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Aryne Acyl-Alkylation in the General and Convergent Synthesis of Benzannulated Macrolactone Natural Products: An Enantioselective Synthesis of (−)-Curvularin

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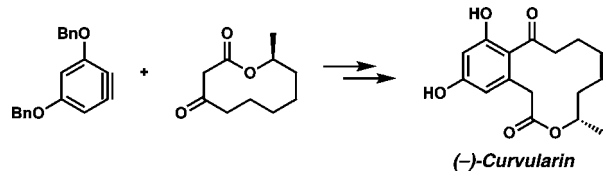
ABSTRACT



A general approach for the synthesis of benzannulated macrolactone natural products utilizing an aryne acyl-alkylation reaction is described. Toward this end, the total syntheses of the natural products (−)-curvularin, curvulin, and (−)-diplodialide C are reported. Furthermore, the aryne insertion technology has enabled the rapid conversion of simple diplodialide natural products to curvularin, thereby connecting these two biosynthetically distinct classes of compounds via synthetic methods.

Benzannulated macrolactones are an ever-growing class of natural products with potential therapeutic and agrochemical applications (e.g., **1**−**3**) (Scheme 1).[1] As part of our ongoing research in aryne methodology, we targeted these natural products using an acyl-alkylation reaction between an aryne and a β-ketolactone.[2] We chose as our initial target (−)-curvularin (**1**),[3,4] a polyketide natural product isolated from several species of the mold *Curvularia* and recently shown to be an inhibitor of human-inducible nitric oxide synthase expression.[5] By applying this retrosynthetic disconnection to curvularin, we recognized that the β-ketolactone fragment mapped onto the carbon framework of the diplodialide natural products (**4**−**7**), revealing an unusual synthetic (i.e., nonbiomimetic) link between the two natural product families. Thus, the development of a general synthesis of benzannulated macrolactones via ring-expansive aryne insertion chemistry from the diminutive macrolactone would provide access to these valuable natural products and various synthetic analogues for biological evaluation.

(−)-Curvularin possesses a 12-membered lactone fused to a resorcinol aromatic ring, which we disconnected by an

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(2) (a) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341. (b) Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 161–171.

(3) For isolation, see: (a) Musgrave, O. C. *J. Chem. Soc.* **1956**, 4301–4305. (b) Musgrave, O. C. *J. Chem. Soc.* **1957**, 1104–1108. (c) Birch, A. J.; Musgrave, O. C.; Richards, R. W.; Smith, H. *J. Chem. Soc.* **1959**, 3146–3152.

(4) For previous total syntheses, see: (a) Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039–3044. (b) Bracher, F.; Schulte, B. *Nat. Prod. Lett.* **1995**, *7*, 65–68. (c) Bracher, F.; Schulte, B. *Liebigs Ann./Recueil* **1997**, 1979–1982. (d) Mohapatra, D. K.; Rahaman, H.; Pal, R.; Gurjar, M. K. *Synlett* **2008**, 1801–1804.

(5) Yao, Y.; Hausding, M.; Erkel, G.; Anke, T.; Forstermann, U.; Kleinert, H. *Mol. Pharmacol.* **2003**, *63*, 383–391.

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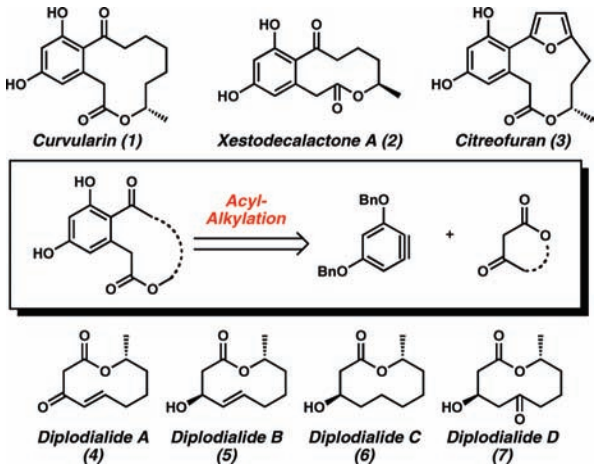
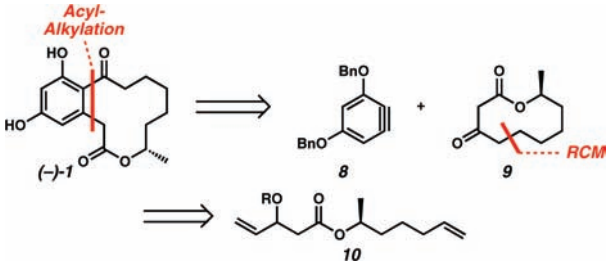
Scheme 1. Aryne Acyl-Alkylation as a General Strategy toward the Synthesis of Benzannulated Macrolactone Natural Products



