Natural Product Synthesis

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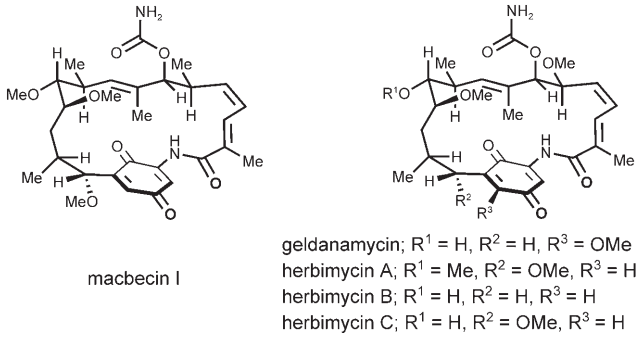
Total Synthesis of Macbecin I**

*Justin K. Belardi and Glenn C. Micalizio**

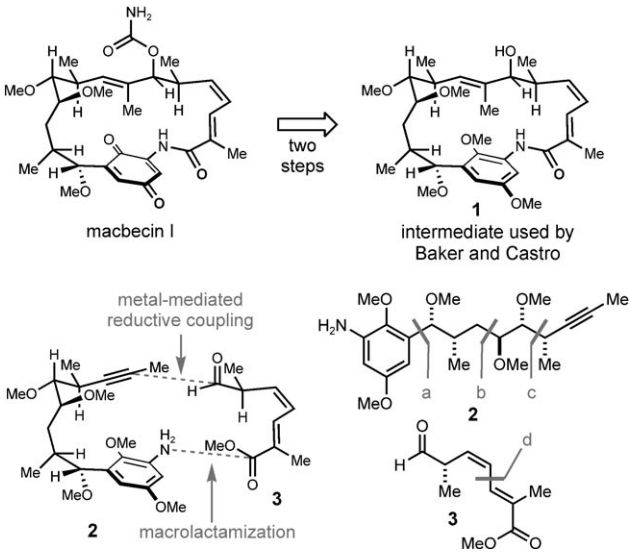
Structurally complex natural products continue to serve as stimuli for the development of synthetic organic chemistry. While numerous total syntheses of complex targets have been achieved, a remaining concern in the evolution of organic chemistry is the efficiency with which such architectures can be prepared. With the aim of establishing more efficient pathways to complex targets, we have been developing new strategies for the cross-coupling of a variety of highly functionalized π systems. Herein, we describe the application of one such process as the key step in a concise total synthesis of macbecin I (Scheme 1), a benzoquinone ansamycin antibiotic.

The benzoquinone ansamycin antibiotics are a class of polyketide-derived natural products that display a range of antitumor, antibacterial, antifungal, and antiprotozoal activities.[1] Members of this class (Scheme 1) have been targets for synthesis since the early 1980s, with the first total synthesis appearing in 1989.[2a] Their unique chemical structures, which have in common a 19-membered macrocyclic lactam that houses a functionalized quinone, seven stereocenters, and three stereodefined olefins, have continued to challenge synthetic chemists for nearly twenty years.[2] Interest in this class of macrocyclic compounds as potential therapeutics has risen dramatically since the discovery that they are potent inhibitors of Hsp90.[3] Numerous reports have described synthetic pathways to access less complex nonnatural benzoquinone ansamycins in an effort to optimize their biological properties.[4] Herein, we describe a total synthesis of macbecin I that proceeds with high step economy[5] with respect to previous studies in this area[2] and highlights the utility and mild nature of titanium-mediated cross-coupling reactions between functionalized alkynes and chiral aldehydes.[6]



Scheme 1. Representative benzoquinone ansamycin antibiotics.

Our retrosynthesis for macbecin I relied on a two-step functionalization of the macrocyclic lactam **1** (Scheme 2), a process previously described by Baker and Castro.[2a,b] We envisioned that this complex intermediate could be derived from the coupling of the aniline-containing alkyne **2** with the stereochemically defined, and likely sensitive, β,γ,δ,ε-unsaturated aldehyde **3**. Alkyne **2** should be accessible through three key C–C bond-forming processes (highlighted as a–c), whereas aldehyde **3** could be prepared by the formation of a central C–C bond (d). We describe herein the application of this ambitious coupling process to the total synthesis of the benzoquinone ansamycin macbecin I.



Scheme 2. Key bond constructions targeted for a synthesis of macbecin I. a) nucleophilic addition, b) nucleophilic substitution, c) propargylation, d) palladium-catalyzed cross-coupling.

