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THE SYNTHESIS OF ANGULARLY FUSED AROMATIC RING SYSTEMS. THE SYNTHESIS OF 3-DEOXYRABELOMYCIN

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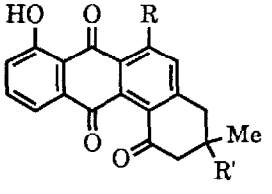
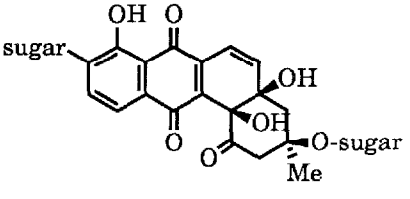
Summary: 3-deoxyrabelomycin was synthesized from the electron-deficient naphthoquinone **21** in four steps in 17% overall yield. The angularly-fused ring system was made by the conjugate addition of 5-methylcyclohexane-1,3-dione to **21** followed by methylation and base-induced cyclization.

The discovery of the anthracycline anticancer agents such as daunomycin and aclacinomycinone stimulated intense interest in the synthesis of linearly-fused aromatic ring systems. Recently, natural products researchers have determined the structures of tetracyclic aromatic compounds such as rabelomycin (**1**),[1] ochromycinone (**2**)[2] and AC5Y (**3**)[3] which are angularly fused. Quinones **1** and **2** exhibit good antibiotic activity. Quinone **3** exhibits antitumor and



1: R = R' = OH
2. R = R' = H



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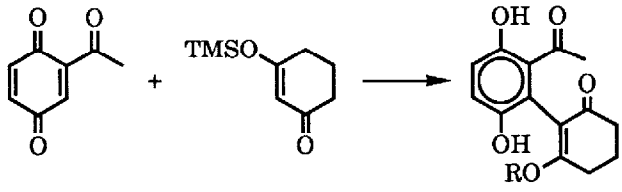
antibacterial activity. Among a growing number of synthetic approaches to **1**, **2** and **3**, only two total syntheses of **2** have been recorded. In the first synthesis of ochromycinone, Snieckus and coworkers assembled the angularly-fused tetracyclic ring system by means of their elegant directed ortho-metallation protocol.[4] A second approach to quinone **2** by Guingant featured a Diels-Alder reaction of juglone.[5] In our pathway the angularly-fused ring system is assembled by a strategy which is dramatically different from the previously reported pathways. Moreover, our strategy is applicable to the synthesis of **1**, **2** and **3**.

Our synthetic plan is depicted in Scheme 1. The construction of the angularly-fused network is readily accomplished by reaction of the enol silyl ether of a cyclohexane-1,3-dione with either

Scheme 1



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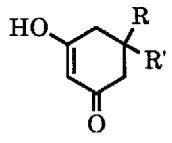
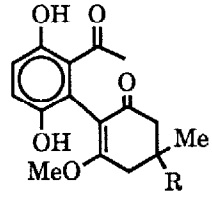
8: R = H
9: R = Me



4: R = R' = H
5: R = Me, R' = H
6: R = R' = Me

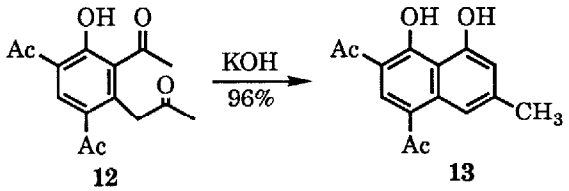


10: R = H
11: R = Me

acetylbenzoquinone or 2-acetyl-1,4-naphthoquinone followed by base-mediated cyclization The conjugate addition of synthetically-useful nucleophiles to electron deficient quinones was initially studied by Eugster and coworkers who demonstrated that both dicarbonyl compounds and furans could be employed.[6] Recently, we and others have shown that enol silyl ethers, allylic silanes and electron-rich dienes also react with electron-deficient quinones in good yields.[7]

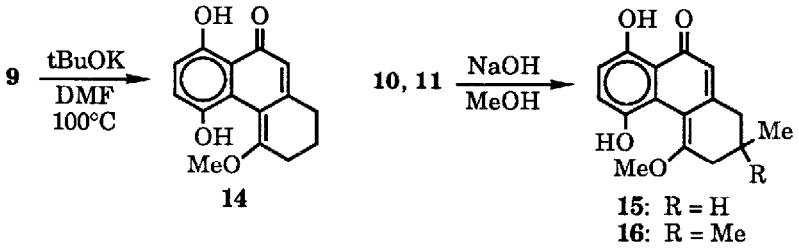
Since cyclohexanediones **4**, **5** and **6** are almost completely enolic in anhydrous solvents,[8] we initially studied the reactions of diketone **4** with acetylbenzoquinone. Although a trace of the desired adduct was formed, the major product seemed to be derived from intermolecular O-alkylation. In order to block this undesired reaction, we prepared the trimethylsilyl enol ether **7**. Acetylbenzoquinone reacted with **7** to provide diketone **8**, which was insoluble in most organic solvents and was adsorbed very strongly on silica gel. Both adduct **8** and its gem-dimethyl analog had been reported by Eugster[6]. Treatment of **8** with methyl iodide and potassium carbonate in boiling acetone afforded ether **9** in 56% overall yield. The reaction of the enol silyl ethers of **5** and **6** with acetylbenzoquinone followed by O-methylation furnished ethers **10** and **11** in 83% and 68% overall yield, respectively. Related additions of dicarbonyl compounds to quinone monoketals had been achieved by both Parker and by Duthaler[9].

