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Selective Synthesis of the *para*-Quinone Region of Geldanamycin

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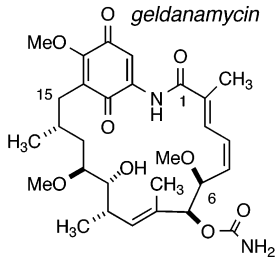
ABSTRACT

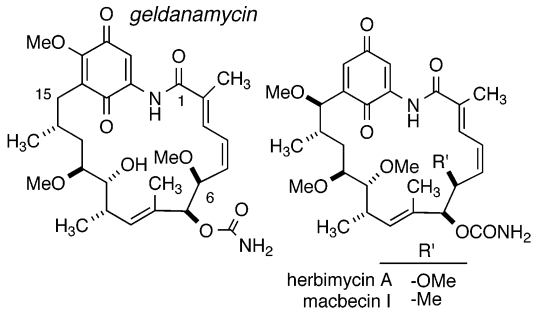


The quinone portion of the ansamycin geldanamycin was made with complete selectivity from the 1,4-dihydroquinone generated from a 1,4-bis-methoxymethyl (MOM) ether intermediate. Palladium catalysis with air gave the desired product in 98% isolated yield. The structure was established using NMR, UV, and X-ray analysis with comparisons to geldanamycin, *ortho*-quino-geldanamycin and a model compound.

The total synthesis of the antitumor antibiotic geldanamycin (GA) was recently reported.[1] Key steps included the development of two asymmetric glycolate aldol reactions and a dealkylative quinone-forming step with nitric acid. This compound has generated considerable interest due to its ability to bind heat shock protein 90 (Hsp90) and lower cellular levels of various oncogenic kinases.[2] Geldanamycin is the most potent member of the ansamycin family, which includes both the herbimycins and macbecins (Scheme 1). 17-Allylamino-GA, a semisynthetic analogue, is currently in clinical trials.[3]

Geldanamycin presents a unique challenge in that it possesses a trisubstituted quinone with a methoxyl group at C17. The trimethoxylactam precursor employed in the synthesis of GA provided some unexpected results. Unlike the dimethoxy precursors employed for the synthesis of the other ansamycins,[4] the trimethoxylactam precursor for GA **1** gave either an unusual azaquinone product or decomposition upon treatment with the standard oxidants.[5] Only with nitric acid was GA generated as a minor component along with the nonnatural *ortho*-quinone product **2** in a 1:10 ratio (Scheme 2). The low yield and poor selectivity of the dealkylative approach prompted the investigation of a new route to the desired methoxy-*p*-quinone portion of GA using

Scheme 1



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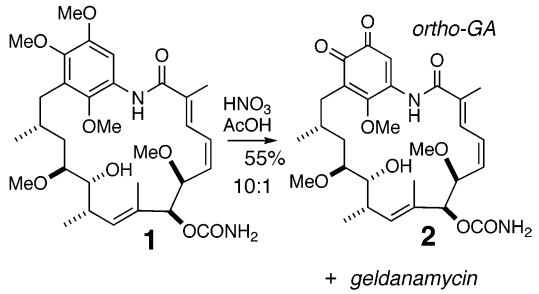
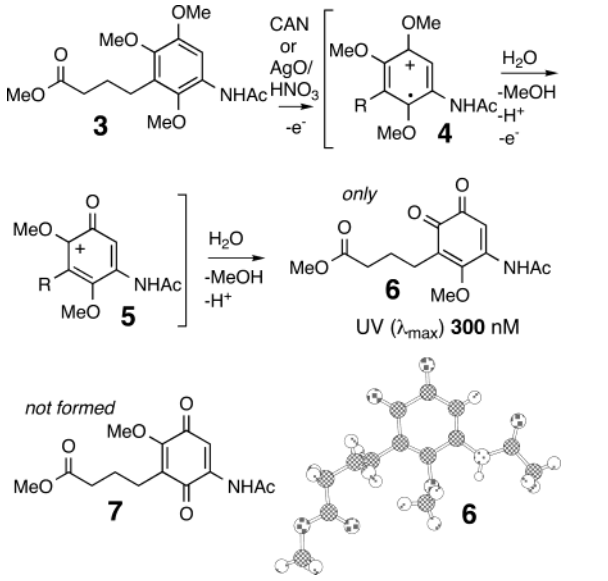
Scheme 2



Scheme 3



phenol and dihydroquinone intermediates. The new approach establishes, for the first time, a selective route to the GA quinone, opening up a new route to GA and analogues of this important template. In addition, the structure of the methoxyquinone product is unambiguously established using NMR, UV, and X-ray analysis with comparison to GA, *ortho*-quino GA **2**, and a simple model compound.

