A Photochemical [4 + 4] Method for the Construction of Annulated Eight-Membered Rings

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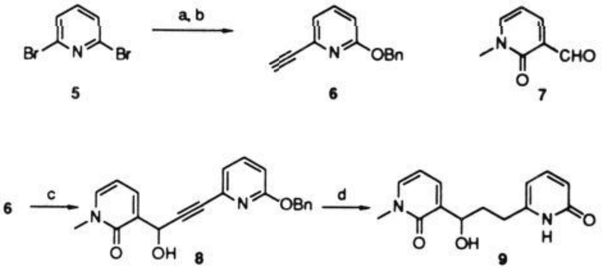
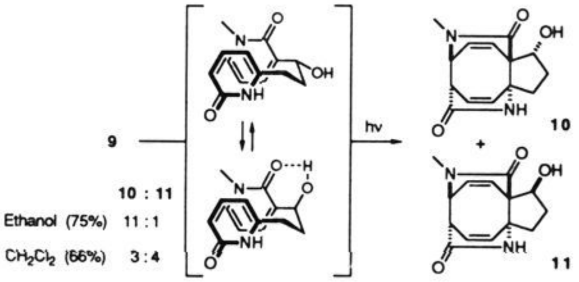
Natural products that incorporate an eight-membered carbocyclic ring, exemplified by fusicoccin A (**1**) and taxol (**2**), remain prominent synthetic challenges[1,2] because of their combination of imposing architectural complexity, a fascinating array of biological activities,[3] and the difficulties associated with cyclooctane chemistry.[4] Despite intensive synthetic effort, particularly with regard to **2**,[5] total synthesis of these molecules remains largely elusive.[6] Among the options for cyclooctane construction,[7] cycloaddition chemistry has received the least synthetic attention[8] but holds great potential for efficient assembly of these complex polycycles. We now report the first intramolecular [4 + 4]

Scheme I[a]

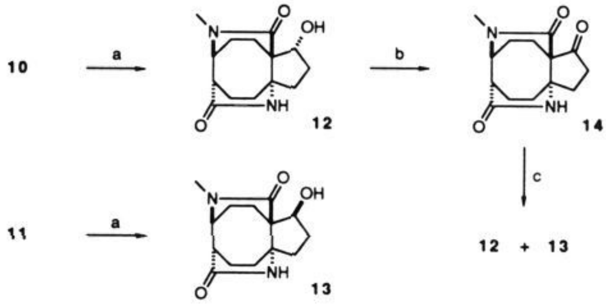


[a] (a) $NaOCH_2Ph$, DMF, 94%; (b) (1) $HC\equiv CC(CH_3)_2OH$, Et_2NH, $Pd(OAc)_2$, CuI; (2) KOH, toluene, reflux, 75%; (c) LDA, **7**, 84%; (d) (1) H_2, Raney nickel; (2) H_2, 10% $Pd–CaCO_3$, 95%.

Scheme II



Scheme III[a]



[a] (a) H_2, PtO_2, 94%; (b) PDC, DMF, 63%; (c) $NaBH_4$, 79%.

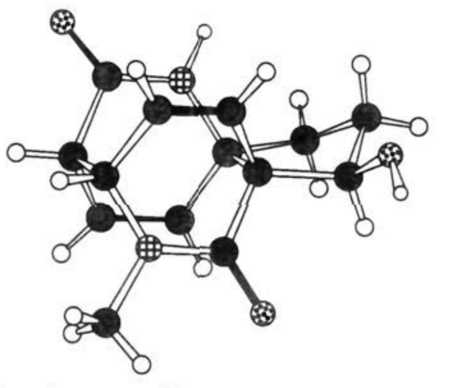


Figure 1. Crystal structure of **10**.

