ORGANIC LETTERS

2002
Vol. 4, No. 20
3549−3552

Total Synthesis of (+)-Geldanamycin and (−)-*o*-Quinogeldanamycin with Use of Asymmetric *Anti*- and *Syn*-Glycolate Aldol Reactions

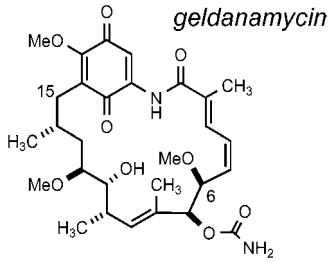
Merritt B. Andrus,* Erik L. Meredith, Bryon L. Simmons, B. B. V. Soma Sekhar, and Erik J. Hicken

Brigham Young University, Department of Chemistry and Biochemistry, C100 BNSN, Provo, Utah 84602-5700

mbandrus@chemdept.byu.edu

Received August 16, 2002

ABSTRACT



Geldanamycin (GA), an antitumor Hsp90 inhibitor, was made for the first time by using an oxidative demethylation reaction as the final step. A biaryldioxanone auxiliary set the *anti* C11–12 hydroxy-methoxy functionality and a methylglycolate auxiliary based on norephedrine was used for the *syn* C6–7 methoxy-urethane. *p*-Quinone-forming oxidants, CAN and AgO, produced an unusual aza-quinone product. Nitric acid gave GA from a trimethoxy precursor in 55% yield as a 1:10 mixture with nonnatural *o*-quino-GA.

Unlike the related anasamycin antibiotics,[1] macbecin I and herbimycin which have received considerable synthetic attention including total syntheses,[2] the synthesis of geldanamycin (*S. hydroscopicus*)[3] has not been reported.[4] These compounds possess various biological activities, including great potential as antitumor agents. Geldanamycin (GA), the most potent family member, shows broad activity with the NCI 60 cell-line panel (13 nM).[5] Its cellular target has only recently been uncovered. GA binds to the ATP binding site of the chaperone heat shock protein 90 (Hsp90), inhibiting its folding and ATPase activity leading to cell cycle disruption.[6] Hsp90 inhibition by geldanamycin significantly and selectively lowers cellular levels of various oncogenic tyrosine kinases including v-Src, Bcr/Abl, and ErbB-2, while the serine/threonine-specific kinases, PKA and PKC, remain unaffected.[7] In addition, recent X-ray structures of the Hsp90·

(1) Rinehart, K. L. *Acc. Chem. Res.* **1972**, *5*, 57.

(2) Herbimycin A: (a) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuda, K. *Tetrahedron Lett.* **1991**, *32*, 6015. Macbecin I: (b) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans.* **1990**, 47. (c) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471. (d) Panek, J. S.; Xu, F.; Rondon, A. C. *J. Am. Chem. Soc.* **1998**, *120*, 4413.

(3) (a) De Boer, C.; Meulman, P. A.; Wnuk, R. J.; Peterson, D. H. *J. Antibiot.* **1970**, *23*, 442. (b) Rinehart, K. L.; Sasaki, K.; Slomp, G.; Grostic, M. F.; Olson, E. C. *J. Am. Chem. Soc.* **1970**, *92*, 7591.

(4) 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. 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. (c) Kuduk, S. D.; Harris, C. R.; Zheng, F. F.; Sepp-Lorenzino, L.; Ouerfelli, Q.; Rosen, N.; Danishefsky, S. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1303.

(5) Whitesell, L.; Shifrin, S. D.; Schwab, G.; Neckers, L. M. *Cancer Res.* **1992**, *52*, 1721.

