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Synthesis of the Left-Hand Portion of Geldanamycin Using an Anti Glycolate Aldol Reaction

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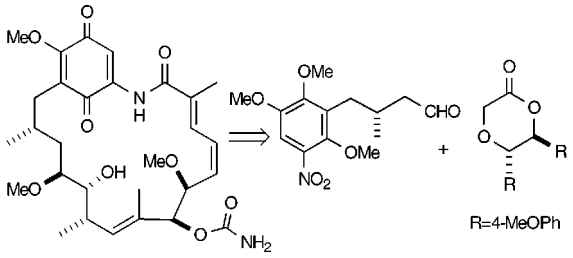
ABSTRACT



A synthesis of the left-hand portion of the ansamycin antitumor natural product geldanamycin is reported. An advanced intermediate incorporates the methoxyquinone precursor as a pentasubstituted benzene with a 10-carbon chain that contains 4 of the 6 stereocenters. The key reaction is a novel anti glycolate aldol reaction with a new diaryl-4-oxapyrone used to generate the C-11, C-12 hydroxy, methoxy functionality.

While the closely related anasamycin antibiotics[1] macbecin I and herbimycin have garnered considerable synthetic attention including total syntheses,[2] no efforts directed toward the original member of the family, geldanamycin,[3] have been reported.[4] These compounds possess numerous and varied biological activities,[5] including great potential as antitumor agents. Geldanamycin, the most potent in the family, shows broad activity with the NCI cell line panel (13 nM) and possesses a unique mode of action.[6] Details of this activity have only recently been uncovered. Geldanamycin binds very tightly to the ATP binding domain of the chaperone heat shock protein 90 (Hsp90), inhibiting its protein folding activity and ATPase activity leading to cell cycle disruption.[7]

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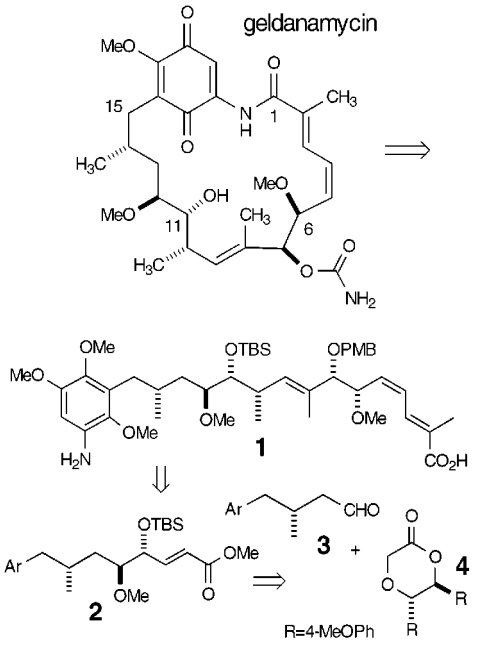
Scheme 1

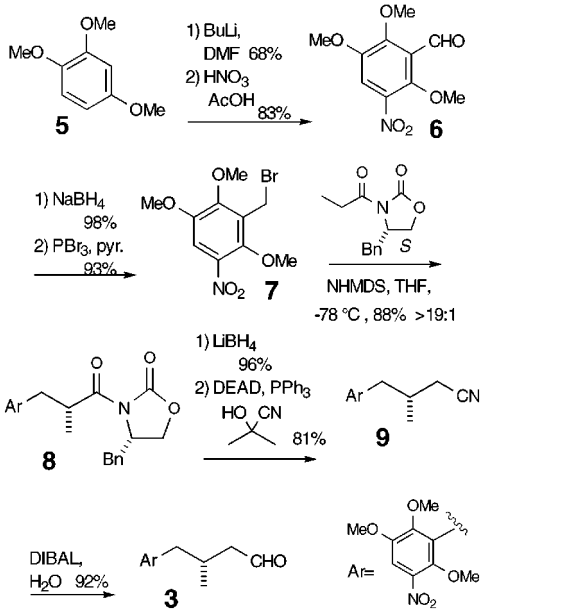


In addition, the crystal structure of the Hsp90−geldanamycin complex suggests modifications that may lead to enhanced activity.[8] Hsp90 binding and inhibition are thought to be responsible for the ability of geldanamycin to significantly and selectively lower levels of various oncogenic tyrosine kinases including v-Src, Bcr/Abl, and ErbB-2.[9] Importantly, levels of serine/threonine-specific kinases, PKA and PKC, remain uneffected. Initially geldanamycin was considered to be a specific kinase inhibitor, yet no direct kinase interaction could be established. These recent findings together with the distinct structure of geldanamycin clearly warrant the development of a total synthesis. We now report the synthesis of the left-hand portion of the molecule that includes an aromatic precursor to the methoxyquinone seco acid **1** and a key asymmetric anti-selective glycolate aldol reaction using diaryl-4-oxapyrone **4** to set the C-11, C-12 hydroxy, methoxy functionality (Scheme 1).

