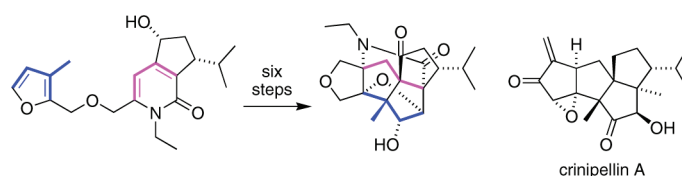


Tetraquinanes via [4 + 4]
Photocycloaddition/Transannular Ring
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ABSTRACT



Intramolecular [4 + 4] photocycloaddition of a furan and a cyclopentane-annulated 2-pyridone yields a cyclooctadiene product with four new stereogenic centers. Transannular ring closure produces the 5–5–5–5 fused ring system of the crinipellins, including three contiguous quaternary carbons, with the correct absolute stereochemistry derived from (–)-carvone.

Among the many polyquinane natural products,¹ the crinipellins remain the only tetraquinane, incorporating both linear and angularly fused triquinane substructures (Figure 1).² This challenging synthetic target, with its eight stereogenic centers, three contiguous quaternary carbons, and notable biological activity,³ has stimulated many approaches⁴ and two total syntheses of (±)-crinipellin B **2**.⁵ We describe here completion of a model system that assembles the four

stereogenic centers and the three quaternary carbons of **1** with the correct absolute stereochemistry using a 2-pyridone/furan [4 + 4] photocycloaddition followed by transannular ring closure as the central synthetic strategy.^{6,7}

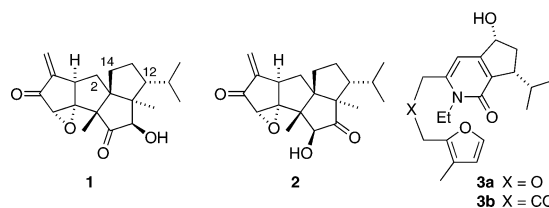


Figure 1. Crinipellin A **1**, B **2**, and potential precursor **3**.

Pyridone **4** is a promiscuous partner in photo-[4 + 4] cycloadditions, undergoing reactions with itself, 1,3-dienes,

(6) Transannular ring closure of cyclooctanoids to diquinanes can be effected in many ways. For lead references see: Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D.; Sieburth, S. McN. *Org. Lett.* **2001**, *3*, 2165–2167.

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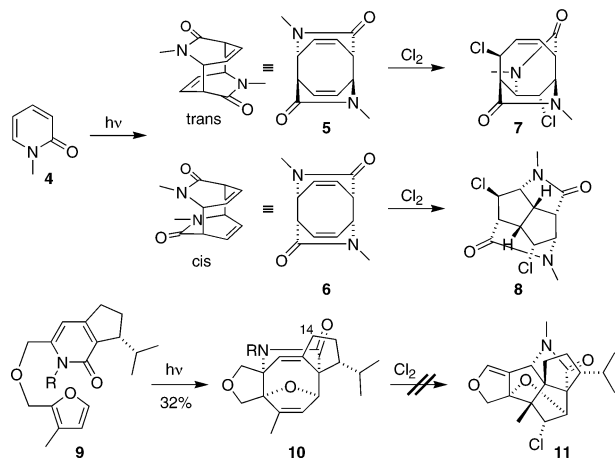
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naphthalene and other heterocycles including furan.^{8,9} Studies of 2-pyridone photodimerization as a route to cyclooctane-containing natural products demonstrated that highly strained photoproducts containing substructures **5** and **6** could be prepared with stereocontrol, and that subsequent reactions were also highly stereoselective.¹⁰ Two postphotocycloaddition reactions are shown in Scheme 1. Trans dimer **5**

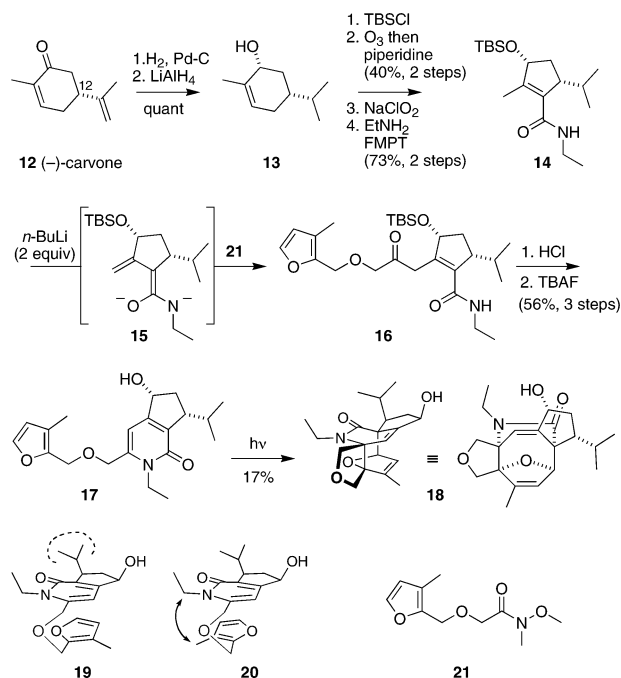
Scheme 1. Pyridone Photodimers, Their Halogenation Reactions, and an Approach to the Tetraquinanes



