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"Decahydroquinoline Construction Through Aza-Annulation: A Stereoselective Synthesis of (±)-5-Epipumiliotoxin C."

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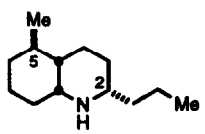
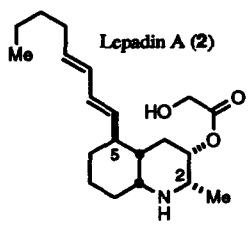
Abstract: Aza-annulation of activated acrylic acid derivatives with 3-benzylamino-2-cyclohexenone led to the efficient formation of the corresponding bicyclic lactam. Stereospecific hydrogenation of this unsaturated lactam resulted in the selective formation of the cis fused bicyclic alkaloid, and subsequent elaboration at C-5 and C-2 completed the synthesis of the decahydroquinoline alkaloid (±)-5-epipumiliotoxin C.

The decahydroquinoline alkaloids display a variety of biological activities due to the structural diversity of these compounds.[1] Despite the apparent differences in structural features of alkaloids containing the cis-fused decahydroquinoline skeleton, such as pumiliotoxin C (**1**),[1] lepadin A (**2**),[2] and gephyrotoxin 287C (**3**),[1] variance from the typical dialkyl substitution pattern does not occur very often. For example, alkyl substituents on the carbon framework are positioned at C-2 and C-5 for each of the compounds shown below (**1-3**). This pattern, common to most compounds in this class of alkaloids, led us to explore the use of intermediate **4** as an approach to constructing the bicyclic skeleton, introducing the cis ring fusion, and controlling stereochemistry of the C-2 and C-5 substituents. The target chosen to explore this approach was pumiliotoxin C (**1**).[3]

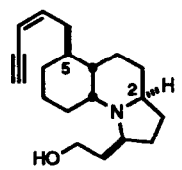
Pumiliotoxin C (**1**)

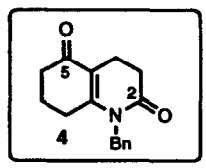


Lepadin A (**2**)

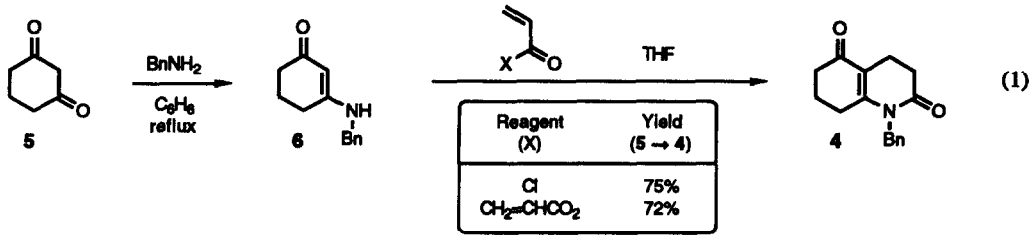


Gephyrotoxin 287C (**3**)





