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SYNTHESIS OF THE CIS-DECAHYDROQUINOLINE RING SYSTEM VIA AN INOC REACTION OF A 1-ACYLDIHYDROPYRIDINE

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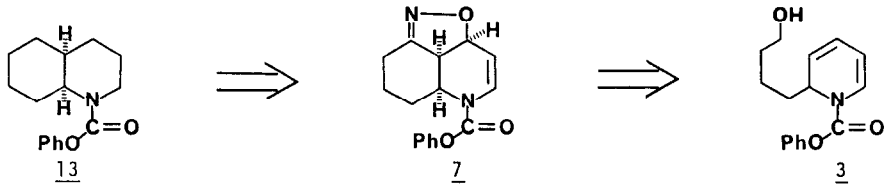
Summary: The intramolecular nitrile oxide cycloaddition (INOC) reaction has been utilized in the synthesis of the cis-decahydroquinoline ring system.

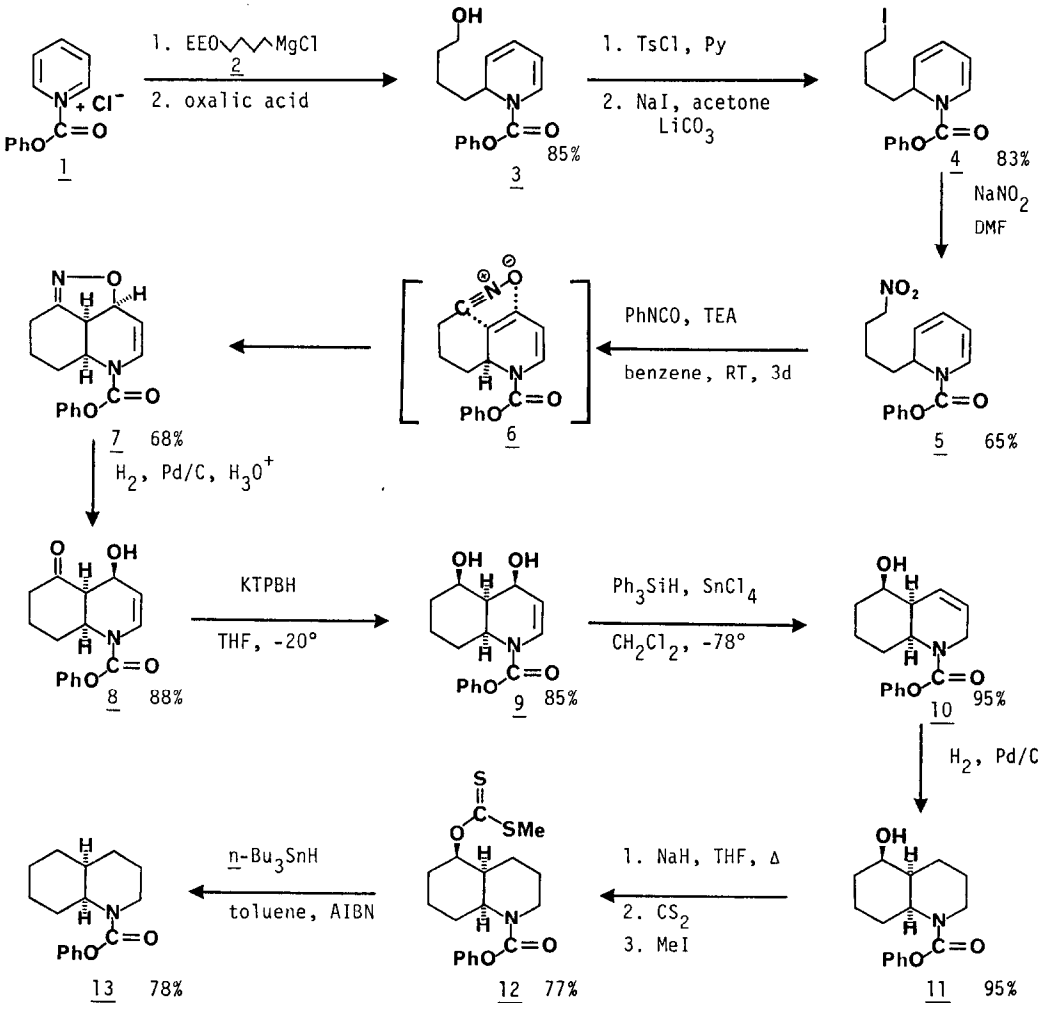
Although the intermolecular[1] and intramolecular[1,2] Diels-Alder reactions of 1,2-dihydropyridines have proven very useful in synthesis, the 1,3-dipolar cycloaddition to dihydropyridines has received relatively little attention. Knaus has reported the intermolecular 1,3-dipolar cycloaddition reactions of cyanogen azide[3] and phenylsulfonyl cyanide N-oxide[4] with N-substituted 1,2-dihydropyridines. We report herein the first intramolecular 1,3-dipolar cycloaddition of a dihydropyridine and application of this reaction to the synthesis of the cis-decahydroquinoline ring system. Our synthetic plan followed the retrosynthetic analysis shown below.