Unlike the herbimycins and macbecin I, the methoxyquinone of geldanamycin requires the use of a pentasubstituted benzene precursor **1** (Scheme 1). The 1,4-disposed methoxyls will be converted to the quinone carbonyls at a later stage.[2] The absence of a benzylic C-15 hydroxyl group in geldanamycin makes the use of a benzyldehyde aldol reaction, a step used previously for herbimycin and macbecin,[2b,c] at that position problematic. Also the C-11 hydroxyl in geldanamycin, not being a methoxyl as with herbimycin A and macbecin I, requires differential protection at the C-11 and C-12 hydroxyls. The C-10 methyl will be introduced through the unsaturated precursor **2** or using the extended Wittig adduct shown below. Aldehyde **3** reacted with the boron enolate of pyrone **4**, an extension of our recently disclosed report, gives the anti aldol product with high selectivity.[10] The new bis-*p*-methoxyphenylpyrone allows for convenient removal following the aldol step. Ceric ammonium nitrate (CAN) can now be used in the presence of the arylnitro group for conversion to **2**.

Aldehyde **3** is constructed starting with 1,2,4-trimethoxybenzene **5** which was formylated and nitrated to give benzaldehyde **6** (Scheme 2).[11] Treatment with sodium

Scheme 2



borohydride produces a benzyl alcohol that was converted to the stable and very hindered bromide **7**.[12] Gratifyingly the Evan's asymmetric alkylation with the *S*-propionyloxazolidinone occurred with high selectivity and yield to produce **8**.[13] Other strategies investigated to set this C-14 methyl stereocenter, asymmetric conjugate cuprate, and

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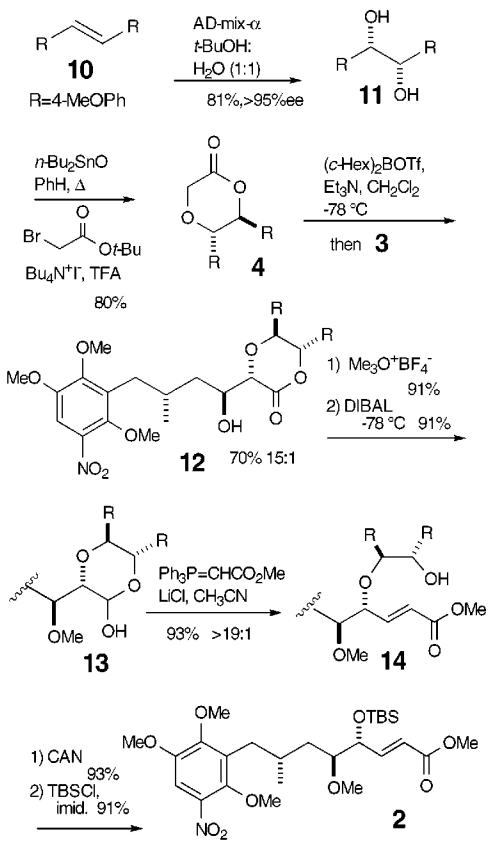
(13) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

diisopinocampeylcrotylborane addition reactions gave low yields and selectivities.[14] The difficulties were most likely due to the steric effect of the bis-*o*-methoxyls, a functionality unique to geldanamycin as mentioned above. The auxiliary was removed by lithium borohydride, and the resultant alcohol was converted to the cyanide **9** under Mitsunobu conditions using acetone cyanohydrin.[15] Reduction with DIBAL followed by exposure to water gave aldehyde **3**.

Synthesis of the new bis-4-methoxyphenylpyrone follows the two step procedure reported previously for the diphenyl substrate (Scheme 3).[10] The trans stilbene **10** was dihydroxy-

Scheme 3



lated with catalytic osmium tetroxide−bis-dihydroquinine complex using Sharpless' AD-mix-α reagent to give *S,S*-**11** in high yield and selectivity.[16] Analysis of a Mosher's ester formed from **11** was used to confirm the enantioselectivity.[17] Pyrone formation using dibutyltin oxide and *tert*-butyl bromoacetate gave **4** in 80% isolated yield.[18] The enolate was formed using dicyclohexylboron triflate and triethylamine at low temperature and treated with aldehyde **3** to generate alcohol **12** following peroxide hydrolysis.[19] The 70% yield was obtained at 1:1.2 aldehyde to enolate stoichiometry. The 15:1 selectivity was determined by ^{1}H NMR. The stereoinduction of the major anti isomer product **12** is in accord with the previous study where the aldehyde approaches the *E*-enolate face, in a closed Zimmerman−Traxler arrangement, opposite to the C-5 pyrone aryl group which is adjacent to the ether oxygen.[10] A crystal structure was solved for the methylated form of alcohol **12** confirming both the aldol stereochemistry and the C-14 methyl stereocenter.[20] Use of an acyclic glycolate as an alternative approach would be problematic in that known auxiliaries generally give syn products through *Z*-enolates.[10,21] Also, asymmetric dihydroxylation with osmium tetroxide works very well for syn diols from *E*-olefins but is not selective for applications with *Z*-alkenes leading to anti diols.[22] In addition, allylmetals are generally limited to *Z*-γ-alkoxy reagents that give syn products.[23] However, a notable exception is a recent indium-mediated allyltin addition of Marshall.[24] To continue, methylation of **12** followed by treatment with DIBAL produced the lactol **13**. The lactol, which is in equilibrium with the hydroxy-aldehyde, reacted with methyl carbethoxymethylidine triphenylphosphorane in high yield generating the *E*-unsaturated ester **14**. The *p*-methoxyphenyl functionality now allowed for easy removal of the pyrone fragment using ceric ammonium nitrate in 93% yield.[25] The *p*-methoxybenzaldehyde byproduct was easily removed by chromatography. While the pyrone is destroyed at this point, it should be noted that it is produced in a catalytic fashion in only two steps from stilbene using the AD-mix reagent. Overall, the process converts the stilbene syn diol to a specific, differentially protected anti diol corresponding to the desired target. Protection of the C-12 hydroxyl as the TBS ether generated the unsaturated ester **2** to finish the sequence.

