Synthesis of Angularly-Fused Benzocyclobutenedione Monoketals: Useful Synthetic Intermediates to Angucyclines

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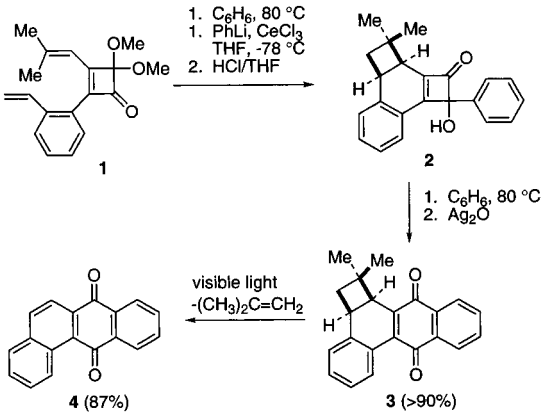
Recently, we reported a dual annulation method that is applicable for the synthesis of polycyclic angularly fused quinones. This involves the well-known ring expansions of

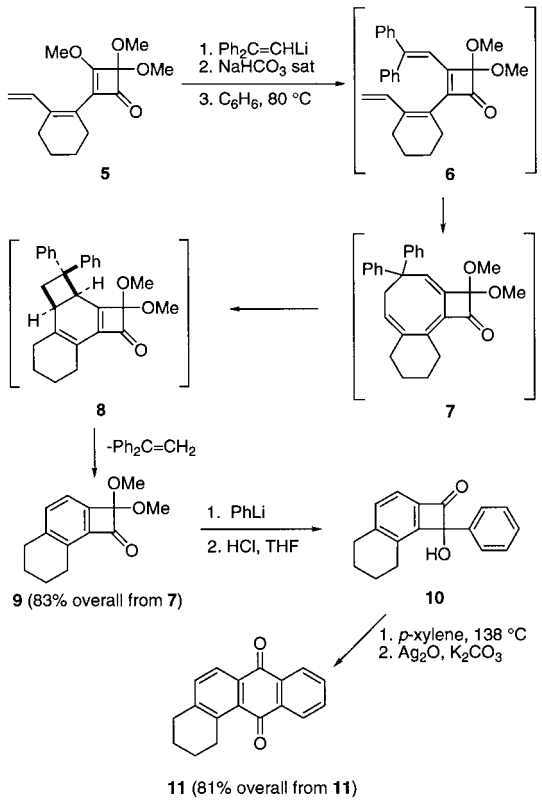
Scheme 1



appropriately substituted cyclobutenones and a new metathesis sequence leading to aromatic rings arising from a photofragmentation of cyclobutyl-substituted quinones as the ultimate step.[1,2] For example, thermolysis of 2-(2-ethenylphenyl)-4,4-dimethoxy-3-(2-methyl-1-propenyl)cyclobutenone **1** (refluxing benzene) induced an 8π electrocyclic ring closure to a cyclooctatriene intermediate followed by a 6π electrocyclic ring closure to give the corresponding bicyclo[4.2.0]octadiene derivative (90%).[3] This was easily converted to **2** which gave the quinone **3** (>90%) upon mild thermolysis followed by oxidation of the resulting hydroquinone. Photolysis of **3** using visible light then gave the angularly fused quinone **4** in 87% yield (Scheme 1). We now report a modification of this method that allows the facile synthesis of the angularly fused regioisomeric benzocyclobutenedione monoketals **9** and **19**, compounds envisaged to be useful synthetic precursor to angucycline antibiotics.[4]

The salient points of this new dual annulation procedure are outlined in Scheme 2. Treatment of **5** with 1-lithio-2,2-diphenylethene[5] gave an 84% yield of a mixture of **6**, **7**, and **8** in a respective ratio of 1:1.15:1.25 (^{1}H NMR analysis). This

Scheme 2



mixture was directly subjected to thermolysis (refluxing benzene) to give the annulated benzocyclobutenedione monoketal **9** in 83% overall yield from **5**. The second annulation step was accomplished upon treatment of **9** with phenyllithium followed by hydrolysis of the ketal leading to the benzocyclobutenone **10**. This was not isolated but directly heated in refluxing *p*-xylene followed by oxidation of the initially formed hydroquinone to give quinone **11** in 81% overall yield.

