Pergamon

Tetrahedron Letters 40 (1999) 4007–4010

TETRAHEDRON LETTERS

FUSICOCCIN RING SYSTEM BY [4 + 4] CYCLOADDITION. 2. A MODEL STUDY

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Received 18 February 1999; accepted 30 March 1999

Abstract: A synthetic approach to fusicoccin A utilizing intramolecular photocycloaddition of tethered 2-pyridones has been completed. This study has led to the first solvent-dependent 2-pyridone photocycloaddition yielding either cis or trans products. Epoxidation of the cis photoproduct is selective for the disubstituted alkene, stabilizes the product, and is properly located for installation of the trans-1,2-diol. Activation of the secondary amide by reaction with an isocyanate led to the reduction of the neopentyl amide carbonyl to a methyl group.

Keywords: cycloaddition, natural products, photochemistry, pyridones.

Among the cyclooctane-containing compounds, the tricyclic 5-8-5 ring fusion can be found in a number of natural products and natural product classes.[1] The fusicoccins are a representative example, with well over a dozen members. These have received substantial attention because of their biological activity[2] and their complex architecture, however none have been prepared by total synthesis.[3,4] We report here the results of a model study for synthesis of fusicoccin A, using an intramolecular 2-pyridone [4 + 4] photocycloaddition.[5]

Retrosynthetically, fusicoccin A (**1**) can be derived from pyridone/pyrindinone **3a**.[6] As an initial exploration of this disconnection, and to study the transformations that would be necessary to manipulate photoproduct **2**, we have prepared and studied **3b**, containing one stereogenic center and carrying a cyclopentane ring.

Among the challenges confronting this synthetic approach, was the desirability of a cis-selective cycloaddition that would set the relative stereochemistry of the methyl groups at C7 and C11 in **1** (the carbonyl groups in **2**). The solution to cis selectivity proved to be the simple combination of two hydrogen bonding pyridones, intramolecularity, and the use of a non-polar solvent.[5] All other examples of 2-pyridone [4 + 4] photocycloaddition have produced the trans isomer as the major, or exclusive product.[7] For photoreactions of **3b**, use of polar and/or hydrogen bonding solvents led to a high selectivity for trans product **6**, whereas nonpolar solvents result in highly cis-selective reactions (**4**, Figure 2).[5]

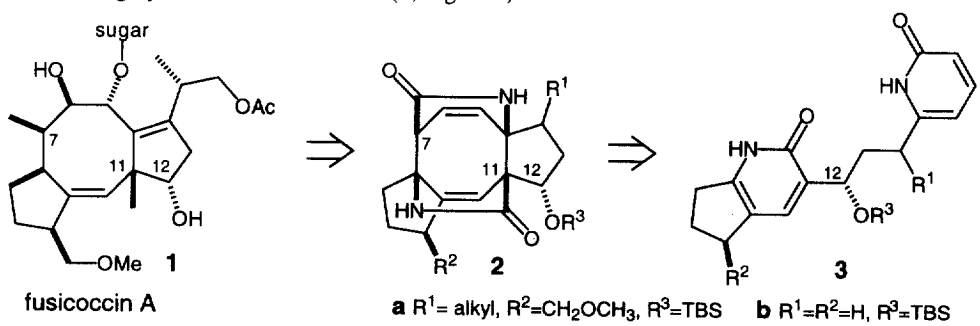

Figure 1. Retrosynthetic disconnection of fusicoccin A.

