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Novel Reaction Pathways for 2-Pyridone [4+4] Photoadducts

Peiling Chen, Yanping Chen, Patrick J. Carroll,[§] and Scott McN. Sieburth*

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19010, and Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

scott.sieburth@temple.edu

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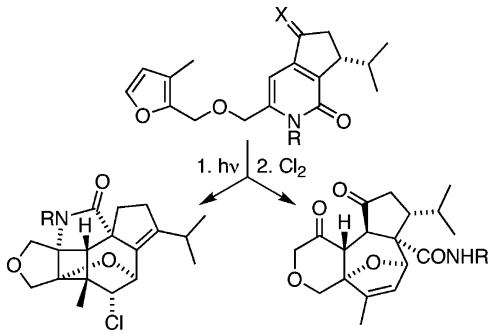
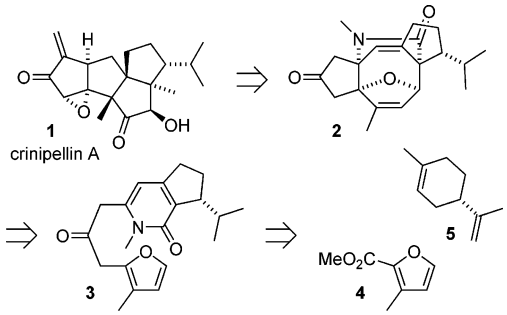
ABSTRACT



Transannular ring closure of a pyridone–furan [4+4] photoadduct has been evaluated in a model system. A combination of nitrogen substitution and an isopropyl group gave full control of the four new stereogenic centers. Chlorination transformed the 1,5-cyclooctadiene to a [4.2.0] ring system instead of to the expected [3.3.0] ring system. Changing an alkene to an enone suppressed this pathway and led to a new rearrangement, converting the 5-8-5 ring system to a 6-7-5 system.

Cycloadditions, such as the Diels−Alder reaction, are prized for the controlled leap in complexity that they engender.[1] Higher-order cycloadditions such as the [4+4] cycloaddition of 2-pyridones exhibit similar traits of regio- and stereoselectivity, but within the more difficultly accessible cyclooctadiene framework.[2] As part of our exploration of 2-pyridone photocycloadditions, we have investigated a pyridone−furan approach to the challenging tetraquinane natural product crinipellin A **1** (Scheme 1).[3] The two published syntheses of **1** utilized either sequential cyclopentane annulation[4] or an arene−alkene cycloaddition route.[5,6]

Scheme 1. Approach to the Crinipellins



As outlined in Scheme 1, we envisioned that intramolecular cycloaddition of a furan with a cyclopentane-substituted 2-pyridone **3** would carry all but one carbon of the natural

[§] University of Pennsylvania.

(1) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807. Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(2) Sieburth, S. McN. Photochemical Reactivity of Pyridones. In *CRC Handbook of Organic Photochemistry and Photobiology;* Horspool, W., Lenci, F., Eds.; CRC: Boca Ratan, 2004; pp 103/1−103/18.

(3) Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 709−711.

(4) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590−602.

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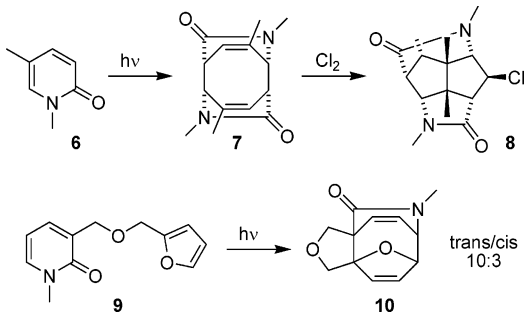
product. An isopropyl group, derived from (−)-limonene **5**, would block one face of the pyridone, and cis-selective cycloaddition would lead to pentacyclic 1,5-cyclooctadiene **2**. Transannular ring closure would then form a product with stereochemistry and functionality closely related to the natural product in only two steps from **3**. We report here our first two generations of this investigation.

