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A New Route to Benzo[4,5]cyclohepta[1,2-*b*]naphthalenes: Synthesis of Radermachol‡

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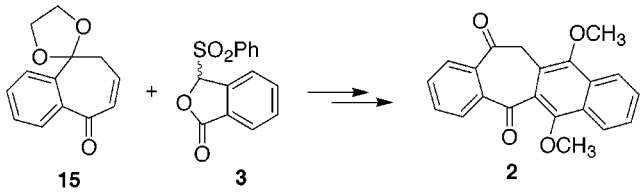
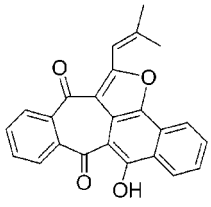
ABSTRACT



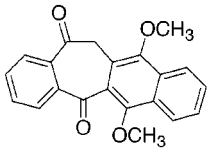
15 3 2

Condensation of 3-phenylsulfonyl-1,3-isobenzofuranone (3) with benzocyclohept-6,7-en-5-ones such as 4 and 15 provides a straightforward, general method for synthesis of functionalized benzo[4,5]cyclohepta[1,2-*b*]naphthalenes (e.g., 5 and 16). This finding was used to achieve a brief and efficient preparation of 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (2), an established intermediate to the naturally occurring red pigment radermachol (1).

The isolation and structure elucidation of the red pigment radermachol (**1**) was originally reported by Joshi et al.[1] Subsequently, the same group accomplished a total synthesis of **1**, in which the benzocycloheptadiene[1,2-*b*]-naphthalene dione **2** was employed as a key intermediate.[2]



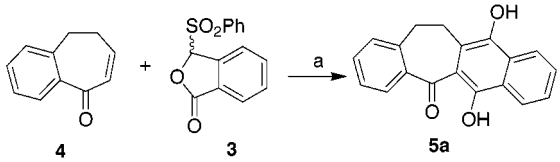
1



2

Our work with the isobenzofuranone annulation suggested that **5**, a potential precursor to **2**, might be readily prepared through condensation of the phenylsulfonyl isobenzofuranone **3** with the benzocyclohepten-5-one (**4**) (Scheme 1).[3]

Scheme 1[a]



4 3 5a

[a]a. LiOtBu, THF, 85%

Since the use of benzcyclohepten-5-ones in the isobenzofuranone annulation had not been previously explored and because this approach would provide a new route to benzo[4,5]cyclohepta[1,2-*b*]naphthalenes, we decided to investigate this approach.

To test the feasability of using the annulation methodology to generate the objective ring system, the anion of the phenylsulfonyl isobenzofuranone **3** was condensed with 8,9-

‡ Dedicated to the memory of the late Arthur G. Schultz (1942−2000).

(1) Joshi, B. S.; Gawad, D. H.; Pelletier, S. W. Kartha, G.; Bhandary, K. *Tetrahedron Lett.* **1984**, *25*, 5547.

(2) Joshi, B. S.; Jiang, Q.; Rho, T.; Pelletier, S. W. *J. Org. Chem.* **1994**, *59*, 8220. Jiang, Q.; Joshi, B. S.; Pelletier, S. W. *Tetrahedron Lett.* **1991**, *32*, 5283.

(3) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. For use of this reaction in natural products syntheses, see: Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984**, *40*, 4711. Hauser, F. M.; Chakrapani, S.; Ellenberger, W. P. *J. Org. Chem.* **1991**, *56*, 5248. Hauser, F. M.; Tommasi, R. A. *J. Org. Chem*, **1991**, *56*, 5758.

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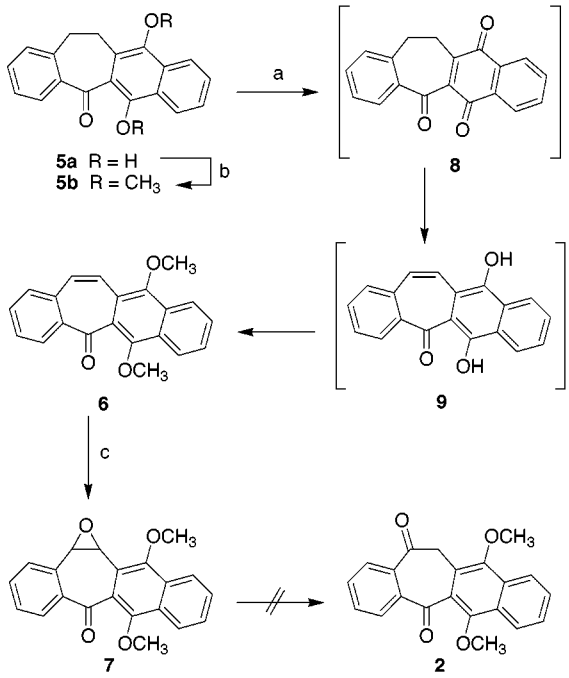
dihydrobenzocyclohepten-5-one[4] (**4**). Indeed, gram quantities of the expected benzo[4,5]cyclohepta[1,2-*b*]naphthalene **5a** were produced in 85% yield. A distinctive feature of the ^{1}H NMR spectrum of **5a** was the presence of multiplets at 3.13 and 3.27 ppm for the protons on the methylene groups at C-12 and C-13.

