

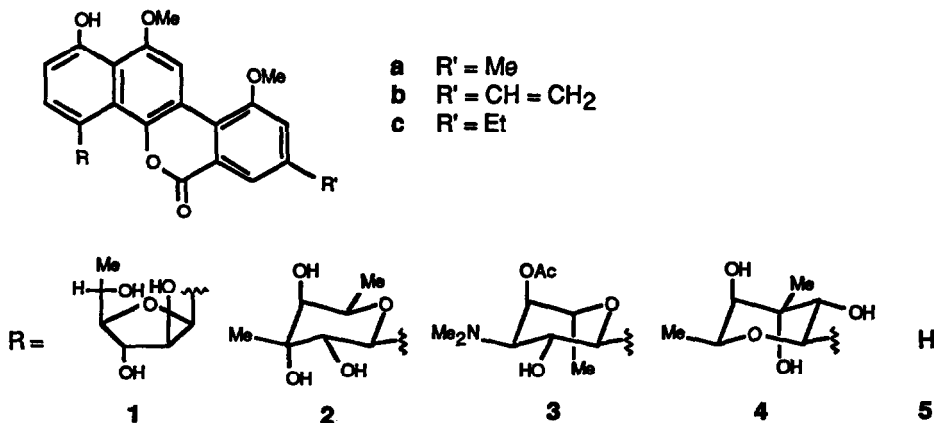
TOTAL SYNTHESIS OF THE AGLYCONE OF THE 8-METHYL BENZONAPHTHOPYRONE ANTIBIOTICS,
GILVOCARCIN M, VIRENOMYCIN M, AND ALBACARCIN M

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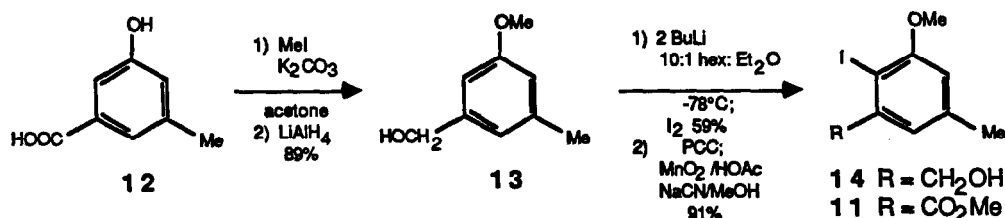
Abstract: A short, convergent synthesis of the aglycone 5a of the 8-methyl benzonaphthopyrone antibiotics is described which utilizes as a key step a Suzuki biaryl coupling.

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 albaccarcin M and V, 4ab.^{5,6} Recent reports^{5cd} that albaccarcin M and V 4ab both have good antitumor (P388) activity (V being about twice as potent as M) seems to contradict an earlier report⁷ 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 D).

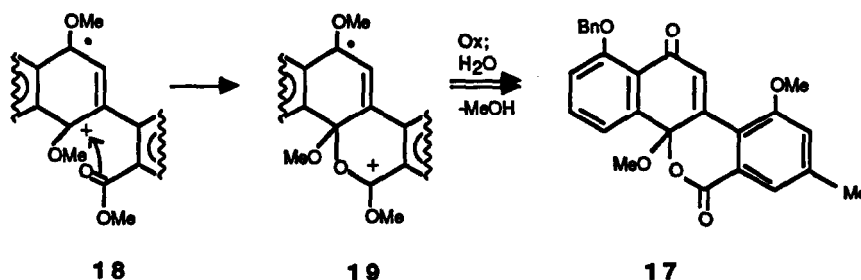


Some time ago we described our work on the mechanism of the conversion of 1,5-diacetoxynaphthalene 6 into 2-bromo-5-hydroxynaphthoquinone 7, which proceeds in two steps in greater than 90% yield.^{8b} Benzoylation of

