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THE BC RINGS OF TAXOL BY [4+4] PHOTOCYCLOADDITION

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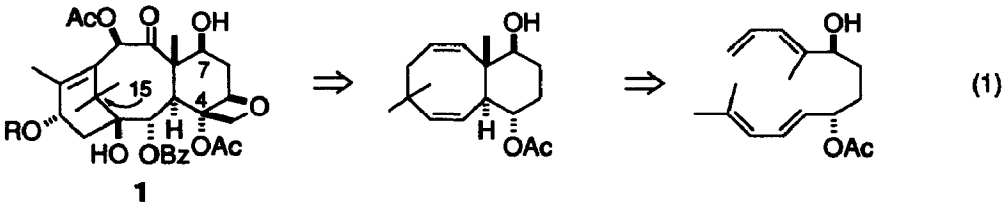
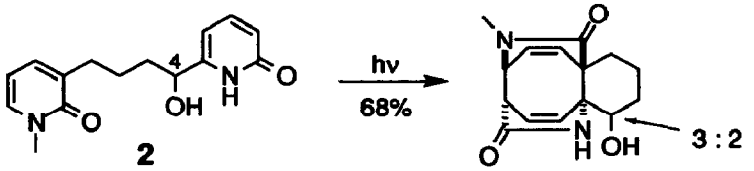
Abstract: Intramolecular photocycloaddition of 2-pyridones joined by a four-carbon chain will form the fused 8-6 ring system of taxol with both of the quaternary carbons. A C-7 silyloxy group on the tether fully controls stereogenesis to give the photoproduct as a single isomer.

Among the numerous synthetic strategies for the total synthesis of taxol (**1**),[1] construction of eight-membered rings[2] by intramolecular [4+4] cycloaddition[3] and equivalent transformations[4] has received modest attention. In an earlier report we noted the formation of 8-6 fused carbocycles in the irradiation of four-carbon tethered pyridones (e.g., **2**, equation 2).[5] Only trans isomers were observed in this photoisomerization, but stereogenic control by the tether alcohol at C-4 (taxol numbering) was poor.

Adapting this reaction for the synthesis of taxol required a methyl group at C-15 and a higher degree of stereogenic control. Toward this objective we have prepared **3**, incorporating the methyl group and a *tert*-butyldimethylsilyloxy group at C-7. In the case of a three-carbon tether, a silyloxy group at this position was found to give a high degree of stereogenic control.[6]

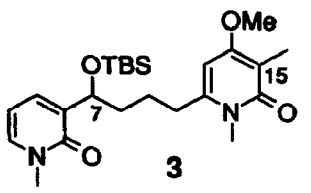


(1)



(2)

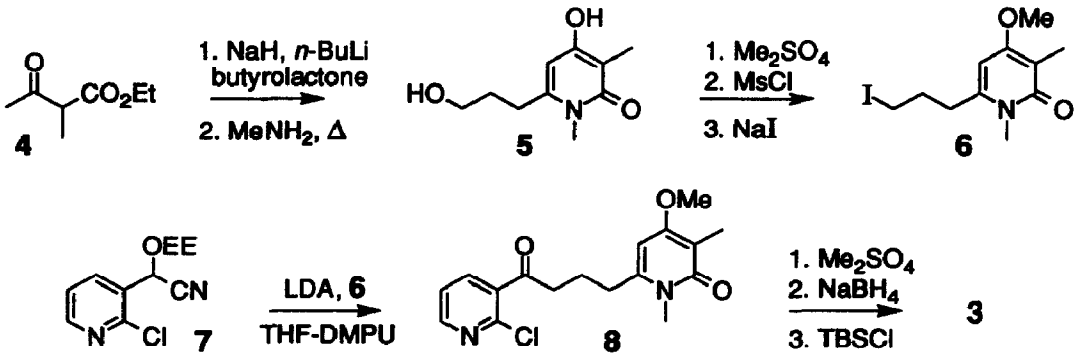
We also elected to incorporate a methoxy substituent on one of the pyridones. The methoxy group differentiates the two alkenes in the [4+4] product and alkoxy pyridones are readily prepared (see Scheme 1). However, the use of alkoxy pyridones is potentially troublesome as Kaneko has reported that 4-alkoxy-2-pyridones *do not* undergo [4+4] photodimerization.[7] The suitability of 4-alkoxy-2-pyridones for [4+4] photocycloaddition with different pyridones, as in **3**, has not been investigated.