As a model for the GA synthesis, trimethoxy benzamide **3** was produced and explored for dealkylative quinone formation (Scheme 3). An early GA-model study reported by Schill and co-workers employed a trimethoxy substrate that was dealkylated to the hydroxyquinone.[6] The α,β-unsaturated precursor to **3** was made from the corresponding benzaldehyde, which was described in a previous report.[7] Treatment with the standard oxidants, ceric ammonium nitrate (CAN)[8] or silver oxide, rapidly produced quinone product in essentially quanitative isolated yields. CoF_2 and MnO_2 gave lower yields of product, 50 and 25%, respectively.[9] Hypervalent iodine-based oxidants failed to give product in this case.[10] Unlike lactam **1** where conformational effects appear to govern the reaction outcome, no trace of aza-quinone was detected with **3**. In this case, one-electron removal gives radical cation **4** where the *p*-methoxyls stabilize the charge through lone-pair donation. Addition of water, loss of methanol, a proton, and an additional electron gives intermediate **5**.[11] Water can then attack either ortho or para to the carbonyl prior to quinone formation. In contrast to previous reports of 1,2,4-trimethoxybenzenes where *para*-quinone products were obtained,[5] quinone **6** was also shown to be the unexpected *ortho*-quinone. Single-crystal X-ray analysis unambiguously identified the structure as shown.[12] UV data of **6** was also obtained and compared to GA and *ortho*-quino-GA **2**. The λ_{max} at 300 nm for the $\pi-\pi^*$ ($CHCl_3$, K-band) of **6** is very close to the energy of this transition for **2** (λ_{max} 303 nm).[13] The corresponding value for GA is much higher at 311 nm. Attack at the ortho position may be due to steric factors or destabilization of the allylic cation at the para position of **5**. The amide may force the methyl ether at this position to adopt a conformation that does not promote lone-pair donation in this case.

The shortcomings of the dealkylation route prompted the investigation of the phenol and dihydroquinone strategies. An unsaturated amide with additional functionality was considered to be an improved model for GA. The route to the *p*-di-MOM-protected hydroquinone began with methoxyhydroquinone **8** (Scheme 4). Protection, formylation,[14] and nitration gave **10a** (R = MOM) in high overall yield.

(3) GA derivatives: (a) Rinehart, K. L.; McMillan, M. W.; Witty, T. R.; Tipton, C. D.; Shield, L. S. Li, L. H.; Reusser, F. *Bioorg. Chem.* **1977**, *6*, 353. (b) Schnur, R. C.; Corman, M. L *J. Org. Chem.* **1994**, *59*, 2581. (c) Schnur, R. C.; Corman, M. L.; Gallaschun, R. J.; Cooper, B. A.; Dee, M. F.; Doty, J. L.; Muzzi, M. L.; Moyer, J. D.; DiOrio, C. I.; Barbacci, E. G.; Miller, P. E.; O'Brien, A. T.; Morin, M. J.; Foster, B. A.; Pollack, V. A.; Savage, D. M.; Sloan, D. E.; Pustilnik, L. R.; Moyer, M. P. *J. Med. Chem.* **1995**, *38*, 3806.

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(5) Trimethoxy substrates normally give *p*-quinone products: (a) Cameron, D. W.; Feutrill, G. I.; Patti, A. F.; Perlmutter, P.; Sefton, M. A. *Aust. J. Chem.* **1982**, *35*, 1501. (b) Witiak, D. T.; Loper, J. T.; Ananthan, S.; Almerico, A. M.; Verhoef, V. L.; Filppi, J. A. *J. Med. Chem.* **1989**, *32*, 1636. (c) Kozuka, T.; *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2415. (d) Cheng, A. C.; Castagnoli, N. *J. Med. Chem.* **1984**, *27*, 513. (e) Michael, J. P.; Cirillo, P. F.; Denner, L.; Hosken, G. D.; Howard, A. S.; Tinkler, O. S. *Tetrahedron* **1990**, *46*, 7923. (f) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745. (g) Kitahara, Y.; Nakahara, S.; Shimizu, M.; Yonezawa, T.; Kubo, A. *Heterocycles* **1993**, *36*, 1909.

(6) Schill, G.; Merkel, C.; Zürcher, C. *Liebigs Ann. Chem.* **1977**, 288. Trimethoxyamide was converted to the hydroxyquinone with boron tribromide and alkylated with diazomethane. These conditions led only to decomposition with **1**, and other precursors led to GA.

(7) Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett.* **2001**, *3*, 259.

(8) Krohn, K.; Frese, P.; Flörke, U. *Chem. Eur. J.* **2000**, *6*, 3887.

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(10) Tohma, H.; Morioka, H.; Harayama, Y.; Hashizume, M.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6899.