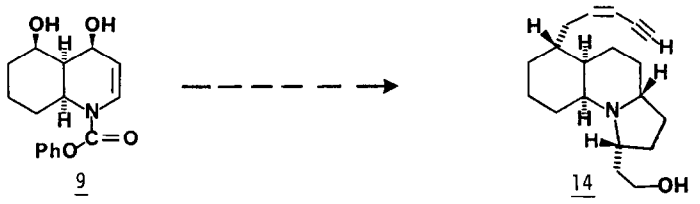
13 7 3

The desired 1-acyldihydropyridine 3 was readily prepared by the dropwise addition of Grignard reagent 2 to 1-(phenoxycarbonyl)pyridinium chloride (1) in THF at -20 °C,[5] followed by treatment of the crude product with oxalic acid. The iodide 4 was prepared from 3 via the tosylate in 83% overall yield. The presence of lithium carbonate (1 equiv) as a buffer was essential to the success of the Finkelstein reaction. Treatment of 4 with sodium nitrite[6] in DMF gave the 2-(nitrobutyl)-1,2-dihydropyridine 5. Intramolecular [3+2] cycloaddition via nitrile oxide 6 was effected using Mukaiyama's procedure[7] for nitrile oxide formation. A single crystalline product was isolated and assigned structure 7. From consideration of non-bonded interactions in the two possible diastereomeric transition states leading to cycloaddition, we anticipated the formation of the cis-fused product 7. This assignment is in accord with the stereochemistry obtained from other intramolecular nitrile oxide cycloaddition (INOC) reactions reported by various groups.[8] Since the tricyclic product results from a stereospecific syn addition, the relative stereochemistry of all three asymmetric

centers in 7 can be determined by resolving the stereochemistry of the six-six ring junction. To this end we carried out the following synthetic sequence. The isoxazoline 7 was converted to the keto-alcohol 8 using Takei's procedure.[9] Reduction with potassium triisopropoxyborohydride (KTPBH) gave diol 9.[10] The γ-hydroxy enecarbamate moiety of 9 is an N-acyliminium ion precursor.[12] Treatment with triphenylsilane and stannic chloride provided olefin 10 in 95% yield. Catalytic reduction gave 11, which was converted to xanthate 12 in good yield. Deoxygenation[13] provided carbamate 13, which was identical with an authentic sample prepared from cis-decahydroquinoline.[14] None of the trans isomer[15] was detected in 13 by ^{1}H or ^{13}C NMR.



This synthesis[16] of carbamate 13 confirmed our stereochemical assignment of isoxazoline 7, and serves as a model study for an approach to the synthesis of the cis-decahydroquinoline alkaloid, gephyrotoxin.[17] An effort to synthesize gephyrotoxin (14) from diol 9 is in progress.



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Acknowledgments. We wish to express appreciation to the National Institutes of Health for support of this project from Grant GM 30255.

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16. All new compounds exhibited the expected ^{1}H NMR, ^{13}C NMR, and IR spectra. Satisfactory analytical data (±0.4% for C, H, N) were also obtained for compounds 7, 8, and 9.

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