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TOTAL SYNTHESIS OF THE AGLYCONE OF THE 8-METHYL BENZONAPHTHOPYRONE ANTIBIOTICS, GILVOCARCIN M, VIRENOMYCIN M, AND ALBACARCIN M

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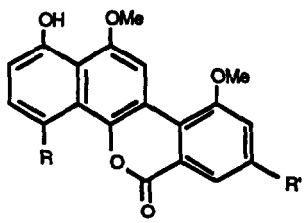
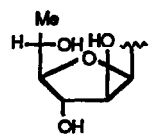
Abstract: A short, convergent synthesis of the aglycone **5a** of the 8-methyl benzonaphthopyrone antibiotics is described which utilizes as a key step a Suzuki biaryl coupling.

Recently a large group of antitumor antibiotics have been isolated from various strains of *Streptomyces*,[2-5] which all share the same general aglycone structure - 1-hydroxy-10,12-dimethoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one - with a substituent at C-8 (Methyl, Vinyl, Ethyl) and differ mainly in the sugar moiety attached at C4. They include gilvocarcin M **1a**, V **1b** (also called toromycin), and E **1c**;[2] virenomycin M and V (also called chrysomycin A and B), **2ab**;[3] ravidomycin **3b**;[4] and albacarcin M and V, **4ab**.[5,6] Recent reports[5cd] that albacarcin M and V **4ab** both have good antitumor (P388) activity (V being about twice as potent as M) seems to contradict an earlier report[7] that the vinyl group was necessary for antitumor activity. Because of our long-standing interest in the use of functionalized juglones in synthesis,[8] we decided to pursue a synthesis of the aglycone of the M series of these antibiotics which would potentially be applicable to the V series as well. We now report a short, convergent total synthesis of the aglycone of the 8-methyl benzonaphthopyrone antibiotics **5a** (Scheme I).



a R' = Me
b R' = CH = CH_2
c R' = Et

R =



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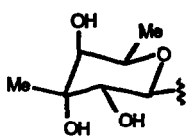

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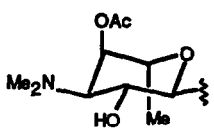

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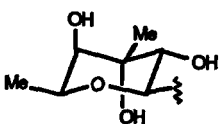

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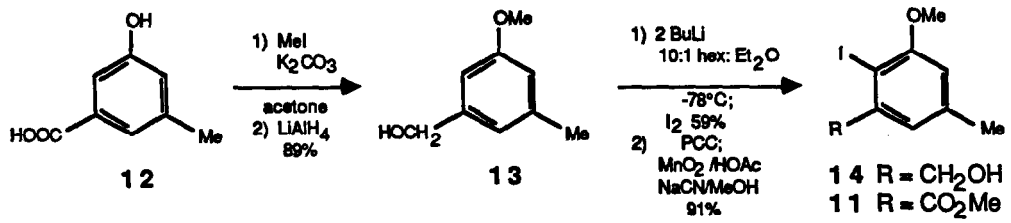
5

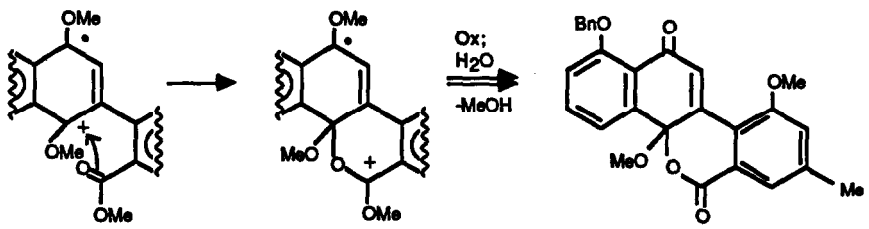
Some time ago we described our work on the mechanism of the conversion of 1,5-diacetoxynaphthalene **6** into 2-bromo-5-hydroxynaphthoquinone **7**, which proceeds in two steps in greater than 90% yield.[8b] Benzylation of

