Organic LETTERS

Letter

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Toward the Total Synthesis of Hygrocin B and Divergolide C: Construction of the Naphthoquinone−Azepinone Core

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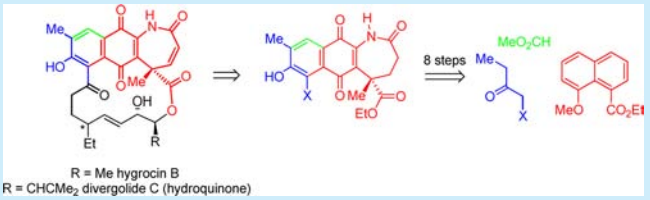
Supporting Information

ABSTRACT: A highly regioselective Diels−Alder approach toward the bioactive natural products hygrocin B and divergolide C is presented. The route uses an unusual benzoquinone−azepinone dienophile prepared in 8 steps from ethyl 8-methoxy-1-naphthoate, by a route which includes, as key steps, a Birch alkylation and a Beckmann rearrangement of a tetralone oxime, both of which are demonstrated on multigram scale. The naphthoquinone−azepinone core is suitably functionalized for addition of the ansa-chain, found in the natural products.



The ansamycin antibiotics are a group of structurally diverse, biologically active, and historically important natural products that have been known for over 50 years.[1] This class of compounds has provided humanity with a number of important drugs that are used worldwide; for example rifabutin **1** and other semisynthetic derivatives of the rifamycins are current frontline treatments for tuberculosis (Figure 1).[2,3] Hence, the isolation of new members of this class of compounds continues to draw interest from the chemical community. Recently, the ansamycin divergolide C **2** was isolated along with a number of its congeners from the bacterium *Streptomyces* sp. HKI0576,[4] exhibiting a highly unusual naphthoquinone−azepinone core as well as moderate antibacterial activity. The only previously reported example of this ring system is found in the closely related naphthoquinone ansamycin hygrocin B **3**, isolated in 2005 along with hygrocin A **4** from *Streptomyces hygroscopicus*,[5] an organism that has proved to be a goldmine of powerful bioactive compounds such as milbemycin, geldanamycin, and rapamycin. Indeed, the hygrocins were first isolated by chemists at Wyeth as impurities in a batch of rapamycin. However, despite this auspicious provenance, they display none of the characteristic biological activity of their more famous coisolates, exhibiting only very weak antibiotic activity, a fact attributed to their remarkably short 13 carbon aliphatic chains, which place them among the smallest known ansamycins. Additionally, the hygrocins C−G were recently isolated from the bacterium gdmAI-disrupted *Streptomyces* sp. LZ35.[6]

Considering the structures of these compounds, hygrocin A **4** appears to be an immediate biosynthetic precursor to hygrocin B **3**,[7] requiring just enolization and cyclization of the macrocyclic ester. Indeed, the biosynthesis of the hygrocins has been the subject of a recent article by Shen and co-workers.[8] However, despite this relationship, the synthesis of **3** *via* **4** is a daunting prospect, due to the challenge of forming the macrocycle of A, which contains a trisubstituted *Z*-olefin adjacent to a highly active methylene group. Furthermore, although hygrocin A is reported as quite unstable as a result of this functionality, the degradation products obtained are those of cyclization of the ansa chain onto the quinone *carbonyl* rather than the quinone *olefin*.[5] Even if the desired azepinone formation could be carried out, it is unclear whether the newly formed quaternary center would have the required configuration or how the stereochemical outcome of this reaction might be controlled. It should also be noted that, in the case of divergolide C **2**, the putative precursor **5** to the azepinone-forming cyclization has not yet been isolated, although, as for hygrocin A, products of the 'unwanted' cyclization onto the quinone carbonyls such as divergolide D **6** do occur in Nature. This suggests that the mode of cyclization required to form the azepinone found in divergolide C may not be particularly favorable and designing a synthesis that relies on carrying out this step at a late stage may be unwise.