undergoes nitrogen migration when treated with chlorine, while cis **6** undergoes transannular ring closure to diquinane **8**.¹¹ Amalgamation of these studies led to a synthetic plan for the crinipellins, explored using ether **9**. Conditions for cis-selective photocycloaddition to give **10** were found (see below); however, the key electrophilic reorganization step to give **11** was frustrated by conversion of the cyclooctadiene to a 4–6 ring system, among others (e.g., **23**, Scheme 3), instead of the anticipated 5–5 ring system.¹²

Reformulation of chlorination substrate **10** with an additional carbonyl situated at C14 (crinipellin numbering) led to **17** as the photosubstrate, Scheme 2. The role of this ketone in **22**, Scheme 3, was to forestall tertiary carbocation generation at the adjacent carbon, preventing the undesired formation of a 4–6 ring system over the desired 5–5 product. To introduce this ketone, preparation of the photosubstrate began with (–)-carvone **12**, carrying the correct absolute stereochemistry of the isopropenyl corresponding to the C-12 isopropenyl of target **1**. Reduction of the isolated alkene and the ketone gave the known cis-alcohol **13**. Protection of this alcohol followed by oxidative cleavage of the alkene to the keto-aldehyde, and then piperidine-mediated aldol condensation, formed the cyclopentene carboxaldehyde.

Scheme 2. Preparation of the Photosubstrate and Cycloaddition



Oxidation of the aldehyde and coupling with ethyl amine gave **14**. Double deprotonation of **14** gave the dienolate **15** which condensed with Weinreb amide **21** to yield ketone **16** which could be cyclized to the desired pyridone under acidic conditions. Removal of the *tert*-butyldimethylsilyl group then gave photosubstrate **17**.

Two different selectivities are at play in the photocycloaddition of **17**. Irradiation of **17** gave a slow conversion to [4 + 4] product **18**. The isopropyl group was anticipated to provide steric shielding of one face of the pyridone **17** (as well as **9**), augmented by the cis alcohol group, and led to >90% facial selectivity for the furan approach.¹³ This pyridone face selectivity was supplemented by cis/trans selectivity engendered by the furan methyl group and its potential interaction with the pyridone *N*-ethyl group, disfavoring the pro-trans addition **20**.¹⁴ These two interactions yield cis isomer **18** via conformation **19**. Notably, three fully substituted carbons are formed in this cycloaddition step as well as four stereogenic centers.

The expectation that C-14 ketone would inhibit formation of the 6–4 ring system and compel formation of the desired

(7) For a related, elegant approach to polyquinanes based on [4 + 4] photocycloaddition of a 2-pyrone with a furan, see: Li, L.; McDonald, R.; West, F. G. *Org. Lett.* **2008**, *10*, 3733–3736.

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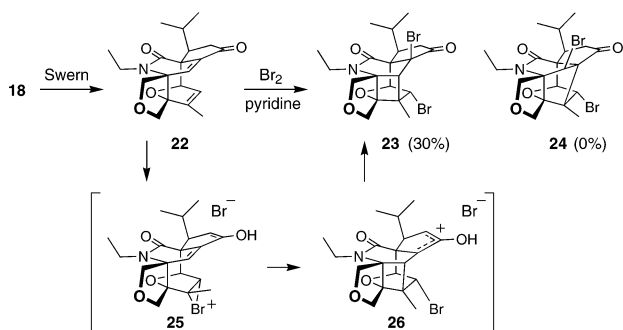
(12) Initial studies Chen, P.; Chen, Y.; Carroll, P. J.; Sieburth, S. McN. *Org. Lett.* **2006**, *8*, 3367–3370.

(13) In a closely related study of the effect of stereochemistry on 2-pyrone-furan [4 + 4]-photocycloaddition, with the opposite steric effect, see: Song, D.; McDonald, R.; West, F. G. *Org. Lett.* **2006**, *8*, 4075–4078.

(14) For a recent discussion of cis-trans stereoselectivity in 2-pyrone-furan [4 + 4]-photocycloadditions, see: Li, L.; Chase, C. E.; West, F. G. *Chem. Commun.* **2008**, 4025–4027. Li, L.; Bender, J. A.; West, F. G. *Tetrahedron Lett.* **2009**, *50*, 1188–1192.

5–5 ring system was, however, overly optimistic. Treatment of **22** with chlorine gave a 6–7 carbon ring system by rearrangement of the 5–8 rings.¹² In contrast, when **22** was treated with bromine in pyridine, the 4–6 ring formation was revisited, incorporating both halogen atoms for the first time.¹⁵ A possible reaction path leading to **23** is shown in Scheme 3, trapping the bromonium ion intermediate by the enone dienol, **25**.¹⁶ No trace of **24** was detected.

