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Studies toward Total Synthesis of Divergolides C and D

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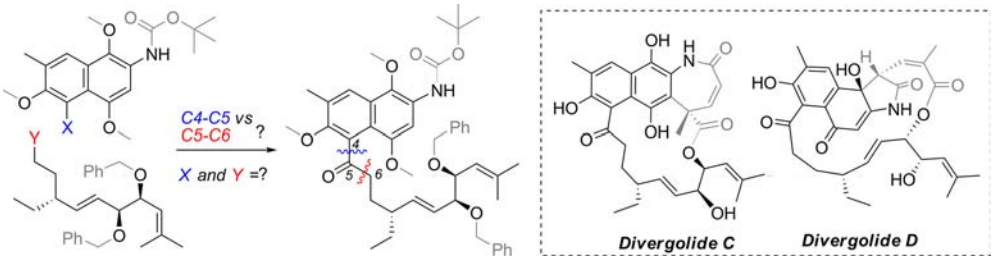
ABSTRACT



A facile synthesis of the western segment of divergolides C and D has been developed. Exploratory studies with two disconnections, i.e., *C4−C5* vs *C5−C6*, for elaboration of the ansa bridge to the sterically demanding hexasubstituted naphthalenic aromatic core using a chiral synthon assembled from D-glucose via a stereoselective Johnson orthoester rearrangement is described. The studies set the stage for the completion of the total synthesis of the biologically important novel ansamycins, divergolides C and D, and their structural congeners.

Ever since the discovery of the antibacterial rifamycin B, ansamycins continue to evoke interest of synthetic and medicinal chemists as antibiotic and antineoplastic agents.[1] Recently, structurally unique ansa macrolides have been isolated from *Streptomyces* sp. HKI0576, an endophyte of the mangrove tree *Bruguiera gymnorrhiza*, and have been named divergolides A−D (**1**−**4**) (Figure 1) due to the possibility of divergent biosynthetic origin.[2]

Divergolides C and D (**3** and **4**) are structurally very close to hygrocins A and B (**5** and **6**), another family of metabolites isolated from *Streptomyces hygroscopicus*.[3] However, divergolides C and D (**3** and **4**) differ from hygrocins A and B (**5** and **6**) in their unprecedented isobutenyl side chain at C12 and oxidation states of the

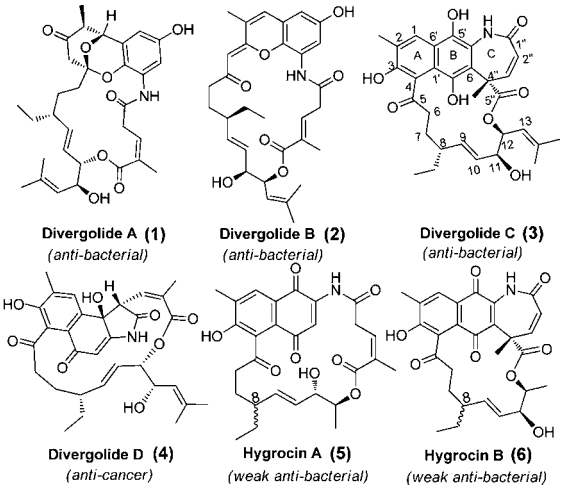


Figure 1. Ansa macrolides isolated from *Streptomyces* sp.

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(1) For recent reviews on ansamycin natural products, see: (a) Wrona, I. E.; Agouridas, V.; Panek, J. S. *C. R. Acad. Sci., Paris* **2008**, *11*, 1483. (b) Floss, H. G.; Yu, T. W. *Chem. Rev.* **2005**, *105*, 621. (c) Funayama, S.; Cordell,G. A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 2000; Vol. 23, p 51. (d) Bryskier, A. In *Antimicrobial Agents*; Bryskier, A., Ed; ASM Press: Washington, DC, 2005, 906.

