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Communication

Alkaloids

Enantioselective Synthesis of Caprolactam and Enone Precursors to the Heterocyclic DEFG Ring System of Zoanthenol

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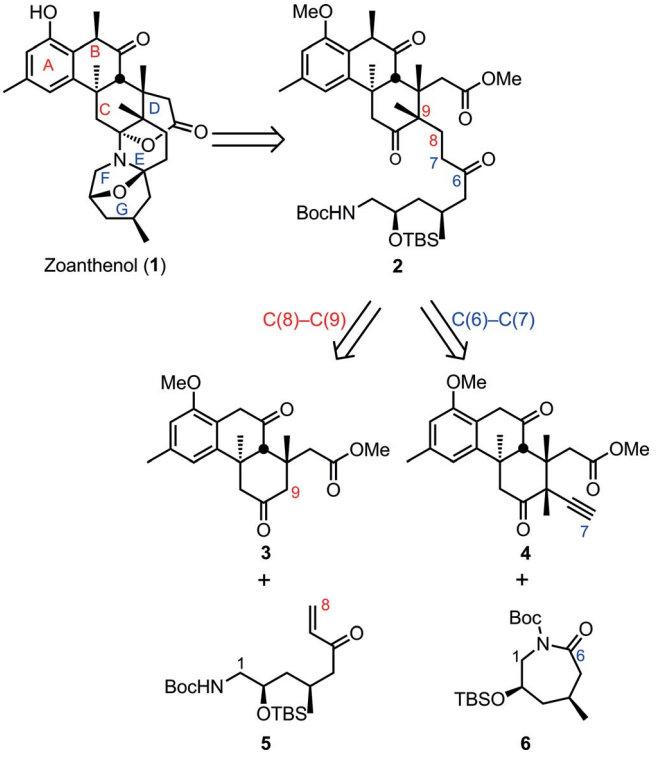
Abstract: The enantioselective synthesis of both caprolactam and enone synthons for the DEFG ring system of zoanthenol are described. The evolution of this approach proceeds first through a synthesis using the chiral pool as a starting point. Challenges in protecting-group strategy led to the modification of this approach beginning with (±)-glycidol. Ultimately, an efficient approach was developed by employing an asymmetric hetero-Diels–Alder reaction. The caprolactam building block can be converted by an interesting selective Grignard addition into the corresponding enone synthon. Addition of a model alkyne provides support for the late-stage addition of a hindered alkyne to the caprolactam building block.

Introduction

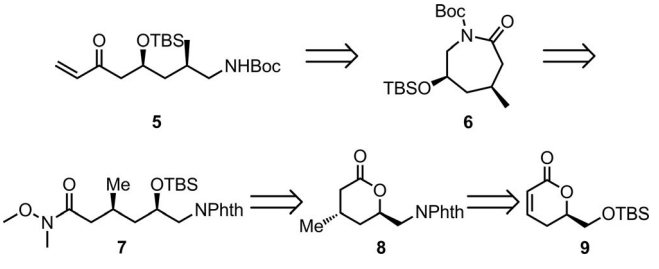
Zoanthenol (**1**) is a complex, polycyclic alkaloid belonging to the zoanthamine family of natural products.[1] These compounds exhibit a range of biological activities including anti-osteoporotic, anti-inflammatory, cytotoxic (P-388 murine leukaemia), and antibacterial activity.[2] Significant synthetic efforts toward the zoanthamines have been disclosed by a number of research groups, including the syntheses of norzoanthamine and zoanthenol by Miyashita in 2004 and 2009[3] and norzoanthamine by Kobayashi in 2008.[4] Our efforts toward the zoanthamines has focused on zoanthenol (**1**), which features an unusual oxidized aromatic A ring with collagen-selective anti-platelet aggregation activity.[5] In addition to Miyashita's total synthesis of zoanthenol (**1**), both Hirama and co-workers[6] and our own group[7] have reported advanced strategies for its completion. In this communication, we disclose the enantioselective synthesis of substituted caprolactam and enone precursors, which enable two potential routes toward the synthesis of the DEFG ring system of zoanthenol.[8,9]