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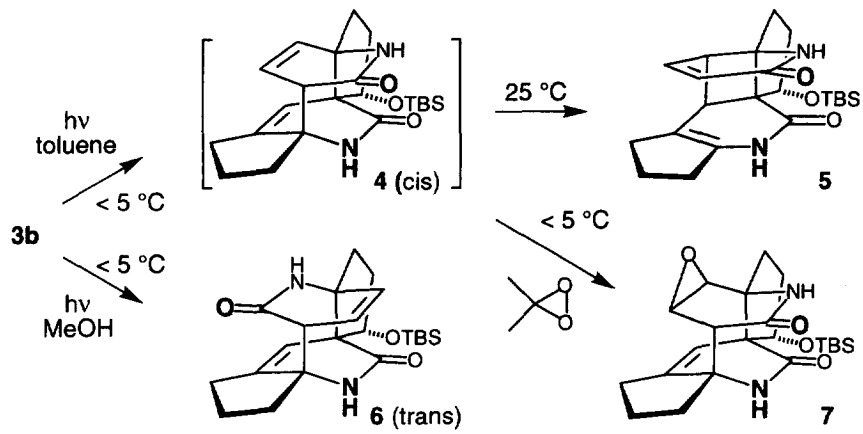


Figure 2. The photocycloaddition of **3b** is solvent dependent. Epoxidation of **4** is selective for the less-substituted olefin and prevents Cope rearrangement.

The utility of these cis selective reaction conditions was initially frustrated by the finding that **4** was unstable and underwent a Cope rearrangement at ambient temperature, the most facile Cope rearrangement found for these systems.[7] This rearrangement was very clean, but irreversible, and we therefore required a second reaction to intercept **4** and arrest the rearrangement. After some experimentation, it was determined that treatment of the crude photoproduct with dimethyldioxirane resulted in a single epoxide **7**, precisely where a trans 1,2-diol is located in the natural product. The facial and site selectivity of this epoxidation are most likely a result of steric effects.[8] When the photocycloaddition of **3b**[9] and the epoxidation were both carried out between 0 and 5 °C, epoxide **7** was isolated in 90% overall yield (Figure 2).

With epoxide **7** in hand, cleavage of the amide bonds was investigated. Secondary amides formed by [4 + 4] 2-pyridone photocycloaddition have been activated using di-*tert*-butyl dicarbonate[10] following Grieco's procedure.[11] However the neopentyl nature of the amide nitrogens in **7** did not allow for the use of this, or sulfonyl chloride reagents, and treatment with either returned starting **7** unchanged. As an alternative, isocyanates were tested because of the potential for these linear electrophiles to react in a sterically encumbered environment.[12] This reaction proved to be both efficient and selective, although incorporating a single isocyanate unit (Figure 3). Based on the relative hindrance of the two amide nitrogens in **7**, the structure **8** was proposed.[13] A variety of isocyanates (R = ethyl, *iso*-propyl, cyclohexyl, and phenyl) gave similar products and yields (74 - 87%). Further experimentation utilized the isopropyl isocyanate derivative.

The structure of **8**, with its seven stereogenic centers and the proposed site of isocyanate incorporation was definitively determined by X-ray crystallography (Figure 3).[14] This structure also revealed an intramolecular hydrogen bond of the urea hydrogen in **8**. This hydrogen bond was anticipated, based on the observation of a well defined signal at 8.1 ppm in the ^{1}H NMR spectrum.

Following reaction with the isocyanate, reductive opening of the amide of **8** was addressed. Reductive opening of **8** is similar to reductive cleavage of products from oxazolidinone and imidazolidinone chiral auxiliaries, albeit with an alternate ring connectivity. This reaction proved to be capricious however, yielding both the desired carbinol **9a** and also **7**, the latter from reductive removal of the isocyanate unit. Experimentation led to the finding that the reaction pathway is critically dependent on the concentration of the lithium borohydride, with higher yields of **9** produced with higher borohydride concentration (e.g. 64% at 0.4 M).[15]

Alcohol **9a** was converted to mesylate **9b** (76%) and reduced using zinc and sodium iodide in DMF.[16] Product **10** was isolated from this reaction in excellent yield (90%).

