Toward the Total Synthesis of Divergolides C and D

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Abstract: The divergolides are a family of structurally unprecedented *ansa* macrocycles. We describe a synthetic strategy toward divergolides C and D that hinges on the biomimetic diversification of a common intermediate. An advanced precursor that incorporates all the carbon atoms of divergolide C and D is presented, and atropisomerism in a sterically crowded acyl naphthalene is studied.

Key words: natural products, ansamycins, macrolides, divergent synthesis, atropisomerism

Divergent synthesis is an attempt to employ a common intermediate that can be readily diversified to reach several related targets.[1] Such an approach can be justified on biosynthetic grounds, since the variation of a metabolite is frequently found in nature. A case in point are the divergolides, a small family of *ansa* macrolides that have been recently reported (Figure 1).[2]

The divergolides were isolated by Hertweck and co-workers from *Streptomyces* sp. HKI0576 that was derived from the stem of *Bruguiera gymnorrhiza*, a Chinese mangrove tree.[2] Divergolides A–D (**1**–**4**) inhibit the growth of several types of bacteria and were found to be toxic to a variety of cancer cell lines.[2] In addition to their promising biological activities, the divergolides are marked by very attractive molecular architectures. As such, they have spurred significant interest in the community resulting in several synthetic approaches which recently surfaced in the literature.[3] One of them utilized a key intermediate,[3b] the synthesis of which we published earlier as a part of a PhD thesis.[4] Motivated by these reports, we now disclose our own efforts toward the synthesis of divergolides C and D.

Structurally, divergolides C and D (**3** and **4**) differ from the other two newly isolated family members. They both exhibit a macrolactone that contains four stereocenters. Divergolide C (**3**) features a naphthohydroquinone that is fused to a seven-membered lactam, whereas divergolide D (**4**) possesses a butyrolactam adjacent to a naphthalene-1-(4*H*)-one with a tertiary alcohol at one of the fusion points. Due to their strained 15- and 19-membered macrocycles, the *ansa* chains of divergolides C and D, respectively, could also represent stereogenic elements.

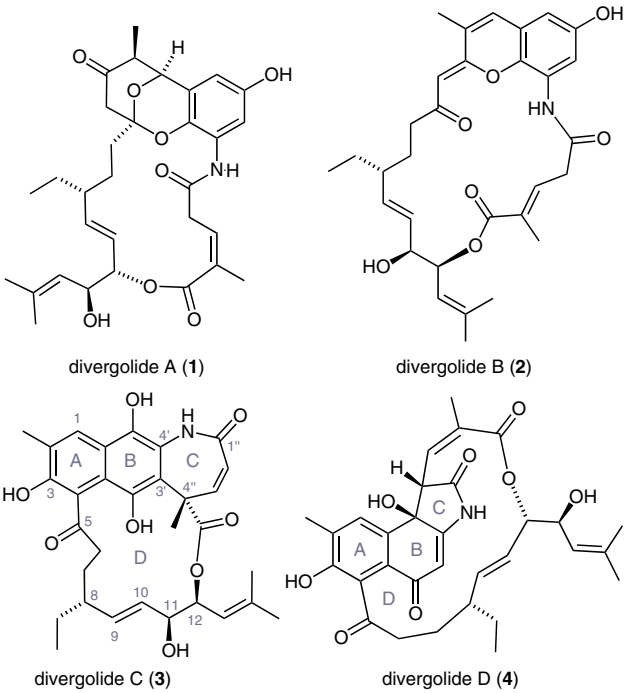

Figure 1 The recently isolated divergolides A–D (**1**–**4**)