With seven rings and nine stereocenters, zoanthenol is a densely functionalized, topographically complex target molecule. Our initial simplifying disconnection involved unravelling the heterocyclic bis-hemiaminal portion of zoanthenol (**1** ⇒ **2**) based on the pioneering work of the Kobayashi and Williams groups (Scheme 1).[10] We envisioned that the resulting tethered side chain could be severed at either the C(8)–C(9) bond to reveal tricyclic core **3** and enone **5** or at the C(6)–C(7) bond to unveil carbocyclic core **4** and caprolactam **6**.

It was anticipated that enone **5** could be derived directly from caprolactam **6**, thus allowing entry into either synthetic



Scheme 1. Retrosynthesis of zoanthenol.



Scheme 2. Retrosynthetic analysis of DEFG synthons.

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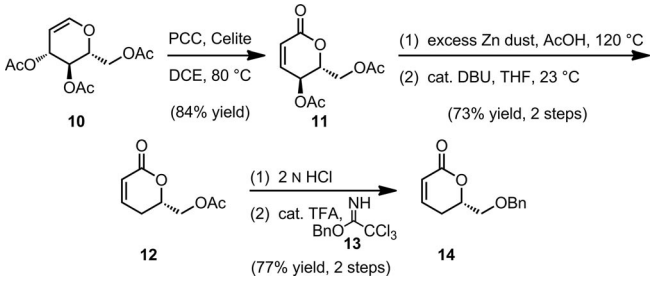
approach from a single DEFG synthon (Scheme 2). Caprolactam **6** was disconnected across the amide C–N bond to reveal Weinreb amide **7**. Phthalimide **7** could in turn be derived from δ-lactone **8**, accessible from α,β-unsaturated lactone **9**.

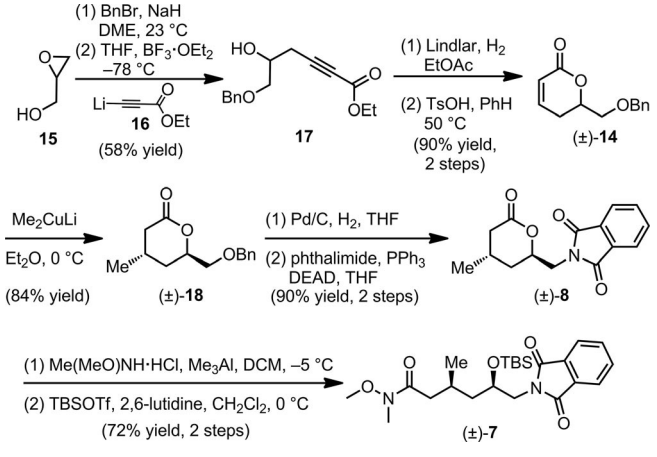
Results and Discussion

Our synthetic efforts began by targeting a lactone such as **9** in enantioenriched form. Initially, we investigated an approach beginning from tri-*O*-acetyl-D-glucal **10**. Unsaturated lactone **11** was accessed in good yield by PCC oxidation according to known methods (Scheme 3).[11] The extraneous acetate was removed by reduction with activated Zn dust in acetic acid followed by reconjugation upon treatment with catalytic DBU to provide **12**.[11] Following removal of the acetate group, our initial attempts at protection with a more suitable group were unproductive, because intermediates related to **12** were very sensitive to base. However, mild acidic conditions for benzyl protection ultimately were developed to provide δ-lactone **14** using trichloroacetimide **13**.[12]