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

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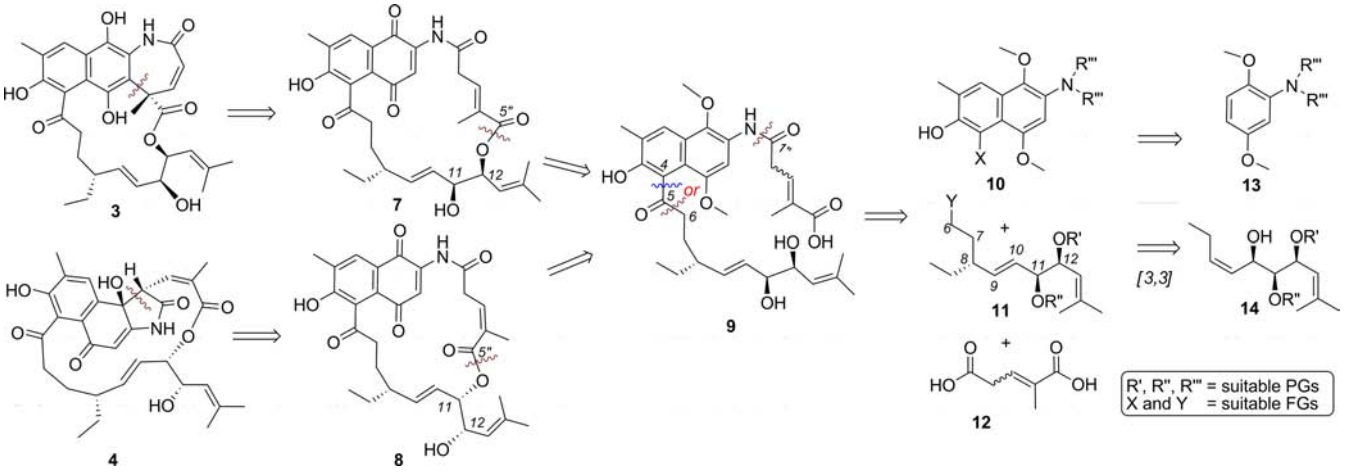
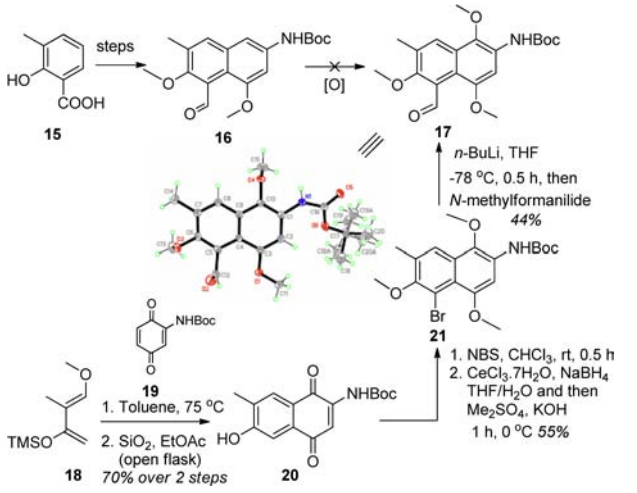
Scheme 1. Retrosynthesis of Divergolides C and D (**3** and **4**)



aminonaphthoquinone, while the overall topology is conserved, except for the shorter bridge seen in divergolide D (**4**). Although the aromatic cores of divergolides C and D differ profoundly from one another, a common biosynthetic proposal involving an amino hydroxybenzoic acid (AHBA)-primed common naphthoquinone polyketide precursor has been proposed.[2,4] The differences in the aromatic cores and in the sizes of the ansa bridge are reflected in the diverse bioactivities of divergolides A−D (**1**−**4**). For example, divergolide D (**4**) showed promising anticancer activities while divergolides A−C (**1**−**3**) exhibited decent antibacterial activities. As aptly pointed by Hertweck et al., this unique macrolide family offers the opportunity for undertaking a natural product based medicinal chemistry approach for developing novel leads for antibacterial and anticancer activities. Because of their structural complexity and diversity in biological acitivities, divergolides A−D (**1**−**4**) have attracted the attention of synthetic chemists, and the first reports describing synthetic approaches have been published recently.[5] We set out to develop a total synthesis of divergolides C (**3**) and D (**4**), amenable to large-scale production of structural analogues, to explore their biomedicinal potential.