Hertweck et al. proposed that biosynthesis of the divergolides involves 3-amino-5-hydroxybenzoic acid (AHBA, **6**) as a starter unit and several extender units that include malonyl-CoA, methylmalonyl-CoA, and the unusual ethylmalonyl-CoA and isobutyrylmalonyl-CoA.[2,5] Assembly of these components on a polyketide synthase could afford a common macrocyclic intermediate **5**, which may subsequently be diversified to reach both divergolides C and D (Scheme 1). According to this biosynthetic scheme, the seven-membered lactam ring in divergolide C (**3**) could be formed via conjugate addition of an enolate formed by deprotonation of the pentenedioic acid derived moiety in the 'northeastern' sector onto the naphthoquinone portion (path a in Scheme 1). By contrast, acyl shift, followed by aldol addition of an analogous enolate to a carbonyl of the naphthoquinone would give rise to divergolide D (path b in Scheme 1). It is possible that the acyl migration proposed for the formation of **4** takes place after the cyclization process. Based on these considerations, it is conceivable that the macrocyclic precursor **5** is a natural product itself and could possibly be isolated.[6]

We found it worthwhile to test this biosynthetic hypothesis and explore whether both natural products could be made from one common intermediate in the laboratory.

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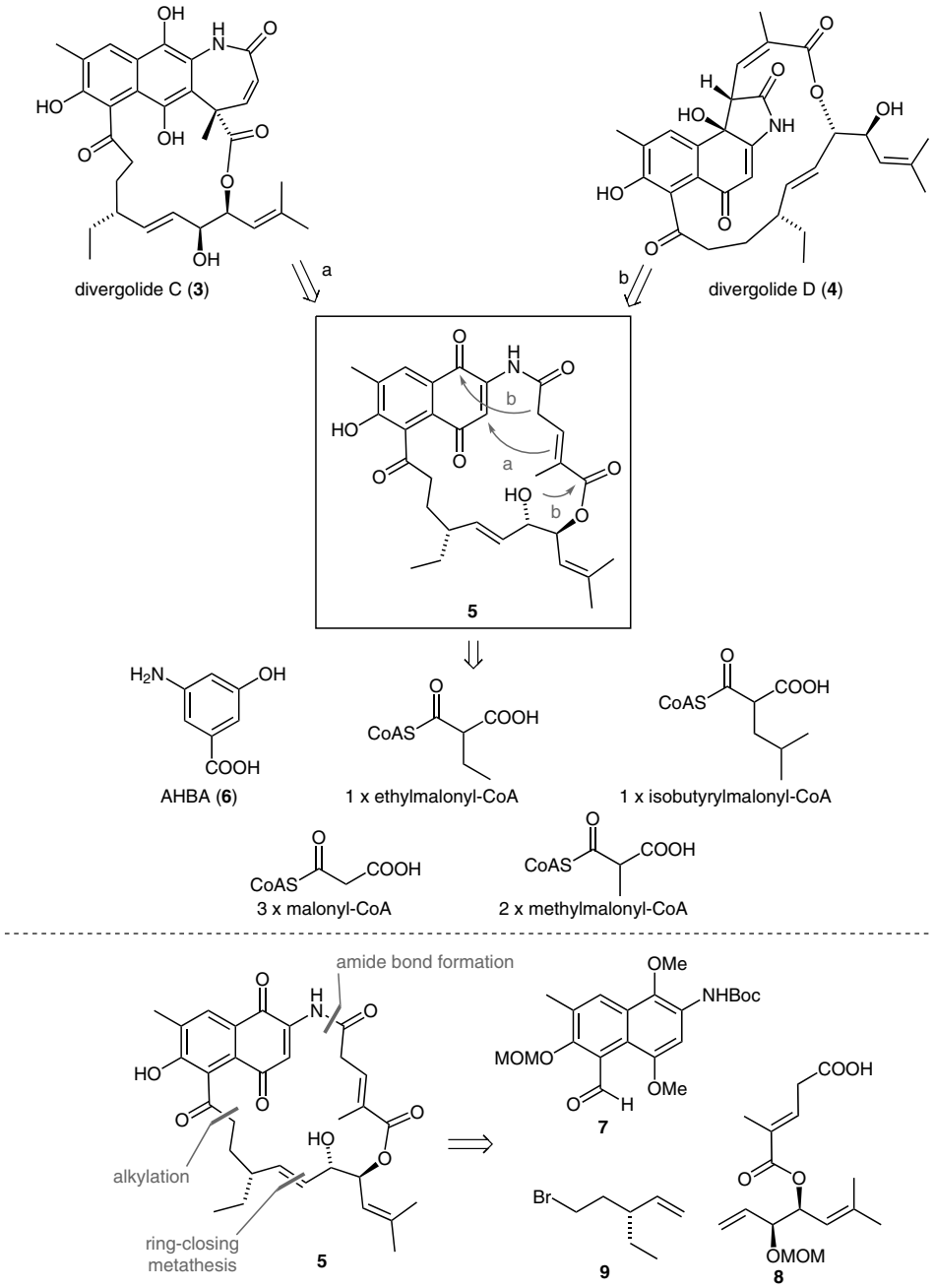
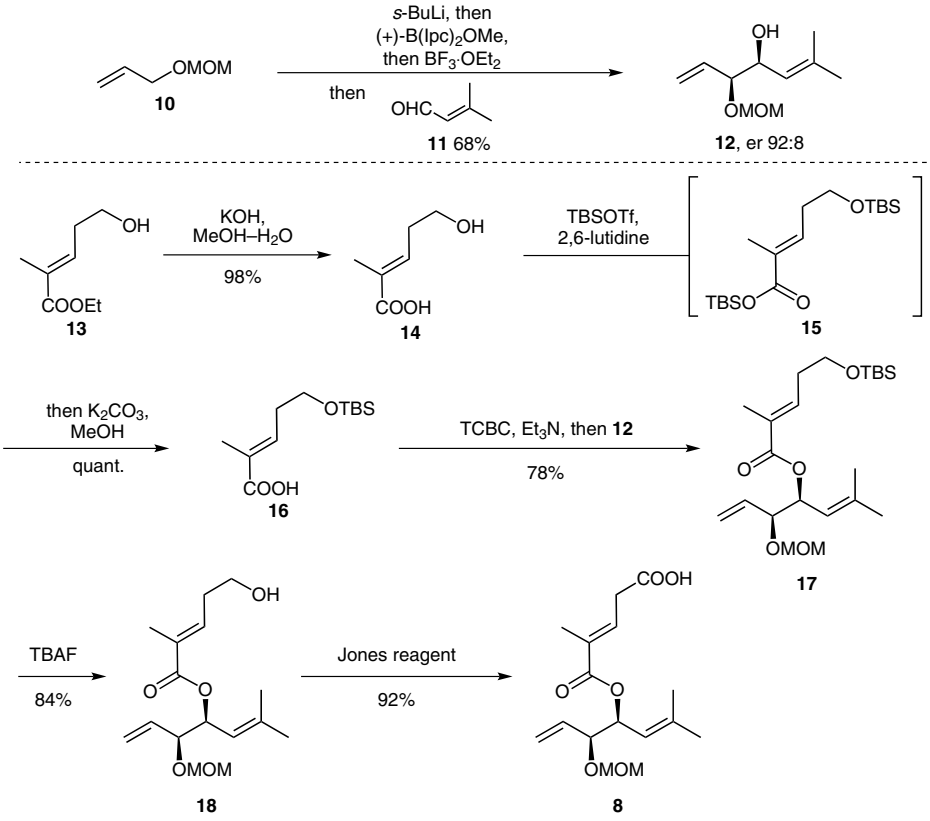
Retrosynthetically, macrocycle **5** can arise from three building blocks that represent the 'northwestern' naphthalene moiety **7**, the 'eastern' flank including an ester bond, compound **8**, and the 'southwestern' zone that features an unusual ethyl side chain **9**.

