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Diels–Alder Cycloaddition of Chiral Nonracemic 2,5-Diketopiperazine Dienes

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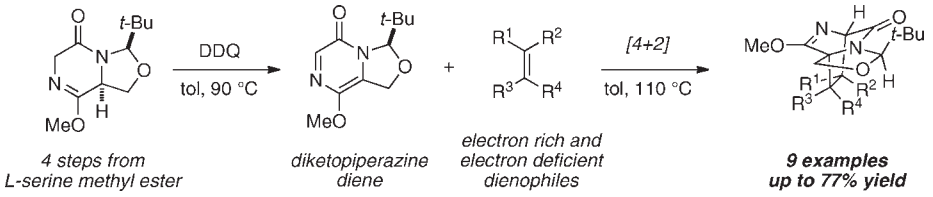
ABSTRACT



Preparation of a chiral, nonracemic 2,5-diketopiperazine diene has enabled the investigation of intermolecular hetero-Diels–Alder cycloadditions. The diketopiperazine diene is reactive with both electron-rich and -deficient alkene substrates. Diastereofacial control in the cycloaddition is enforced with a removable aminal substituent. This study partly illuminates the regiochemical, stereoelectronic, and reactivity preferences of the diketopiperazine cycloaddition as well as provides a direct diastereoselective synthetic route to bicyclo[2.2.2]diazaoctane structures.

Brevianamide A was the first isolated fungal metabolite that displayed a [2.2.2]-diazabicyclic core.[1] In the decades since this initial discovery, a large family of prenylated indole alkaloids has been revealed, including the paraherquamides, stephacidins, and notamides.[2] Many of these natural products possess potent and varied biological activities including antitumor, antihelmintic, antibacterial, and insecticidal properties.[3] The [2.2.2]-diazabicyclic structural motif shared among these alkaloids is postulated to arise through a biogenic intramolecular hetero-Diels–Alder cycloaddition between an unactivated terminal alkene and a 2,5-diketopiperazine (DKP) tautomeric azadiene intermediate (Figure 1).[4]

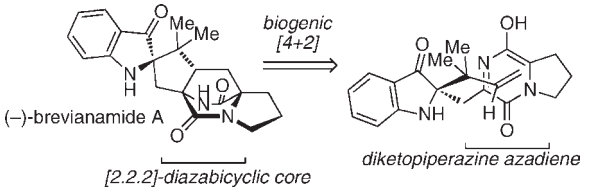


Figure 1. Structure of brevianamide A, a representative [2.2.2]-diazabicyclic indole alkaloid, and the proposed biosynthesis.

Support for this biosynthetic hypothesis was first realized by Porter and Sammes when they demonstrated the Diels–Alder cycloaddition of a symmetric pyrazine with both a strained alkene and dimethyl acetylenedicarboxylate (Figure 2).[5] More recently, Williams and co-workers have explored intramolecular variants of the DKP Diels–Alder in the context of several elegant biomimetic total syntheses.[6,2] To date, three distinct dieneophiles have been employed in the DKP cycloaddition: unactivated alkenes (including intramolecular variants), acetylene dicarboxylate,

(1) Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, 644–645.

(2) (a) Williams, R. M. *Chem. Pharm. Bull.* **2002**, *50*, 711–740. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127–139.

(3) (a) Qian-Cutrone, J. F.; Huang, S.; Shu, Y. Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556–14557. (b) Martinez-Luis, S.; Rodriguez, R.; Acevedo, L.; Gonzalez, M. C.; Lira-Rocha, A.; Mata, R. *Tetrahedron* **2006**, *62*, 1817–1822. (c) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97–173.

(4) (a) For reviews of biogenic Diels–Alder reactions, see: (a) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115. (b) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. Biosynthesis of Prenylated Alkaloids Derived from Tryptophan. *Biosynthesis: Aromatic Polyketides, Isoprenoids, Alkaloids*; Springer-Verlag Berlin: Berlin, 2000; Vol. 209, pp 97–173.

(5) Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1970**, 1103.

(6) For reviews, see: (a) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160–3174. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127–139.

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and diazodicarboxylate.[7] These mostly symmetric or tethered substrates validate the reaction with dieneophiles of disparate electronic character but offer only a limited view of other reaction attributes including the regiochemical and stereochemical preferences of the DKP Diels–Alder cycloaddition.