Coupling with a larger fragment, which represents most of the remaining geldanamycin features, was also facilitated

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(17) Full details of the synthesis and reactivity of the new pyrone will be reported shortly.

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(20) X-ray data: for the methyl ether of **12**, orthorhombic space group $P2_12_12_1$, $a = 9.629(6)$, $b = 17.661(3)$, $c = 19.081(3)$, $B = 24.98(2.13)°$, $V = 3245(2)$ Å, $Z = 4$, independent data 3385 ($R_{int} = 0.0121$) $R_1 = 0.0505$ [$I > 2\sigma(I)$] (see Supporting Information).

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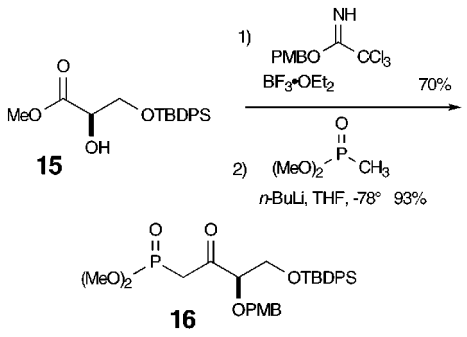
(25) Johansson, R.; Samuelsson, B. *Chem. Commun.* **1984**, 201.

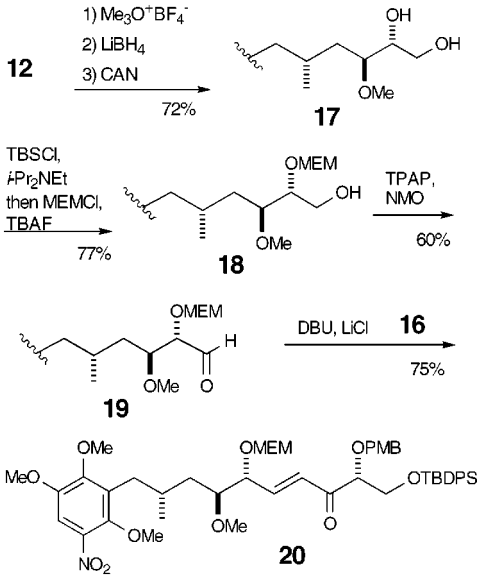
by the aldol intermediate **12**. The requisite phosphonate **16** needed for this strategy was made in two steps from the known protected glycerate methyl ester **15**[26] which was reacted with *p*-methoxybenzyl trichloroacetimidate[27] followed by lithio methylphosphonate addition (Scheme 4).[28]

Scheme 4



Diol **17** was formed by methylation, reduction, and treatment with CAN in high overall yield (Scheme 5). A one pot sequence was developed to generate the protected terminal alcohol **18**.[29] Treatment with TBSCl and Hünig's base followed by addition of methoxyethoxymethyl chloride (MEMCl) and then tetra-*n*-butylammonium fluoride (TBAF) produced **18** in 77% yield in one operation. Oxidation gave aldehyde **19**, which was then subjected to Horner−Emmons coupling with *β*-ketophosphonate **16** under the Roush−Masamune conditions.[30] Enone **20** was isolated in 75% yield. Both **2** and **20** now open up a variety of routes for the completion of the final target. These will include additions to set the methyl C-10 stereocenter and couplings to generate the remaining trisubstituted olefin and the diene amide. The C-10 methyl-trisubstituted olefin region has been troubling in the past ansamycin routes but has been solved using cuprate addition,[2b,g] aldol reaction,[2c] or directed hydroboration.[2a]

Scheme 5



Intermediates **2** and **20** now allow for a number of these and other routes to be explored to develop a more efficient approach to the bottom domain of geldanamycin.

A key piece leading to the synthesis of the important Hsp90 inhibitor geldanamycin has been made. An anti-selective glycolate aldol reaction with a new bis-methoxyphenylpyrone, made using catalytic asymmetric dihydroxylation, was used to set the C-11, C-12 stereocenters with high selectivity. Removal of the pyrone was accomplished using CAN allowing for the production of two key advanced intermediates. Completion of the route and further studies with nonnatural variants will be reported in due course.

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Supporting Information Available: Experimental details, NMR, MS, and X-ray data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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