Our synthetic efforts started with the assembly of the 'eastern' part **8**, which was accessible in a short sequence from alcohol **12** and acid **16** (Scheme 2). First, the two adjacent stereocenters in **12** were set by a diastereo- and enantioselective Brown allylation[7] of 3-methylcroton aldehyde **11** and vinyl methyl methoxy ether **10**[7b,8] that gave the product as a single diastereoisomer with an enantiomeric ratio of 92:8. Next, acid **14** was procured from known ethyl ester **13**.[9] Hydrolysis of **13** followed by global protection of acid **14** provided compound **15**. Hydrolysis under mild conditions gave rise to the free acid **16**, which was then combined with secondary alcohol **12** using Yamaguchi conditions. Subsequent deprotection of **17** using TBAF gave access to alcohol **18**, which was oxidized to the free acid **8** under Jones conditions. Other oxidation protocols, such as DMP, TPAP/NMO/H_2O or TPAP/BAIB/H_2O led to decomposition of the starting material.

The synthesis of the 'southwestern' chain **9** started with the acylation of Koga's auxiliary[10] **19** with activated *trans*-2-pentenoic acid (Scheme 3). Subsequent conjugate addition of divinyl magnesiocuprate to **20** proceeded smoothly, and the corresponding alkene **21** could be pre-



Scheme 1 Proposed biogenesis of divergolides C and D (**3** and **4**) and retrosynthetic analysis of the key intermediate **5**

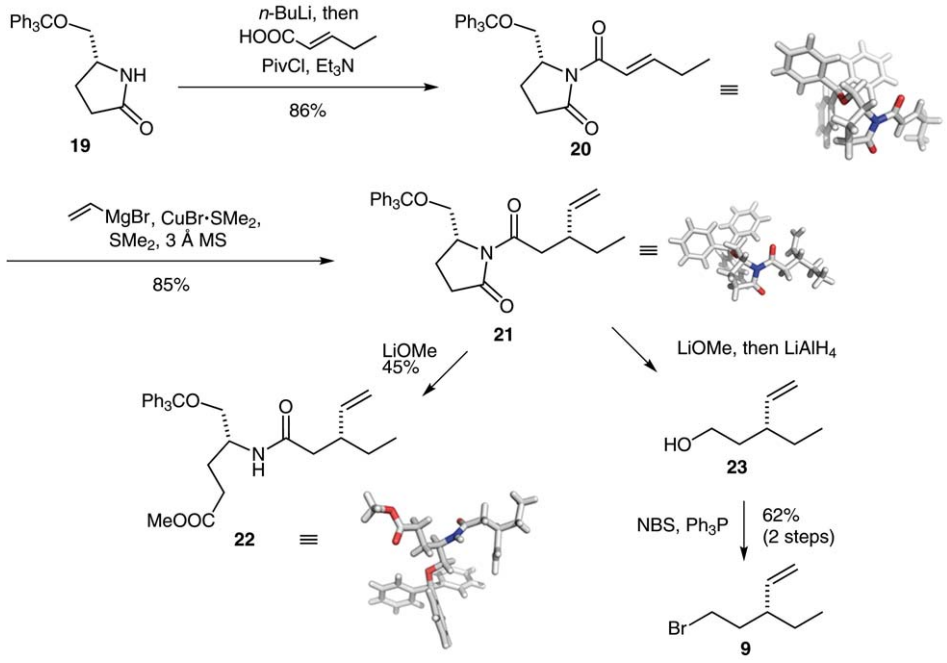


Scheme 2 Synthesis of the 'eastern' chain **8**. TCBC = 2,4,6-trichlorobenzoyl chloride.

pared on a gram scale. The desired stereochemical outcome of the reaction was secured by single-crystal X-ray analysis of **21** and related compound **22**.[11]

Cleavage of the auxiliary group proved more difficult than anticipated. Lithium methoxide only delivered undesired amide **22**. However, a combination of lithium methoxide and $LiAlH_4$ gave alcohol **23**, which was converted into the volatile bromide **9** using Appel-type conditions.