Once it was established that the isobenzofuranone condensation provided the ring system, various methods for introduction of a C-13 ketone functionality in **5a** were explored to complete construction of the intermediate **2**. The conceptualized plan, as outlined in Scheme 2, was to convert

Scheme 2[a]



[a]a. $(CH_3O)_2SO_2$, K_2CO_3, acetone, reflux, 15h, 46%; b. $Bu_4N^+F^-$, CH_3I, DMF, 75%; c. MCPBA, CH_2Cl_2, rt, 4 h, 78%.

5a to the dimethyl ether derivative **5b** and then introduce C-12/C-13 unsaturation in **6**, possibly through benzylic bromination/dehydrobromination. It was anticipated that the epoxide **7**, derived from **6**, would undergo regioselective rearrangement to the objective ketone **2**,[5] as a result of resonance stabilization by the neighboring methoxyl group. We were pleased but not entirely surprised to discover that the unsaturated compound **6** was directly formed in 46% yield on attempted methylation of **5a** with $(CH_3O)_2SO_2$ and K_2CO_3, thereby obviating the need for alternative methods for introduction of C-12/C-13 unsaturation. Formation of **6** was confirmed by the ^{1}H NMR spectrum. There were no absorptions between 3.1 and 3.3 ppm for the protons on the ethano bridge. Instead, a one-hydrogen doublet at 6.95 ppm (J = 12.4 Hz) was observed, indicating the presence of a vinyl hydrogen. Proton decoupling established that the other vinyl hydrogen was buried in the aromatic absorptions. Apparently the presence of oxygen in the medium resulted in oxidation of the hydroquinone **5a** to the quinone **8**, which underwent tautomerization to **9** and then methylation. Although we had seen this phenomena before and even refined and capitalized on it for anthracycline syntheses,[6] the facility of this transformation was nevertheless striking. In fact, preparation of the dimethyl ether **5b**, uncontaminated with the unsaturated dimethyl ether **6**, proved challenging.[7]

Although epoxidation of **6** (MCPBA, CH_2Cl_2) produced **7** in 78% yield, attempted rearrangement of **7** with CF_3CO_2H or BBr_3 failed to give the expected ketone **2**. A possible explanation is that, as shown in Figure 1, the ring system is

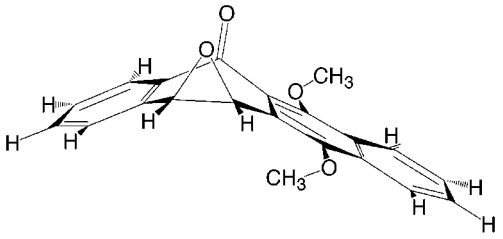
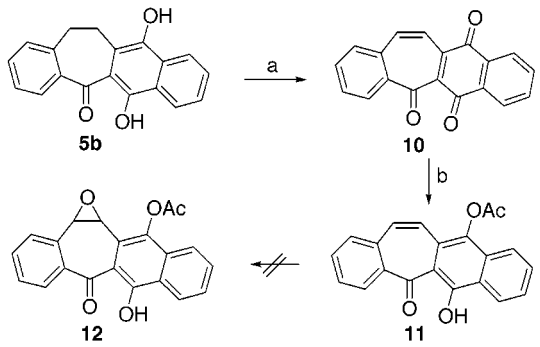


Figure 1. Three-dimensional representation of **7** showing the cupped geometry.

cup-shaped and opening of the epoxide to form a carbocation would result in additional ring strain. Moreover, attempted reductive opening (H_2, Pd/$BaSO_4$) of the epoxide in **7** was also unsuccessful. In this case, the catalyst probably cannot access the concave face.

Based on the expectation that regiospecific reductive opening of a 12,13-epoxide or regioselective reductive removal of a 12-hydroxyl group would be possible, the route shown in Scheme 3 was explored. To access appropriately functionalized intermediates, our previously developed procedure for oxidative tautomerization of quinones was exploited.[6] Treatment of the hydroquinone **5a** with Fetizon's

Scheme 3[a]

