center in the cyclobutene ring in ratios of 1:1.5 and 1:1.2, respectively. The diastereomers were separated by recycling preparative HPLC for structure assignment; see the Supporting Information.

[14] Products *cis*-**11** and *trans*-**11** were obtained as mixtures of diastereomers in ratios of 1:3.2 and 1:1.4, respectively. The diastereomers were separated by recycling preparative HPLC for structure assignment; see the Supporting Information.

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[17] Product **13** was obtained as a mixture of diastereomers in a 1:3.4 ratio. The diastereomers were separated by preparative TLC for structure assignment; see the Supporting Information.

[18] The reaction of **15** gave *cis*-**16** as the only isolable product; thus, the reaction proceeded with high *cis* selectivity.

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