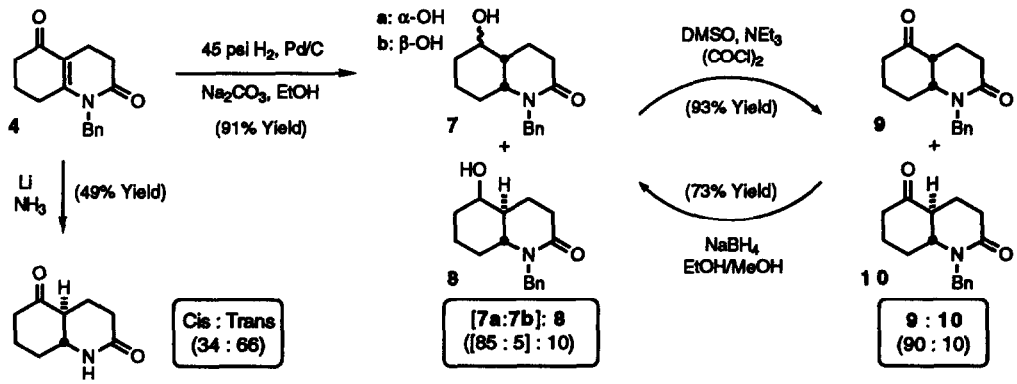
Several factors led to the selection of **4** as the key synthetic intermediate. The most appealing feature of this route was the accessibility of this compound through aza-annulation of **5**, and the report that similar 1,3-dione derivatives underwent aza-annulation with acryloyl chloride in 40-50% yields.[4] In addition, the use of a cyclic β-enamino ketone complemented our previous studies with imines[5] and β-enamino esters[6] (eq. 1). Condensation of **5** with benzylamine produced enamine **6**,[7] which was isolated in 89% yield, or could be directly treated with the acrylic acid derivatives without prior isolation to efficiently generate **4**. Enamine formation through the reaction of **5** with benzylamine, with azeotropic removal of H_2O by benzene, followed by subsequent reaction with either acryloyl chloride or acrylic acid anhydride in THF, resulted in formation of **4** in 75% and 72% yields, respectively, for the two-step condensation/aza-annulation of **5** to **4**.[8]



(1)

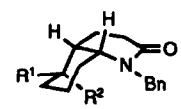
The cis fusion of the bicyclic skeleton was established through catalytic hydrogenation of **4**.[9] Hydrogenation of **4** in the presence of Pd/C and Na_2CO_3 resulted in reduction of both the alkene and the ketone to produce an 85:5:10 mixture of the three products **7a**:**7b**:**8** (Scheme I). Swern oxidation of this mixture gave a 90:10 mixture of **9**:**10**. Overall, the stereochemistry of **9** was established in 85% yield from **4**, which represents an overall 64% yield from **5**.

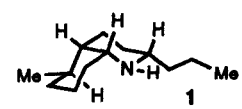
Scheme I. Establishing the Cis Ring Fusion of the Decahydroquinoline Framework.



The most problematic step of the synthesis proved to be the stereochemically correct introduction of the C-5 methyl substituent. In this case, the bicyclic lactam ring system provided a significant stereofacial bias for nucleophilic attack, however, the thermodynamic preference for equatorial *versus* axial substituents at C-5 was less than expected for the quinolone. Hydrolysis and equilibration of enol ether **11a** produced only a 42:58 ratio of **11b**:**11c**, and imine or 1,3-dithiane formation from the aldehyde did little to improve the equatorial (R^1) to axial (R^2) selectivity.

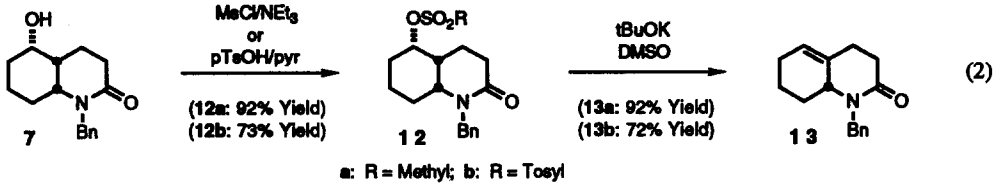
11a: R^1,R^2 = CHOMe
11b: R^1 = CHO, R^2 = H
11c: R^1 = H, R^2 = CHO





Attempts to take advantage of the existing hydroxyl stereochemistry of α-**7**, by introducing the methyl substituent from the least hindered face of the ring skeleton through S_N2 displacement, proved unsuccessful. Although mesylate **12a** and tosylate **12b** formation occurred as expected, treatment of **12** with a variety of methyl nucleophiles, such as Me_2CuLi, $Me_2CuCNLi_2$, MeMgBr, and MeLi, was unproductive. These reagents either did not react with **12**, or they gave only the product of sulfonate elimination (**13**) due to the