Initial attempts to prepare the regioisomeric benzocyclobutenedione monoketal **19** by an analogous sequence of reaction failed. Specifically, treatment of dimethyl squarate (**12**) with 1-lithio-2,2-diphenylethene and then trifluoroacetic anhydride (TFAA) and methanol gave **13** in 98% yield (Scheme 3).[6] This was converted to **14** upon treatment with 1-lithio-2-ethenylcyclohexene[7] in THF at −78 °C. Immediate thermolysis of **14** in refluxing diethyl ether gave **15** (64% overall from **13**), which unlike its regioisomer **8**, was stable in refluxing benzene. Apparently, the diradical intermediate

(1) Heileman, M. J.; Tiedemann, R.; Moore, H. W. *J. Am. Chem. Soc.* **1998**, *120*, 3801.

(2) For a recent review on the ring expansion of cyclobutenones, see: Moore, H. W.; Yerxa B. R. *Adv. Strain Org. Chem.* **1995**, *4*, 81−162.

(3) For an elegant application of this electrocyclic cascade in natural products synthesis, see: Nicolaou, K. C.; Petasis, N. A.; Zipin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555.

(4) For a recent review on these compounds, see: Rohr, J.; Thiericke, R. *Natural Prod. Rep.* **1992**, 103. Also see: (a) Krohn, K.; Ballwanz, F.; Baltus, W. *Liebigs Ann. Chem.* **1993**, 911. (b) Larsen, D. S.; O'Shea, M. D. *Tetrahedron Lett.* **1993**, *34* 1373. (c) Krohn, K.; Khanbabaee, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 99. (d) Larsen, D. S.; O'Shea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1019. (e) Kim, K.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2397. (f) Matsuo, G.; Miki, Y.; Nakata, M.; Matsumura, S.; Toshima, K. *Chem. Commun.* **1996**, 225. (g) Carreno, M. C.; Urbano, A.; Fischer, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 1621. (h) Larsen, D. S.; O'Shea, M. D.; Brooker, S. *Chem. Commun.* **1996**, 203.

(5) Köbrich, G.; Stöber, I. *Chem. Ber.* **1970**, *103*, 2744.

(6) For examples of analogous synthetic methodology, see: (a) Gayo, L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. (b) Santora, V. J.; Moore, H. W. *J. Am. Chem. Soc.* **1995**, *117*, 8486.

(7) Denmark, S. E.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 195. A better yield of 1-bromo-2-ethenylcyclohexene can be obtained by doing a Peterson instead of a Wittig olefination. Specifically, treatment of 2-bromo-1-cyclohexene-1-carbaldehyde with trimethylsilylmethyllithium followed by acidic workup (concentrated HCl) furnished the bromodiene in 80% yield.

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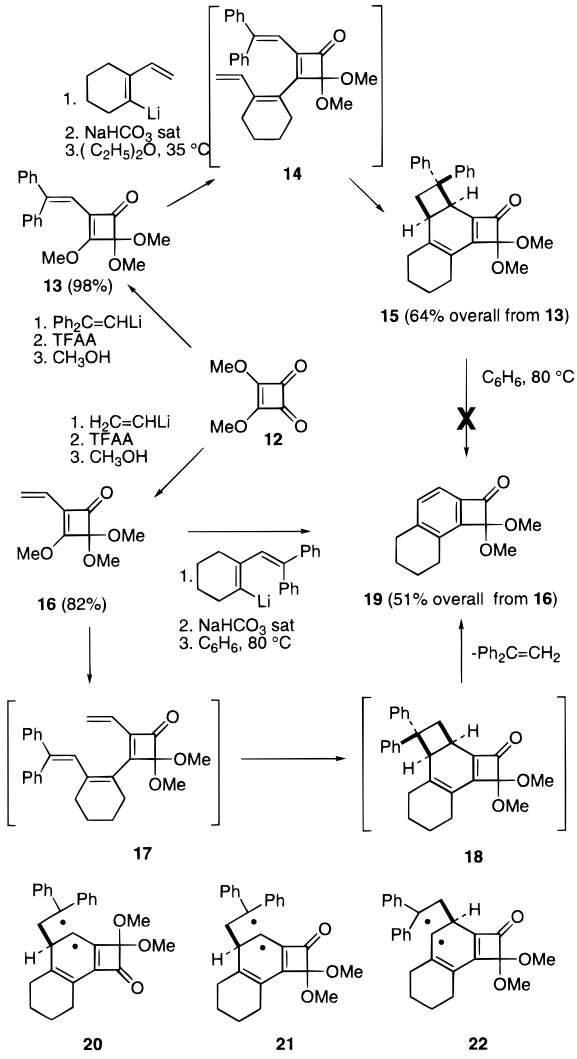
Scheme 3