In view of these considerations, we decided to eschew the 'macrocycle-first' approach recently reported by Rasapalli[9−11] and Trauner[12] and, instead, consider two potential synthetic routes: the first employing an ambitious intramolecular Diels−Alder approach from the pendant diene-containing benzoquinone-azepinone **7**, and the second aiming to prepare the tricyclic naphthoquinone−azepinone core **8**, common to both divergolide C **2** and hygrocin B **3**, to which suitable ansa chains could later be attached, either by modifying a pendant ester, nitrile, or allyl group or by introducing a halogen or a formyl group *ortho* to the naphthol (Scheme 1) (cf. Rasapalli).[9−11] By focusing initially on the second approach, it was anticipated that the core **8**, bearing a point of attachment for the ansa chain, could be prepared by a Diels−Alder reaction of a suitable diene such as **10**−**13** with a benzoquinone−azepinone **9**. This dienophile could itself be prepared from a suitable tetralone using classic aromatic chemistry. This strategy will allow the

Received: February 5, 2014
Published: March 25, 2014

dx.doi.org/10.1021/ol5003847 | *Org. Lett.* 2014, 16, 1896−1899

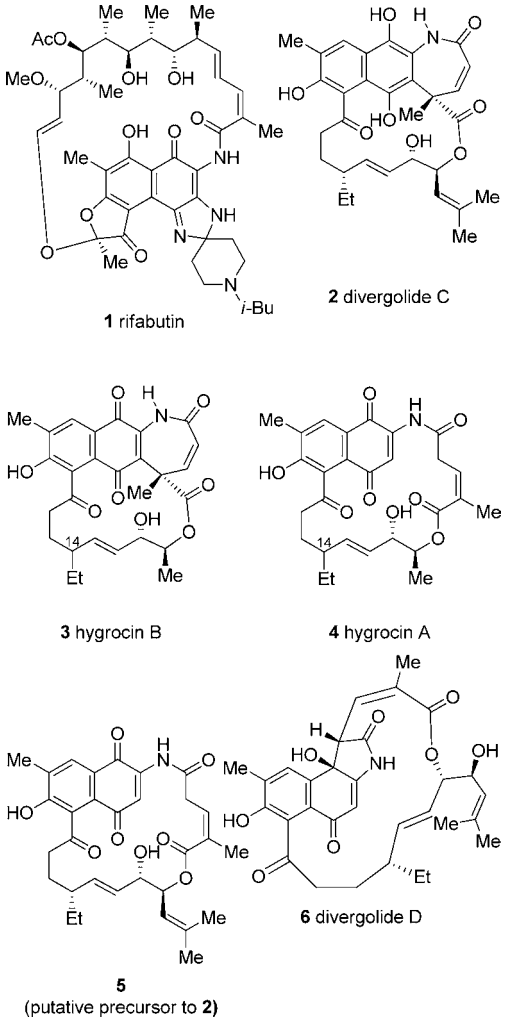
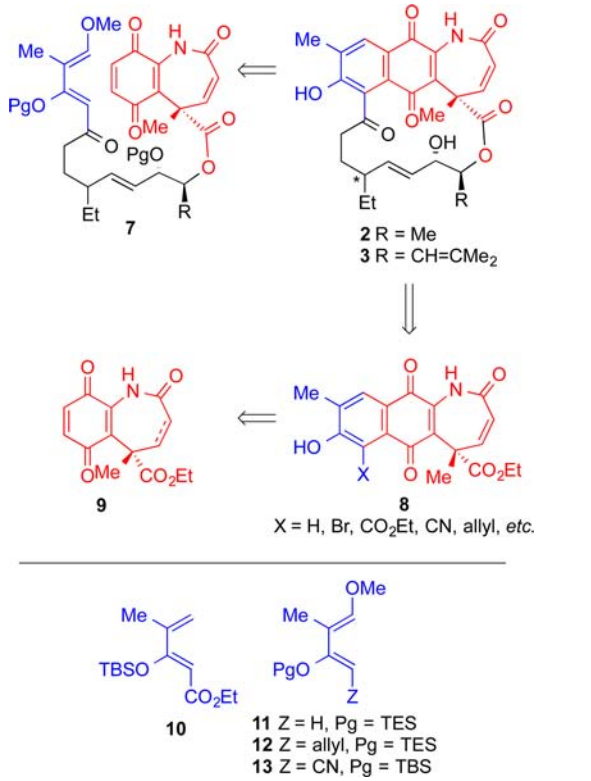


Figure 1. Selected naphthoquinone ansamycins, including hygrocins and divergolides.

challenging quaternary center present in these natural products to be set early on in the synthesis, and the divergent nature of the route should allow access to both natural products from a common late-stage intermediate.