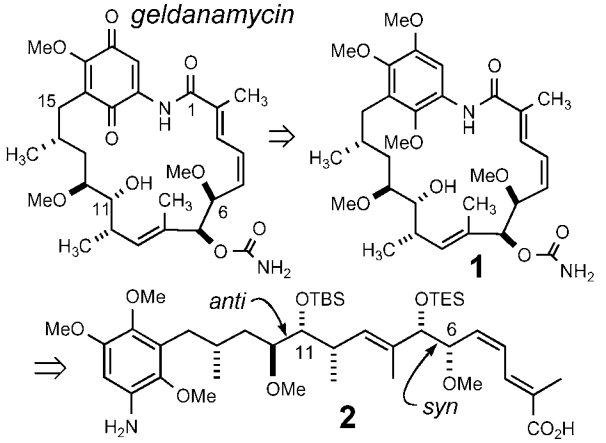
(6) Whitesell, L.; Mimnaugh, E. G.; De Costa, B.; Myers, C. E.; Neckers, L. M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 8324.

(7) Lawrence, D. S.; Niu, J. *Pharmacol. Ther.* **1998**, *77*, 81.

10.1021/ol0267432 CCC: $22.00
Published on Web 09/11/2002

GA complex suggest modifications that may lead to enhanced activity.[8] These findings together with its distinct structural features clearly warrant the development of a total synthesis. We now report the first total synthesis of GA along with *o*-quino-GA using a nitric acid oxidation of trimethoxylactam **1** (Scheme 1). This establishes the absolute stereo-

Scheme 1

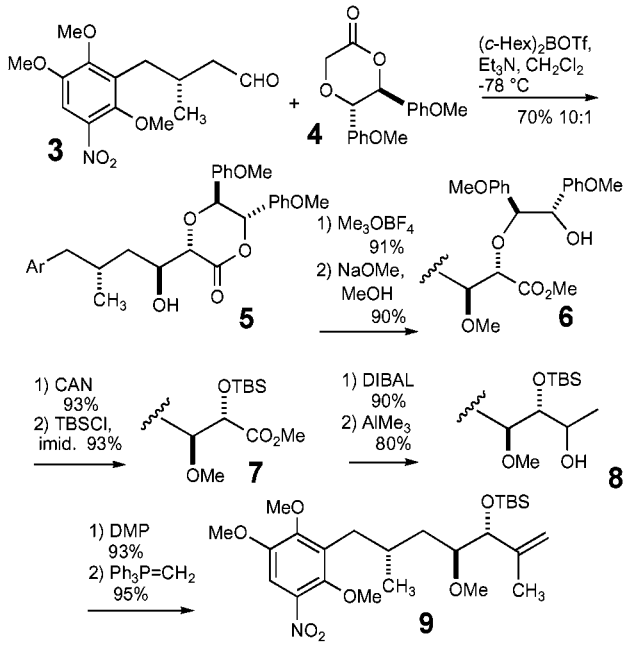


chemistry and resolves the ambiguity of the C14 methyl substituent. The structure of Pavletich indicated an *R* configuration, while that of Pearl was *S* at C14.[8] Key steps to access seco acid **2** include a novel *anti*-selective glycolate aldol reaction using the recently developed diaryldioxanone auxiliary and a new *syn*-selective glycolate aldol using a norephedrine based approach.

Unlike the herbimycins and macbecins, the methoxyquinone of GA requires the use of a pentasubstituted benzene precursor **1** (Scheme 1). On the basis of previous ansamycin syntheses, including other trimethoxybenzenes, oxidative removal of the 1,4-disposed methoxyls at C18,21 of **1** was anticipated to directly generate GA with high selectivity.[2] The lack of a benzylic C15-hydroxyl together with the added hindrance of an additional C17-methoxyl precludes the use of an aldol reaction for GA C14−15 bond formation as employed previously with herbimycin and macbecin.[2b,c] Also, C11 bears a hydroxy group, not a methoxy as with herbimycin and macbecin, thus requiring a distinct approach for formation of the *anti*-C11−12 hydroxy-methoxy functionality.

