

Studies on the Syntheses of Benzoquinone Ansamycin Antibiotics. Syntheses of the C(5)–C(15) Subunits of Macbecin I, Geldanamycin, and Herbimycin A

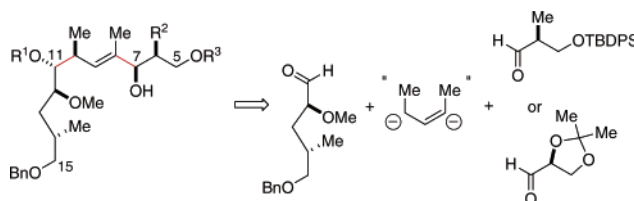
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ABSTRACT



A general and convergent route to the C(5)–C(15) subunits of the benzoquinone ansamycin antibiotics macbecin I, geldanamycin, and herbimycin A is described. Each subunit is prepared by the stepwise coupling of differentially functionalized aldehydes with a pentenyl dianion equivalent derived from diastereoselective pentynylation and regioselective reductive coupling.

The benzoquinone ansamycin antibiotics, including the macbecins, herbimycins, and geldanamycin, are a family of benzoquinone-containing ansa-bridged macrocyclic lactams that possess a significant range of antitumor, antibacterial, antifungal, and antiprotozoal activities (Figure 1).¹ Binding of the ansamycin antibiotics to Hsp-90 results in a significant decrease in cellular levels of various oncogenic tyrosine kinases, while not affecting levels of the serine/threonine

kinases PKA or PKC.² As such, members of the ansamycin class of natural products have been targets for total synthesis,³ and have been explored as leads for the development of novel anticancer therapeutics, with 17-allylaminogeldanamycin currently in phase-II clinical trials.⁴ To date, the search for more effective members of this class has been dominated by semisynthesis (from derivatization of geldanamycin) and engineered biosynthesis—approaches that are limited in their ability to provide structurally diverse ansamycins.⁵ Although a number of elegant syntheses of members of this class have been described,³ new strategies are needed that enable the preparation of diversely functionalized synthetic benzoquinone ansamycins to fuel the discovery of novel therapeutics.⁴

With the long-term goal of developing a synthetic pathway of use for the discovery of novel benzoquinone ansamycins with unique biological profiles, we initiated research aimed

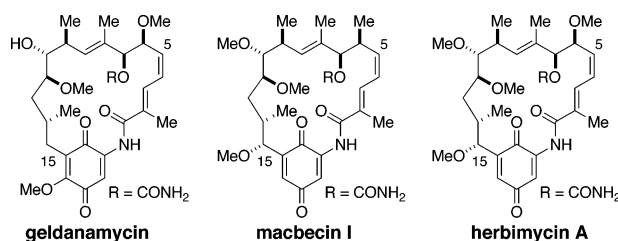


Figure 1. Structures of benzoquinone ansamycin antibiotics.

(1) DeBoer, C.; Meulman, P. A.; Wnuk, R. J.; Peterson, D. H. *J. Antibiot. (Tokyo)*, **1970**, *23*, 442–447.

(2) Goetz, M. P.; Toft, D. O.; Ames, M. M.; Erlichman, C. *Ann. Oncol.* **2003**, *14*, 1169–1176.

at developing a general route to the stereochemically dense region of these targets. Central to this goal was to define a synthetic pathway that could address the natural structural perturbations observed among the members of this class (Figure 2), as well as to provide possibilities for additional skeletal diversification.

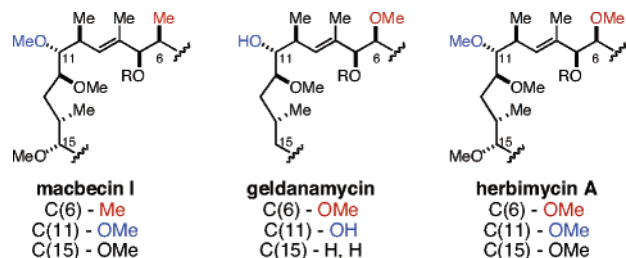


Figure 2. Structural diversity in the C(5)–C(14) segments of the natural benzoquinone ansamycins: C(6), C(11), and C(15).