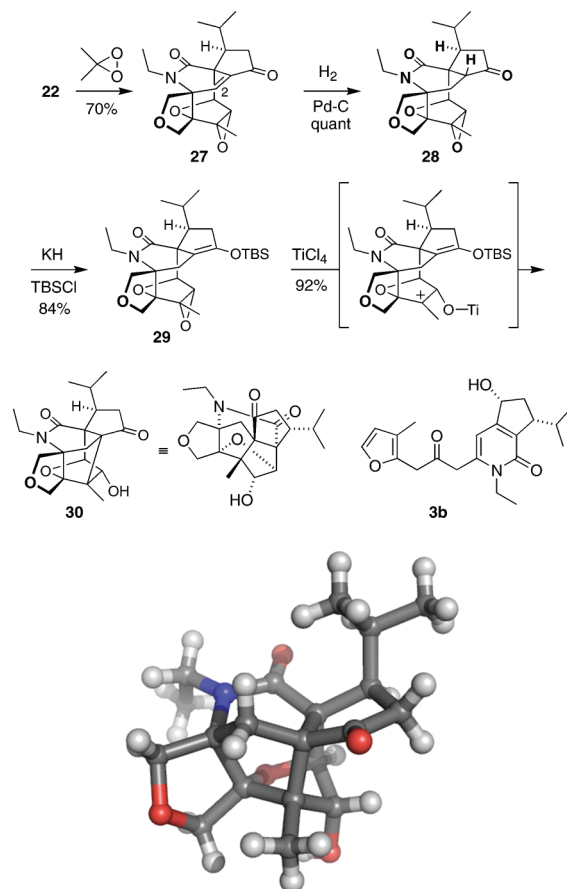
Scheme 3. Bromination of Enone **22** Converts Cyclooctadiene to a 4–6 Fused Ring System



It was clear that unsaturation at C-2 was the Achilles heel of the proposed transannular cyclization, and an alternative sequence was explored, Scheme 4. Epoxidation of the more electron rich alkene gave **27**. Hydrogenation of the interfering enone alkene, followed by thermodynamic enolization of the resulting ketone **28** in the presence of *tert*-butyldimethylsilyl chloride gave enol ether **29** as the sole product.¹⁷ It was anticipated that the epoxide and enol ether juxtaposition would ensure formation of the long sought C–C bond and two new quaternary carbons. In the event, treatment of **29** with titanium tetrachloride at $-78\text{ }^{\circ}\text{C}$ for ten minutes gave tetraquinane **30** in near quantitative yield! The desired bond construction and stereochemistry of **30** was confirmed by X-ray crystallography, Scheme 4.¹⁸

In this approach to the crinipellins, an intramolecular furan/2-pyridone [4 + 4] photocycloaddition forms a cycloocta-

Scheme 4. Completion of the Tetraquinane Construction and Crystal Structure of **30**



(15) Compound **23** crystallizes in the orthorhombic space group $P2_12_12_1$, with $a=6.6549(5)\text{ \AA}$, $b=13.8696(11)\text{ \AA}$, $c=21.495(2)\text{ \AA}$, $V=1984.0(3)\text{ \AA}^3$ and $Z=4$. Solution using direct methods gave $R_1=0.0392$ and $wR_2=0.0843$. See Supporting Information.

(16) A reviewer has made the very reasonable suggestion that the formation of **23** could also be explained by addition of a radical bromination process.

(17) Brown, C. A. *J. Org. Chem.* **1974**, 39, 1324–1325. Brown, C. A. *J. Org. Chem.* **1974**, 39, 3913–3918. Hudrlik, P. F.; Takacs, J. M. *J. Org. Chem.* **1978**, 43, 3861–3865.

(18) Compound **30** crystallizes in the orthorhombic space group $P2_12_12_1$, with $a=7.4039(5)\text{ \AA}$, $b=13.4534(10)\text{ \AA}$, $c=17.6386(13)\text{ \AA}$, $V=1756.9(2)\text{ \AA}^3$ and $Z=4$. Solution using direct methods gave $R_1=0.0370$ and $wR_2=0.0850$. See Supporting Information.

diene with four new stereogenic centers. Five additional steps are then used to set up and execute the transannular bond construction that completes formation of four contiguous five-membered rings. One of the natural product's three contiguous quaternary carbons is formed in the cycloaddition, and the other two are formed during the transannular bond formation, all with the correct absolute stereochemistry, derived from (–)-carvone.

To adapt this chemistry to preparation of the natural product **1**, the central ether of **3a** must be replaced with a ketone, **3b**. These studies are in progress.

Supporting Information Available: Experimental details, characterization data, proton and carbon NMR spectra for new compounds and crystal structure data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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