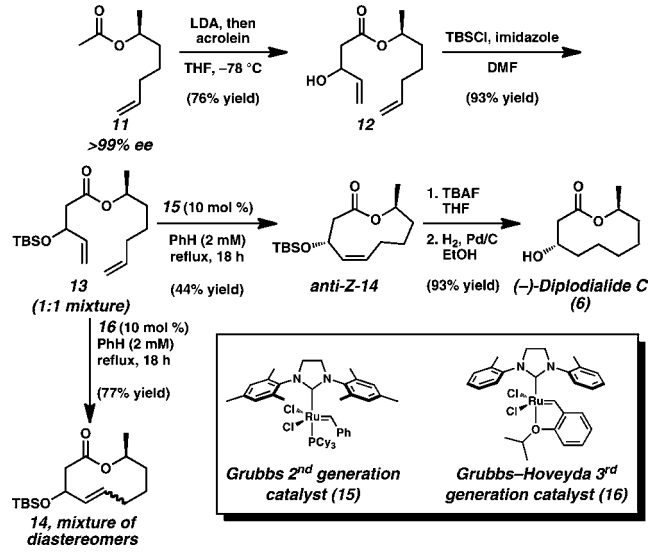
acyl-alkylation between resorcinylic aryne **8** and 10-membered β-ketolactone **9**[6] (Scheme 2). This formal C−C bond insertion into β-ketolactone **9** forms two new C−C bonds in a single step. Furthermore, β-ketolactones, such as **9**, represent a substrate class that had not previously been investigated in aryne acyl-alkylation reactions and would be amenable to the preparation of other members of this class of natural products. β-Ketolactone **9** could be accessed in turn by ring-closing metathesis (RCM) of linear α,ω-diene **10**.

Scheme 2. Retrosynthetic Analysis of (−)-Curvularin



We began the forward synthesis by targeting β-ketolactone **9**. Aldol reaction of known acetate **11**[7] with acrolein provided β-hydroxyester **12** as a 1:1 mixture of diastereomers (Scheme 3). Initial attempts to generate 10-membered ring products by RCM proved challenging. Unfortunately, β-hydroxyester **12** was a poor substrate for RCM with a number of different

Scheme 3. RCM of Silyl Ether **13** and Synthesis of (−)-Diplodialide C (**6**)



catalysts.[8] However, conversion of the allylic alcohol to the silyl ether (**13**) led to significantly improved reactivity. We were intrigued to find that treatment of silyl ether **13** with Grubbs' second-generation catalyst (**15**) in refluxing benzene resulted in the formation of a single diastereomer having the cis olefin geometry (***anti-Z*-14**) in 44% yield.[9] The relative stereochemistry of lactone ***anti-Z*-14** was determined by conversion to (−)-diplodialide C[6c,8,10] (**6**) by desilylation and hydrogenation. While the resolution of the diastereomers of silyl ether **13** by RCM was notable, the moderate yield hindered our efforts. To our delight, use of the sterically less encumbered Grubbs−Hoveyda third-generation catalyst[11] **16** led to the formation of a mixture of diastereomers and olefin isomers of lactone **14** in 77% yield.

With this key RCM result in hand, we sought to streamline this process by developing a one-pot silylation−RCM−desilylation procedure beginning with allylic alcohol **12**. Gratifyingly, silylation with HMDS followed by RCM with Grubbs−Hoveyda third-generation catalyst (**16**) and acidic hydrolysis of the trimethylsilyl group generated β-hydroxylactone **17** as the expected mixture of diastereomers and olefin isomers (Scheme 4). This mixture was then readily converted to β-ketolactone **9** by hydrogenation and Dess−Martin oxidation. Interestingly, β-ketolactone **9** has been shown previously to be an intermediate in the total syntheses of the diplodialide family of natural products (Scheme 1).[6]

(6) For previous syntheses of β-ketolactone **9**, see: (a) Anand, R. V.; Baktharaman, S.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 3356–3359. (b) Ishida, T.; Wada, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 323–327. (c) Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008–2012. (d) Ishida, T.; Wada, K. *J. Chem. Soc., Chem. Commun.* **1977**, 337–338.

(7) Acetate **11** was prepared by nucleophilic opening of (*S*)-propylene oxide with a butenyl Grignard reagent in the presence of a copper catalyst, followed by acetylation. See: Lin, W.; Zercher, C. K. *J. Org. Chem.* **2007**, *72*, 4390–4395.