the phenol produced in 85% yield the ether **8** (mp 125°C) which was reduced and dimethylated to give the bromotrialkoxynaphthalene **9** (mp 86-7°C) in 87% yield.[9,10] Formation of the boronic acid **10** from **9** was accomplished as follows: treatment of **9** with *n*-butyllithium in THF at -100°C followed by addition of trimethyl borate at -78°C, stirring at -78°C for 1/2h and at 25°C for 2h, and then aqueous acidic workup at 25°C gave **10**, one component of the desired Suzuki coupling.[11] The necessary aryl iodide **11** was prepared from the readily available acid **12**[12] in four steps. Dimethylation (MeI/K_2CO_3) followed by reduction ($LiAlH_4$) afforded the alcohol **13** in 89% yield. Treatment of **13** with 2 eq of *n*-butyllithium in 10:1 hexane:diethyl ether at -78°C followed by addition of iodine produced the iodide **14** (mp 112-3°C) in 59% yield. Finally oxidation to the aldehyde with PCC followed by the oxidation method of Corey[13] (MnO_2/NaCN/HOAc/MeOH) furnished **11** in 91% overall yield.



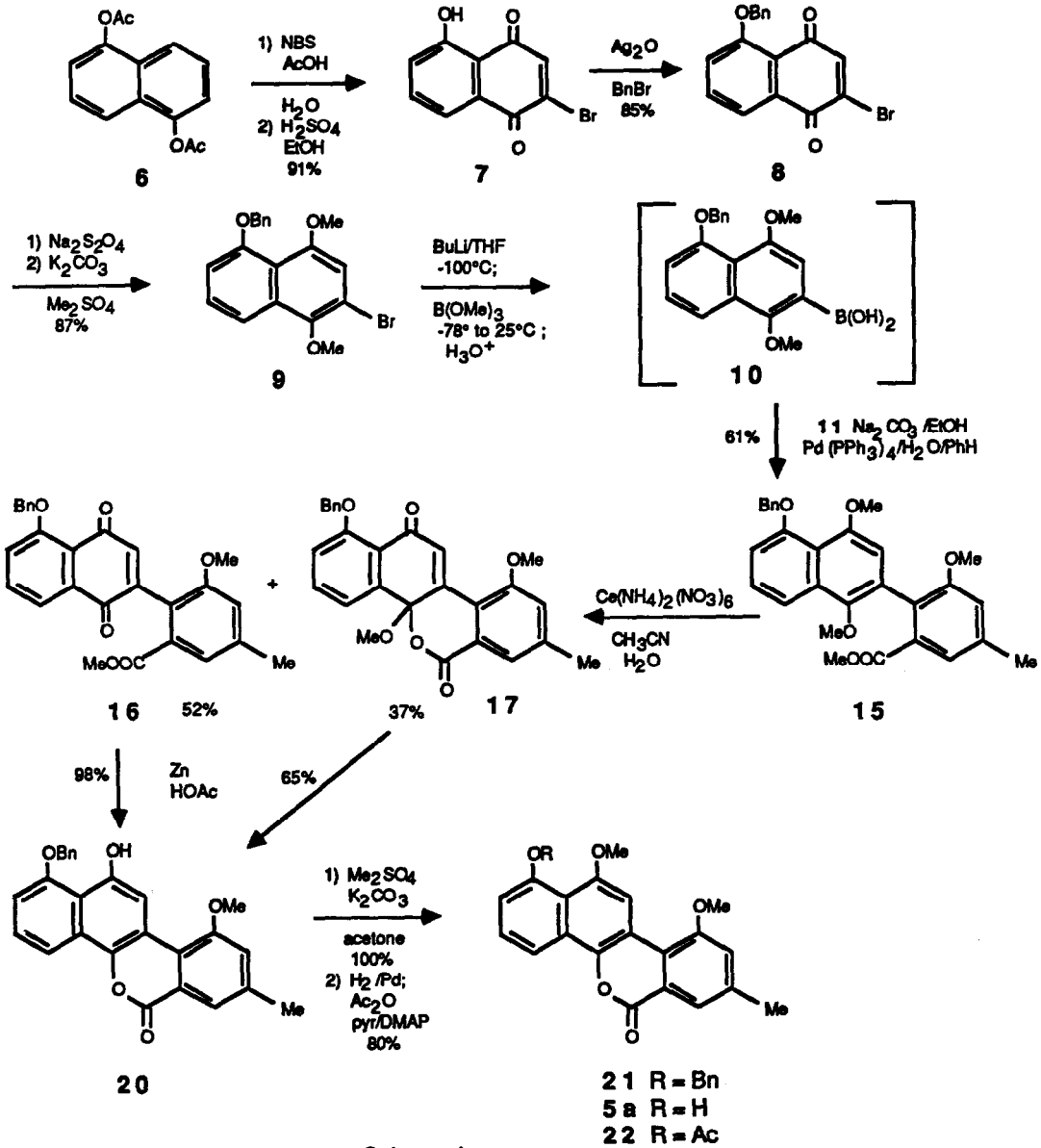
12 **13**

Coupling of **10** with **11** using $Pd(PPh_3)_4$ and Na_2CO_3 in aqueous ethanol/benzene gave the desired biaryl **15** (mp 169.5-170.5°C) in 61% yield.[14] This compound has all the required atoms in the skeleton of **5a** and only minor transformations remained. Oxidative dealkylation[15] of the quinone dimethyl ether of **15** using ceric ammonium nitrate in aqueous acetonitrile afforded a mixture of two compounds which were easily separated by flash chromatography and shown to be the desired quinone **16** (52%, mp 171-3°C) and the quinone monoketal **17** (37%, mp 226-8°C) by virtue of their spectroscopic data.[16] Presumably an intermediate in the oxidation of **15**, e.g. the radical cation **18**, is trapped intramolecularly by the ester to give **19** which is then converted in several steps to **17**,



18 **19** **17**

which is stable under the reaction conditions. Since both of these compounds can be taken on to **5a**, this formation of **17** is more of a curiosity than a nuisance. Treatment of either **16** or **17** with zinc in acetic acid produced the desired hydroxylactone **20** (mp 234-7°C) in 98% and 65% yield, respectively. Methylation of the free phenol of **20** gave