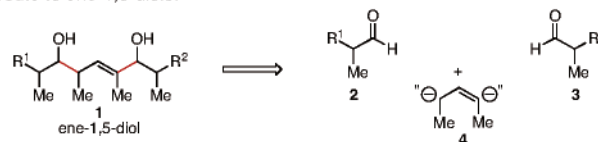
Recently, we reported a two-step process for ene-1,5-diol synthesis based on the coupling of differentially functionalized carbonyl electrophiles with a formal pentenyl dianion equivalent (Figure 3).⁶ Our studies revealed that a dia-

(3) For total syntheses of members of the benzoquinone ansamycin family of natural products, see: (a) Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378–381. (b) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47–65. (c) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Tetrahedron Lett.* **1991**, 32, 6015–6018. (d) Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, 57, 1067–1069. (e) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, 58, 471–485. (f) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, 117, 10587–10588. (g) Panek, J. S.; Xu, F.; Rondon, A. C. *J. Am. Chem. Soc.* **1998**, 120, 4113–4122. (h) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Sekhar, B. B. V. S.; Hicken, E. J. *Org. Lett.* **2002**, 4, 3549–3552. (i) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, 68, 8162–8169. (j) Carter, K. D.; Panek, J. S. *Org. Lett.* **2004**, 6, 55–57. (k) Wrona, I. E.; Garbada, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, 127, 15026–15027. For formal syntheses, or partial syntheses, see: (l) Coutts, S. J.; Whittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1990**, 31, 4301–4304. (m) Coutts, S. J.; Kallmerten, J. *Tetrahedron Lett.* **1990**, 31, 4305–4308. (n) Eshelman, J. E.; Epps, J. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, 34, 749–752. (o) Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, 56, 5496–5498. (p) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Hartmann, M. *J. Org. Chem.* **1992**, 57, 1070–1072. (q) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996**, 52, 3229–3246. (r) Martin, S. F.; Limberakis, C.; Burgess, L. E.; Hartmann, M. *Tetrahedron* **1999**, 55, 3561–3572.

(4) Uehara, Y. *Curr. Cancer Drug Targets* **2003**, 3, 325–330.

(5) For selected examples of geldanamycin derivatization, see: (a) 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, 3806–3812. (b) Schnur, R. C.; Corman, M. L.; Gallaschun, R. J.; Cooper, B. A.; Dee, M. F.; Doty, J. L.; Muzzi, M. L.; DiOrio, C. I.; Barbacci, E. G.; Miller, P. E.; Pollack, V. A.; Savage, D. M.; Sloan, D. E.; Pustilnik, L. R.; Moyer, J. D.; Moyer, M. P. *J. Med. Chem.* **1995**, 38, 3813–3820. (c) Tian, Z.-Q.; Liu, T.; Zhang, D.; Wang, Z.; Dong, S. D.; Carreras, C. W.; Zhou, Y.; Rastelli, G.; Santi, D. V.; Myles, D. C. *Bioorg. Med. Chem.* **2004**, 12, 5317–5329. (d) Rastelli, G.; Tian, Z.-Q.; Wang, Z.; Myles, D.; Lium Y. *Bioorg. Med. Chem. Lett.* **2005**, 15, 5016–5021. (e) Le Brazidec, J.-Y.; Kamal, A.; Busch, D.; Thao, L.; Zhang, L.; Timony, G.; Grecko, R.; Trent, K.; Lough, R.; Salazar, T.; Khan, S.; Burrows, R.; Boehm, M. F. *J. Med. Chem.* **2004**, 47, 3865–3873. For an example of engineered biosynthesis of geldanamycin analogues, see: (f) Patel, K.; Piagentini, M.; Rascher, A.; Tian, Z.-Q.; Buchanan, G. O.; Regentin, R.; Hu, Z.; Hutchinson, C. R.; McDaniel, R. *Chem. Biol.* **2004**, 11, 1625–1633.

route to ene-1,5-diols:



a two-step sequence for convergent union of two carbonyl electrophiles:

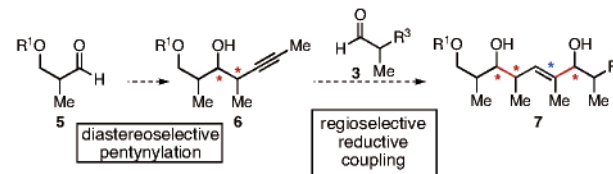


Figure 3. Group 4 metal alkoxide-mediated coupling reactions for polyketide assembly.

stereoselective pentynylation (5 → 6), in conjunction with a titanium alkoxide-mediated coupling (6 → 7)⁷ can provide general and flexible access to complex polyketides.