The synthesis of alkyne **2** commenced with a Myers alkylation of the iodide **4**,[7] followed by reduction to provide the primary alcohol **6** (d.r. 9:1) in 70% yield over two steps (Scheme 3). The oxidation of **6** to the corresponding aldehyde, followed by diastereoselective propargylation with the chiral allenyl stannane **7**, afforded the homopropargylic alcohol **8** in 50% yield over two steps (diastereoselection as judged prior to purification (d.s.) 4:1).[8] While the diastereo-

[*] J. K. Belardi, Prof. G. C. Micalizio
Department of Chemistry, Yale University
225 Prospect Street, New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-6144
E-mail: glenn.micalizio@yale.edu

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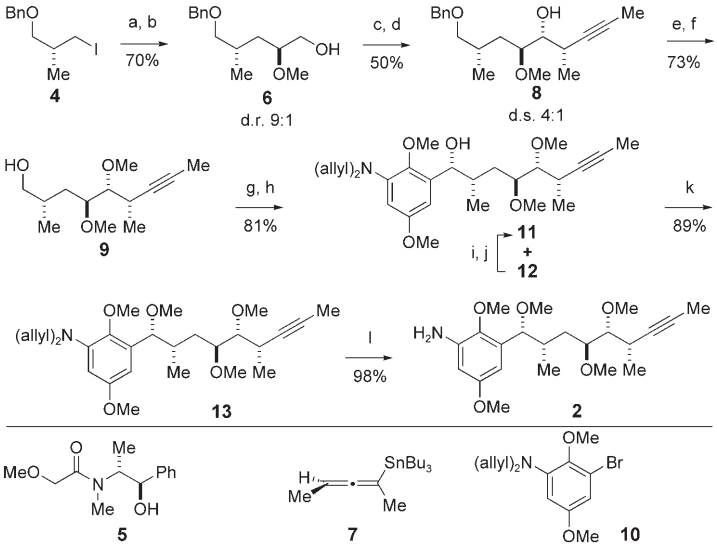
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 3. Preparation of the alkyne coupling partner **2**: a) **5**, LDA, THF, −78 °C→RT (d.r. 9:1); b) $BH_3{\cdot}NH_3$, LDA, THF; c) Dess–Martin periodinane, CH_2Cl_2; d) **7**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; e) NaH, MeI, THF; f) BBr_3, CH_2Cl_2, −78 °C; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; h) **10**, *n*BuLi, Et_2O, −78 °C→RT, then addition of the aldehyde at −78 °C (d.r. 2:1); i) Dess–Martin periodinane, CH_2Cl_2; j) $LiAlH_4$, Et_2O (2 steps, 76%, d.r. 1:1); k) NaH, MeI, THF; l) 1,3-dimethylbarbituric acid, $[Pd(PPh_3)_4]$, CH_2Cl_2. Bn = benzyl, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide.

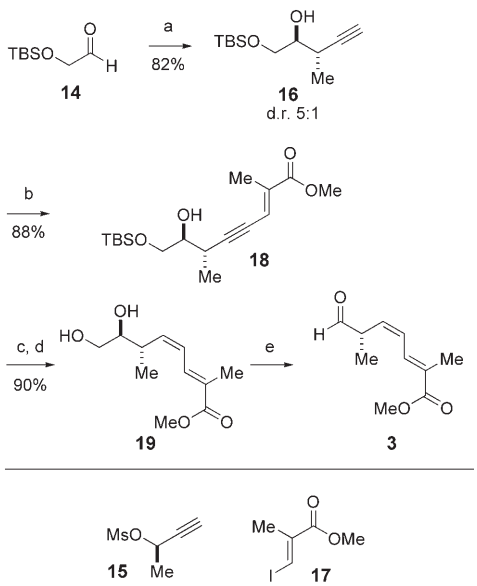
selectivity of this process was expected to be higher based on the results of similar processes described by Marshall and coworkers,[8] we anticipated that an erosion of diastereoselectivity could accompany a partial epimerization of the chiral allenyl stannane by a process that is known to complicate their preparation.[8c] In spite of the moderate diastereoselectivity of the double asymmetric propargylation, we were pleased to obtain the desired alkyne as a single isomer after standard flash column chromatography, and in only four steps from iodide **4**.

Methylation of the secondary alcohol in **8**, followed by BBr_3-promoted debenzylation, provided the primary alcohol **9** in 73% yield. Alcohol **9** was then converted into the coupling partner **2** by oxidation to the aldehyde, nucleophilic addition of a preformed aryl lithium reagent derived from **10**,[2i] methylation, and deallylation. As observed in a related bond construction,[2i] nucleophilic addition of the aryl lithium reagent derived from **10** to the aldehyde derived from **9** proceeded with 2:1 stereoselection. The desired isomer **11** was produced as the major product and easily purified from its diastereomer **12** by column chromatography. Furthermore, the minor diastereomer **12** could be recycled by a two-step oxidation/reduction sequence to provide additional quantities of the desired diastereomer **11**. Overall, this pathway provided a relatively concise and scalable route to the coupling partner **2**, which was prepared in 10 linear steps from iodide **4**.

The preparation of aldehyde **3** began with palladium-catalyzed asymmetric propargylation of the α-silyloxy acetaldehyde **14** with alkyne **15**[9] to provide the *anti* homopropargylic alcohol **16** (d.r. 5:1) in 82% yield (Scheme 4). Sonogashira coupling[10] with the readily available vinyl iodide **17**[11] then delivered enyne **18** in 88% yield. Lindlar reduction of the alkyne, followed by desilylation, provided diol **19** in 90% yield. Finally, oxidative cleavage of the 1,2-diol[12] afforded the desired β,γ,δ,ε-unsaturated aldehyde **3**. This highly sensitive intermediate was used in the subsequent coupling reaction without purification.