As can be seen from our retrosynthetic analysis of the divergolides C (**3**) and D (**4**), shown in Scheme 1, disconnection of the biomimetic macrolide precursors **7**/**8** at the lactam (C1″-N) and lactone (C11/12-OH and C5″) sites provides options to assemble the macrolide skeleton. Our fragment-based approach identified three synthons, namely aromatic core **10**, chiral fragment **11**, and 2-methyl-2-pentenedioic acid **12**. We initially focused our efforts on synthesis of the AB-rings of the tricyclic core of the targets under consideration and planned to rely on the putative biomimetic annulations of *N*-acylated naphthoquinone for the formation of the C-ring of the tricyclic aromatic cores.

Scheme 2. Synthesis of Formyl Naphthalene Core



Our initial foray that involved utilization of 3-methylsalicylic acid (**15**) met with a roadblock in the final conversion of the desoxy-AB core **16** to **17**.[6] Hence, we resorted to a well-established route in the synthesis of aromatic cores of ansamycins, i.e., Diels−Alder reaction of modified Danishefsky's dienes with quinones, to obtain the naphthalenic core **17** and planned to introduce the required C3 carbonyl at a later stage as shown in Scheme 2. Thus, the requisite diene **18** and the quinone **19** were prepared following the literature protocols[7] whose cycloaddition provided the quinone

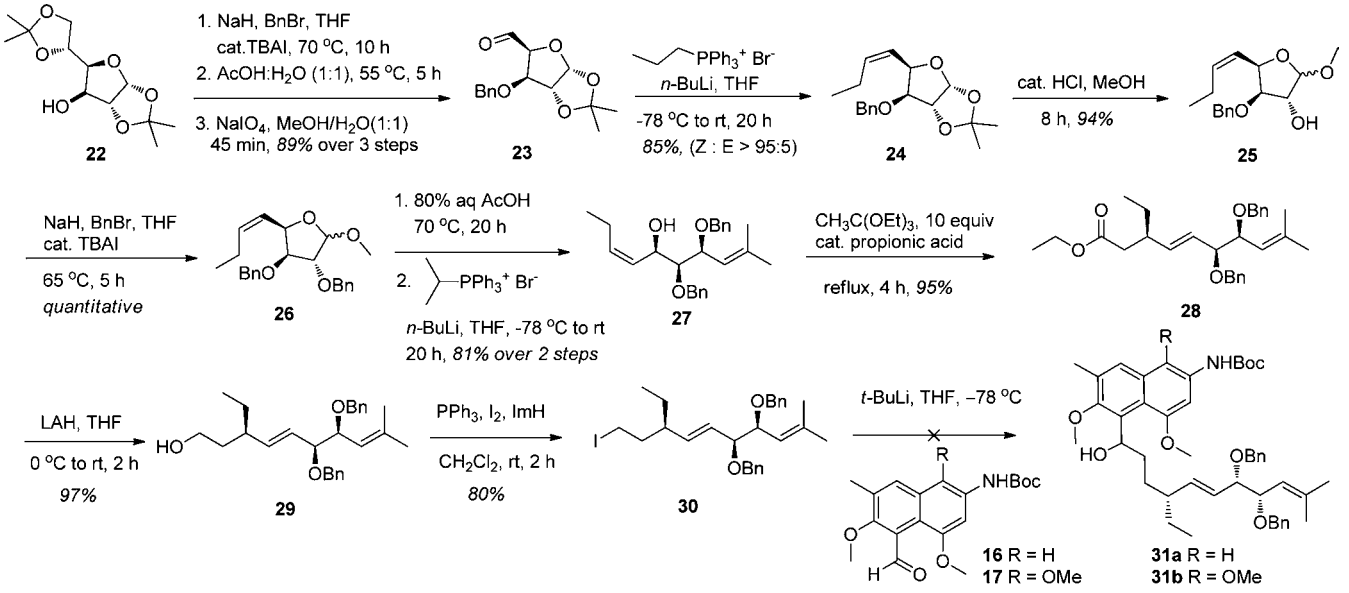
(4) For a recent comprehensive review on the biosynthesis of ansamycins, see: Kang, Q.; Shen, Y.; Bai, L. *Nat. Prod. Rep.* **2012**, *29*, 243.