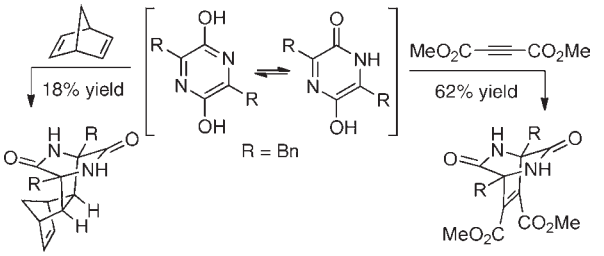


Figure 2. Initial discovery of the DKP Diels–Alder cycloaddition.

Additionally, the prior work by Williams and co-workers in the biomimetic total synthesis of VM55599[8] was of particular interest as the only example of an intermediate bearing a stereogenic center adjacent to the DKP azadiene (Figure 3).[9] In the key cycloaddition step, the exocyclic alkene in the DKP starting material isomerized to the reactive endocyclic azadiene over two weeks in acetyl chloride. Subsequent intramolecular Diels–Alder cycloaddition afforded a mixture of three of the four possible diastereomers (35:15:10:0), the major product resulting from apparent contrasteric cycloaddition on the face *syn* to the C-17 methyl group.[10]

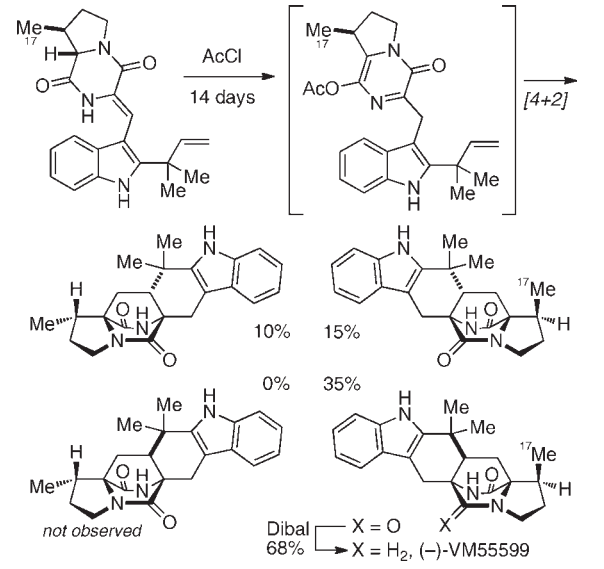
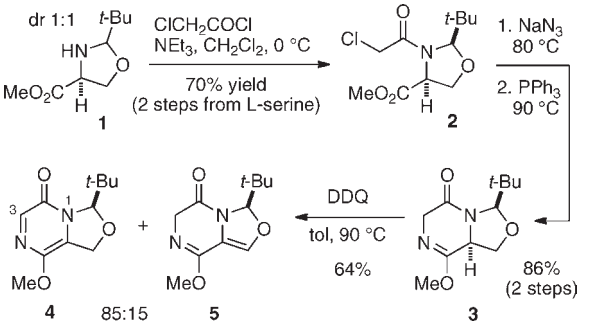


Figure 3. Synthesis of VM55599 via DKP [4 + 2] by Williams.

In the context of this background, we wanted a readily prepared, chiral, nonracemic DKP diene model to explore diastereoselective cycloadditions in greater detail. We envisioned that a removable chiral *tert*-butyl aminal auxiliary could impart a strong facial bias during the cycloaddition and inform selective bond formation. Exploiting the concept of self-regeneration of stereocenters as pioneered by Seebach,[11] we initiated our synthesis of the chiral DKP diene from L-serine methyl ester. Preparation of the desired DKP was facile and required only modifications to precedented procedures.[12] First, the α-amino and *β*-hydroxy functions were engaged to form the derived cyclic *tert*-butyl aminal **1** (Scheme 1).[13] Acylation of the unstable

Scheme 1. Synthesis of Chiral Diketopiperazine Diene



aminal mixture (dr 1:1) with chloroacetyl chloride at 0 °C gave predominantly the kinetic product, *cis*-configured oxazolidine **2** (dr > 10:1). In addition to providing one major diastereomer, acylation also rendered the aminal function configurationally stable to the required subsequent chemical transformations. Staudinger reduction of the derived azide with triphenylphosphine under anhydrous conditions (toluene, 90 °C) permitted cyclization of the resulting aza-Wittig intermediate at the pendant methyl ester, thereby establishing both the DKP ring and the lactim ether moiety.[14] In summary, the DKP diene precursor **3** could be prepared in four steps (two chromatographic separations) and 60% overall yield.