The synthesis of photosubstrate **3** is shown in Scheme 1. Condensation of the dianion[8] of the commercially available **4** with butyrolactone yields a diketoester intermediate that is conveniently carried on without purification. Treatment with methanolic methylamine at reflux gives tetrasubstituted pyridone **5** in 55% overall yield after column chromatography. Methylation of the 4-hydroxy group was effected with dimethylsulfate and potassium hydroxide (71%) and the primary alcohol was then converted to iodide **6** via the mesylate (88%).

The lithium anion of cyanohydrin **7**,[9] prepared from the commercially available 2-chloronicotinic acid, is readily alkylated with iodide **6** in the presence of DMPU. Aqueous workup, incorporating both acid and base treatment, gives ketone **8** (65%). N-methylation of **8** with dimethylsulfate and basic aqueous workup serves to generate the second pyridone (58%). Reduction of the ketone and protection as the *tert*-butyldimethylsilyl ether yields **3** (84%).

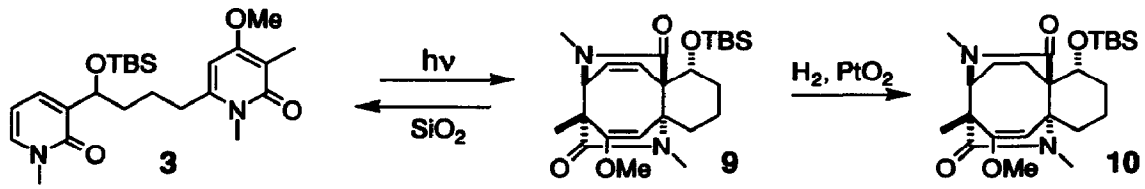
Scheme 1.



Irradiation of **3** under standard conditions[6] (0.05 M in methanol, 450W medium-pressure mercury lamp) was initially followed by TLC, but did not indicate conversion of starting material. Nevertheless, inspection by ^{1}H NMR showed complete and very clean conversion of **3** into [4+4] product **9**, apparently as a single isomer: each of the seven well-resolved methyl groups were sharp singlets.[10] The sensitivity of photoproduct **9**, and the difficulty with TLC analysis, was manifest when column chromatography (silica gel, 95:5 methylene chloride/methanol) gave a near-quantitative recovery of **3**.

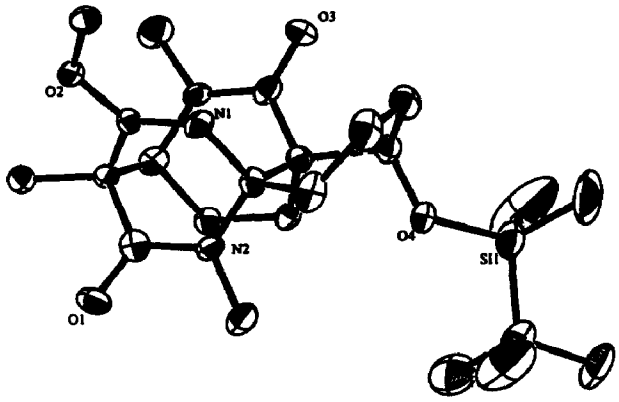
Removing unsaturation in **9** prevents a reversion to pyridones, thereby stabilizing the photoproduct. Thus, hydrogenation followed by silica gel chromatography gave **10** as a colorless solid (84% from **3**).

Scheme 2.



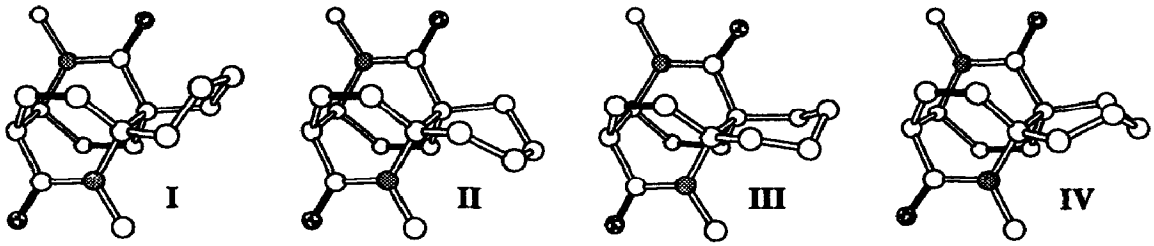
An X-ray structure[11] of **10** confirmed the proposed trans, anti[6] stereochemistry. Remarkably, the cyclohexane ring was found to be in a boat conformation with the *tert*-butyldimethylsilyloxy group at the flagpole position!