The chemistry outlined in Scheme 1 was predicated, in part, on the two reactions shown in Scheme 2. During a study

Scheme 2. Two Reaction Precedents for the Synthetic Plan

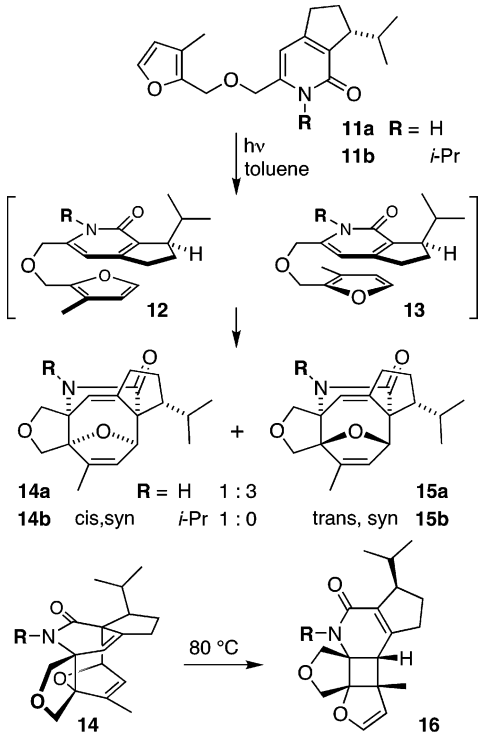


of 2-pyridone photodimer chlorination, the cis dimer **7** derived from 1,5-dimethyl-2-pyridone **6** was treated with chlorine. The major product isolated from that reaction was **8**,[7] with two quaternary carbons created during the chlorination step. A similar assembly of quaternary carbons was anticipated in the reaction of **2** (Scheme 1). The photochemistry of **3** would be analogous to that of **9** from which the [4+4] adduct **10** was isolated as a mixture of cis and trans isomers.[8]

To evaluate the salient features of the proposed synthesis, we elected to use ether **11**, easily derived from the known furan **4**,[9] and the enantiomerically pure isopropyl-substituted 1-pyrindin-2-one, assembled using chemistry described earlier (see Scheme 5).[10] In the four possible transition states leading to [4+4] adducts, we expected the isopropyl to inhibit the approach of the furan from the same face (not shown). Although the lone stereogenic center of **11** is adjacent to one of the carbons participating in the cycloaddition, the degree of this steric control had not been evaluated in earlier studies.[11] A second stereocontrol element, involving the pro-cis and pro-trans conformations **12** and **13**, was also an unsolved challenge. The closely related furan−pyridone photocycloaddition of **9** gave a very low level of stereocontrol, favoring the undesired trans isomer of **10**.

A cycloaddition with two tethered 2-pyridones, both unsubstituted on nitrogen, had been found to heavily favor cis cycloaddition in nonpolar solvents,[12] a consequence of the strong intermolecular hydrogen bonding of 2-pyridones.[13] Although not the same system, a cis-selective cycloaddition motif for **11a** could be imagined. In the event, however, irradiation of nitrogen-unsubstituted **11a** in toluene led to mostly the trans isomer **15a**. In contrast, when the *N*-isopropyl **11b** was irradiated in the same solvent, only the cis isomer **14b** was formed. In both cases, the cis:trans ratio was readily determined by warming the photochemistry product mixture and observing the quantitative Cope rearrangement of the cis isomer to give cyclobutane product **16** by ^{1}H NMR spectroscopy (Scheme 3).

Scheme 3. Steric-Induced Cis-Selective Photocycloaddition



The cis-selective cycloaddition of **11b** was expected to be a consequence of a destabilization of conformation **13**, where the isopropyl group **R** is in close proximity to the methyl group on the furan, thereby favoring conformation **12**.

The anticipated stereocontrol engendered by the isopropyl group on the cyclopentane of **11** was found to be at useful levels, with isomeric products resulting from the approach of the furan to the face of the pyridone syn to the isopropyl group (not shown) making up no more than 20% of the product mixture.