The previously reported *R*-aldehyde **3** was treated with the boron enolate of *S,S*-bis-4-methoxyphenyldioxanone **4** to generate the *anti*-glycolate aldol adduct **5** in 70% yield with 10:1 selectivity (Scheme 2).[9] A four-step sequence was used to generate the differentially protected *anti*-diol ester **7** in high overall efficiency, using catalytic sodium methoxide

Scheme 2



followed by oxidative benzyl ether removal with CAN (ceric ammonium nitrate).[10] Various options were considered and explored for the installation of the C10 methyl group. Finally, the established route with asymmetric hydroboration was followed.[2] The aldehyde derived from **7** was treated with trimethylaluminum, followed by Dess−Martin periodinane to give a ketone that was treated under Wittig conditions to provide **9**. Removal of the silyl ether and hydroboration gave diol **10** with the C10 methyl possessing the proper *S*-configuration (Scheme 3). Protection of the primary and secondary hydroxyls as *tert*-butyldimethylsilyl (TBS) ethers followed by treatment with aqueous camphor sulfonic acid to remove the primary TBS ether gave a primary alcohol intermediate. Oxidation to the aldehyde and Wittig homologation in refluxing toluene provided unsaturated ester **11** with 16:1 *E:Z* selectivity in 98% yield. Enal **12** was produced by using DIBAL reduction followed by Swern oxidation conditions. The boron enolate of the newly developed norephedrine-based glycolate **13** reacted with **12** to generate **14** in greater than 20:1 selectivity and 90% isolated yield.[11] In accord with the norephedryl propionate boron aldol reactions reported by Masamune and co-workers,[12] glycolate **13** gives *syn*-products with a wide range of substrates including branched and unsaturated aldehydes. The auxiliary was removed with LiOH followed by acidification with HCl (pH ∼2) and the crude mixture was converted to ester **15** with

(8) (a) Stebbins, C. E.; Russo, A. A.; Schneider, C.; Rosen, N.; Hartl, F. U.; Pavletich, N. P. *Cell* **1997**, *89*, 239. (b) Roe, S. M.; Prodromou, R. O.; Ladbury, J. E.; Piper, P. W.; Pearl, L. H. *J. Med. Chem.* **1999**, *42*, 260.

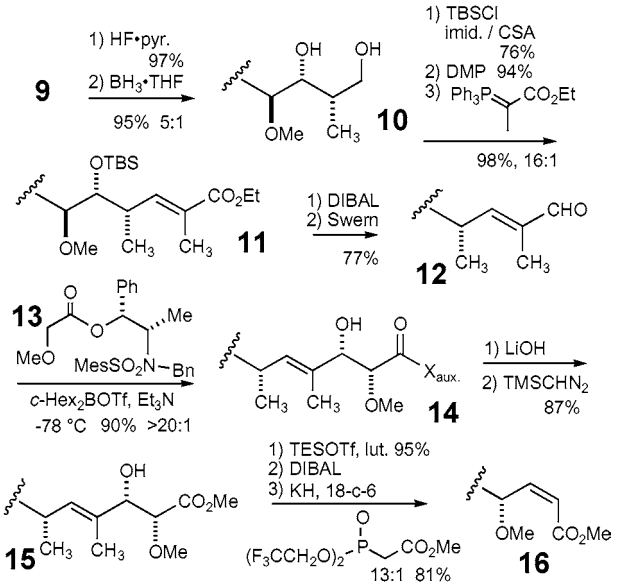
(9) (a) Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035. (b) Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett.* **2001**, *3*, 259.

(10) Andrus, M. B.; Mendenhall, K. G.; Meredith, E. L.; Soma Sekhar, B. B. V. *Tetrahedron Lett*. **2002**, *43*, 1789−1792.