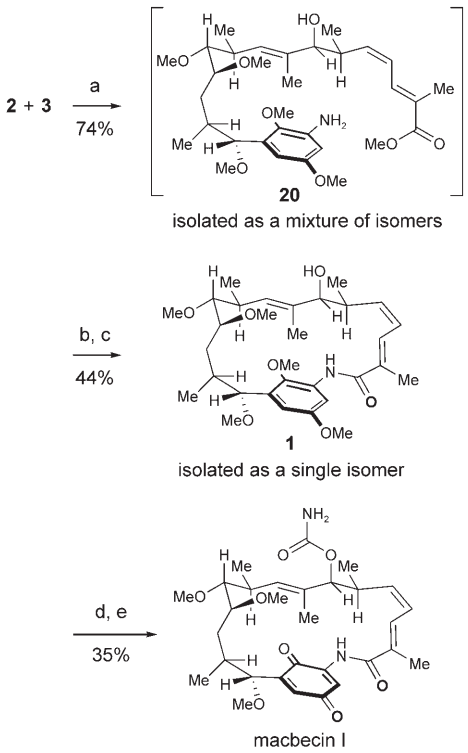
The titanium-mediated coupling of alkyne **2** with aldehyde **3** proceeded in an efficient manner to afford a mixture of coupled products in 74% combined yield (Scheme 5). While chromatographic purification of this mixture was not possible, Baker's intermediate **1** was accessed in 44% yield through a two-step processing of this mixture: 1) saponification (LiOH, THF, MeOH, H_2O) and 2) macrocyclization (BOPCl, iPr_2NEt, toluene). During the course of these two steps, the minor regio- and stereoisomers derived from the coupling of **2** and **3** were effectively removed. This process provided a straightforward preparative means of accessing **1** as a single isomer and completing a formal total synthesis of macbecin I.

With regard to the selectivity of the metal-mediated coupling of alkyne **2** with aldehyde **3**, the desired isomer **20** was obtained as the major product. The precise levels of regio- and stereoselectivity could not be determined by analysis of the spectral data gathered. However, in a related coupling reaction of alkyne **2** with an aldehyde that lacked the terminal methyl ester, the desired regio- and stereoisomer was produced as the major product with 7:1 regioselectivity and 3:1 diastereoselectivity.[13]



Scheme 4. Preparation of the aldehyde coupling partner **3**: a) **15**, $[Pd(PPh_3)_4]$, InI, HMPA, THF; b) **17**, $[Pd(PPh_3)_4]$, CuI, Et_3N; c) Pd on $CaCO_3$/lead, quinoline, benzene, H_2; d) HF·pyridine, pyridine, THF; e) $Pb(OAc)_4$, EtOAc. Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

With the macrocyclic lactam **1** in hand, we turned to a well-established end-game strategy to complete the total



Scheme 5. Fragment coupling and completion of the total synthesis: a) **2**, $ClTi(OiPr)_3$, *c*-C_5H_9MgCl, toluene, −78 to −30 °C, then addition of **3** at −78 °C as a solution in toluene, −78 °C→RT (74% yield of a mixture of regio- and stereoisomers); b) LiOH, THF, MeOH, H_2O; c) BOPCl, iPr_2NEt, toluene; d) Cl_3CONCO, CH_2Cl_2, then K_2CO_3, MeOH; e) CAN, H_2O, CH_3CN. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, CAN = ceric ammonium nitrate.

synthesis of the natural product.[2a,b] The conversion of **1** to the corresponding carbamate followed by the notoriously challenging oxidation of the aromatic ring to the quinone (CAN, H_2O, CH_3CN)[2a,b] completed the total synthesis of macbecin I.

Overall, the use of a titanium-mediated reductive cross-coupling reaction between a highly functionalized alkyne and sensitive chiral aldehyde formed the basis of a convergent total synthesis of macbecin I. The success of this coupling reaction demonstrates the functional-group compatibility and mild nature of the process. Furthermore, the ability to couple **2** with **3** directly led to the total synthesis of a benzoquinone ansamycin antibiotic in only 15 steps from the readily available iodide **4** (longest linear sequence). The titanium-mediated reductive cross-coupling reaction used in this total synthesis is, to our knowledge, among the most complex examples of such reaction methodology and demonstrates the great potential of titanium-mediated coupling processes in the synthesis of complex molecules.[6i–l]

Although the total number of synthetic operations required to access macbecin I through this route remains above thirty (from readily available starting materials), this synthesis represents a significant advance toward the goal of developing a synthetic pathway for the production of collections of complex molecules related to the benzoquinone ansamycins. Such contributions can serve as a foundation to enable the probing of structure–activity relationships and production of significant quantities of benzoquinone ansamycin inspired Hsp90 inhibitors unbound by the constraints of biosynthesis.

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[13] See the Supporting Information for additional information.