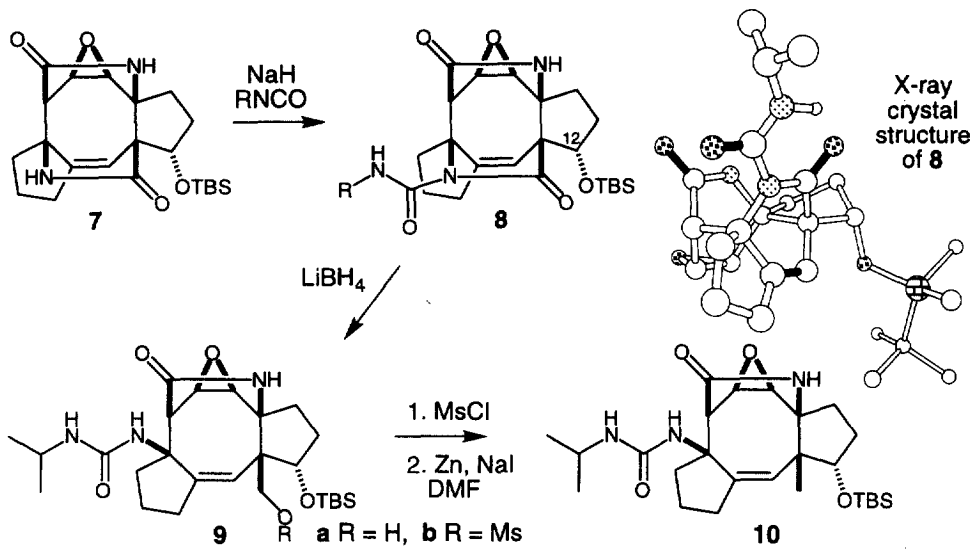


Figure 3. Secondary amide activation by condensation with an isocyanate allows for a mild reductive opening. Alcohol **9a** is readily reduced to a methyl group.

Transformation of bis-2-pyridone **3b** to **10** in five steps has laid the foundation for a synthesis of fusicoccin A **1** via [4 + 4] cycloaddition. During this investigation, we have discovered the first *cis*-selective 2-pyridone photocycloaddition, demonstrated an efficient method for activation of an amide using readily available and sterically insensitive isocyanates, found an unusual hydride concentration effect for reduction of **8**, and demonstrated for the first time that the amide carbonyl groups of pyridone photoproducts can be readily reduced to methyl groups. Further investigations will be reported in due course.

Acknowledgment: Support for this work by the National Institutes of Health is gratefully acknowledged. We thank Brian Dinkelmeyer and David Rucando for assistance with the X-ray structure determination.

References

1 Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757-5821.

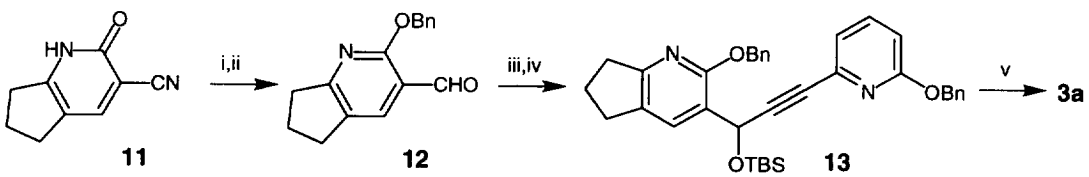
2 The high affinity fusicoccin receptor in plants is associated with the H^+-ATPase of the plasma membrane. See: Piotrowski, M.; Morsomme, P.; Boutry, M.; Oecking, C. *J. Biol. Chem.* **1998**, *273*, 30018-30023.

3 For synthetic approaches to the fusicoccins and related 5-8-5 ring systems, see: Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977**, *42*, 922-923. Begley, M. J.; Mellor, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1905-1912. Grayson, D. H.; Wilson, J. R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1695-1696. Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541-3557. Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201-205. Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319-1321. Dauben, W. G.; Warshawsky, A. M. *J. Org. Chem.* **1990**, *55*, 3075-3087. Mehta, G.; Murty, A. N. *J. Org. Chem.* **1990**, *55*, 3568-3572. Rigby, J. H.; McGuire, T.; Senanayake, C.; Khemani, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3449-3457. Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705-3716. Williams, D. R.; Coleman, P. J. *Tetrahedron Lett.* **1995**, *36*, 39-42. Harmata, M. *Tetrahedron* **1997**, *53*, 6235-6280. Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478-1479. Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suárez-Sobrino, A.; Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908-4909. Total synthesis of a biosynthetically related natural product, fusicocca-2,10(14)-diene, has recently been reported: Kato, N.; Zhang, C.-S.; Matsui, T.; Iwabuchi, H.; Mori, A.; Ballio, A.; Sassa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2473-2474. see also reference 5.