(5) Wender, P. A.; Dore, T. M. *Tetrahedron Lett.* **1998**, *39*, 8589−8592.
(6) See also: Curran, D. P.; Sisko, J.; Balog, A.; Sonoda, N. K. N.; Ryu, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, *10*, 1591−1593. Mehta, G.; Rao, K. S.; Reddy, M. S. *J. Chem. Soc., Perkin Trans. 1* **1991**, *4*, 693−700. Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272−9284.
(7) Kuznetsova, L. SUNY Stony Brook. Research notes, 1999.
(8) Sieburth, S. McN.; McGee, K. F. J.; Zhang, F.; Chen, Y. *J. Org. Chem.* **2000**, *65*, 1972−1977.
(9) Burness, D. M. *Org. Synth.* **1963**, *Coll. Vol. IV*, 649−652.
(10) Chen, Y.; Li, T.; Sieburth, S. McN. *J. Org. Chem.* **2001**, *66*, 6826−6828.
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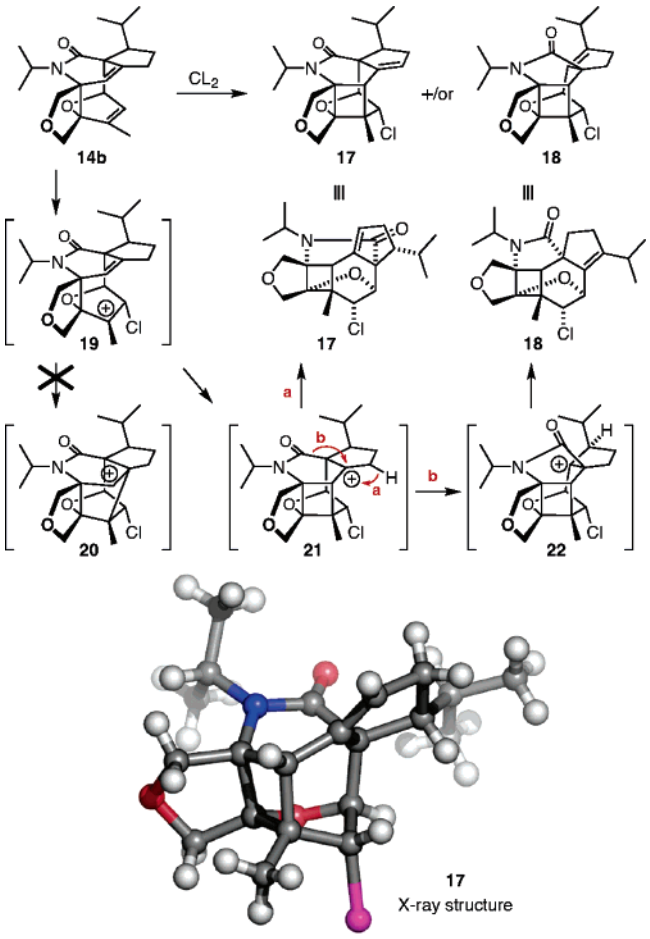
(13) Krackov, M. H.; Lee, C. M.; Mautner, H. G. *J. Am. Chem. Soc.* **1965**, *87*, 892−896. Beak, P.; Covington, J. B.; Smith, S. G.; White, J. M.; Zeigler, J. M. *J. Org. Chem.* **1980**, *45*, 1354−1362. Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787−5789.

With **14b** in hand, the critical chlorination reaction was investigated. Addition of a chlorine solution in methylene chloride to **14b** in the same solvent led to two products. Each contained a single alkene, and in the ^{1}H NMR, the chemical shift of the vinyl methyl singlet of **14b** (1.44 ppm) had shifted upfield to 1.28 ppm, characteristic of an aliphatic methyl group. The spectral data were difficult to rationalize as the hoped for product, however. When the chlorination solvent was changed to DMF, two products again resulted, one of which was the same. Use of ICl in methylene chloride also gave two products, each closely related (NMR) to the unique products formed in the two chlorination reactions (**17** and **18**). The structures of two products were determined by X-ray crystallography. Each of these resulted from a transannular closure of the cyclooctadiene of **14b** to a 4-6 ring system instead of the anticipated 5-5 product. This can be rationalized (Scheme 4) as involving a chloronium ion that opens