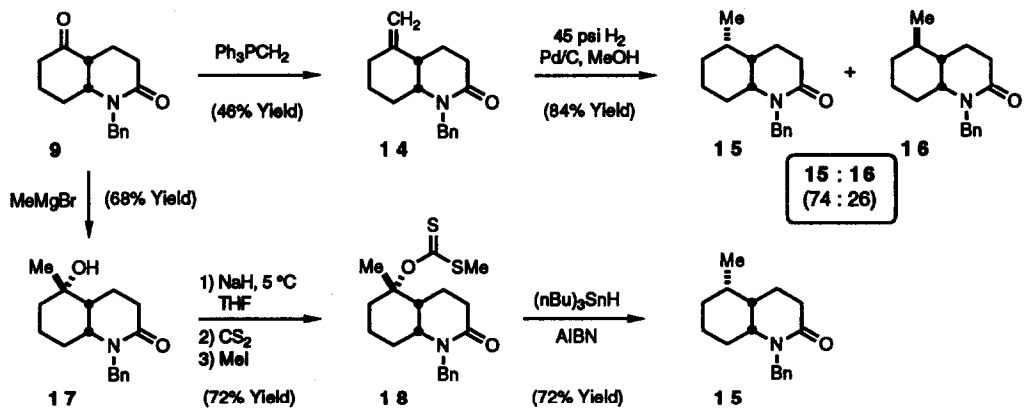
optimal anti periplanar alignment of the methine hydrogen with respect to the sulfonate leaving group. This same transformation was achieved more efficiently by treatment of **12** with tBuOK in DMSO.



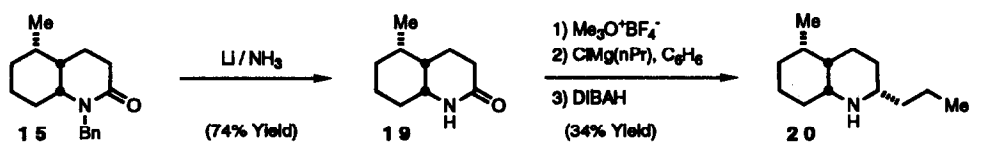
a: R = Methyl; b: R = Tosyl

Due to the difficulties encountered in selective formation of **16**, similar strategies of stereofacial attack were employed to selectively produce **15** (Scheme II). Starting from the 90:10 mixture of **9**:**10**, Wittig methylenation was used for generation of **14**, which was isolated as a single diastereomer in 46% yield. However, initial hydrogenation produced poor stereoselective formation of **15**:**16**, and the use of other potential hydrogenation catalysts was not explored. Instead, carbon-carbon bond formation was accomplished by Grignard reaction with the ketone, and a single isomer of **17** was isolated in 68% yield. Removal of the hydroxyl substituent was accomplished by xanthate formation (**18**) followed by radical generation and hydrogen abstraction from the least hindered face of the bicyclic structure to give **15** as the only stereoisomer.[12] Transformation of the ketone to the methyl substituent was accomplished in 37% yield for the three-step sequence.

Scheme II. Stereoselective Introduction of the C-5 Methyl Substituent.



Lactam **15** was transformed into (±)-5-epipumiliotoxin C (**20**) through procedures already established for the synthesis of **1** from **16** (eq. 3).[13] Removal of the benzyl protecting group, followed by *O*-methylation of the lactam, produced the corresponding imidate. Subsequent reaction of the imidate with nPrMgCl in C_6H_6 and then reduction with DIBAH produced **20** in 25% yield for the four-step sequence from **15**.



Several important transformations were illustrated by this synthesis of (±)-epipumiliotoxin C. A key feature in this sequence was the rapid and efficient construction of the ring skeleton through generation of **4**. From this intermediate, the cis ring fusion was selectively generated by catalytic hydrogenation, and oxidation of the hydroxyl group provided the versatile synthetic intermediate **9**. Selective reaction at the different carbonyl groups led to sequential stereoselective introduction of the alkyl substituents at C-5 and C-2, respectively. Overall, the synthesis of **19** was accomplished in 6% yield from **5**.

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