The synthesis of dienophile **9** began from ethyl 8-hydroxy-1-naphthoate **14** (Scheme 2),[13] which was readily prepared from commercial naphthalic anhydride or naphtholactam using known chemistry (see Supporting Information for details).[14,15] This was protected as its methyl ether and subjected to Birch reductive alkylation by treatment with lithium in liquid ammonia−THF−*t*-BuOH, followed by quenching with iodomethane to give ester **15**. This reaction proceeded in excellent yield, even on decagram scale and was found to be tolerant of various *O*-protecting groups including TES and TIPS ethers as well as several different esters (methyl, ethyl, and *tert*-butyl). Furthermore, as asymmetric Birch alkylations are well precedented,[16] this step could be adapted to provide a single enantiomer. Allylic oxidation was carried out using Corey's procedure,[17] which proved superior to chromium based methods on a large scale, even with very low catalyst loadings (1 mol % Pd), and the resulting enone **16** was converted into the corresponding oxime **17**. Surprisingly, this second step required quite forcing conditions involving the use of a large excess of hydroxylamine hydrochloride in anhydrous pyridine at 80 °C in order to achieve good conversion. Oxime **17** was

Scheme 1. Initial Retrosynthetic Analysis

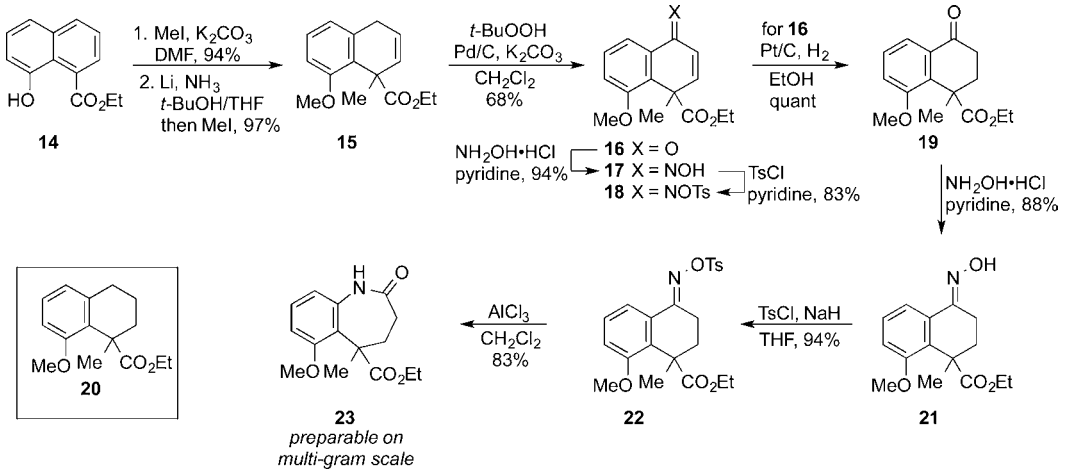


found to be inert toward standard Beckmann conditions, so was activated by tosylation, and a range of conditions were screened for the key rearrangement. Unfortunately, no desired product benzazepinone was obtained under Brønsted (PPA, H_2SO_4, HCl, TFA) or Lewis ($AlCl_3$,[18] $CuSO_4$, $BF_3{\cdot}OEt_2$[19]) acid activation of **18**, even at high temperatures. In view of this failure, and the very limited literature precedent for Beckmann rearrangement of α,β-unsaturated oximes, we decided to prepare the corresponding saturated tosyl oxime **22** in order to compare its reactivity to that of **18**. As