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Intramolecular Photocycloaddition of a Tethered Bis-2,3-dihydro-4-pyridone: Stereochemistry and Reactivity of the Cycloadduct

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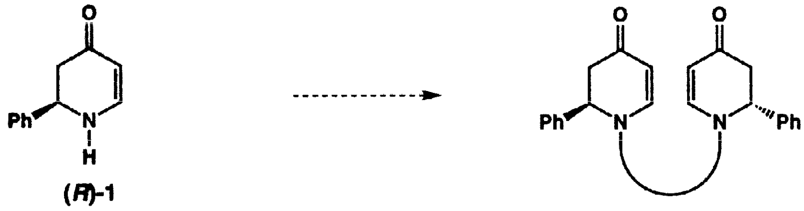
Abstract: *The photocycloaddition of enantiopure bis-dihydropyridone 4 provided a single cycloadduct in high yield. Treatment of the cycloadduct with SmI_2 effected ring opening and intramolecular aldol addition to give pentacyclic β-hydroxyketone 7.*

To expand the utility of chiral 2,3-dihydro-4-pyridones as building blocks for synthesis,[1] we have been examining intramolecular [2 + 2] photocycloaddition reactions of these heterocycles. Novel ring systems can be prepared using this reaction as was first demonstrated by Neier.[2] We recently used this approach to build the ring system of the alkaloid, perhydrohistrionicotoxin.[3] Beckwith used a similar approach to prepare indolizidine and quinolizidine derivatives.[4] In addition to its utility in alkaloid synthesis, the potential for preparing new chiral ligands appeared worthy of investigation. To this end, we initiated a study of the intramolecular [2+2] photodimerization of 2(*R*)-phenyl-2,3-dihydro-4-pyridone (**1**) tethered at the nitrogen atoms of the heterocycle.



(*R*)-1

tethered photosubstrate

The photodimerization of *N*-benzoyl-5,6-dihydro-4-pyridone leads to a mixture of head-to-head and head-to-tail cycloadducts containing the cis,anti,cis stereochemistry.[5] Keana and coworkers[6] reported the photodimerization of tethered bis-4-pyridone **2**. In this case, the cyclobutane product **3** formed with the *cis,syn,cis* configuration. We were interested in determining if the related bis-dihydropyridone photosubstrate **4** would provide a photodimer of similar stereochemistry to that found in **3**, or whether the stereogenic centers at C-2 and C-2′ of **4** would control the stereochemistry of the cyclobutane formation giving a cis,anti,cis arrangement. The bis-*N*-acyl derivative **4** was chosen for its ease of preparation and the potential for facile