(7) (a) Jin, S.; Wessig, P.; Liebscher, J. *J. Org. Chem.* **2001**, *66*, 3984–3997. (b) Alen, J.; Smets, W. J.; Dobrzanska, L.; De Borggraeve, W. M.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2007**, 965–971. (c) Sanz-Cervera, J. F.; Williams, R. M.; Marco, J. A.; Lopez-Sanchez, J. M.; Gonzalez, F.; Martinez, M. E.; Sancenon, F. *Tetrahedron* **2000**, *56*, 6345–6358.

(8) (a) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1675–1683. (b) Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2556–2559.

(9) The synthesis of versicolamide B intercepts a chiral spriooxindole; however in this case, the stereogenic center is removed from the DKP diene functionality and imparts only modest facial selectivity: Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63–68.

(10) The DKP Diels–Alder cycloaddition pertinent to VM99955 has been modeled: Domingo, L. R.; Zaragoza, R. J.; Williams, R. M. *J. Org. Chem.* **2003**, *68*, 2895–2902.

(11) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708–2748.

(12) (a) Brunner, M.; Saarenketo, P.; Straub, T.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2004**, 3879–3883. (b) Cagnon, J. R.; LeBideau, F.; MarchandBrynaert, J.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 2291–2294.

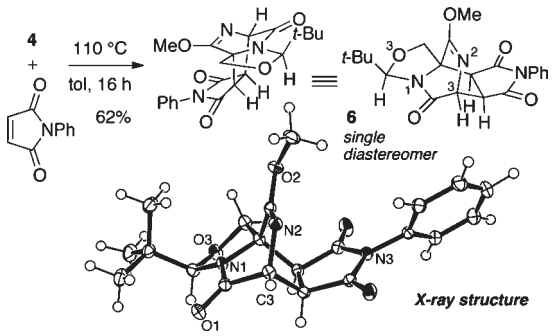
(13) Seebach, D.; Stucky, G.; Renaud, P. *Chimia* **1988**, *42*, 176–178.

(14) Nicolaou, K. C.; Lizos, D. E.; Kim, D. W.; Schlawe, D.; de Noronha, R. G.; Longbottom, D. A.; Rodriquez, M.; Bucci, M.; Cirino, G. *J. Am. Chem. Soc.* **2006**, *128*, 4460–4470.

Oxidation of bicycle **3** with DDQ gave a mixture of the desired DKP diene **4** and the regioisomeric exocyclic diene **5** (64% combined yield, 85:15 ratio). The diene isomers were inseparable by chromatography, and the desired diene **4** decomposed on exposure to air.[15] Consequently, the acidic hydroquinone byproduct was removed by filtration and base wash, and the resulting diene mixture was submitted directly to the Diels–Alder without purification.

With the aim of obtaining a crystalline cycloadduct, *N*-phenylmaleimide was first examined in the Diels–Alder reaction with DKP diene **4**. We observed efficient reaction on heating in toluene (110 °C, 0.1 M) to afford cycloadduct **6** as a single diastereomer (dr >95:5) in 62% yield. The structure of product **6**, verified by single crystal X-ray analysis, reveals that cycloaddition occurred on the DKP face opposite the *tert*-butyl aminal substituent and from the *endo* transition state (Scheme 2).

