Fusicoccin Ring System by [4 + 4] Cycloaddition. Control of Diastereoselectivity through Hydrogen Bonding

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The dicyclopenta[*a*,*d*]cyclooctane ring system is common to several classes of natural products, including the ophiobolins and the fusicoccins,[2] and is also a substantial portion of more complex natural products such as the cardiotoxic kalmanol[3] and the termite defense secretion longipenol.[4] These challenging and biologically active molecules have stimulated many synthetic studies,[5] however, construction of the ring system via higher order cycloaddition chemistry[2,6] has only recently been reported.[7]

A retrosynthetic approach to fusicoccin A is outlined in Figure 1, in which linked 2-pyridones (**3**) undergo an intramolecular [4 + 4] cycloaddition. During the cycloaddition, two stereogenic centers (C-3 and C-12) should cooperatively influence stereogenesis at C-11.[8] Control of the stereogenic center C-7 would optimally be addressed by a cis-selective[9] cycloaddition to give **2**. The *trans*-8,9-diol would be derived via epoxidation of the disubstituted alkene.

Stereoinduction by a C-12 substituent has been reported;[9] however, 2-pyridone cycloadditions are generally selective for the trans isomer, an outcome that would require inversion at C-7. Selectivity for the trans product is variable, but cis-selective cycloadditions have been reported only for 2-pyridone dimerizations in micelles.[10] We report here a surprisingly high degree of stereoselectivity for the cycloaddition of **3b**,**c** and an equally high and unprecedented solvent-dependent stereoselectivity of **3a** that allows for selective formation of *either* trans or cis products from this substrate.

The annulated cyclopentane in **3** was initially expected to promote formation of the cis photoproduct **2**. Inspection of the conformations pro-trans **4** and pro-cis **5** reveals a steric interaction derived from the cyclopentane in **4** that could destabilize it relative to **5**. Without the cyclopentane in **3**, the trans selectivity is modest (66−74%),[9] and therefore a small steric interaction could greatly enhance the percentage of the cis photoproduct.

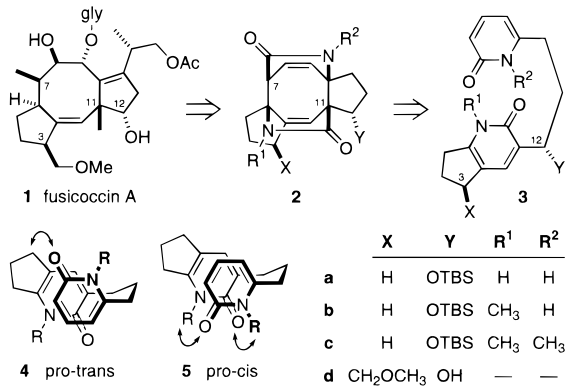
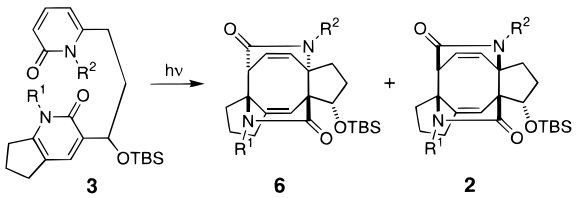


Figure 1. Retrosynthesis of fusicoccin A and trans/cis cycloaddition conformations.

Table 1. Solvent and Substituent Effect on the Trans/Cis Ratio of the Photoproduct



entry	cmpd	R^1	R^2	solvent	E_T	**6**:**2**
1	**3a**	H	H	MeOH	55.4	9:1
2	**3a**	H	H	DMSO	45.1	>98:<2
3	**3a**	H	H	CH_2Cl_2	40.7	3:1
4	**3a**	H	H	pyridine	40.5	9:1
5	**3a**	H	H	$C_6H_5CF_3$	38.5	1:4
6	**3a**	H	H	AcOEt	38.1	1:1
7	**3a**	H	H	THF	37.4	2:1
8	**3a**	H	H	C_6H_5Cl	36.8	5:95
9	**3a**	H	H	MBTE	35.5	1:9
10	**3a**	H	H	ether	34.5	1:2
11	**3a**	H	H	C_6H_6	34.3	<1:>99
12	**3b**	Me	H	MeOH	55.4	>99:<1
13	**3b**	Me	H	C_6H_6	34.3	>99:<1
14	**3c**	Me	Me	MeOH	55.4	>99:<1
15	**3c**	Me	Me	C_6H_6	34.3	>99:<1