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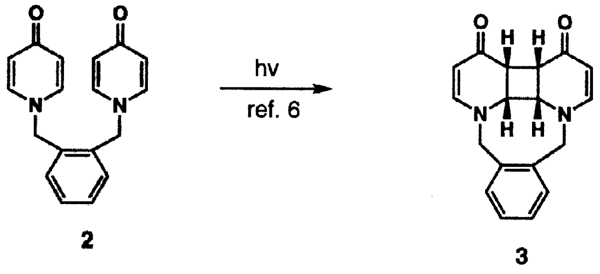
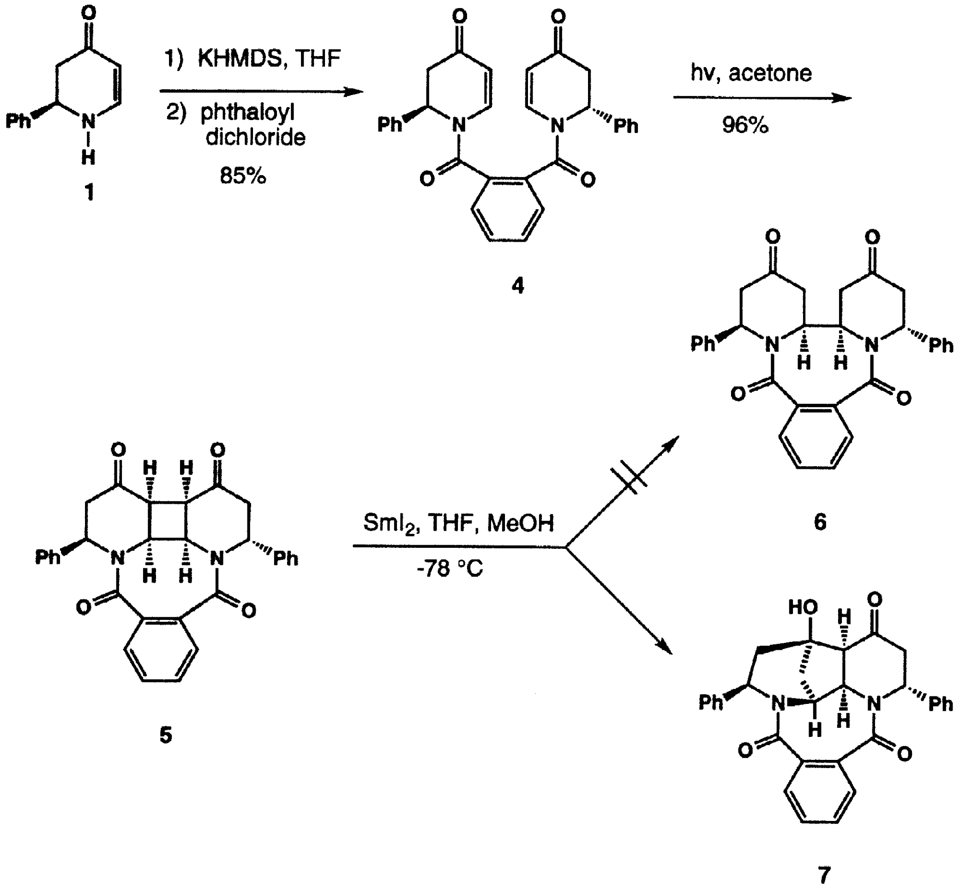
removal of the tether at the appropriate stage by hydrolysis. The enantiopure starting material, dihydropyridone **1**, is readily prepared in multigram quantities by phenyl Grignard addition to chiral 1-acylpyridinium salts.[7]

Treatment of dihydropyridone **1** with KHMDS and phthaloyl dichloride gave the tethered bis-dihydropyridone **4** in 85% yield (mp 240-242 °C, $[\alpha]^{22}_{D}$ + 498 (*c* 2.1, $CHCl_3$)). Irradiation (460 W Hanovia Hg lamp, rt, 2.5 h) of **4** (300 mg) in 250 mL of acetone provided a single cycloadduct **5** in 96% yield (mp 175-177 °C, $[\alpha]^{23}_{D}$ - 58 (*c* 1.4, CH_2Cl_2)). The stereochemistry was determined by X-ray crystallographic analysis (Figure 1). The cyclobutane ring contains the cis,syn,cis configuration, which suggests that the tether controls the stereochemical outcome of the dimerization rather than the stereocenters in **4**.





The enantiopure pentacyclic compound **5** has an interesting core structure, containing one four-, one eight- and three six-membered rings. In an attempt to open the cyclobutane ring to give bis(2-phenylpiperidine) derivative **6**, compound **5** was treated with SmI_2 (2 equiv) in THF. We have previously reported that an αketocyclobutane can be ring-opened using SmI_2.[3] From the initial reaction was isolated a single product in 38% yield after chromatography. The yield was improved to 65%, along with 20% of recovered **5**, when the reaction was performed in the presence of MeOH at -78 °C. The observed ^1H and ^{13}C NMR spectra were not indicative of structure **6**. The correct structure was determined by single-crystal X-ray analysis to be β-hydroxyketone **7** (Figure 2). In the SmI_2-mediated cyclobutane ring-opening step, a subsequent regiospecific aldol addition reaction occurred. We assume that the ring-opening step leads to a bis-samarium enolate, which on protonation gives diketone **6**. A facile base-promoted intramolecular aldol reaction would then provide ketoalcohol **7**.

Interestingly, only one of four possible diastereomers is formed from the aldol addition step. Molecular mechanics (MMX)[11] and semiempirical (AM1)[12] calculations indicate that the two diastereomers **7** and **8** are lowest in energy. Of these two, diastereomer **8** was computed to be more stable by 13.1 kcal (AM1), which suggests that aldol **7** may result from a kinetic process.

Other reactions of **5**, and the possibility of using derivatives of **5** as chiral ligands, are under study.