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(3) Examples include pleuromutilin (an antibiotic): Arigoni, D. *Pure Appl. Chem.* **1968**, *17*, 331. Taxol (antineoplastic agent and inhibitor of tubulin depolymerization): Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. Ophiobolin A (calmodulin inhibitor and phytotoxin): Nozoe, S.; Morisaki, M.; Tsuda, K.; Iitaka, Y.; Takahashi, N.; Tamura, S.; Ishibashi, K.; Shirasaka, M. *J. Am. Chem. Soc.* **1965**, *87*, 4968. Cotylenin A (plant growth regulator): Sassa, T.; Takahama, A. *Agric. Biol. Chem.* **1979**, *43*, 385. Vinigrol (antihypertensive and platelet aggregation inhibitor): Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292. Kalmanol (cardiotoxic): Burke, J. W.; Doskotch, R. W.; Ni, C.-Z.; Clardy, J. *J. Am. Chem. Soc.* **1989**, *111*, 5831. Variecolin (an inhibitor of angiotensin II receptor binding): Hensens, O. D.; Zink, D.; Williamson, J. M.; Lotti, V. J.; Chang, R. S. L.; Goetz, M. A. *J. Org. Chem.* **1991**, *56*, 3399.

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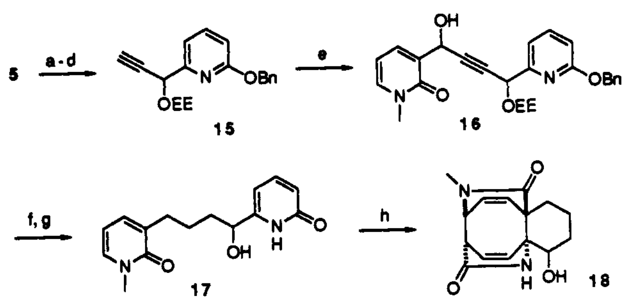
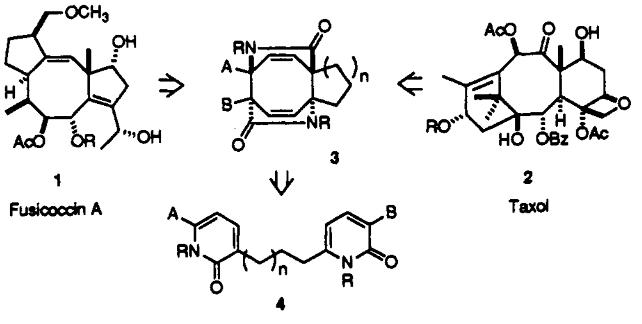
Scheme IV[a]



[a] (a) $NaOCH_2Ph$, DMF, 94%; (b) *s*-BuLi, DMF, 73%; (c) TMSC≡CLi, 90%; (d) (1) $EtOCHCH_2$, TsOH; (2) KF, 91%; (e) *n*-BuLi, 7, 64%; (f) H_2, 10% Pd–$CaCO_3$, 52%; (g) 10% HCl, THF, 72%; (h) $h\nu$, 63%.

photocycloaddition of tethered 2-pyridones: a reaction that forms fused 8–5 and 8–6 carbocyclic ring systems strategically functionalized for the synthesis of natural products such as **1** and **2**.



This approach to eight-membered-ring construction employs the known photodimerization of 2-pyridones, described independently by Taylor and Paquette 30 years ago.[9] Direct photolysis of concentrated solutions of 2-pyridones forms the trans, anti (head-to-tail) product, to the near exclusion of the other three [4 + 4] and 12 [2 + 2] possible dimers.[10] Despite the intrinsic regio- and stereocontrol demonstrated by this reaction, it has not been employed in natural product synthesis. The potential utility of this transformation, however, can be seen in the correspondence of the carbonyl groups in **3** with the methyl groups in **1** and **2** and a similar correspondence of the olefin carbons in **3** and the sites of oxidation in **1** and **2**. An intramolecular [4 + 4] pyridone photocycloaddition, e.g., **4** → **3**, has not been reported,[11] and relatively little is known about the electronic and geometric requirements of the reaction.[12]