(5) (a) Kuttruff, C. A.; Geiger, S.; Cakmak, M.; Mayer, P.; Trauner, D. *Org. Lett.* **2012**, *14*, 1070. (b) Zhao, G.; Wu, J.; Dai, W.-M. *Synlett* **2012**, *23*, 2845. (c) Pennington, L. L.; Moody, C. J. *Abstracts of Papers*, 238th ACS National Meeting, Washington, DC; American Chemical Society: Washington, DC, 2009.

(6) Rasapalli, S.; Jarugumilli, G.; Yarrapothu, G. R.; Golen, J. A.; Rheingold, A. L. *Tetrahedron Lett.* **2013**, http://dx.doi.org/10.1016/j.tetlet.2013.03.022.

(7) (a) Nawrat, C. C.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2011**, *76*, 7872. (b) Kuttruff, C. A.; Geiger, S.; Cakmak, M.; Mayer, P.; Trauner, D. *Org. Lett.* **2012**, *14*, 1070.

Scheme 3. Synthesis of Ansa C6–C12 Fragment



20 in decent yield. Quinone **20** was subjected to a series of transformations involving bromination, reduction, *O*-methylation, lithiation, and formylation to obtain the aldehyde **17** in good overall yield.[8]

Having obtained the required AB-aromatic core **17** with pendent aldehyde for further elaboration, we turned our focus to the synthesis of the chiral fragment **11**. At the outset, we wanted to develop a scalable and cost-effective stereoselective route for the (C6–C12) fragment **11** that allows orthogonal protection of the C11 and C12 hydroxyl groups while accommodating different substituents at C12.[9] Keeping the above criteria and our resources in focus, the stereochemistry of the target molecules was mapped via the chiral pool synthesis through the stereoselective Johnson orthoester variant of the Claisen rearrangement, whose synthetic utility is underlined by its predictable high diastereoselectivity.[10]

Our synthetic efforts commenced with the commercially available D-glucose diacetonide **22** to obtain the fragment **11** with the requisite stereochemistry and functional groups, as shown in Scheme 3. Thus, D-glucose diacetonide **22** was converted to aldehyde **23** following the literature procedure.[11] Wittig olefination of aldehyde **23** with *n*-propylidenetriphenyl phosphorane (generated in situ from $n\text{-}C_3H_7PPh_3{}^+Br^-$ and *n*-BuLi) at −78 °C gave the *Z*-olefin **24**[12] with good (>95:5 *Z*/*E*) stereoselectivity. Treatment of the *Z*-olefin **24** with a catalytic amount of concentrated HCl in MeOH provided a 1:1 mixture of anomers **25** whose free secondary hydroxyl group is ideally placed for orthogonal protection. However, with the intention of establishing the chemistry required for the elaboration of the ansa bridge onto aromatic core **17**, we converted the secondary hydroxyl group of **25** to benzyl ether **26** under NaH and BnBr conditions. Compound **26** was in turn converted to hemiacetal as 1:1 mixture of α and β anomers whose Wittig olefination with isopropylidenetriphenyl phosphorane[13] (generated in situ from $i\text{-}C_3H_7PPh_3{}^+Br^-$ and *n*-BuLi) gave allylic alcohol **27** in good yield.

