

# Efficient Entry to the [2.2.2]-Diazabicyclic Ring System via Diastereoselective Domino Reaction Sequence

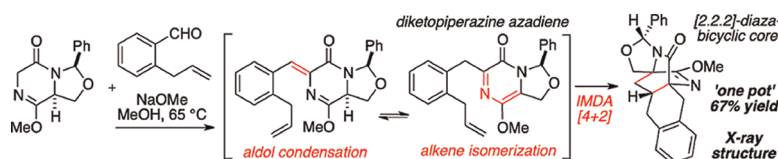
Kaila A. Margrey, Alex J. Chinn, Stephen W. Laws, Robert D. Pike, and Jonathan R. Scheerer\*

Department of Chemistry, The College of William & Mary, P.O. Box 8795, Williamsburg, Virginia 23187, United States

jrscheerer@wm.edu

Received March 20, 2012

## ABSTRACT



A domino reaction sequence involving aldol condensation, alkene isomerization, and intramolecular hetero-Diels–Alder cycloaddition for the synthesis of [2.2.2]-diazabicyclic structures is reported. Excellent diastereofacial control during the cycloaddition is enforced with a removable chiral phenyl aminal diketopiperazine substituent. The reaction sequence rapidly generates molecular complexity and is competent with both enolizable and nonenolizable aldehyde substrates (nine examples total). Progress toward the synthesis of malbrancheamide B, a prototypical member of the [2.2.2]-diazabicyclic natural product family, is also disclosed.

The [2.2.2]-diazabicyclic ring skeleton is shared among a number of prenylated indole alkaloids including the brevianamides, paraherquamides, stephacidins, notamides, and malbrancheamides (Figure 1).<sup>1</sup> These fungal-derived natural products possess a wide spectrum of biological activities including antitumor, antihelminthic, antibacterial, calmodulin inhibition, and insecticidal properties.<sup>2</sup> Impressive structural diversity is observed across the alkaloid family, although all members share a [2.2.2]-diazabicyclic core. In addition to potent bioactivity and remarkable chemical structure, there are engaging biosynthetic questions regarding the origin of the [2.2.2]-diazabicyclic structural motif. The functionality is putatively derived from a biogenic intramolecular hetero-Diels–Alder cycloaddition (IMDA).<sup>3</sup>

Alkaloids within this family have attracted significant attention from the synthetic community. In the context of

total synthesis, five general synthetic strategies have been successfully employed to prepare the [2.2.2]-diazabicyclic core:<sup>4</sup> (1) biomimetic Diels–Alder cycloaddition<sup>5</sup> (Williams, Liebscher), (2) radical cyclization<sup>6</sup> (Myers, Simpkins), (3) oxidative enolate coupling<sup>7</sup> (Baran), (4)  $S_N2'$  enolate alkylation<sup>8</sup> (Williams), and (5) cation–olefin cyclization<sup>9</sup> (Simpkins).

Because the Diels–Alder reaction establishes two bonds in concerted fashion, the biomimetic IMDA approach pioneered by Williams provides one of the most efficient

(1) (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.

(2) (a) Qian-Cutrone, J. F.; Huang, S.; Shu, Y. Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klotz, 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.

(3) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. Biosynthesis of Prenylated Alkaloids Derived from Tryptophan. In *Biosynthesis: Aromatic Polyketides, Isoprenoids, Alkaloids*; Springer-Verlag: Berlin, 2000; Vol. 209, pp 97–173.

(4) Synthetic approaches to [2.2.2]-diazabicyclics have been reviewed: Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160–3174.