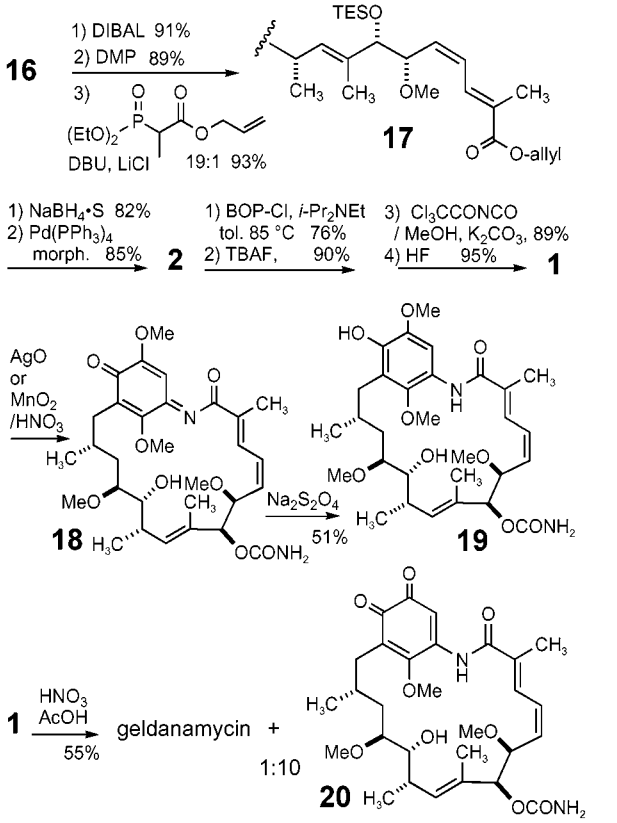
(11) Andrus, M. B.; Soma Sekhar, B. B. V.; Turner, T. M.; Meredith, E. L. *Tetrahedron Lett.* **2001**, *42*, 7197.

(12) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (b) Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978. (c) Abiko, A.; Liu, J.-F.; Buske, D. C.; Moriyama, S.; Masamune, S. *J. Am. Chem. Soc.* **1999**, *121*, 7168. (d) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873.

Scheme 3



Scheme 4



trimethylsilyldiazomethane in 4:1 benzene/methanol solution.[13] The norephedrine auxiliary was also recovered at this stage of the sequence. Protection as the triethylsilyl (TES) ether, followed by half reduction with DIBAL, and treatment of the resultant aldehyde with the Still−Gennari phosphonate gave *Z*-**16** with 13:1 *Z:E* selectivity in 81% yield.[14] In contrast, asymmetric aldol reaction with α-branched enal **12** using the well-known methylglycolate oxazolidinone boron enolate gave a much reduced 2:1 mixture of diastereomeric *syn*-aldol products.[15]

Z-Enal from **16** was generated by using DIBAL reduction and Dess−Martin periodinane. Treatment with the allyl ester phosphonate shown in the presence of DBU and lithium chloride gave *E,Z*-diene **17** with 19:1 *E:Z* selectivity in high yield (Scheme 4).[16] Hydrolysis of the analogous methyl ester of **17** with aqueous base led only to decomposition, not to the desired unsaturated carboxylic acid. The nitro group was first reduced to the aniline through the action of $NaBH_4$ with added sulfur, following the precedure of Lalancette,[17] as employed recently by Panek.[2c] The allyl ester was then removed by using catalytic $Pd(PPh_3)_4$ in the presence of morpholine to give the seco acid **2**. Generation of **1** proved uneventful, including cyclization with BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride, 0.001 M) to form the lactam in 76% yield.[2] Urethane formation, following TES ether removal at C7, was performed by using 2 equiv of trichloroacetylisocyanate then treatment with potassium carbonate in methanol in 89% yield according to the procedure of Kocovsky.[18] Previous ansamycin routes have used excess sodium cyanate for this transformation.[2] These conditions, in the case of the GA intermediate, gave urethane product in less than 50% yield. Aqueous HF in acetonitrile was then used to remove the C11-TBS ether generating trimethoxy-GA **1** in high yield. Use of either HF•pyridine or tetrabutylammonium fluoride for this step failed to provide **1**. The sensitivity of GA to aqueous acid and base has been noted previously.[3]