4 Ophiobolin C and the ceroplastols have been prepared by total synthesis: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735-2737. Boeckman, R. K., Jr.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737-2739. Paquette, L. A.; Wang, T.-Z.; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676-1683. Okamoto, H.; Arita, H.; Kato, N.; Takeshita, H. *Chem. Lett.* **1994**, 2335-2338. Kato, N.; Okamoto, H.; Takeshita, H. *Tetrahedron* **1996**, *52*, 3921-3932. Total synthesis of the structurally related epoxydictymene has been achieved: Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5505-5506. Paquette, L. A.; Sun, L.-Q.; Friedrich, D.; Savage, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 8438-8450.

5 The solvent-dependent stereoselectivity for the photocycloaddition of **3b** has been reported: Sieburth, S. McN.; McGee Jr., K. F.; Al-Tel, T. H. *J. Am. Chem. Soc.* **1998**, *120*, 587-588.

6 Compound **3a** was prepared in five steps from **11**.[17] *O*-Alkylation with benzyl bromide using Tieckelmann's conditions[18] was followed by reduction of the nitrile to the aldehyde. Coupling **12** with the magnesium bromide acetylide derived from 2-benzyloxy-6-ethynyl pyridine and protection of the alcohol with *tert*-butyldimethylsilyl chloride gave **13**. Hydrogenation then yields **3a**.



i. BnBr, Ag_2CO_3 ii. DIBAL iii. 2-benzyloxy-6-(BrMgC≡C)-pyridine iv. TBSCl v. H_2, 5% Pd-C.

7 Sieburth, S. McN. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI: Greenwich, CT, 1999; Vol. 5; 85-118.

8 Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811-822.

9 A toluene solution of **3b** (0.025M) in a pyrex test tube was strapped to the side of a water-cooled quartz immersion well surrounding a medium-pressure mercury lamp inside of a pyrex filter. The entire apparatus was placed in an ice bath during irradiation (ca. 3h). Following the irradiation, the cooled photoproduct solution was transferred to a flask and treated with an acetone solution of dimethyldioxirane (2 equivalents of a 0.07 M solution.

10 Sieburth, S. McN.; Rucando, D.; Lin, C.-H. *J. Org. Chem.* **1999**, *64*, 954-959.

11 Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426.

12 Sera, A.; Itoh, K.; Yamaguchi, H. *Tetrahedron Lett.* **1990**, *31*, 6547-6548.

13 The C12 carbinol proton in **2** is found at 4.67 ppm, presumably due to the deshielding of the adjacent carbonyl. Reduction of **8** to **9a** results in a substantial upfield shift in this proton signal.

14 Compound **8** crystallizes from acetonitrile in the monoclinic space group $P2_1/c$ with a = 15.126 (4) Å, b = 12.900 (3) Å, c = 15.592 (4) Å, β = 111.70 (2)°, V = 2826.9 (5) Å^3, and Z = 4. Final least squares refinement using 2229 unique reflections with $I > 3\sigma(I)$ gave $R(R_w) = 0.069$ (0.088).

15 Despite apparently ample precedent for hydride reduction of acylated ureas, we are not aware of a report concerning an effect of reducing agent concentration on product distribution. Studies in this area will be reported elsewhere.

16 Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 3325-3326. Matsumoto, T.; Terao, H.; Wada, M.; Imai, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2762-2765.

17 Paine, J. B., III *J. Heterocycl. Chem.* **1987**, *24*, 351-355.

18 Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040-4044.