Pergamon

Tetrahedron Letters, Vol. 37, No. 9, pp. 1367-1370, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00055-X

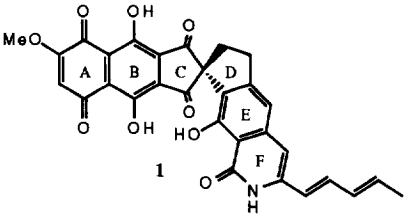
Palladium Catalyzed Cross–Coupling Acylation Approach to the Antitumor Antibiotic Fredericamycin A

P. Andrew Evans* **and Thomas A. Brandt**

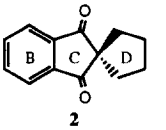
Lammot du Pont Laboratory, Department of Chemistry and Biochemistry,
University of Delaware, Newark, DE 19716.

Abstract: *The palladium catalyzed cross-coupling of the organozinc reagent derived from 2-bromobenzaldehyde ethylene ketal* ***4*** *with the acyl chlorides* ***5*** *and* ***8*** *provides an expeditious route to the BCD* ***2*** *and BCDE* ***3*** *ring systems of Fredericamycin A* ***1****.*

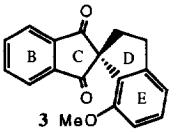
Fredericamycin A **1** (NSC-305263), a quinone antitumor antibiotic, is the major component present in a fermentation broth of the strain *Streptomyces griseus* (FCRC-48) isolated from a soil sample in Frederick, Maryland by Pandey and coworkers in 1981.[1] FM-A **1** has a hexacyclic structure with a novel spiro[4.4]nonane moiety linking the naphthoquinone and isoquinolone subunits. The unique quaternary stereogenic center in the spiro[4.4]nonane is a function of the asymmetry created by the remote methoxy group in the A ring of the naphthoquinone subunit.[2] *X*-ray crystallography was used to determine the structure after spectroscopic studies failed to resolve the tautomeric structures.[3] FM-A **1** possesses both potent *in vitro* cytotoxic activity and *in vivo* antitumor activity. Preliminary studies aimed at elucidating the mode of action of FMA **1**, while still inconclusive, have in part attributed the biological activity to reversible inhibition of the DNA processing enzymes topoisomerase I, II and DNA polymerase α.[4]