Cyclization of compounds similar to ketones **9**, **10** and **11** had considerable literature precedent For example, the synthesis of naphthalene **13** from diketone **12** had been accomplished in high yield at ambient temperature.[10] The aldol cyclization of **9** was not as readily effected.



12 13

Heating compound **9** and excess tBuOK in DMF in a sealed tube at 100°C afforded hydroquinone **14** in 32% yield. Optimized conditions for the cyclization of compounds **10** and **11** involved reaction of the ketones with an excess of NaOH in MeOH in a sealed tube at 120°C. Compounds **15** and **16** were generated in 60% and 53% yield, respectively. *Although we had expected to isolate a naphthoquinone, the functionality in **15** should be even more useful for eventual conversion to **3**.*



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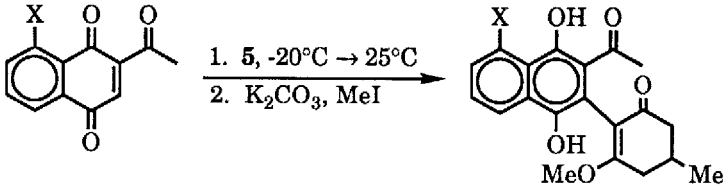
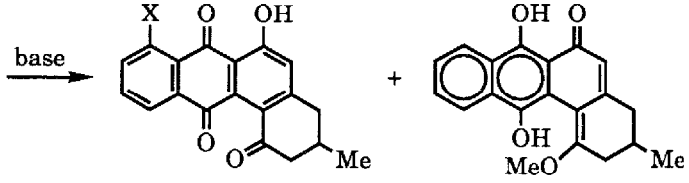
15: R = H
16: R = Me

The reaction of diketone **5** with 2-acetyl-1,4-naphthoquinone (**17**) at subambient temperature followed by methylation afforded a 52% yield of compound **18**. Attempted cyclization of **18** with NaOH in MeOH at reaction temperatures ranging from 25°C to 120°C afforded recovered starting material at lower temperatures and largely decomposition products at higher temperatures. The reaction of **18** in DMF with tBuOK at 100°C provided anthraquinone **19** in 16% yield and naphthalene **20** in 1% yield. Naphthoquinone **21** was readily available by way of our cyanophthalide annulation chemistry.[11] Quinone **21** could be prepared from 7-methoxy-3-cyanophthalide and methyl vinyl ketone in 70% yield. The reaction of **21** with diketone **5** followed by methylation gave compound **22** in an overall yield of 64%. The reaction of **22** with NaOH in MeOH at 140°C for 14 hours provided anthraquinone **23** in 27% isolated yield.



17: X = H
21: X = OMe

18: X = H
22: X = OMe



19: X = H
23: X = OMe
24: X = OH

20

Anthraquinone **23** contains the entire skeleton of **1**. Conversion into 3-deoxyrabelomycin requires the deprotection of the phenol at C-8. In contrast with our successful results with the anthracyclines[12], attempted demethylation of **23** using boron trichloride in methylene chloride led to recovered starting material. Demethylation had previously been achieved using aluminum chloride.[13] Reaction of **23** with $AlCl_3$ at 25°C afforded a 58% yield of 3-deoxyrabelomycin (**24**)

The direct preparation of **24** from naphthoquinone **21** illustrates the potential of our methodology. Anthraquinone **24** is available in four steps in approximately 30% overall yield. Additionally, naphthalene **15** represents an attractive precursor to compound **3**.

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References

1. Liu, W.; Parker, W. L.; Slusarchyk, D. S.; Greenwood, G. L.; Graham, S. F.; Meyers, E *J. Antibiot*, **1970**, *23*, 437.
2. Bowie, J. H.; Johnson, A. W. *Tetrahedron Lett.*, **1967**, 1499.
3. Otake, N.; Hayakawa, Y.; Adachi, K.; Imamura, K. Jpn. Kokai Tokkyo Koho JP 61 50,976. Chem. Abstracts, **1986**, *105*, 59453q.
4. Katasuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9.
5. Guingant, A.; Barreto, M. *Tetrahedron Lett.* **1987**, *28*, 3107.
6. Fumagalli, S. E.; Eugster, C. H. *Helv. Chim. Acta* **1971**, *54*, 959.
7. Enol silyl ethers: Kraus, G. A.; Shi, J. *J. Org. Chem.*, **1990**, *55*, 4922.
   Enolate anions: Trueb, W.; Eugster, C.H. *Helv. Chim. Acta*, **1972**, *55*, 969.
   Allylic stannanes: Naruta, Y.; Uno, H.; Maruyama, K. *J. C. S. Chem. Commun.* **1981**, 1277.
   Dienes: Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1986**, *51*, 114. Kraus, G.A.; Walling, J.A. *Tetrahedron Lett.*, **1986**, *27*, 1873.
8. Gould, E. S. "Mechanism and Structure in Organic Chemistry" (Holt and Co., New York, 1959) p 376-379.
9. Parker, K.A.; Kang, S.-K. *J. Org. Chem.*, **1980**, *45*, 1218. Duthaler, R. O.; Wegmann, U. H.-U. *Helv. Chim. Acta*, **1984**, *67*, 1755.
10. Tan, S. F. *J. Chem. Soc. Supplement 1*, **1964**, 5646.
11. Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sujimoto, H.; Prugh, S. *J. Org. Chem.*, **1983**, *48*, 3439.
12. Kraus, G.A.; Liras, S.; Man, T.O.; Molina, M.T. *J. Org. Chem.*, **1989**, *54*, 3137.
13. Uemura, M.; Take, K.; Hayashi, Y. *J. Chem. Soc. Chem. Commun.*, **1983**, 858.

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