Herein, we describe a succinct and convergent approach to the preparation of the stereochemically dense regions of these natural products—the C(5)–C(15) subunits of macbecin I, geldanamycin, and herbimycin A (8)—by the convergent assembly of functionalized aldehyde 9 with either the α -methyl- β -silyloxy aldehyde 11 or glyceraldehyde acetonide 12 (Figure 4).

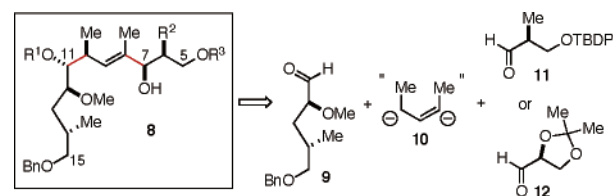


Figure 4. Synthetic strategy for the C(5)–C(15) subunit of the benzoquinone ansamycin antibiotics.

Our initial efforts focused on the synthesis of the macbecin I C(5)–C(15) fragment 18 (Figure 5). Myers' alkylation⁸ of the Roche iodide 13,⁹ followed by LAB reduction (BH₃·NH₃, LDA, THF)⁸ of the amide provided the stereochemically defined primary alcohol 15 (dr 9:1). Oxidation to the aldehyde (Dess–Martin periodinane, CH₂Cl₂),¹⁰ followed by a double asymmetric¹¹ pentynylation with the allenylstannane

(6) (a) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, 127, 3694–3695. (b) Bahadoor, A. B.; Micalizio, G. C. *Org. Lett.* **2006**, 8, 1181–1184.

(7) For examples of titanium alkoxide-mediated coupling of internal alkynes and aldehydes, see: (a) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, 36, 3203–3206. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, 100, 2835–2886.

(8) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, 119, 6496–6511.

(9) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, 57, 5292–5800.

(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 48, 4155–4156.

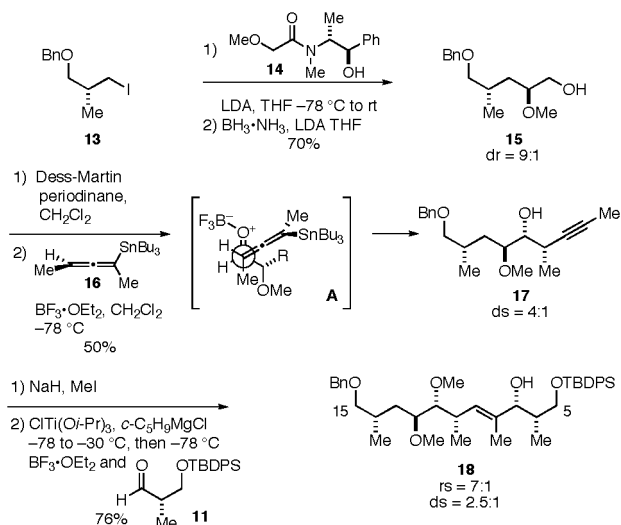


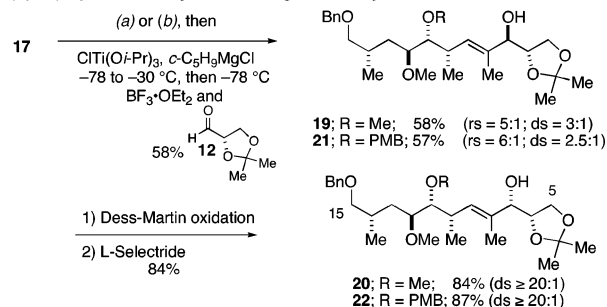
Figure 5. Synthesis of the C(5)–C(15) segment of macbecin I.

16 ($\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C) provided the homopropargylic alcohol **17** (50% yield over two steps).¹² Conversion to the methyl ether (NaH, MeI, THF), followed by a regio- and diastereoselective titanium alkoxide-based reductive coupling with the α -methyl- β -silyloxy aldehyde **11**¹³ ($\text{ClTi}(\text{Oi-Pr})_3$, $c\text{-C}_5\text{H}_9\text{MgCl}$, -78 to -30°C , then -78°C , $\text{BF}_3 \cdot \text{OEt}_2$ and **11**) provided the fully functionalized C(5)–C(15) subunit of macbecin I **18** ($rs = 9:1$, $ds = 2.5:1$). Although the product was formed as a 2.5:1 mixture of diastereomers (favoring the desired isomer), realization of this bond construction results in a six-step linear synthesis of this complex polyketide from the Roche iodide **13**.⁹ Importantly, the pure Felkin isomer was obtained by simple column chromatography of the diastereomeric mixture of products.