1



2

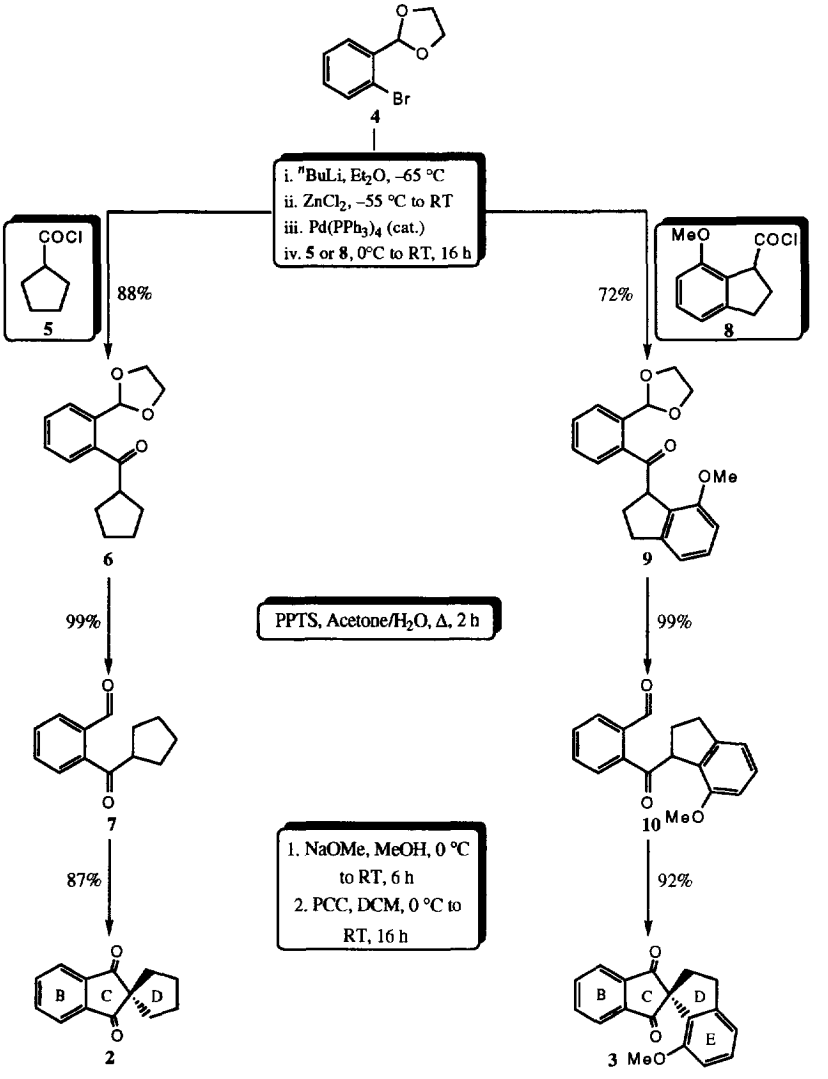


There has been considerable effort aimed at synthesizing this molecule, particularly with respect to the spiro[4.4]nonane system. However, despite exhaustive synthetic studies[5,6] a practical synthesis of this extremely important molecule has not been forthcoming. Therefore, potent antitumor activity and the unusual mode of action coupled with the need for an expeditious route to this important molecule provides the incentive for further synthetic studies.

We now report that the key spiro[4.4]nonane system of FM-A **1** can be readily assembled *via* a modified Negishi palladium catalyzed cross-coupling acylation reaction.[7,8] The palladium mediated cross coupling reaction of organozinc reagents with acyl chlorides provides an efficient route to a variety of

ketones. The advantage of this strategy, is that the newly formed C-C bond is at the correct oxidation state, thus minimizing the capricious oxidation chemistry associated with FM-A **1**.[5f] Furthermore, the methodology is inherently versatile and tolerant of an array of sensitive functionality.

Scheme 1



Halogen metal exchange of 2-bromobenzaldehyde ethylene ketal **4** with *n*-butyllithium in diethyl ether afforded the aryllithium, which was transmetalated with zinc chloride to afford the corresponding organozinc species. Treatment of the aryl organozinc species with the acyl chloride **5** or **8**[9] in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) furnished the aryl ketones **6** and **9** in 88% and 72% yield respectively (**Scheme 1**).[10] The coupling was particularly amenable to

scale-up and sensitive to the quality of the zinc chloride.[11,12] Deprotection of the cyclic ketals **6** and **9** with pyridinium *p*-toluenesulfonate (PPTS) furnished the corresponding aldehydes **7** and **10** in quantitative yields.[10] Treatment of the keto-aldehydes **7** and **10** with catalytic sodium methoxide in methanol to effect the intramolecular aldol reaction, analogous to Boger and Jacobson in their approach to FM-A **1**,[5f] afforded the cyclized adducts which after an aqueous work-up were oxidized with pyridinium chlorochromate to furnish the model spiro[4.4]nonane systems **2** and **3** in 87% and 92% yield.[10] This represents an overall yield of 76% and 66% for the 4 step reaction sequence from the acyl chlorides **5** and **8** to the BCD **2** and BCDE **3** model systems respectively. The BCDE **3** ring system has been used extensively as a model for synthetic studies directed towards the natural product. The novel palladium catalyzed cross-coupling acylation approach outlined herein represents one of the most versatile and efficient methods available for constructing the spirocyclic moiety of FM-A **1**.[6]

In conclusion, we have developed a practical and efficient synthetic strategy for the synthesis of the spiro[4.4]nonane system of FM-A **1** using a palladium catalyzed cross-coupling acylation reaction. This method is currently being applied to more advanced systems applicable to a synthesis of FM-A **1**.

Acknowledgments

We thank the University of Delaware Research Foundation and Zeneca Pharmaceuticals (Wilmington) for generous financial support. We also thank Professor Philip Fuchs for stimulating discussions.

References and Footnotes

1. Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389.

2. For an enantioselective approach to FM-A **1**, see: Trypke, W.; Steigel, A.; Braun, M. *Synlett* **1992**, 827. Boger and coworkers have recently demonstrated through resolution, that the enantiomers of FM-A **1** have almost identical cytotoxic potency *in vitro* against the L1210 tumor cell line.[5f]

3. Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478.

4. (a) Dalal, N. S.; Shi, X. *Biochemistry* **1989**, *28*, 748. (b) Latham, M. D.; King, C. K.; Gorycki, P.; Macdonald, T. L.; Ross, W. E. *Cancer Chemother. Pharmacol.* **1989**, *24*, 167 and references therein.