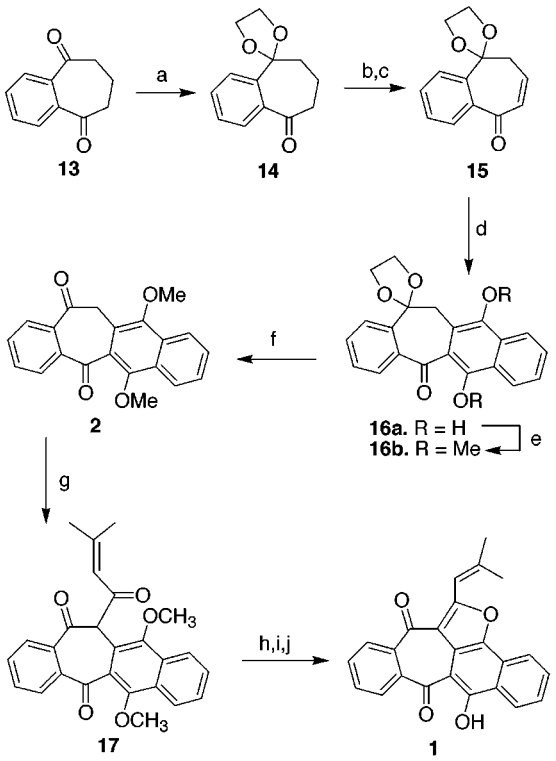


[a]a. Ag_2CO_3, Et_3N, CH_2Cl_2, rt, 30 min, 99%; b. Zn, Ac_2O, AcOH, rt

(4) Ito, S.; Kasai, M.; Ziffer, H.; Silverton, J. V. *Can. J. Chem.* **1987**, *65*, 574.

(5) Hauser, F. M.; Prasanna, S. *Synthesis* **1980**, 621.

Scheme 4[a]



[a]a. Ethylene glycol, PPTS, PhH, reflux, 15 h, 97%; b. LDA, TMSCl, CH_2Cl_2, -78 °C to rt, 1h; c. $Pd(OAc)_2$, CH_3CN, reflux, 15h, 95%; d. LiO*t*-Bu, **3**, THF, -78 °C to rt, 3h; e. Bu_4NF, CH_3I, DMF, rt ,15h, 75%; f. PPTS, acetone/water, reflux, 20 h, 97%; g. $AlCl_3$, dimethylacryloyl chloride, CH_2Cl_2, reflux, 1 h; h. TMSI, $CDCl_3$, rt, 30 h; i. MeOH; j. PTSA, PhH, reflux Dean-Stark, 6 h.

reagent[8] in the presence of Et_3N directly furnished the unsaturated quinone **10** in quantitative yield.[9] As expected, under reductive acetylation conditions, **10** was converted to the monacetylated intermediate **11**. Unexpectedly, **11** proved resistant not only to epoxidation with MCPBA but also to dihydroxylation (catalytic OsO_4 with either TMNO or *t*-BuOOH).

The route shown in Scheme 4, which leads directly to the masked ketone **16**, was investigated next. Ketalization of the known 5,8-diketone **13**[10] with ethylene glycol and PPTS furnished exclusively the monoketal **14**.[11] Treatment of **14** with LDA and TMSCl produced the expected TMS ether, which smoothly underwent oxidation with $Pd(OAc)_2$ to the unsaturated enone **15**.

Condensation of **15** with the anion of the sulfone **3** gave **16a**, which was directly methylated ($Bu_4N^+F^-$, CH_3I, DMF)[7] to furnish the dimethyl ether **16b** (75% overall yield). Hydrolysis of **16b** (PPTS, acetone/water, 97%) produced **2**, which had physical and spectral properties (^1H and ^{13}C NMR) identical to those reported by Joshi et al.[2] The sequence reported by them, involving acylation of **2** with dimethylacryloyl chloride to **17**,[12] followed by demethylation and cyclization furnished **1**.

In summary, we have shown that condensation of benzocycloheptenones with an isobenzofuranone provides straightforward access to functionalized benzocycloheptadiene[1,2-*b*]naphthalenes.

Acknowledgment. This work was generously supported by the National Cancer Institute of the National Institutes of Health under grant CA 18141.

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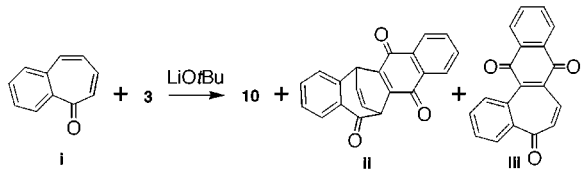
(6) Hauser, F. M.; Takeuchi, C.; Yin, H.; Corlett, S. A. *J. Org. Chem.* **1994**, *59*, 258 and references therein.

(7) Ultimately, the dimethyl ether **5b** was cleanly prepared in 75% yield from **5a** by rigorously removing oxygen from the reaction medium and using an alternative methylation procedure ($Bu_4N^+F^-$, CH_3I, DMF). Slater, G. P.; Haskins, R. H.; Hogge, L. R.; Nesbitt, L. R. *Can. J. Chem.* **1967**, *45*, 92.

(8) Fetizon, M.; Golfiner, M. *Compt. Rend.* **1968**, 267, 900.

(9) In conjunction with the work described in this paper, condensation of the anion of the isobenzofuranone **3** with the benzocycloheptenone *i* was performed. This reaction produced, after incipient oxidation, the quinone **10** (15%), the bridged bicyclic product *ii* (7%), and *iii* (28%).



(10) Barltrop, J. A.; Johnson, A. J.; Meakins, G. D. *J. Chem. Soc.* **1951**, 181.

(11) Even under forcing conditions, excess ethylene glycol and prolonged reflux, only trace quantities of the bisketal were observed. This selectivity is probably a consequence of relief of ring strain.

(12) Our yield for the $AlCl_3$ promoted acylation of **2** to **17** was only 13%, in contrast to the reported 69%.