Next, we examined the flexibility of this synthetic pathway for the preparation of fragment precursors to the ansa chains of herbimycin A and geldanamycin. As previously discussed, the structural differences between these targets reside at three positions in the ansa chain: C(6), C(11), and C(15). On the basis of our synthetic route to the macbecin subunit **18**, substitution at C(6) can be varied by coupling of the homopropargylic ether with a differentially functionalized carbonyl electrophile, whereas the nature of the C(11) substituent can be varied simply by protection of the homopropargylic alcohol **17**. These simple modifications of our pathway are described in Figure 6.

First, the C(5)–C(15) subunit of herbimycin A (**20**) was prepared from homopropargylic alcohol **17** by methylation (NaH, MeI, THF), regioselective reductive coupling ($\text{ClTi}(\text{Oi-Pr})_3$, $c\text{-C}_5\text{H}_9\text{MgCl}$, -78 to -30°C , then -78°C ,

C(5)–C(15) of herbimycin A and geldanamycin:



(a) NaH, MeI, THF; (b) NaH, PMBCl, DMF

Figure 6. Synthesis of C(5)–C(15) segments of herbimycin A and geldanamycin.

$\text{BF}_3 \cdot \text{OEt}_2$ and **12**), oxidation (Dess–Martin periodinane, CH_2Cl_2),¹⁰ and diastereoselective reduction (L-Selectride, THF; $ds \geq 20:1$).¹⁴ In a similar fashion, the geldanamycin fragment **22** was prepared via conversion of **17** to the corresponding PMB ether (NaH, PMBCl, DMF), regioselective reductive coupling, oxidation, and diastereoselective reduction.

In summary, we have defined a synthetic pathway to the C(5)–C(15) polyketide fragments of the benzoquinone ansamycin antibiotics macbecin I, geldanamycin, and herbimycin A. The route is highly convergent, providing the stereochemically dense region of these natural products by the stepwise construction of three C–C bonds (C(12)–C(13), C(10)–C(11), and C(7)–C(8)). Overall, the sequence proceeds in just six to eight steps from the Roche iodide **13**, and features a Myers' alkylation, a diastereoselective pentynylation, and a regioselective titanium-mediated coupling reaction with a functionalized aldehyde. On the basis of the generality of these bond constructions, and the convergent nature of the pathway to the ansa chains of these targets (Figure 7), we expect that this pathway will be useful for

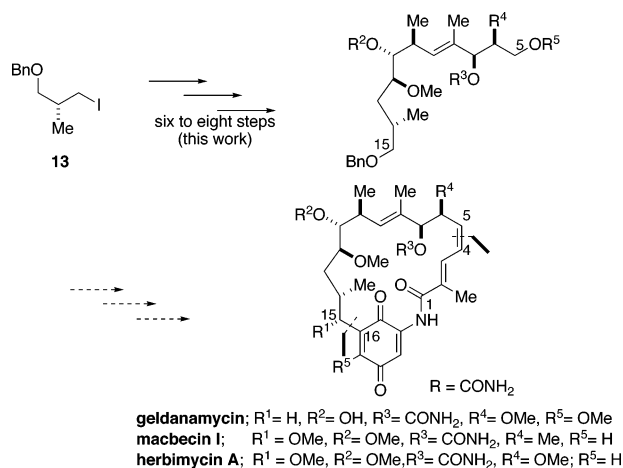


Figure 7. Summary and future direction.

(11) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.

(12) (a) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1992**, *57*, 1242–1252. For a review of chiral allenylmetal reagents, see: (b) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31–47. For the synthesis of allenylstannanes, see: (c) Marshall, J. A.; Chobanian, H. *Org. Synth.* **2005**, *82*, 43–54.

(13) Heathcock, C. H.; Young, S. D.; Hagan, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095–2105

total syntheses of each member of this natural product class, as well as for the synthesis of diverse benzoquinone ansamycins. Progress made along these lines will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Sun, C.; Bittman, R. *J. Org. Chem.* **2004**, 69, 7694–7699.