Our first test substrate for this intramolecular reaction was bis-2-pyridone **9**,[13] prepared in five steps from 2,6-dibromopyridine (**5**) (Scheme I). It was anticipated that a three-carbon chain between the pyridones would permit ready access to a conformation suitable for cycloaddition. Furthermore, the alcohol in **9** would allow us to probe the control of stereogenesis by a chiral center on the tether, although the alcohol itself was expected to exert little effect on the product ratios. In the event, Pyrex-filtered irradiation of an ethanol solution[14] of **9** for 5 h resulted in the complete consumption of **9** and isolation of two crystalline products in a ratio of 11:1, with a combined isolated yield of 75%. The ratio of these products proved to be solvent dependent. When the photolysis was performed in methylene chloride, under otherwise identical conditions, the previously minor isomer became the major isomer (3:4, 66% isolated yield). The structures of these products were assigned as **10** and **11**, respectively (Scheme II). The assignment of the relative configuration of the two lactams was based on intermolecular reaction precedent.[10] The assignment of the relative configuration of the alcohol qualitatively follows from the solvent dependence of the reaction. The alcohol and carbonyl groups in **9** will hydrogen bond to a protic solvent (ethanol), resulting in a large apparent size of these groups, favoring formation of **10**.[15] Alternatively, the alcohol and the adjacent carbonyl can hydrogen bond intramolecularly in the absence of a hydrogen-bonding solvent (methylene chloride), favoring **11**.

The structure of isomer **10**, containing a chair-like cyclooctadiene ring trans fused to the cyclopentane ring, was confirmed by X-ray analysis[16] (Figure 1). Correlation of structure **11** with **10** was accomplished through chemical transformations:[17] hydrogenation of **10** and **11** individually gave **12** and **13** (94% and 86%, respectively, Scheme III); oxidation of **12** with PDC gave ketone **14** (63%); reduction of **14** with sodium borohydride in ethanol gave both **12** and **13** (4:3, 79%).

Access to the fused 8–6 rings comprising rings B and C of taxol using this method would require pyridones tethered by a four-carbon chain. Inspection of models suggested that the conformation required for cycloaddition of **17** would be higher in energy than the corresponding conformation of three-carbon-tethered **9**, and therefore the outcome was more uncertain. Bis-2-pyridone **17**, which incorporates a four-carbon chain, was prepared with the sequence outlined in Scheme IV. Gratifyingly, photolysis of an ethanol solution of **17** for 5 h fully consumed this bis-2-pyridone and led to the isolation of two crystalline products, assigned as carbinol epimers **18** (2:3, 63%, Scheme IV). The assignment of structure **18** rests on the excellent correlation of spectral data for these two isomers with **10** and **11**[18] and chemical correlation of the two isomers.[19]

The successful conversion of tethered bis-2-pyridones to [4 + 4] cycloadducts containing conformationally defined 8–5 and 8–6 bicyclic carbon skeletons sets the stage for further studies aimed at understanding the parameters that control stereogenesis at the four new sp^3 centers and the application of this method to total synthesis.

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Supplementary Material Available: X-ray data for compound **10** and spectroscopic data for compounds **6** and **8–18** (17 pages). Ordering information is given on any current masthead page.

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(11) For examples of sensitized photocycloaddition of N,N′-tethered pyridones which yield exclusively [2 + 2] and [4 + 2] products, see: Nakamura, Y.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1976**, *59*, 2841.

(12) Sharp, L. J.; Hammond, G. S. *Mol. Photochem.* **1970**, *2*, 225. Matsushima, R.; Terada, K. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1445.

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(14) Typical reactions were run at 0.01 M using a 450-W medium-pressure mercury lamp at ambient temperature (ca. 28 °C).

(15) Consistent with this rationale is the observation that photolysis of the *tert*-butyldimethylsilyl ether of **9** in ethanol yields the silyl ether of **10**, to the near exclusion of **11**.

(16) Crystal data for **10**: monoclinic, $C2/c$, $a = 21.42$ (1) Å, $b = 8.610$ (7) Å, $c = 13.066$ (3) Å, $\beta = 94.30$ (3)°, $V = 2403$ (2) Å^3, $Z = 8$, λ(Mo Kα) = 0.71069 Å, $T = -167$ °C. Final least-squares refinement with all the non-hydrogens anisotropic gave R (R_w) = 0.091 (0.096) using 649 observations, $I > 3.00\sigma(I)$. For additional data, see the supplementary material.

(17) Both **10** and **11** could be directly oxidized to the same ketone using PDC; however, this reaction proved to be highly variable in yield.

(18) Attempts to obtain suitable crystals of isomers of **18** for X-ray analysis have not been successful.

(19) Each isomer of **18** was hydrogenated (PtO_2) and oxidized (PDC), as described for **10** and **11**. These sequences yielded the same ketone, requiring that the isomers of **18** be carbinol epimers.