Figure 1. X-ray structure of **10**



The rigid [6.2.$2^{1,6}$.$2^{2,5}$] photoproduct of 2-pyridone photodimerization requires that four of the six atoms of the cyclohexane ring in **9** and **10** be planar, much like cyclohexene. Cyclohexene, however, exists as a half-chair, with the boat conformation more than 5 kcal/mol higher in energy.[12] To probe this point further, the conformations of the parent system of **9** was examined by molecular mechanics (Figure 2). For this structure, two nonequivalent conformations for both the boat and the half-chair are possible. MM3* and MM2* calculations[13] for these four isomers found both of the boat conformations to be more stable than either of the half-chairs, with the half-chairs (III and IV) 4-6 kcal/mol above the lowest energy boat form (I). The enthalpy for conformation IV was not found by MM3*, as this structure minimized to I. The preference for boat over half-chair in these structures is likely due, in part, to the hybridization of the ring fusion carbons and the resulting bond angles for the cyclohexane at these centers (109° and 111°) which are quite different from those of boat cyclohexene (119°, MM3*). A preference of boat over half-chair for these photoproducts may be general.[14]

Figure 2. Calculated relative enthalpies of conformers in kcal/mol.



MM3*	0	1.41	6.07	—
MM2*	0	1.21	6.99	4.00

Photocycloaddition of **3** is the first example of the formation of a *single* diastereomeric product from the intramolecular [4+4] photocycloaddition of 2-pyridones.[5,6,15] It is also notable for the first use of 4-alkoxy-2-pyridones in a [4+4] cycloaddition reaction. Further studies of the chemistry of photoproduct **9** are underway and will be reported in due course.

Acknowledgment is made to the National Institutes of Health for support of this work (GM45214). We also thank Professor Stephen Koch and Michael Rickenbach for determination of the crystal structure of **10**.

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10. ^{1}H NMR data ($CDCl_3$): Cmpd **3**: δ 7.45 (dd, 1 H, J = 7.2, 1.5 Hz), 7.20 (dd, 1 H, J = 7.2, 1.5 Hz), 6.19 (t, 1 H, J = 7.2 Hz), 5.90 (s, 1 H), 4.9 (t, 1 H, J = 3.6 Hz), 3.8 (s, 3 H), 3.5 (s, 3 H), 3.4 (s, 3 H), 2.5 (m, 2 H), 1.96 (s, 3 H), 1.67 (m, 4 H), 0.89 (s, 9 H), 0.04 (s, 3 H), -0.08 (s, 3 H).
    Cmpd **9**: δ 6.4 (dd, 1 H, J = 9.0, 6.9 Hz), 6.2 (dd, 1 H, J = 9.0, 1.2 Hz), 5.16 (s, 1 H), 4.2 (t, 1 H, J = 4.2 Hz), 3.5 (s, 3 H), 3.38 (dd, 1 H, J =6.9, 1.2 Hz), 2.86 (s, 3 H), 2.82 (s, 3 H), 2.5 (m, 2 H), 1.85 (m, 4 H), 1.4 (s, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.02 (s, 3 H).
    Cmpd **10**: δ 5.17 (s, 1 H), 4.06 (t, 1 H, J = 4.0 Hz), 3.5 (s, 3 H), 3.29 (dd, 1 H, J = 6.3, 1.2 Hz), 3.0 (s, 3 H), 2.8 (s, 3 H), 2.6 (m, 2 H), 2.0 (m, 2 H), 1.8 (m, 4 H), 1.48 (m, 2 H), 1.4 (s, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.02 (s, 3 H).
11. Compound **10** crystallizes in the orthorhombic space group $Pca2_1$ with a = 7.5801 (8) Å, b = 23.513(1) Å, c = 14.147 (2) Å, V = 2521.4 (7) Å^3, and Z = 4. Final least squares refinement using 3263 unique reflections with $I > 3\sigma(I)$ gave $R(R_w)$ = 0.064 (0.076).
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