Scheme 4. Chlorination of Cis Adduct **14**

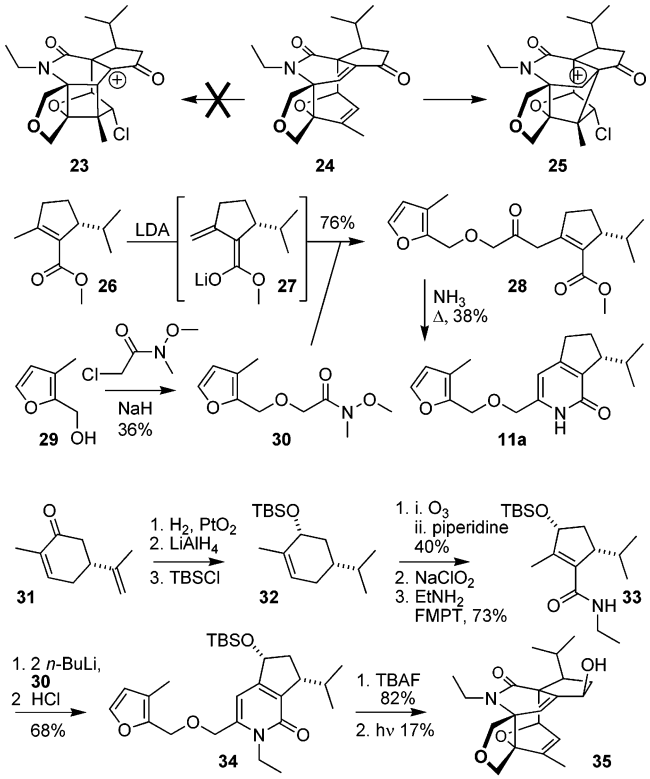


to the tertiary carbocation **19**. This cation is then intercepted by the proximal alkene, but instead of closing to the desired 5-5 ring system and a secondary carbocation **20**, the 4-6 ring system and a tertiary carbocation **21** are formed. This, in turn, either loses a proton to give alkene **17** (path a) or undergoes a migration of the amide carbonyl group to generate another tertiary carbocation (path b) and then loses a proton to yield tetrasubstituted alkene **18**. The third isolated product appears to be closely related to **18** (NMR), but its full identity is unresolved.

The migration of the amide carbonyl (**21**, path b) may appear unusual, but it has been observed in other 2-pyridone photodimer chlorinations. Indeed, product **8** in Scheme 2 results from carbonyl migration (although the desired diquinane structure and two quaternary carbons *were* formed in this case). A cationic ring closure of a constrained cyclooctadiene to yield a 4-6 ring system has been observed with 2-methoxy naphthalene photodimers.[14]

Considering the proposed pathways outlined in Scheme 4, a ketone adjacent to the undesired carbocation **21**, e.g., **24** (Scheme 5), was expected to shut down the cyclobutane

Scheme 5. Anticipated Effect of Ketone Substitution and Preparation of the Photosubstrates



formation (**23**) and favor the desired diquinane product formation via **25**. The preparation of **24**, however, would require a different starting point. Photosubstrate **11** had been prepared from (−)-limonene **5** via the known ester **26**[15] and the sequence shown in Scheme 5. Deprotonation of ester **26** and condensation with the Weinreb amide **30**, followed by refluxing with ammonia, led to substrate **11a**.

To introduce the desired ketone and prepare **24**, we began with (−)-carvone **31** in place of limonene **5**. Hydrogenation,

(14) Teitei, T.; Wells, D.; Sasse, W. H. F. *Tetrahedron Lett.* **1974**, 367−370. Teitei, T.; Wells, D.; Spurling, T. H.; Sasse, W. H. F. *Aust. J. Chem.* **1978**, *31*, 85−96.

(15) Chuman, T.; Noguchi, M. *Agric. Biol. Chem.* **1975**, *39*, 567−568. Chen, Y.; Li, T.; Sieburth, S. McN. *J. Org. Chem.* **2001**, *66*, 6826−6828.