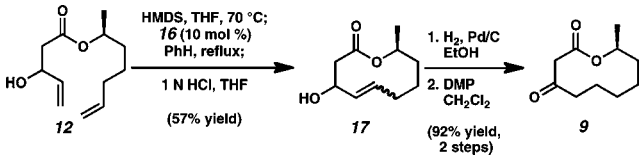
(8) In our hands, β-hydroxyester **12** was not a suitable substrate for RCM with multiple catalysts. However, for RCM of **12**, see: Sharma, G. V. M.; Reddy, K. L. *Tetrahedron: Asymmetry* **2006**, *17*, 3197–3202.

(9) To our knowledge, only two other examples of a resolution of diastereomers by RCM using an achiral catalyst are known: (a) Bajwa, N.; Jennings, M. P. *Tetrahedron Lett.* **2008**, *49*, 390–393. (b) Magauer, T.; Martin, H. J.; Mulzer, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6032–6036.

(10) For previous total syntheses, see: Wakamatsu, T.; Akasaka, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *32*, 2755–2758.

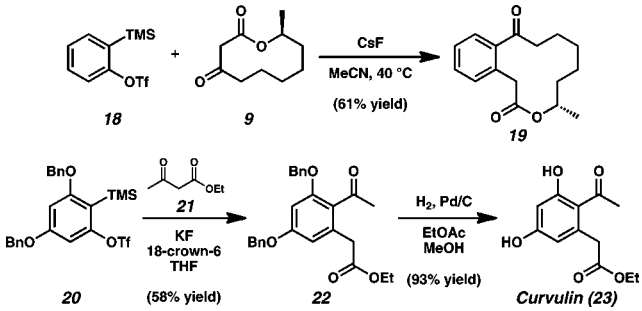
(11) (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592. (b) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

Scheme 4. Synthesis of β-Ketolactone **9**



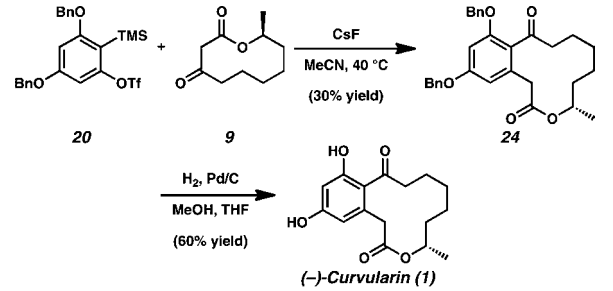
Preliminary acyl-alkylation studies showed that β-ketolactone **9** reacted competently with unsubstituted silyl aryl triflate **18**,[12] producing macrolactone **19** in 61% yield (Scheme 5). Furthermore, in the insertion reaction between silyl aryl triflate **20**[13] and ethyl acetoacetate (**21**), arene **22** was produced in 58% yield as a single isomer. The regiochemistry of this product was confirmed by debenzylation of arene **22** to yield the natural product curvulin[14,15] (**23**).

Scheme 5. Model Acyl-Alkylation Studies and Synthesis of Curvulin (**23**)



Encouraged by these results, we turned our attention to the key aryne acyl-alkylation toward curvularin. We were pleased to find that treatment of aryne precursor **20** and β-ketolactone **9** with CsF resulted in formation of benzannulated macrolactone **24**, albeit in lower yield than macrocycle **19** (Scheme 6). Finally, hydrogenolysis of the benzyl groups[4a] produced (−)-curvularin (**1**) in 8% overall yield and in only six steps from acetate **11**.

Scheme 6. Completion of (−)-Curvularin



In conclusion, we have successfully completed syntheses of the natural products (−)-curvularin (**1**), (−)-diplodialide C (**6**), and curvulin (**23**). A unique resolution of diastereomers by RCM allowed for the preparation of (−)-diplodialide C from a mixture of diastereomeric dienes. Application of the aryne acyl-alkyation en route to curvularin resulted in a general synthesis that we anticipate will be applicable to a number of related natural and non-natural analogues. Furthermore, the aryne insertion technology has enabled the formal conversion of the diplodialide natural products to curvularin, two biosynthetically distinct classes of compounds. The utilization of these methods in additional complex settings is currently underway in our laboratories.

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Supporting Information Available: Experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.

(13) Silyl aryl triflate **20** was prepared in five steps from phloroglucinol: Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, DOI: 10.1021/ol1000796.

(14) For isolation, see: Coombe, R. G.; Jacobs, J. J.; Watson, T. R. *Aust. J. Chem.* **1968**, *21*, 783–788.

(15) For total synthesis, see: Bracher, F.; Krauss, J. *Nat. Prod. Lett.* **1998**, *12*, 31–34.