With the optically pure allylic alcohol **27** in hand, the stage was set to ascertain the efficacy of Johnson orthoester rearrangement.[14] Pleasingly, refluxing compound **27** at 130 °C for 3 h in triethyl orthoacetate (10 equiv) in the presence of a catalytic amount of propionic acid provided ester **28** exclusively as a single diastereomer in quantitative yield.[15] In light of our successful model studies[6] for C5–C6 bond formation, it made sense to convert the ester to the appropriate halide for the eventual conversion into the organomagnesium derivative of the chiral C6–C12 fragment. Accordingly, ester **28** was reduced with $LiAlH_4$ to give primary alcohol **29**, which in turn was converted to primary iodide **30** under Appel reaction conditions.[16]

Having accessed both synthons, i.e., **17** and **30**, on a multigram scale, we attempted the formation of organomagnesium with the iodide **30**, albeit unsuccessfully. After a few

(8) For an alternative approach to **17**, see: Kuttruff, C. A. Dissertation, Ludwig-Maximilians-Universität München, 2012, ISBN 9783843906005.

(9) We plan on extending this route to the total synthesis of hygrocins A and B.

(10) Fernandes, R. A.; Ingle, A. B.; Chaudhari, D. A. *Eur. J. Org. Chem.* **2012**, 1047.

(11) Schwörer, C. J.; Oberthür, M. *Eur. J. Org. Chem.* **2009**, 6129.

(12) (a) Byrne, P. A.; Gilheany, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 9225. (b) Tortosa, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3950. (c) Sharma, G. V. M; Vepachedu, S. R. *Tetrahedron* **1991**, *47*, 519. (d) Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4786.

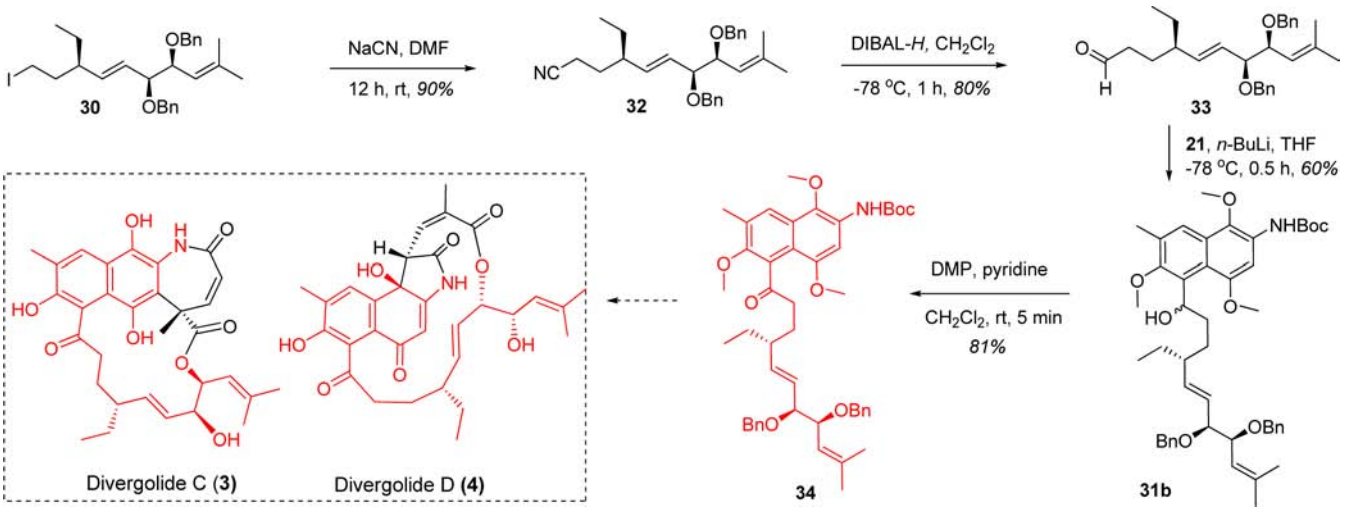
(13) Tzirakis, M. D.; Alberti, M. N.; Orfanopoulos, M. *Org. Lett.* **2011**, *13*, 3364.