In the event, irradiation[11] of *N*,*N*-dimethyl **3c** in a mixture of methanol and methylene chloride (for solubility) led to a rapid cycloaddition and the formation of a single product isomer. Despite the steric consideration discussed above, NMR analysis suggested that this product was the trans isomer **6c**, a conclusion confirmed by X-ray crystallography.[12,13] Similar to systems studied earlier,[9] this cycloaddition was solvent independent, yielding the same single product in methanol or in benzene (Table 1, entries 14 and 15). Solvent-insensitive stereoselectivity of 2-pyridone cycloadditions has been noted for both inter-[14] and intramolecular[9] reactions, although tether substituents have been found to exert solvent-dependent effects.[15]

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(8) A bulky group at C12 leads to a high degree of stereoinduction (see ref 9). The influence of a stereogenic center on a peripheral ring is unknown; however, if it blocks one face of the pyridone, it will lead to an enhanced selectivity at C-12.
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(11) Irradiations utilized a 450 W medium-pressure mercury lamp (Hanovia) and a Pyrex filter in a quartz water-cooled jacket. For additional experimental details, see ref 9. See also ref 17.
(12) All stable new compounds have been characterized by NMR, IR, MS, exact mass, and combustion analysis.
(13) Compound **6b** crystallizes in the monoclinic space group $P2_1/n$ with $a = 10.541(3)$ Å, $b = 16.593(2)$ Å, $c = 26.791(6)$ Å, $\beta = 90.36(1)°$, $V = 4686$ (2) Å^3 and $Z = 4$. Final least-squares refinement using 1622 unique reflections with $I > 3\sigma(I)$ gave R (R_w) = 0.060 (0.055). An ORTEP view of the crystal structure is included in the Supporting Information.
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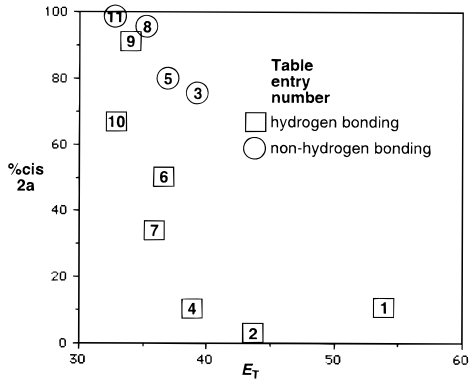

Figure 2. Percentage of cis **2** as a function of E_T indicating hydrogen-bonding solvents.

Irradiation of **3a**, lacking the *N*-methyl groups, in the same methanol/methylene chloride mixture, also led exclusively to trans product **6a**; however, a significant solvent dependence of the trans/cis ratio was found (Table 1). Entries in Table 1 are ranked according to the empirical solvent polarity parameter E_T.[16] For polar solvents, the trans isomer **6a** dominates (entries 1−4), while for much less polar solvents, the cis isomer dominates (entries 8−11).[17,18] Use of benzene (entry 11) yields exclusively the cis isomer! This dramatic change in stereoselectivity may be due to intramolecular hydrogen bonding (see below).

The relationship of E_T to the percentage of cis **2a** is illustrated in Figure 2, with hydrogen-bonding and non-hydrogen-bonding solvents indicated by squares and circles, respectively. Cis **2a** dominates the photoproducts for all of the non-hydrogen-bonding solvents, with the least polar (benzene and chlorobenzene, Table entries 11 and 8) yielding high cis selectivity. The more polar ((trifluoromethyl)benzene and dichloromethane, entries 5 and 3) are only 75−80% selective.

Comparison of the three ethers (THF, *tert*-butyl methyl ether, and diethyl ether, entries 7, 9, and 10) demonstrates that solvent polarity alone is not sufficient to explain the trans/cis selectivity. *tert*-Butyl methyl ether (entry 9) is more polar than ether (entry 10), yet it is much more selective for cis **2a**. Selectivity for trans **6a** parallels the ability of the ethers to hydrogen bond. The good hydrogen-bond acceptors methanol, DMSO, and pyridine (entries 1, 2, and 4) are highly selective for **6a**.