5. Total syntheses: (a) Kelly, T. R.; Armstrong-Chong, R. J.; Ohashi, N.; Bell, S. H. *J. Am. Chem. Soc.* **1986**, *108*, 7100. (b) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y. -J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Chem. Soc., Chem. Commun.* **1992**, 1489. (c) Rama Rao, A. V.; Singh, A. K.; Rao, B. V.; Reddy, K. M. *Tetrahedron Lett.* **1993**, *34*, 2665. (d) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Soc. Chim. Fr.* **1993**, *130*, 447. (e) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921. (f) Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839.

6. Fredericamycin A ABCDE ring system and simplified skeletons, see: (a) Rama Rao, A. V.; Reddy, D. R.; Deshpande, V. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1119. (b) Kende, A. S.; Ebetino, F. H.; Ohta, T. *Tetrahedron Lett.* **1985**, *26*, 3063. (c) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 4725. (d) Braun, M.; Veith, R. *Tetrahedron Lett.* **1986**, *27*, 179. (e) Bennett, S. M.;

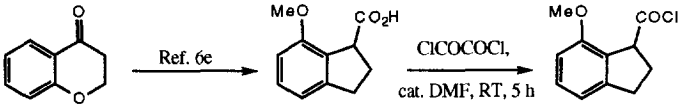
Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878. (f) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1986**, *27*, 1983. (g) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171. (h) Mehta, G.; Subrahmanyam, D. *Tetrahedron Lett.* **1987**, *28*, 479. (i) Naik, S. N.; Pandey, B.; Ayyangar, N. R. *Synth. Commun.* **1988**, *18*, 633. (j) Rama Rao, A. V.; Rao, B. V.; Reddy, D. R.; Singh, A. K. *J. Chem. Soc., Chem. Commun.* **1989**, 400. (k) Toyota, M.; Terashima, S. *Tetrahedron Lett.* **1989**, *30*, 829. (l) Boger, D. L.; Jacobson, I. C. *Tetrahedron Lett.* **1989**, *30*, 2037. (m) Aiden, I. S.; Narasimhan, N. S. *Tetrahedron Lett.* **1989**, *30*, 5323. (n) Watanabe, M.; Morimoto, H.; Furukawa, S. *Heterocycles* **1993**, *36*, 2681 and pertinent references cited therein.

7. Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T. *Tetrahedron Lett.* **1983**, *24*, 5181.

8. Evans, P. A.; Nelson, J. D.; Stanley, A. L. *J. Org. Chem.* **1995**, *60*, 2298.

9. The carboxylic acid **12** was prepared *via* a 5 step literature procedure from commercially available 4-chromanone **11** (**Scheme 2**).[6e] Treatment of the carboxylic acid **12** with oxalyl chloride and a catalytic amount of dimethylformamide furnished the acid chloride **8** in 97% yield.

Scheme 2



11 **12** **8**

10. All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}C NMR) and analytical (HRMS) data in accord with the assigned structure.

11. Commercial zinc chloride in diethyl ether was found to be significantly inferior in this reaction.

12. Experimental Procedure for the Cross-Coupling Acylation Reaction: 2-Bromobenzaldehyde ethylene ketal **4** (1.262 g, 5.5 mmol) was dissolved in anhydrous diethyl ether (22 ml) and cooled with stirring to –70 °C. *n*-Butyllithium (2.65 ml, 6.63 mmol, 2.5 M soln. in hexanes) was then added dropwise keeping the internal temperature ≤–65 °C and stirred for 1 hour forming a yellow solution. Zinc chloride (0.917 g, 6.73 mmol) was flame dried under high vacuum and suspended in anhydrous ether (20 ml). The freshly prepared zinc chloride solution was cooled to 0 °C and added dropwise, keeping the internal temperature ≤–55 °C. The reaction mixture was then allowed to warm to room temperature during which a white precipitate formed. After 1 hour the reaction mixture was cooled to 0 °C and tetrakis(triphenylphosphine) palladium(0) (0.295 g, 5 mol%) was added followed by the dropwise addition of the acyl chloride **8** (1.054 g, 5.00 mmol) in anhydrous ether (14 ml) *via* Teflon cannula. The reaction mixture was then allowed to warm to room temperature and stirred for *ca.* 19 hours affording a yellow colored solution, which was poured into a mixture of saturated $NaHCO_3$ solution (100 ml) and ethyl acetate (50 ml) shaken and separated. The aqueous phase was then back-extracted with ethyl acetate (2 x 25 ml). The organic layers were combined, washed with saturated NaCl solution (50 ml), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with ethyl acetate/hexane 1 : 4) furnished **9** (1.174 g, 72%) as a pale yellow colored solid; mp 75-78 °C.

(*Received in USA* 30 *November* 1995; *accepted* 18 *December* 1995)