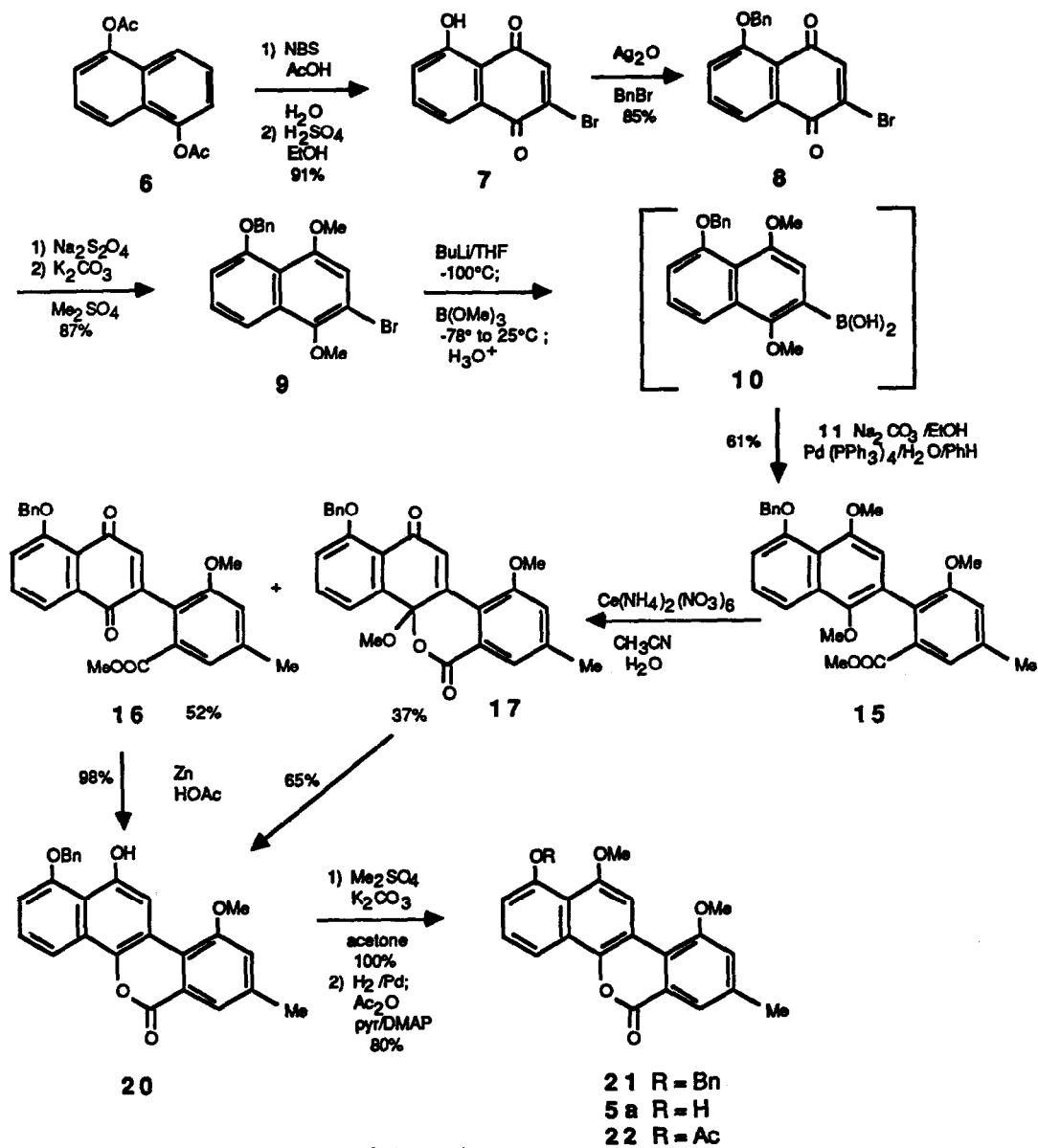
the phenol produced in 85% yield the ether **8** (mp 125°C) which was reduced and dimethylated to give the bromotrialkoxynaphthalene **9** (mp 86-7°C) in 87% yield.^{9,10} Formation of the boronic acid **10** from **9** was accomplished as follows: treatment of **9** with *n*-butyllithium in THF at -100°C 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/K₂CO₃) followed by reduction (LiAlH₄) 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 Corey¹³ (MnO₂/NaCN/HOAc/MeOH) furnished **11** in 91% overall yield.