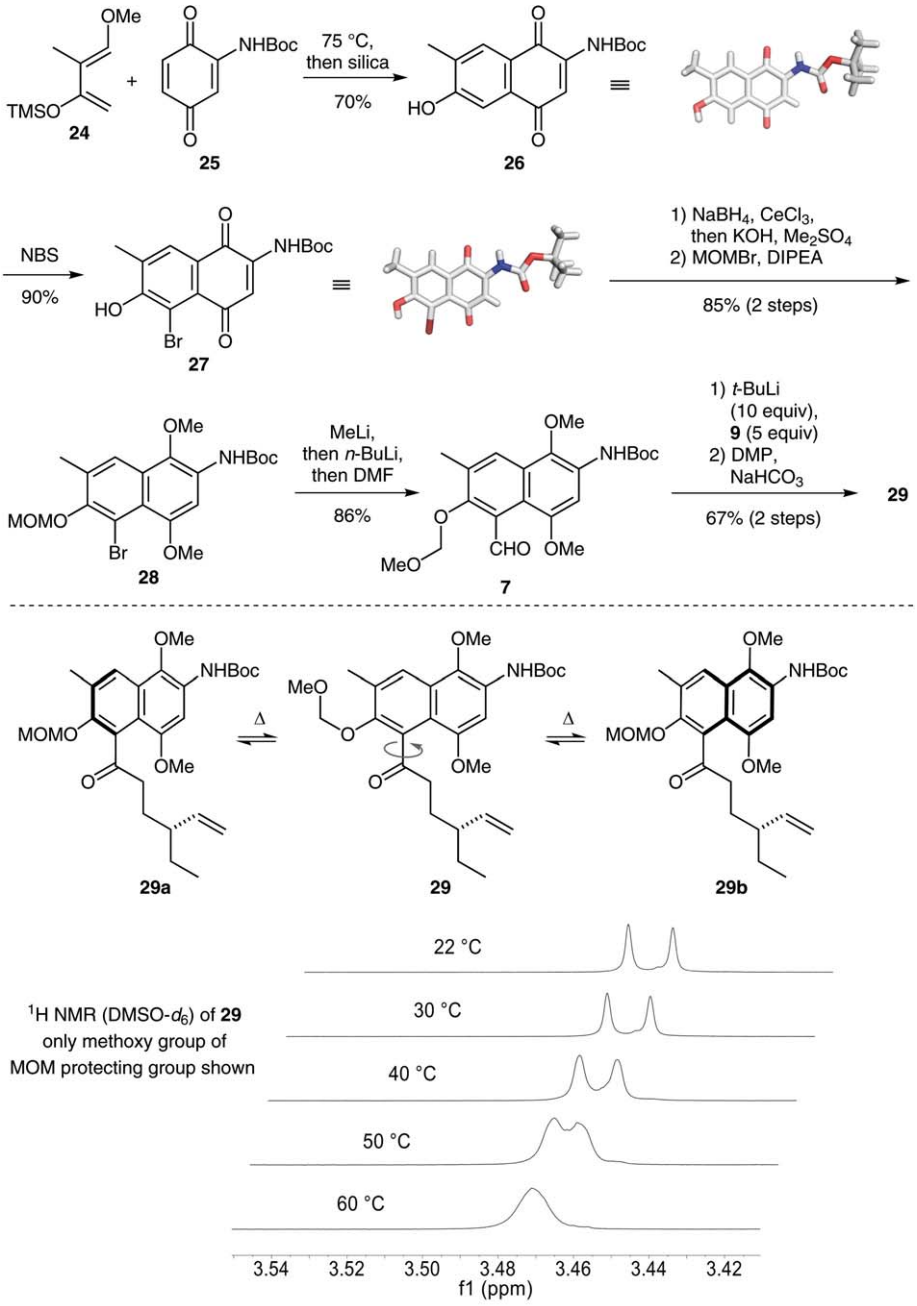
The synthesis of formyl naphthalene **7** was achieved in five steps starting from known Danishefsky-type diene **24**[12] and *p*-benzoquinone **25**[13] (Scheme 4).[14] Diels–Alder reaction of the two compounds under optimized condi-