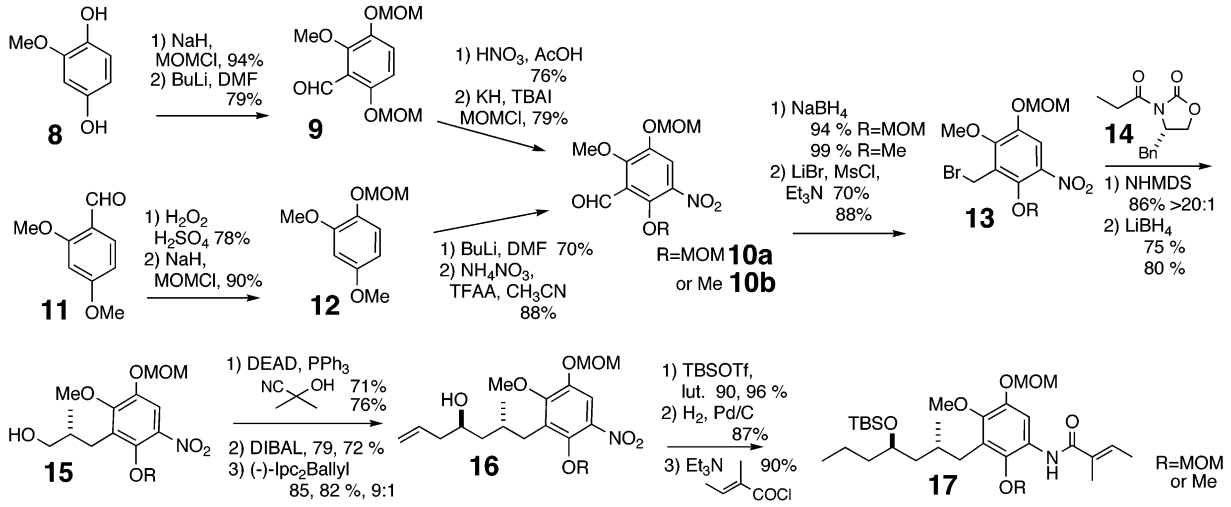
(11) For a recent mechanistic investigation of dealkylative quinone formation, see: Rathore, R.; Bosch, E.; Kochi, J. K. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1157.

(12) X-ray data: orthorhombic space group *P*212121, $a = 7.359$, $b = 8.645$, $c = 21.12$ Å, independent data $R1 = 0.038$. The Supporting Information contains full details.

(13) For a discussion of UV−structure correlation, see: *Spectrometric Identification of Organic Compounds*, 5th ed.; Silverstein, R. M., Bassler, G. C., Morrill, T. C., Eds.; John Wiley & Sons: New York, 1991; Chapter 7.

(14) Gilman, H.; Thirtle, J. R. *J. Am. Chem. Soc.* **1944**, *66*, 858.

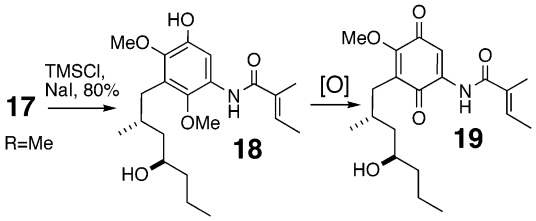
Scheme 4



Under these conditions, the extra protection step was needed because the C3-MOM group was removed during the nitration step. For the phenol approach, 2,4-dimethoxybenzaldehyde **11** underwent Baeyer−Villiger oxidation,[15] protection, formylation, and nitration with ammonium nitrate in trifluoroacetic anhydride[16] to give **10b** (R = Me). Surprisingly, use of ammonium nitrate with **9** as with nitric acid, also led to MOM removal. Alternative conditions for nitration at this point gave multiple products or lower yields.[17] These intermediates were separately converted to the benzyl bromides **13** using sodium borohydride and MsCl in the presence of lithium bromide and triethylamine according to Kajiwara's conditions.[18] Use of standard conditions, PBr_3 and pyridine or Ph_3P with carbon tetrabromide, led to MOM removal or low yield. Evans asymmetric alkylation with *S*-oxazolidinone **14** proceeded with high yield and selectivity.[19] Reduction with lithium borohydride provided the alcohols **15** (R = MOM, Me). Mitsunobu homologation, with acetone cyanohydrin under the conditions of Ito,[20] gave the intermediate cyano compounds. Reduction to the aldehydes, with DIBAL followed by addition of water, gave the corresponding aldehydes. Asymmetric allylborane addition following the conditions of Brown[21] gave homoallylic alcohols **16**. Protection as the TBS ether, reduction of the arylnitro group to the aniline, and treatment with tigloyl chloride[22] gave the unsaturated benzamides **17** (R = MOM, Me).