removal of the double bond at the oxime stage was anticipated to be problematic, hydrogenation of enone **16** was investigated instead. However, to our surprise, reduction of enone **16** using palladium-on-carbon under an atmosphere of hydrogen at room temperature did not give tetralone **19** but instead yielded tetralin **20**. This unexpected reaction appeared to be quite rapid, and complete conversion into the tetralin occurred in just 2 h. Further investigation revealed that the desired product could not be obtained by simply shortening the reaction time, as this only produced mixtures of both products. Fortunately it was found that hydrogenation over a platinum catalyst, in the form of platinum dioxide or platinum-on-carbon, prevented over-reduction and gave the desired tetralone in quantitative yield. Oxime formation and tosylation gave Beckmann precursors **21** and **22**, whose rearrangement was now investigated. Although oxime **21** and tosyl oxime **22** proved quite unreactive toward Brønsted acid activation, it was found that rearrangement to the desired lactam **23** could be effected in good yield upon treatment of **22** with 4 equiv of aluminum chloride at 0 °C,[18] even on gram scale.

Initially we had planned to demethylate benzazepinone **23** prior to oxidation to the quinone, as oxidation of phenols is far easier than that of anisoles and can be achieved under mild and specific conditions using salcomine or Frémy's salt. However,

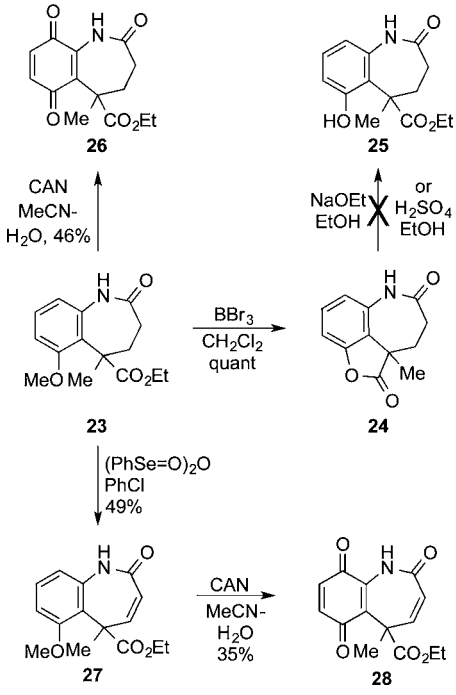
dx.doi.org/10.1021/ol5003847 | *Org. Lett.* 2014, 16, 1896−1899

Scheme 2. Synthesis of a Suitable Benzazepinone Precursor



this deprotection proved challenging; although demethylation occurred rapidly, the product tended to undergo lactonization to **24** under the reaction conditions (Scheme 3). Attempted

Scheme 3. Oxidation of Lactam 23 to the Quinone 26 and Reintroduction of the α,β-Unsaturation with Subsequent Oxidation to the Benzoquinone−Azepinone 28