Strong intermolecular hydrogen bonding of 2-pyridones has long been known.[19] This hydrogen bonding often holds the 2-pyridones coplanar[19] and has been suggested as a source of the trans, head-to-tail photodimer.[20] Imposition of a three-carbon tether is incompatible with a planar hydrogen-bonding arrangement. A conformation compatible with a hydrogen bond between the closest groups on the photosubstrate, and slightly biased toward a cis [4 + 4] product, is shown as **A** (Figure 3).[21] This nine-membered ring is similar to the preferred ring size found by Gellman in his studies of polyamide hydrogen bonding.[22] Two hydrogen bonds can only be attained with a very cis-like conformation (**B**). The highly bent hydrogen bonds in **B** and the use of nonoptimal carbonyl orbitals counsels against a two-hydrogen bond effect;[23] nevertheless, both acidic 2-pyridone protons in **3a** are well defined in the ^{1}H NMR spectrum in C_6D_6 near 14 ppm, consistent with a hydrogen-bonded species.[24]

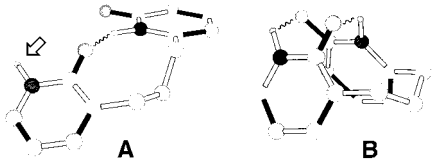

Figure 3. Molecular modeling of intramolecular hydrogen-bonded 2-pyridones showing the effect of one (**A**) and two (**B**) intramolecular hydrogen bonds.

To probe this effect further, mono *N*-methylated bis-2-pyridone **3b** was prepared, replacing the hydrogen in conformation **A** marked with an arrow. This single methyl group would prevent a two-hydrogen-bonded conformation **B**. In benzene, the lone acidic pyridone proton of **3b** is found at 12 ppm, in contrast to the 14 ppm found for **3a**. Compound **3b** yields exclusively the trans [4 + 4] product in methanol and in benzene (Table 1, entries 12 and 13). The NMR spectra and photochemical results are consistent with **3a** adopting conformation **B** in nonpolar, non-hydrogen-bonding solvents.

The features responsible for the unusually high trans selectivity for **3b**,**c** are presently unclear; however, the use of intramolecular hydrogen bonding to control stereogenesis in intramolecular reactions may be a general phenomenon.[25] The chemistry described here is an efficient pathway to the dicyclopenta[*a*,*d*]-cyclooctane ring system from simple precursors with full control of stereochemistry. Further studies are in progress.

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Supporting Information Available: A synthetic scheme for the synthesis of **3** and proton NMR spectra for compounds **2**, **3**, **6**, and synthetic intermediates, as well as the X-ray structure of **6c** (16 pages). See any current masthead page for ordering and Internet access instructions.

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(17) Reactions were performed with the starting bis-2-pyridone **3** as a 0.25 M solution in the appropriate solvent. Irradiation of the samples as described in ref 11 were conducted for 3 h at ambient temperature. Cis **2a** undergoes a facile Cope rearrangement at ambient temperature. The **2**:**6** ratio was determined by ^{1}H NMR spectroscopy after allowing **2a** to rearrange. See reference 18.

(18) *cis*-1,2-Divinylcyclobutane quantitatively rearranges to 1,5-cyclooctadiene (Vogel, E. *Liebigs Ann. Chem.* **1958**, *615*, 1−14). In contrast, cis polycyclic products of [4 + 4] cycloaddition such as **2a**, with a tub-shaped 1,5-cyclooctadiene, rearrange under rather mild conditions to the divinylcyclobutane. This instability is generally considered to originate from nonbonded steric interactions. For an application of this rearrangement and lead references, see: Sieburth, S. McN.; Lin, C.-H. *J. Org. Chem.* **1994**, *59*, 3597−3599.

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(21) Hydrogen bonds were modeled within Macromodel 4.0 (MacroModelV4.0; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467) by enforcing a distance of 1.8 Å between the hydrogen and the oxygen and then minimizing the structure.

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