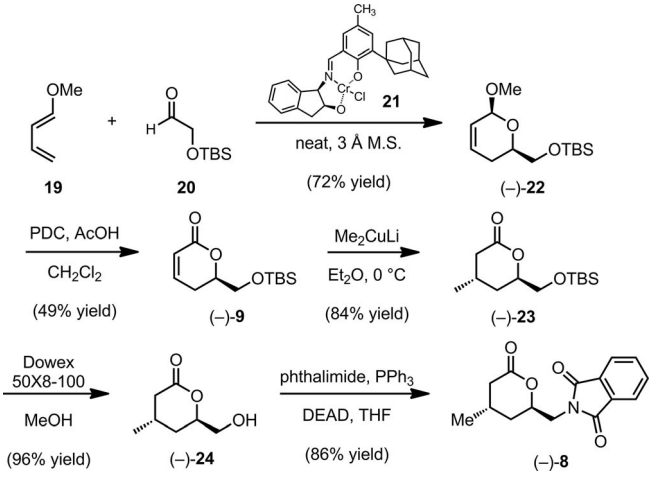
Scheme 3. Synthesis of a chiral unsaturated δ-lactone.

Despite the initial appeal of utilizing the chiral pool as the starting point for the synthesis of enone **14**, the necessity to shuffle protecting groups prompted the exploration of a route starting from racemic glycidol **15** (Scheme 4). The enantioselective route could be secured upon completion of the racemic route from readily available (*S*)-glycidol.[13,14] According to literature preparations, the sequence began with benzyl protection of racemic glycidol **15**, followed by nucleophilic epoxide opening with the anion of ethyl propiolate (**16**) to provide known alkyne **17**.[15] Unsaturated lactone **14** was quickly accessed through Lindlar reduction of alkyne **17**, followed by cyclization upon exposure to mild acid. With suitably protected lactone **14** in hand, a highly diastereoselective cuprate addition with the Gilman reagent proceeded smoothly, yielding scaleable quantities of saturated lactone **18** as a single observed diastereomer.[13a] Installation of the primary amine was accomplished through hydrogenolysis of the benzyl ether, followed by Mitsunobu reaction with phthalimide, providing the crystalline intermediate **7**.



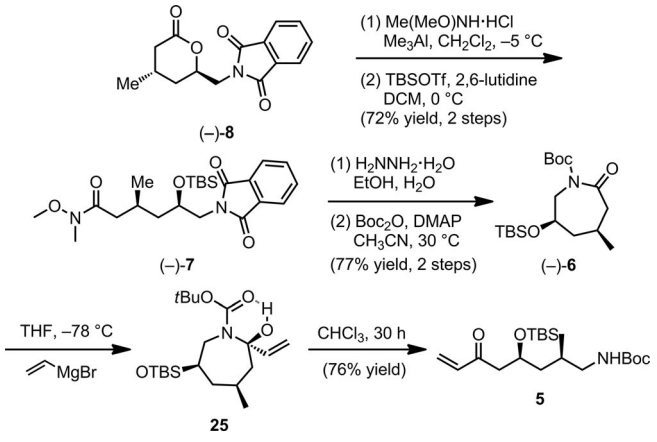
Scheme 4. Access to Weinreb amide **7** from (±)- or (*S*)-glycidol.

Ultimately, we were able to access δ-lactone **9** more directly by employing the hetero-Diels–Alder catalyst developed by Jacobsen and co-workers (**21**; Scheme 5).[16] Thus, following reaction of diene **19**, aldehyde **20**, and catalyst **21**, desired dihydropyran **22** was isolated in 72 % yield and >99 % *ee* and could be converted into the necessary lactone **9** using acidic pyridinium dichromate conditions. At this point, selective 1,4-addition was accomplished by treatment of **9** with Gilman's reagent to afford **23** as a single diastereomer.[17] Treatment with acidic resin induced desilylation to provide alcohol **24**, and subsequent Mitsunobu reaction provided phthalimide derivative **8**.[18]