Dimethoxy **17** (R = Me) was treated with TMSCl and sodium iodide to give the phenol **18** (Table 1).[23] The deprotection was accompanied by TBS ether removal. The standard oxidants in this case,[24] CAN and DDQ (2,3-

Table 1. Oxidation Conditions for Quinone Formation



entry	reagent	% yield[a]
1	CAN	19
2	DDQ	20
3	AgO/HNO_3	b
4	HNO_3/AcOH	b
5	PhIO	15
6	$CuCl_2/O_2$	
7	Salacomine/O_2	27
8	Co(salen)/O_2	26
9	$K_3Fe(CN)_6$	14

[a] Isolated yield following silica gel chromatography. [b] Multiple products were obtained without formation of **19**.

(15) Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, *49*, 4740.
(16) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056.
(17) (a) $NO_2^+BF_4^-$: Dwyer, C. L.; Holzapfel, C. W. *Tetrahedron* **1998**, *54*, 7843. (b) $Cu(NO_3)_2 \cdot (H_2O)_{2.5}$: Boger, D. L.; Garbaccio, R. M. *J. Org. Chem.* **1999**, *64*, 8350. (c) Nitropyridinium: Olah, G. A.; Narang, S. C.; Olah, J. A.; Pearson, R. L.; Cupas, C. A. *J. Am. Chem. Soc.* **1980**, *102*, 3507. (d) $La(NO_3)_3$, Ouertani, M.; Girard, P.; Kagan, H. B. *Tetrahedron Lett.* **1982**, *23*, 4315.
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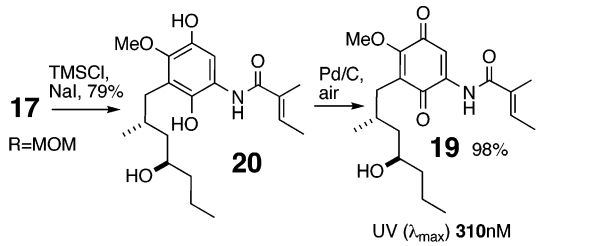
Scheme 5



dichloro-5,6-dicyanoquinone), gave only a very low yield of the desired product **19** (entries 1 and 2). The product **19** was shown to be the *p*-quinone. Spectral comparisons and NMR data are discussed below. Silver oxide and nitric acid gave multiple products without formation of **19** (entries 3 and 4). Iodosobenzene, as used recently for the synthesis of saframycin and longithorone, [25] was also low yielding, producing **19** in only 15% isolated yield (entry 5). At this point, various catalysts with oxygen as oxidant that have been used with more complex substrates were explored (entries 6−8). Copper(II) chloride failed to give product, while salcomine,[17b] used for CC-1065, and Co(salen)[26] again gave only low yields of **19**. Potassium ferricyanide (entry 9) also gave a low yield.

Treatment of di-MOM **17** (R = MOM) with TMSCl and sodium iodide gave dihydroquinone **20** in 79% yield (Scheme 5). Again, the TBS ether was removed. Looking ahead, silyl ether removal at C11 is needed prior to quinone formation in the route to GA. Use of HF·pyridine could be used to selectively remove the TBS ether and maintain the MOM ethers in this case (82%). TBAF and HF·Et_3N were not effective for this transformation. Gratifyingly, it was found that treatment of **20** with catalytic palladium on carbon (10%), following the conditions of Rapoport,[27] with the flask open to air gave quinone **19** in near quantitative yield. The UV spectra showed a λ_{max} at 310 nm consistent with the same $\pi-\pi^*$ band observed for geldanamycin (311 nm). These *p*-quinone UV bands are clearly distinct from the $\pi-\pi^*$ bands seen with the *o*-quinones **2** and **6** (303 and 300 nm, respectively). Additional NMR experiments were also performed to confirm the structure of **19**. DEPT and HETCOR were used to assign the ^{13}C NMR shifts and ^{1}H correlations for **19**. HMBC was then used to establish the connectivity and rule out alternatives. A key observation in this regard was the through-bond coupling observed for the amide hydrogen to the adjacent carbonyl of the quinone. In the alternative *o*-quinone in this case, the amide hydrogen would be found four and five bonds removed from the ring carbonyls and a correlation would not be observed.

A new route to the *p*-quinone portion of geldanamycin has been developed involving dihydroquinone oxidation using 1,4-di-MOM protection. For the first time, selective access to this unique trisubstituted quinone has been achieved. New routes to this important target can now be undertaken with confidence.

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Supporting Information Available: Experimental procedures and characterization, including two-dimensional NMR and X-ray data for **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) (a) Lipshutz, B. H.; Mollard, P.; Pfeiffer, S. S.; Chrisman, W. *J. Am. Chem. Soc.* **2002**, *124*, 14282. (b) With Cu, see: Matsumoto, M.; Kobayashi, H.; Hotta, Y. *Synth. Commun.* **1985**, *15*, 515.

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