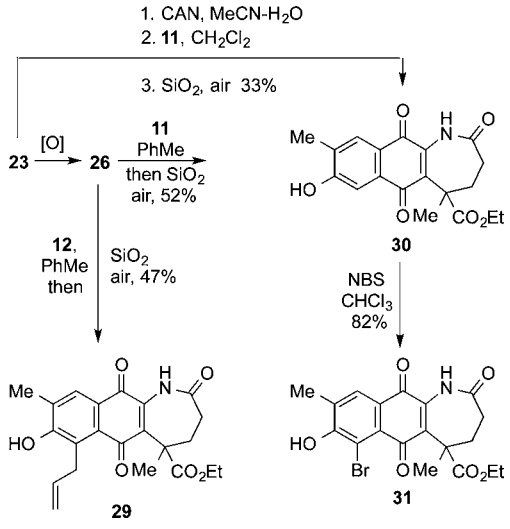


opening of lactone **24** to obtain the desired phenol **25** was not successful, generally resulting in decomposition and mixtures of products. Nucleophilic removal of the methyl group was unsuccessful, and thus we were forced investigate the possibility of oxidizing **23** directly to the quinone. The use of Dess-Martin periodinane for this transformation as recently described by Rasapalli was unsuccessful,[10] as was the use of IBX as described by Nicolaou and co-workers for the oxidation of a range of acetanilides.[20−23] Our previously reported conditions employing bis(trifluoroacetoxy)iodobenzene and di(acetoxy)iodobenzene did result in formation of some product (15−20%),[24] but the best conditions involved the use of excess cerium(IV) ammonium nitrate in aqueous acetonitrile, which delivered the desired quinone **26** in moderate yield. Unfortunately, the yields decreased on scale-up beyond 100 mg, although owing to the efficiency of the rest of the synthetic route enough material could be obtained to allow examination of the pivotal Diels−Alder reaction.

At this stage oxidation of benzazepinone **23** to reintroduce the α,β-unsaturation was investigated. Although such a transformation is commonplace in the γ-lactam series,[25] it is almost unknown in benzazepinones and was crucial to the viability of the proposed route.[26] Fortunately, after screening a number of oxidants known to effect this transformation, it was found that simply heating **23** with 2 equiv of benzeneselenic anhydride in chlorobenzene gave a reasonable yield of the desired compound in a single step (Scheme 3).[25] Benzazepinone **27** could also be oxidized successfully to the corresponding benzoquinone−azepinone **28**.

With dienophiles **26** and **28** in hand, their reactivity in the key Diels−Alder step was now investigated (Scheme 4). Disappointingly, **26** did not undergo a reaction with the ester containing diene **10**[24] and did not appear to tolerate the relatively high reaction temperatures (130−150 °C) typically

Scheme 4. Diels−Alder Reactions of Quinone 26; Synthesis of the Naphthoquinone−Azepinone Core



dx.doi.org/10.1021/ol5003847 | Org. Lett. 2014, 16, 1896−1899

required for this partner. Next, we prepared and tested Trauner's nitrile-containing diene **13**,[27] which has been shown to be somewhat more reactive than **10** and quite amenable to Lewis acid catalyzed Diels–Alder reactions, but this was also unproductive. Additionally, studies on fully unsaturated benzoquinone–azepinone **28** were unsuccessful. Although an initial reaction occurred with diene **12**, no desired product was observed. Fortunately, quinone **26** did undergo a Diels–Alder reaction with diene **12** to give the naphthoquinone–azepinone **29** in reasonable yield, with the allyl group serving as a latent aldehyde, as has already been demonstrated in the context of aminonaphthoquinone synthesis.[24] Alternatively, allylic/benzylic oxidation would give an enone suitable for attaching the ansa-chain by the organocatalytic asymmetric conjugate addition methodology developed by Gellman and coworkers,[28] allowing access to both configurations of the stereocenter at position 14, as yet undetermined in the hygrocins A and B (Figure 1). The simpler diene **11**[29] was also found to be a suitable reaction partner, allowing tricyclic quinone **30** to be prepared in moderate yield. This was slightly improved by employing a telescoped procedure, avoiding purification of the somewhat sensitive quinone **26**, giving the Diels–Alder adduct **30** in 33% yield over 2 steps. In both Diels–Alder reactions, there was no sign of the alternative regioisomer, and the regiochemistry of this product was confirmed by HMBC NMR spectroscopy experiments and is in accordance with those previously observed for the reactions of aminonaphthoquinones.[22,24,30] Further functionalization of **30** was also shown to be possible: bromination of the aromatic ring[9−11] gave the bromoaminonaphthoquinone–azepinone **31** in excellent yield. This allows for lithium–halogen exchange and trapping of the aryllithium with a suitable electrophile.

In conclusion, a Diels–Alder based strategy to reach the naphthoquinone–azepinone core of divergolide C and hygrocin B has been realized. Central to this was the development of a highly scalable route to key benzazepinone building block **23**, which should be easily adapted to allow an asymmetric synthesis of these natural products through the use of a chiral auxiliary in the Birch reductive alkylation step. Further development of this transformation, optimization of the Diels–Alder chemistry, and investigations into the potential of an intramolecular Diels–Alder approach are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC for funding.

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