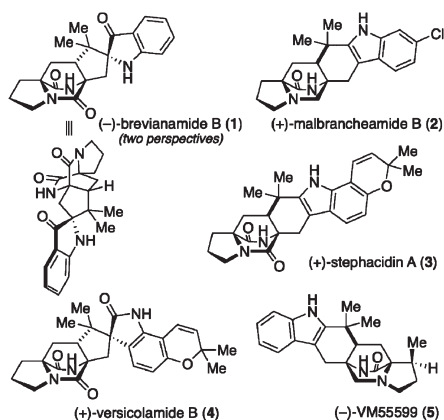
(5) (a) Williams, R. M. *Chem. Pharm. Bull.* **2002**, *50*, 711–740. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127–139. (c) Jin, S.; Wessig, P.; Liebscher, J. *J. Org. Chem.* **2001**, *66*, 3984–3997.

(6) (a) Herzog, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342–5344. (b) Crick, P. J.; Simpkins, N. S.; Highton, A. *Org. Lett.* **2011**, *13*, 6472–6475. (c) Simpkins, N.; Pavlakos, I.; Male, L. *Chem. Commun.* **2012**, *48*, 1958–1960.

(7) Baran, P. S.; Hafenstein, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.

(8) (a) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927–5929. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323–9324. (c) Artman, G. D.; Grubbs, A. W.; Williams, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 6336–6342.

(9) (a) Frebault, F. C.; Simpkins, N. S. *Tetrahedron* **2010**, *66*, 6585–6596. (b) Frebault, F.; Simpkins, N. S.; Fenwick, A. *J. Am. Chem. Soc.* **2009**, *131*, 4214–4215.

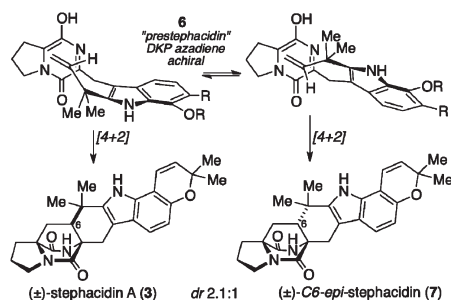


**Figure 1.** Representative [2.2.2]-diazabicyclic indole alkaloids.

entries to the [2.2.2]-diazabicyclic core. In the laboratory, the biomimetic Diels–Alder reaction often suffers from limited stereoselectivity. The elegant synthesis of stephacidin A (**3**) by Williams and co-workers is depicted as an illustrative example (Figure 2).<sup>10</sup> In the key step, prestephacidin **6** (illustrated as the reactive diketopiperazine (DKP) azadiene tautomer) reacts via IMDA to afford diastereomeric [2.2.2]-bicyclic products (±)-**3** and (±)-C6-*epi*-**7** (dr 2.1:1). This modest diastereomeric ratio has been consistent with other related biomimetic DA cycloadditions. Because prestephacidin **6** is achiral, the diastereomeric cycloadducts are necessarily produced as racemic mixtures.

The biosynthesis of **3** likely intercepts an achiral intermediate that closely resembles **6**, although the products isolated from the fungal hosts appear to contain only one stereochemical relationship at C6 and are observed in a single enantiomeric series.<sup>11</sup> This observation adds intrigue to the biosynthesis of this family of alkaloids and possibly indicates the intervention of a desymmetrizing biomolecule, although identification and characterization of a Diels–Alderase enzyme remain elusive.<sup>12</sup>

In the absence of an enzyme or other known catalysts to control the hetero-Diels–Alder cycloaddition, we pursued a general approach based on a chiral DKP azadiene in order to control the facial selectivity of the reaction. We were encouraged by, but hoped to improve upon, the selectivity observed during the synthesis of versicolamide