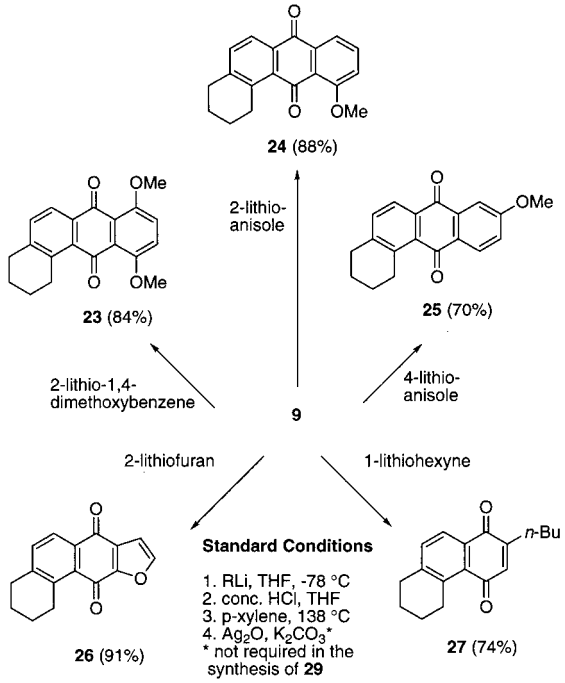


20 arising from **8** is more stable and thus more easily formed than diradical **21** arising from **15**; i.e., the cyclohexenyl radical site in **20**, unlike **21**, is a vinylogously conjugated acyl radical and thus gains additional stabilization by delocalization into the carbonyl group.

On the basis of the above radical stabilization argument, it was reasoned that **18** would readily give **19** via diradical intermediate **22**. Indeed, this was shown to be the case. Treatment of **16**, prepared as indicated in 82% yield from dimethyl squarate (**12**), with 1-lithio-2-(2,2,-diphenylethenyl)cyclohexene[8] gave the cyclobutenone **17**, which was converted to **19** in 51% overall yield from **16** by immediately subjecting crude **17** to thermolysis (refluxing benzene).[9]

The cyclobutenone ring expansions outlined in Scheme 4 illustrate the utility of benzocyclobutenedione monoketals as valuable synthetic intermediates to the angucycline ring systems. For example, in direct analogy to the synthesis of

Scheme 4[a]



[a] Standard conditions: (1) RLi, THF, −78 °C; (2) concd HCl, THF; (3) *p*-xylene, 138 °C; (4) Ag_2O, K_2CO_3* (*not required in the synthesis of **29**).

11, benzocyclobutenedione monoketal **9** was converted to the angularly fused anthraquinones **23** (84%), **24** (88%), **25** (70%), **26** (91%), and **27** (74%) by using, respectively, 2-lithio-1,4-dimethoxybenzene, 2-lithioanisole, 4-lithioanisole, 2-lithiofuran, and 1-lithiohexyne.

The significant points arising from this study include the following: (1) A new direct metathesis reaction starting with readily available 2-(2-ethenylcyclohexenyl)-4,4-dimethoxy-3-(2,2-diphenylethenyl)-cyclobutenone **6** and 2-ethenyl-4,4-dimethoxy-3-(2-(2,2-diphenylethenyl)cyclohexenyl)-cyclobutenone **17** leads to the angularly fused regioisomeric benzocyclobutenedione monoketals **9** and **19**, respectively. The ease of the reaction stems from the diphenylethenyl group, which facilitates cyclobutane ring cleavage to diradical intermediates in the ultimate aryl ring forming step.[10] (2) The benzocyclobutenedione monoketals **9** and **19** are examples of a potentially broad class of such compounds that could be prepared by this method. It is noteworthy that no method has previously been reported that would allow the synthesis of such compounds. (3) The availability of benzocyclobutenedione monoketals is of synthetic importance since their ring expansion reactions provides a potentially general route to highly condensed polycyclic systems.

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Supporting Information Available: Procedures and characterization data.

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(8) 1-Lithio-2-(2, 2,-diphenylethenyl)cyclohexene was generated from 1-bromo-2-(2, 2,-diphenylethenyl)cyclohexene by lithium−halogen exchange with *n*-butyllithium. The bromodiene was prepared by a low-valent titanium-mediated crossed coupling of benzophenone with 2-bromo-1-cyclohexene-1-carbaldehyde using $TiCl_4$ and zinc powder. For a similar procedure, see: Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475.

(9) For a recent review of olefin metathesis in organic chemistry, see: Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.

(10) For a review of [2 + 2]-cycloreversions and relative stabilities of diradical intermediates, see: Schaumann, E.; Ketcham, R. *Angew. Chem., Int. Engl.* **1982**, *21*, 225.