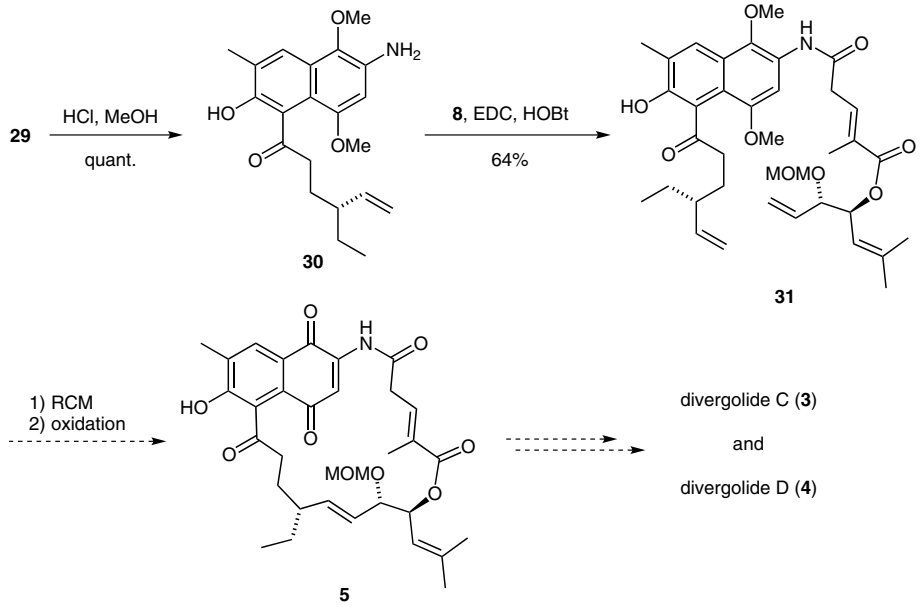
Scheme 3 Assembly of the 'southwestern' chain **9**

tions provided Boc-protected naphthoquinone **26** as a single isomer, the structure of which was unambiguously confirmed through X-ray crystallography. Treatment of **26** with *N*-bromosuccinimide cleanly yielded the monobrominated naphthalene **27**,[15] which was then transformed into hydroquinone dimethyl ether **28** by MOM protection and reductive etherification. Deprotonation of the amide, followed by lithiation of **28** and quenching of the resulting dianion with DMF provided aldehyde **7** in good yield of 86%.

The stage was now set to bring the three building blocks together (Scheme 4). In order to attach the southwestern chain **9**, we had to carefully optimize the reaction conditions. Lithiation of bromide **9** using excess of *t*-BuLi followed by addition of naphthyl aldehyde **7**, aqueous workup, and immediate Dess–Martin oxidation, reliably provided the desired ketone **29** in 67% over two steps. Interestingly, the ^{1}H NMR spectrum of **29** at room temperature showed two different sets of signals as soon as any side chain was attached to the carbonyl group (Scheme 4, bottom). Since we do not observe Boc rotamers on bromonaphthalene **28** and naphthaldehyde **7**, we attribute this observation to a hindered rotation around the axis between the carbonyl group and the naphthalene moiety. As a result, compound **29** exists at room temperature as a mixture of two atropisomers **29a** and **29b** (Scheme 4). In order to show that these diastereomers can be interconverted, we



Scheme 4 Synthesis of the naphthalene building block **7** and attachment of the 'southwestern' chain (top); high-temperature ^{1}H NMR experiments of compound **29** (bottom)



Scheme 5 Completion of the assembly of precursor **31**

performed variable-temperature ^{1}H NMR experiments. Indeed, at 60 °C the signals of the two diastereomers coalesce to one set of peaks, as it is illustrated for the methoxy protons of the MOM group.