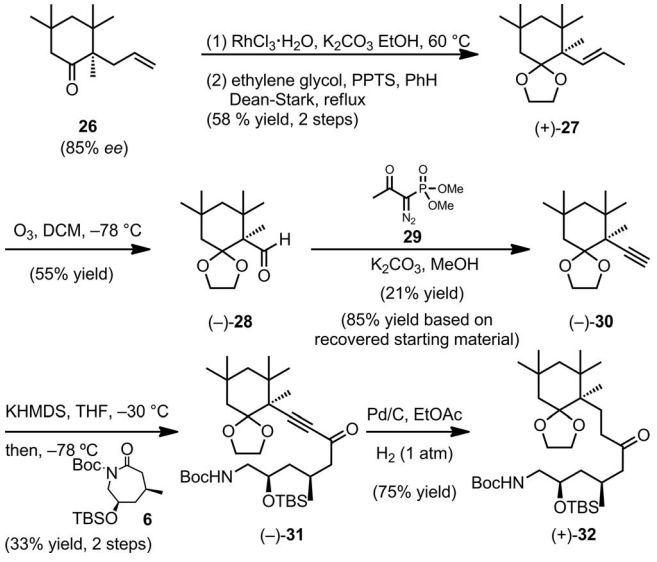
Scheme 5. Toward a catalytic asymmetric synthesis of synthons **5** and **6**.

Chiral lactone **8** was then treated under standard conditions for Weinreb amide formation, and the intermediate alcohol was immediately trapped by addition of TBSOTf and 2,6-lutidine to yield Weinreb amide **7** (Scheme 6). Treatment of **7** with hydrazine hydrate in refluxing ethanol revealed the free primary amine, which spontaneously cyclized to form a caprolactam. Carbamate formation with Boc anhydride provided caprolactam synthon **6**. The final step in accessing enone synthon **5** was to add a single vinyl equivalent to the Boc-protected caprolactam. Thus, treatment of **6** with vinylmagnesium bromide provided isolable Grignard adduct **25**. The chelation of Mg^{2+} between the Boc carbonyl group and the amide carbonyl group encourages addition of a single equivalent of the nucleophile, and we anticipate that a similar hydrogen-bonding event slows the collapse of hemiaminal **25**. Upon standing in $CHCl_3$, desired enone **5** is produced.



Scheme 6. Conversion of the δ-lactone to the ε-lactam and enone synthons.

In order to determine the feasibility of the addition of hindered alkyne **4** to caprolactam **6**, a model alkyne was synthesized. In order to generate a single diastereomer of the addition product, it was necessary to generate the model alkyne as a single enantiomer. Fortunately, α-quaternary allyl ketone **26** was readily available using our asymmetric alkylation methodology[19] and could be advanced to a suitable model system (Scheme 7). Thus, allyl ketone **26** was smoothly isomerized to the internal olefin, which was then ketalized to provide olefin **27**. Ozonolysis with mild reductive workup allowed access to desired aldehyde **28**. Treatment with the Ohira–Bestman reagent (**29**) induced sluggish Gilbert–Seyferth homologation to afford alkyne **30** and recovered aldehyde **28**. Deprotonation of the alkyne with KHMDS and trapping with caprolactam **6** provided alkynone **31**. Hydrogenation of the alkyne readily provided the final side-chain appended model product **32**. This unoptimized approach provides a key proof-of-concept supporting the challenging disconnection of tethered tricycle **2** to carbocyclic core **4** and caprolactam **6**.



Scheme 7. Functionalization of a model ketone with caprolactam **6**.

Conclusions

These studies constitute the synthesis of two fully functionalized, enantiopure DEFG synthons (**5** and **6**) ready for late-stage coupling with our carbocyclic core structures (**3** and **4**). The synthetic approaches described encompass strategies beginning from a chiral glycal, racemic or enantiopure glycidol, and ultimately a catalytic enantioselective approach employing a hetero-Diels–Alder reaction followed by a diastereoselective conjugate addition. Additionally, selective ring-opening and ring-closing events allow for the efficient elaboration of the key δ-lactone. The strategic choice of Boc as the amide protecting group enables selective mono-addition of vinylmagnesium bromide, and ultimately a neopentylalkyne, to the caprolactam. Efforts to combine these synthons with carbocyclic core structures analogous to **3** and **4** are ongoing.

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Keywords: Zoanthamines · Zoanthenol · Enantioselectivity · Hetero-Diels–Alder reaction · Allylation

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