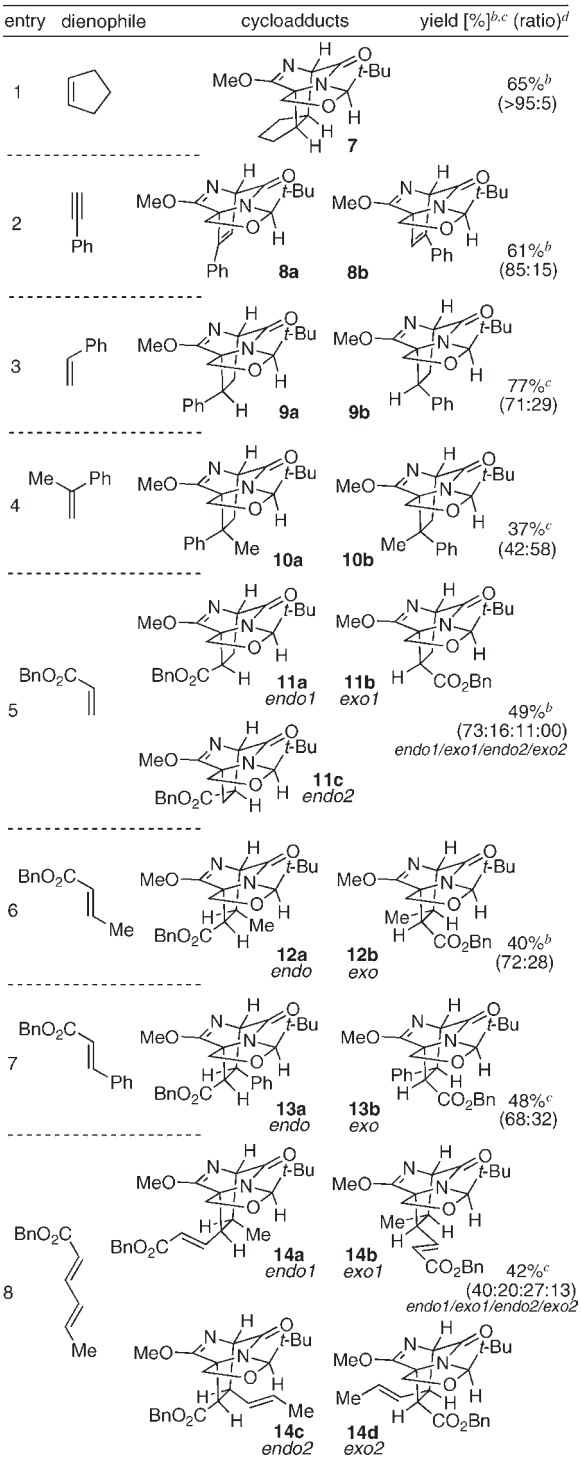
Scheme 2. DKP Diels–Alder with *N*-Phenylmaleimide



Because both the *endo* and *exo* transition states for the DKP diene cycloaddition have possible secondary orbital interactions with π-electrons, the exclusive preference for the *endo* transition state in this case was surprising and is not easily rationalized from related azadiene substrates. Although the preference for the *endo*-approach in the Diels–Alder reaction with carbocyclic dienes is well documented—particularly with maleic acid derivatives—nitrogen-containing dienes often prefer the *exo* approach.[16] In particular, 2-azadiene derivatives generally favor the *exo* approach.[17] DKP **4** behaves distinctly from other known azadienes.

We were encouraged by the reactivity and selectivity of the maleimide example and set out to explore the scope of the thermal cycloaddition with DKP diene **4**. A variety of dieneophilic substrates, both electron-rich and -deficient, were equally competent in the cycloaddition. Representative results are summarized in Table 1. Diene face selectivity was excellent; in no case were products detected from cycloaddition on the DKP diene face *syn* to the *tert*-butyl aminal substituent.

Table 1. Diketopiperazine Diene Diels–Alder Cycloaddition[a]



[a] Standard conditions: **4** (and **5**), tol 110 °C (0.1 M), dieneophile (1.1 equiv), 16 h. [b] Isolated yield of a single (major) isomer. [c] Isolated yield of combined isomers. [d] Determined by ^{1}H NMR spectroscopy of the unpurified product mixture.

(15) DKP dienes rapidly undergo cycloaddition with molecular oxygen: Machin, P. J.; Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 404–409.

(16) *Exo* adducts with maleimide involve heterocyclic dienes. See: Eckroth, D. R. *J. Org. Chem.* **1976**, *41*, 394–395 and references therein.