Unlike the previous ansamycin routes involving dimethoxy intermediates and other trimethoxy model substrates, silver or manganese oxide impregnated with HNO_3 reacted rapidly with **1** to give aza-quinone GA **18** in 77 and 40% yields, repectively. The desired *p*-quinone GA, as anticipated by the precedent noted above, was not formed with these reagents under all conditions investigated.[2] Other reagents, including CAN (ceric ammonium nitrate) in acetonitrile used alone or under phase transfer catalysis conditions, led only to decomposition. In these cases not a trace of **18** or GA was observed. The unique aza-quinone **18** was confirmed by treatment with sodium hydrosulfite to give phenol **19**.[19] Use of CAN with a TBS,TES-protected lactam derived from **1** also led to the formation of an aza-quinone product without a trace of *p*-quinone. The hypervalent iodine based oxidants

(13) Hirai, Y.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1987**, *111*, 3062.
(14) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(15) For a typical use of this approach see: Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113. 2-Methylcinnamaldehyde gave a 3:2:2:1 mixture of products with the methoxyacetyloxazolidinone boron enolate.
(16) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.
(17) Lalancette, J. M.; Freche, A.; brindle, J. R.; Laliberte, M. *Synthesis* **1972**, 526.
(18) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.
(19) Compound **19** was formed by using the conditions found in ref 4b. nOe enhancements for **19**: C17−OH and C18−OMe 1.54%, C20−NH and C21−OMe 4.1%.

bis(trifluoroacetoxy)- and bis(acetoxy)iodobenzene have also been used for oxidative demethylation to form quinones from 1,4-dimethoxy aryl compounds.[20] These reagents also failed to produce geldanamycin from intermediate **1**.

Production of the aza-quinone in the case of silver and manganese oxide is most likely due to nitrogen lone-pair donation to the adjacent trimethoxybenzene moiety. The bound conformation of GA indicates a loss of resonance of the nitrogen lone pair with the amide carbonyl that is twisted out of plane as seen in the Hsp90·GA X-ray structure.[8] It is reasonable to assume that, in solution, **1** would also adopt conformations with reduced amide resonance and enhanced nitrogen−aryl interaction. Upon oxidation with this arrangement, the intermediate radical cation is stabilized by the available nitrogen lone pair and demethylation occurs at C17 to generate **18** instead of C18,21 as anticipated. Indeed, an acyclic *N*-acetyl model substrate produced only *o*-quinone upon treatment with CAN or silver oxide, not aza-quinone.[21] In an effort to deactivate nitrogen−aryl delocalization, BOC and Aloc *N*-protected lactams were formed from **1**. In both cases neither substrate produced the desired *p*-quinone upon oxidation. Gratifyingly, simple treatment of **1** with nitric acid in acetic acid for 1 min[22] followed immediately by sodium bicarbonate quenching produced both (+)-geldanamycin, identical (NMR, TLC, UV) to authentic material, and the new nonnatural compound *o*-quino-GA **20**, $[\alpha]_D^{22}$ −26.7°, in a 1:10 ratio. While the selectivity of the final step proved disappointing, the biological activities of the new geldanamycin variants **1**, **18**, **19**, and **20** can now be evaluated by using cytotoxicity and Hsp90 client protein lowering assays.[6] Efforts are also underway to solve the selectivity of the *p*-quinone formation step by using labile protecting groups at C18,21 together with improved, convergent routes to designed analogues.

Acknowledgment. We are grateful to The NIH (GM57275), The American Cancer Society, and BYU for funding, Bruce Jackson for MS assistance, and Prof. Chaitan Khosla, Kosan Biosciences, for a sample of authentic geldanamycin.

Supporting Information Available: Experimental procedures and characterization for all compounds and spectral data for numbered compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0267432

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

(21) These details will be reported in a full account.

(22) Musgrave, O. C. *Chem. Rev.* **1969**, *69*, 9.