(14) (a) Hiersemann, M.; Nubbemeyer, U. *The Claisen Rearrangement*; Wiley-VCH: Weinheim, 2007. (b) Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939. (c) Nubbemeyer, U. *Synthesis* **2003**, 961. (d) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461.

(15) Fernandes, R. A.; Ingle, A. B.; Chaudhari, D. A. *Eur. J. Org. Chem.* **2012**, 1047 and references cited therein.

(16) Prusov, E.; Röhm, H.; Maier, M. E. *Org. Lett.* **2006**, *8*, 1025.

Scheme 4. Succesful Elaboration of Ansa Bridge via Coupling of the Advanced Synthons



unsuccessful attempts, we found that *t*-BuLi was more effective for lithiation of the iodide **30**. Although this lithiated **30** proved successful in coupling with simple electrophiles,[17] to our dismay it did not react with aldehyde **17**.

The C5−C6 disconnection turned out to be not as simple as it appeared from our model studies; similarly, Trauner et al. have also faced problems with this disconnection.[4,7] We reasoned that electronic factors might be operative in comparison to aldehyde **16** that had been shown earlier to couple with 2-ethylhexylmagnesium bromide.[6] Even our efforts to couple lithiated **30** with aldehyde **16** were of no avail to form the C5−C6 bond to access **31a**, ruling out electrophilicity or steric issues of the aromatic partner as reasons for failure.[18] We finally resorted to the reversal of the polarity of the intermediates and planned the coupling of the two synthons via C4−C5 bond formation.[19] This approach required the homologation of the iodo compound **30** to aldehyde **33**. This task was accomplished via nitrile chemistry under standard conditions with good yields as shown in Scheme 4.

Gratifyingly, the coupling reaction of the lithiated naphthalenic core **21** with aliphatic aldehyde **33** proceeded with moderate yield (65%, unoptimized) to provide the alcohol **31b** as a mixture of diastereomers. Careful oxidation of **31b** under DMP/pyridine conditions provided ketone **34** in good yield as a mixture of atropisomers.[20]

In summary, we have synthesized the western segment of divergolides C and D (**3** and **4**). The requisite aromatic fragments are prepared on large scale via a reliable cycloaddition approach. We have also successfully constructed the variously functionalized chiral fragments with the requisite stereochemistry of the targets, i.e., C8 (R), C9=C10 (*E*), C11(S), C12(S), via a chiron approach. Two complementary strategies for the coupling of the advanced synthons via C4−C5 and C5−C6 disconnections were evaluated, and we established the robustness of the C4−C5 over C5−C6 as a suitable approach for our further studies toward completion of the total synthesis of divergolides C and D (**3** and **4**). The chemistry described herein is also applicable for the synthesis of divergolides A and B (**1** and **2**) as well as hygrocins A and B (**5** and **6**). Our studies in this direction will be reported in due course.

Acknowledgment. This work was supported through the startup and Healey Foundation funds of UMass Dartmouth and partly from Microbiotix, Inc, Worcester.

Supporting Information Available. Complete experimental procedures, including ^{1}H and ^{13}C spectra of all new compounds. X-ray data (CIF) for **17**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

(17) Lithiated **30** reacted succesfully with an amide derived from 3-methylsalicylic acid: Rasapalli, S.; Jarugumilli, G.; Yarrapothu, G. R. Unpublished results.

(18) We are currently exploring the different options for utilizing **16**/**17** in total synthesis of divergolides A−D.

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The authors declare no competing financial interest.