Coupling of **10** with **11** using Pd(PPh₃)₄ and Na₂CO₃ 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 dealkylation¹⁵ 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**,



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 219-222°C) 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

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References and Notes

1. UCLA Gold Shield Faculty Awardee 1986-1988; Glenn T. Seaborg Awardee 1987.
2. a) K. Hatano, E. Higashide, M. Shibata, Y. Kameda, S. Horii, and K. Mizuno, *Agric. Biol. Chem.*, **44**, 1157 (1980). b) H. Nakano, Y. Matsuda, K. Ito, S. Ohkubo, M. Morimoto, and F. Tomita, *J. Antibiot.*, **34**, 266 (1981). c) K. Takahashi, M. Yoshida, F. Tomita, and K. Shirahata, *Ibid.*, **34**, 271 (1981). d) D. M. Balitz, F. A. O'Herron, J. Bush, D. M. Vyas, D. E. Nettleton, R. E. Grulich, W. T. Bradner, T. W. Doyle, E. Arnold, and J. Clardy, *Ibid.*, **34**, 1544 (1981). e) N. Hirayama, K. Takahashi, K. Shirahata, Y. Ohashi, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, **54**, 1338 (1981). f) T. C. Jain, G. C. Simolike, and L. M. Jackman, *Tetrahedron*, **39**, 599 (1983).
3. a) F. Strelitz, H. Flon, and I. N. Asheshov, *J. Bacteriol.*, **69**, 280 (1955). b) U. Weiss, K. Yoshihira, R. J. Highet, R. J. White, and T. T. Wei, *J. Antibiot.*, **35**, 1194 (1982). c) M. K. Kudina, V. V. Kulyaeva, N. P. Potapova, L. M. Rubasheva, T. S. Maksimova, M. G. Brazhnikova, and B. V. Rozynov, *Antibiotiki (Moscow)*, **27**, 507 (1982). d) M. G. Brazhnikova, M. K. Kudina, V. V. Kulyaeva, N. P. Potapova, L. M. Rubasheva, B. V. Rozynov, and G. Horvath, *Ibid.*, **29**, 884 (1984).
4. J. A. Findlay, J.-S. Liu, and L. Radics, *Can. J. Chem.*, **59**, 3018 (1981); **61**, 323 (1983).
5. a) W. T. Bradner, J. A. Matson, J. A. Bush, R. W. Myllymaki, and W. C. Rose, *Proc. Int. Congr. Chemother.*, **13th**, 16, 284/203-284/204 (1983). b) J. A. Bush, J. A. Matson, T. W. Doyle, and W. T. Bradner, *Proc. XXIII ICAAC*, Abst. 218 (1983). c) J. A. Matson, R. W. Myllymaki, T. W. Doyle, and J. A. Bush, *US 4,461,831* (1984); *Chem. Abs.*, **102**, 4456a (1985). d) T. W. Doyle, "Antineoplastic Agents," Chap. 15, in "Annual Reports in Medicinal Chemistry," Vol. 19, Ed. D. M. Bailey, Acad. Press, New York, 1984, pp. 141-2.
6. It is interesting that the structures reported for the virenomyocins (chrysomycins) **2**, and the albacarcins, **4**, are enantiomeric, the sugars being mirror images of each other.
7. R. K. Elespuru and S. K. Gonda, *Science*, **223**, 69 (1984).
8. a) M. E. Jung and J. A. Hagenah, *J. Org. Chem.*, **52**, 1889 (1987) and references therein. b) M. E. Jung and J. A. Hagenah, *Ibid.*, **48**, 5359 (1983).
9. J. A. Hagenah, Ph.D. dissertation, UCLA, 1984. A similar preparation of the trimethyl ether has been published.^{8a}
10. Satisfactory spectral data (NMR, IR, HRMS or analysis) have been obtained for all new compounds reported.
11. For a recent review, see: A. Suzuki, *Pure Appl. Chem.*, **57**, 1749 (1985).
12. a) F. A. Turner and J. E. Gearien, *J. Org. Chem.*, **24**, 1952 (1959). b) H. Mühlemann, *Pharm. Acta Helv.*, **26**, 204 (1951).
13. E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).
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.
15. a) P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, **41**, 3627 (1976). b) L. Syper, K. Kloc, J. Mlochowski, and S. Zdzislaw, *Synthesis*, 521 (1979).
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).
18. After this manuscript had been accepted for publication, another synthesis of **5b**, closely related to the Findlay route, appeared.^{17a} A. D. Patten, N. H. Nguyen, and S. J. Danishefsky, *J. Org. Chem.*, **53**, 1003 (1988).

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