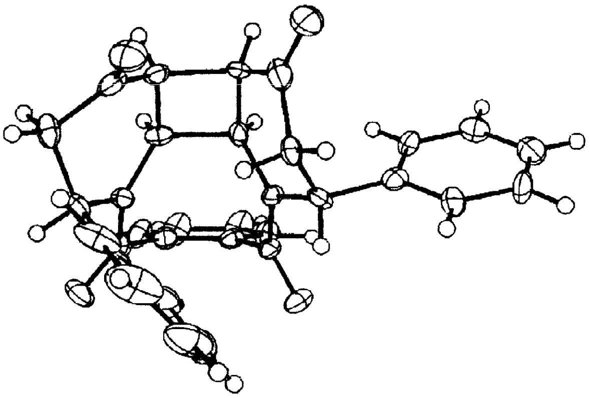


Figure 1. Crystal structure of **5**[8,10]

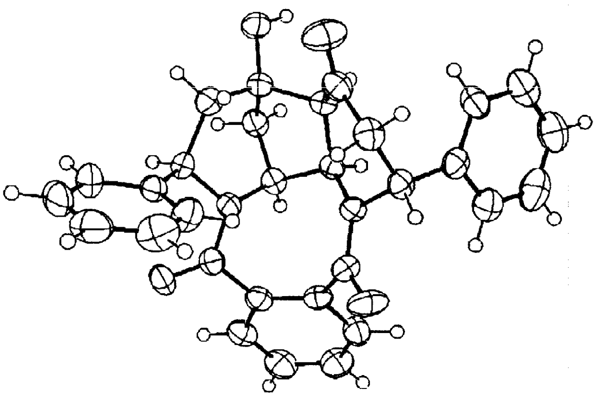
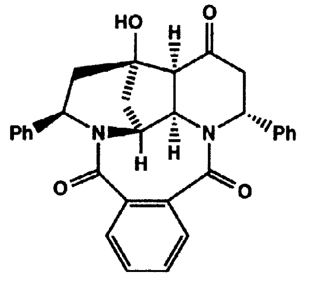
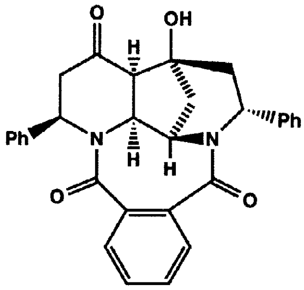


Figure 2. Crystal structure of **7**[9,10]



7



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8. Crystal experimental data for **5**: $C_{30}H_{24}N_2O_4$• $2CH_2Cl_2$, MW 646.39, monoclinic, P 2_1, a = 9.2869 (9), b = 22.7877 (9), c = 14.2242 (6) Å, β = 90.202(5)°, V = 3010.2(3) Å^3. Graphite monochromated MoKα radiation, λ = 0.71073 Å, μ = 0.43 mm^{-1}, 5580 unique reflections collected at -120 °C, 4879 observed, R = 0.074, R_w = 0.053. Structure solved by SIR92, NRCVAX program package used for all other crystallographic calculations. All non-hydrogen atoms refined anisotropically, hydrogens atoms included at idealized positions. The authors kindly thank Dr. P. S. White of UNC-CH for the low temperature data set.
9. Crystal experimental data for **7**: $C_{30}H_{26}N_2O_4$ MW 478.54, orthorhombic, P $2_12_12_1$, a = 8.9058 (7), b = 15.2549 (9), c = 17.4550 (10) Å, V = 2371.4(3) Å^3. Graphite monochromated MoKα radiation, λ = 0.71073 Å, μ = .08 mm^{-1}, 2357 unique reflections collected at room temperature, 1796 observed , R = 0.040, R_w = 0.051. Structure solved by SIR92, NRCVAX program package used for all other crystallographic calculations. All non-hydrogen atoms refined anisotropically, hydrogens atoms were allowed to ride on parent carbon atom.
10. Atomic co-ordinates, bond lengths and angles, and displacement parameters have been deposited with the Cambridge Crystallographic Data Centre.
11. PCMODEL 5.03; Serena Software, Box 3076, Bloomington, IN 47402.
12. Spartan 4.1; Wavefunction, Inc., 18401 Von Karman #370, Irvine, CA 92715.