Next, removal of both protecting groups in **29** under acidic conditions using a solution of HCl in MeOH gave free aminonaphthalene **30** in quantitative yield (Scheme 5). It is worth noting, that due to the absence of the MOM group in **30**, free rotation around the axis is enabled, which is reflected in the NMR spectra. Finally, amide coupling of free amine **30** and carboxylic acid **8** with EDC and HOBt gave ring-closing-metathesis precursor **31** in 64% yield. So far, our attempts to oxidize and cyclize this compound via olefin metathesis to reach key intermediate **5** have been unsuccessful and have only yielded dimeric compounds. A solution to this problem could involve substitutions that ensure that the *s-cis* conformation of the amide conducive to cyclization is energetically attainable.

In summary, we have synthesized an advanced synthetic precursor for divergolides C and D that possesses all carbon atoms of the natural products. Our synthetic study allowed for detailed investigations of atropisomerism in sterically crowded acyl naphthalenes, an issue that needs to be addressed in the final synthesis of the molecules. Our efforts to complete the synthesis of the divergolides and thus support Hertweck's biosynthetic hypothesis are well under way and will be reported in due course.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental details, spectroscopic and analytical data for all new compounds (including X-ray data for **20**, **21** and **22**, as well as for **26** and **27**).

References

(1) For recent examples of divergent total synthesis, see: (a) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (b) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (c) Chiyoda, K.; Shimokawa, J.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 2505.

(2) Ding, L.; Maier, A.; Fiebig, H.-H.; Görls, H.; Lin, W.-H.; Peschel, G.; Hertweck, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 1630.

(3) (a) Zhao, G.; Wu, J.; Dai, W.-M. *Synlett* **2012**, *23*, 2845. (b) Rasapalli, S.; Jarugumilli, G.; Yarrapothu, G. R.; Golen, J. A.; Rheingold, A. L. *Org. Lett.* **2013**, *15*, 1736. (c) Rasapalli, S.; Jarugumilli, G.; Yarrapothu, G. R.; Golen, J. A.; Rheingold, A. L. *Tetrahedron Lett.* **2013**, *54*, 2615.

(4) Kuttruff, C. A. *PhD Thesis*; LMU München: Germany, **2012**.

(5) Xu, Z.; Ding, L.; Hertweck, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 4667.

(6) For a similar situation encountered in the isolation of hygrocins, see: (a) Cai, P.; Kong, F. M.; Ruppen, M. E.; Glasier, G.; Carter, G. T. *J. Nat. Prod.* **2005**, *68*, 1736. (b) Pennington, L. I.; Moody, C. J. *Abstracts of Papers of the ACS 238th National Meeting, August 16th, 2009*; American Chemical Society: Washington, DC, **2009**, Abstract number ORGN 387.

(7) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (b) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Fleming I.; Pergamon Press: Oxford, **1991**, 1.

(8) Yin, N.; Wang, G.; Qian, M.; Negishi, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2916.

(9) Phillips, D. J.; Pillinger, K. S.; Li, W.; Taylor, A. E.; Graham, A. E. *Chem. Commun.* **2006**, 2280.

(10) (a) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369. (b) Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. *Tetrahedron* **2004**, *60*, 2097. (c) Adam, W.; Zhang, A. *Eur. J. Org. Chem.* **2004**, 147.

(11) X-ray structures in cif format for compounds **20**, **21**, and **22** are available at the Cambridge Crystallographic Data Center (registration numbers CCDC 894000, 894001, and 894001, respectively).

(12) (a) Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840. (b) Gupta, R. C.; Larsen, D. S.; Stoodley, R. J.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 739. (c) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976. (d) Miyashita, M.; Yamasaki, T.; Shiratani, T.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1997**, *18*, 1787. (e) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793.

(13) Nawrat, C. C.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2011**, *76*, 7872.

(14) Kuttruff, C. A.; Geiger, S.; Cakmak, M.; Mayer, P.; Trauner, D. *Org. Lett.* **2012**, *14*, 1070.

(15) X-ray structures in cif format for compounds **26** and **27** are available at the Cambridge Crystallographic Data Center (registration numbers CCDC933387 and 933388, respectively).