a quantitative yield of the ether **21** (mp 219-222C) which was hydrogenolyzed in 85% yield to give **5a**, the desired aglycone. The high field ^1H NMR of **5a** was analogous to that reported for the natural materials (minus the sugar resonances) and that of the acetate **22** (prepared in 87% yield) matched the reported spectrum,[2c] thus confirming the structure.



Scheme I

Thus we have completed a short, efficient synthesis of the aglycone 5a which should be applicable to the V and E series as well.[17]

Acknowledgement: We thank the National Institutes of Health (GM31349) for generous support.

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14. In one preparation, we obtained in addition to a 53% yield of **15**, a 33% yield of debenzylated compound corresponding to **15**. On benzylation it afforded **15** and thus increases the overall yield of this key biaryl intermediate.
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16. Spectral data. **16**: mp 171-3°C; IR: 1654, 1714 cm^{-1}; ^1H NMR: δ 2.42 (3H, s), 3.68 (3H, s), 3.74 (3H, s), 5.30 (2H, s), 6.74 (1H, s), 6.97 (1H, bs), 7.25-7.45 (3H, m), 7.32 (1H, dd, *J*= 8.6, 0.8 Hz), 7.48 (1H, bs), 7.56-7.64 (3H, m), 7.78 (1H, dd, *J*=7.4, 0.8 Hz). **17**: mp 226-8°C; IR: 1653, 1734 cm^{-1}; ^1H NMR: δ 2.46 (3H, s), 2.90 (3H, s), 3.97 (3H, s), 5.28 (2H, ABq), 7.08 (1H, bs), 7.13-7.45 (4H, m), 7.48 (1H, s), 7.58-7.67 (4H, m), 7.70 (1H, bs).
17. a) Since the inception of this project, a similar route to the aglycone of ravidomycin, defucogilvocarcin **5b**, using a Meyers oxazoline-based biaryl coupling has appeared. J. A. Findlay, A. Daljeet, P. J. Murray, and R. N. Rej, *Can. J. Chem.*, **65**, 427 (1987). b) Also very recently another synthesis of **22**, using a Meerwein arylation as the key step, has been published. S. J. F. Macdonald, T. C. McKenzie, and W. D. Hassen, *J. Chem. Soc., Chem. Commun.*, 1528 (1987). For earlier work, see: T. C. McKenzie and W. D. Hassen, *Tetrahedron Lett.*, **28**, 2563 (1987); T. C. McKenzie, W. D. Hassen and S. J. F. Macdonald, *Ibid.*, **28**, 5435 (1987). c) For a different approach, see: L. R. McGee, Y.-C. Tse-Dihn, G. M. Cole, and P. N. Confalone, *191st ACS National Meeting*, New York, ORGN 195 (1986).
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