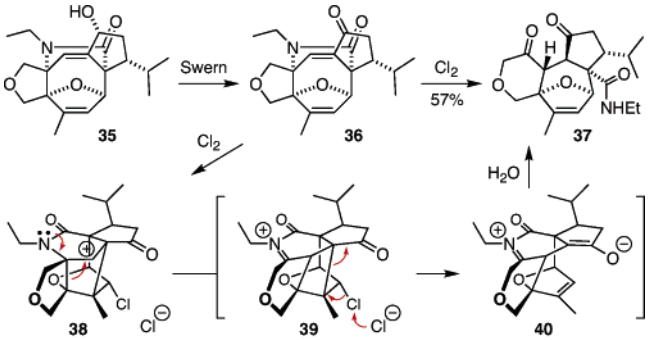
followed by reduction of the ketone and protection with *tert*-butyldimethylsilyl chloride, gave the cis product **32**.[16] Ozonolysis, aldol cyclization, oxidation of the aldehyde, and amide formation with ethylamine led to **33**. Condensation of this amide with Weinreb amide **30** gave **34**. With the silyl ether and the isopropyl groups blocking the same face of the pyridone, the relative stereochemistry of the subsequent cycloaddition was high; however, purification was far easier with the alcohol. Photocycloaddition was therefore run on the alcohol. The size of the nitrogen substitution required to effect the cis selectivity observed for *N*-isopropyl **11b** was titrated with the smaller *N*-ethyl **34**. In this case, cis adduct **35** again dominated the product but was not the exclusive outcome, with a cis/trans ratio of 9:1.

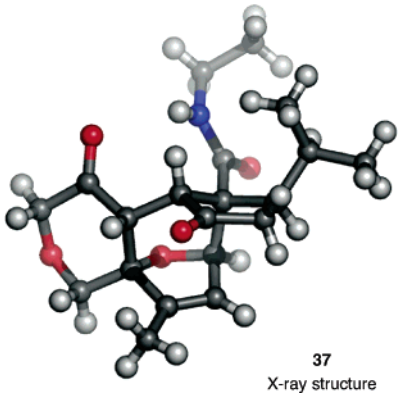
Ketone **36** was then prepared by Swern oxidation of the alcohol (Scheme 6). Treatment of this substrate with chlorine in methylene chloride led to the isolation of largely one new product in good yield. Confusingly, however, this new structure exhibited two ketones in its carbon NMR spectrum, as well as what appeared to be a secondary amide in the proton NMR spectrum. The solution to the structural identity of this product was solved, once again, by X-ray crystallography, which revealed it to be **37**.

The rearrangement leading to **37** can be explained by the mechanism shown in Scheme 6. Chlorinium ion formation at the least-hindered face of the more electron-rich alkene opens to generate a tertiary cation. This cation is then intercepted in the anticipated fashion by the enone alkene to form the tetraquinane **38**. Surprisingly, this cation is not intercepted by migration of the adjacent amide nitrogen[17] but instead suffers migration of the carbon−carbon bond, expanding a furan ring to a pyran and contracting the newly formed cyclopentane to a cyclobutane. The driving force for this rearrangement is presumably the stabilization resulting from conversion of the carbocation to the iminium ion. The strain of the cyclobutane intermediate is then relieved by removal of the intially added chlorine, possibly by the chloride ion, and enol(ate) formation. Hydrolysis of the resulting **40** leads to the observed keto amide product **37**.

Although this was not the anticipated outcome, formation of a 6-7 ring system **37** is the product of an hitherto unseen bond reorganization of [4+4] photoadducts. It is notable that product **40** has close analogy to several natural product structures.[18] These studies are continuing.

Scheme 6. Rearrangement of Enone **36**





37
X-ray structure

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Supporting Information Available: Proton NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Engler, M.; Anke, T.; Sterner, O. *Phytochemistry* **1998**, *49*, 2591−2593. Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79−85. Kobayashi, J.; Morita, H. The Daphniphyllum Alkaloids. In *The Alkaloids;* Cordell, G. A., Ed.; Academic: New York, 2003; Vol. 60, pp 165−205.