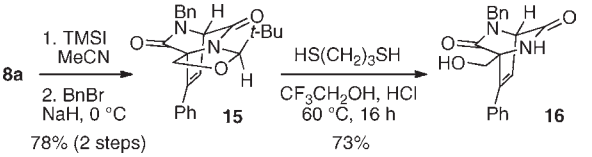
(17) (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617–2618 and references therein. (b) For general reviews of azadienes in the Diels–Alder reaction, see: (b) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939. (c) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471. (d) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987.

Due to the dissonant[18] relationship of heteroatoms in DKP diene **4**, prediction of the major cycloadduct regioisomer was not obvious *a priori*. However, as we explored unsymmetric substrates, two different regiochemical preferences emerged, one for reverse electron demand cycloaddition (electron-rich dieneophiles), another under normal electron demand conditions (electron-deficient dieneophiles). For electron-rich dieneophiles such as phenylacetylene, styrene, and α-methyl styrene (entries 2−4), the more nucleophilic terminus of the dieneophile aligns with the C-3 imino functionality of DKP diene **4**. In contrast, electron-deficient unsaturated esters (entries 5−8) reverse this trend, aligning the less nucleophilic terminus with C-3 of DKP **4**. Unsaturated ester dieneophiles (entries 5−8) also show a preference for the *endo* transition state. Selectivity varies from 84:16 for acrylate (entry 5, combined *endo*/*exo*) to approximately 2:1 for cinnamate, sorbate, and crotonate (entries 6−8). These selectivities, and that of the previously mentioned maleimide derivate (> 95:5 *endo*, Scheme 2), loosely correlate with *endo*/*exo* ratios for thermal Diels−Alder cycloaddition between the illustrated dieneophiles and carbocyclic dienes like cyclopentadiene[19] or cyclohexadiene.[20]

In an attempt to probe the ambiphilic nature of the DKP diene Diels−Alder reaction, benzyl sorbate (entry 8) was selected as a unique dieneophile possessing two alkene functions. Cycloaddition of DKP diene **4** with sorbate indicated a small preference (3:2 ratio) for reaction at the more electron-rich ψ,δ-unsaturation relative to the more electron-deficient α,β-unsaturation (see adducts **14a**−**d**).

Cycloadduct **8a** was chosen as a model substrate to demonstrate cleavage of the *tert*-butyl aminal residue (Scheme 3). In order to facilitate aminal removal, it proved necessary to first convert the basic lactim ether functionality into a lactam. Toward this end, the lactim ether in **8a** was efficiently deprotected by alkylative de-etherification with *in situ* prepared TMSI.[21] The resulting lactam was benzylated on nitrogen to afford intermediate product **15**. The *tert*-butyl aminal was then removed with HCl in the presence of 1,3-propanedithiol as an aldehyde trapping agent.[22] The resulting product **16** was cleanly obtained after removal of the dithiane byproduct. The *N*-benzyl amide protection was not necessary for aminal cleavage but differentiated the two lactams in product **16** and greatly aided solubility; the derived product lacking the benzyl amide was virtually insoluble in common organic solvents (e.g., MeOH, acetone, DMF).

Scheme 3. Cleavage of *tert*-Butyl Aminal Auxiliary



To summarize, we have successfully expanded the scope of the DKP diene Diels−Alder cycloaddition. The reaction is compatible with a variety of alkene (or alkyne) dieneophiles. The dominant product regioisomer is predictable, and stereochemistry favors reaction from the *endo* transition state with electron-deficient α,β-unsaturated esters and imides. The methods explored in this initial report offer a synthetic tool for chemists in the construction of asymmetric molecules that contain a [2.2.2]-diazabicyclic skeleton.

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Supporting Information Available. Experimental procedures and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(18) For explanation of dissonant bond paths, a phrase introduced by David A. Evans, see: Hudlicky, T.; Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*; Wiley-VCH: Weinheim, 2007; Chapter 2.4.5, p 186.

(19) (a) Methyl acrylate (75:25 *endo*/*exo*): Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17–22. (b) Methyl crotonate (1:1 *endo*/*exo*): Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548–6553. (c) Methyl cinnamate (53:47 *endo*/*exo*): Mamaghani, M. *Tetrahedron* **2002**, *58*, 147–151.

(20) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 22–25.

(21) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun*. **1978**, 874–875.

(22) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc*. **1992**, *114*, 10677–10678.