**Figure 2.** Synthesis of (±)-Stephacidin via Biomimetic Diels–Alder cycloaddition by Williams and co-workers.

B<sup>13</sup> (**4**) and VM55599<sup>14</sup> (**5**), the two known asymmetric biomimetic IMDA cycloadditions. The IMDA leading to **4** intercepts a chiral spirooxindole intermediate that does not discriminate the azadiene stereofaces during cycloaddition (dr 1.4:1). The azadiene intermediate leading to **5** contains a vicinal stereocenter that enforces reasonable face selection (dr 7:3:2:0). Based on our experience with a chiral DKP azadiene bearing a *tert*-butyl aminal,<sup>15</sup> we anticipated that a phenyl aminal auxiliary could impart strong facial bias during DKP cycloaddition and offer reductive strategies for aminal cleavage and auxiliary removal (in addition to acidic aminal hydrolysis). Preparation of the desired DKP derivative was accomplished in three steps (two chromatographic separations) starting from *N*-chloroacetyl L-serine methyl ester (Scheme 1).<sup>16</sup> Following the final step of this synthesis, Staudinger reduction with resin-bound phosphine, the diastereomeric DKP lactim ether products **8** and **9** were obtained in 36% and 19% yield over the three steps. The absolute structure of major isomer **8** was validated through X-ray crystallographic analysis (see the Supporting Information).

We explored initial reactions of DKP **8** with **10**, an easily prepared substrate that contained both an aldehyde to engage in enolate-based reactions and an alkene that we anticipated would participate in the DKP azadiene cycloaddition (Scheme 1). We quickly determined that a domino<sup>17</sup> reaction sequence with DKP **8** could be initiated by enolization and subsequent aldol condensation to give intermediate **11**. Under the basic conditions (NaOMe in MeOH at reflux), isomerization of the exocyclic alkene in **11** to the endocyclic DKP azadiene in **12** precedes intramolecular Diels–Alder cycloaddition with the terminal alkene to give the observed cycloadduct **13**.<sup>18</sup>

(10) Greshock, T. J.; Williams, R. M. *Org. Lett.* **2007**, *9*, 4255–4258.

(11) The antipodes of some alkaloids have been isolated from different fungal producers: Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573–3577.

(12) (a) Li, S.; Finefield, J. M.; Sunderhaus, J. D.; McAfoos, T. J.; Williams, R. M.; Sherman, D. H. *J. Am. Chem. Soc.* **2012**, *134*, 788–791. (b) Sunderhaus, J. D.; Sherman, D. H.; Williams, R. M. *Israel J. Chem.* **2011**, *51*, 442–452.

(13) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63–68.

(14) Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2556–2559.

(15) Morris, E. N.; Nenninger, E. K.; Pike, R. D.; Scheerer, J. R. *Org. Lett.* **2011**, *13*, 4430–4433.

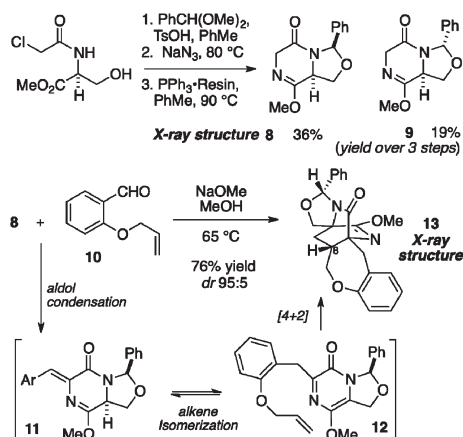
(16) Bedurftig, S.; Wunsch, B. *Bioorg. Med. Chem.* **2004**, *12*, 3299–3311.

(17) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

(18) Alkene isomerization in related systems to the endocyclic DKP azadiene is precedented in neat AcCl for 20 days (see ref 5c) and under basic conditions (KOH in MeOH): Williams, R. M.; Sanz-Cervera, J. F.; Sancenon, F.; Marco, J. A.; Halligan, K. M. *Bioorg. Med. Chem.* **1998**, *6*, 1233–1241.

The one-pot synthetic operation occurs in good yield (76%) and delivers the product in favorable diastereoselectivity (95:5). The structure of pentacyclic adduct **13** was verified by single-crystal X-ray analysis (see the Supporting Information) and confirmed that the cycloaddition occurred on the azadiene face opposite the phenyl aminal substituent from the *endo* transition state to produce the *anti* configuration<sup>19</sup> at C8.

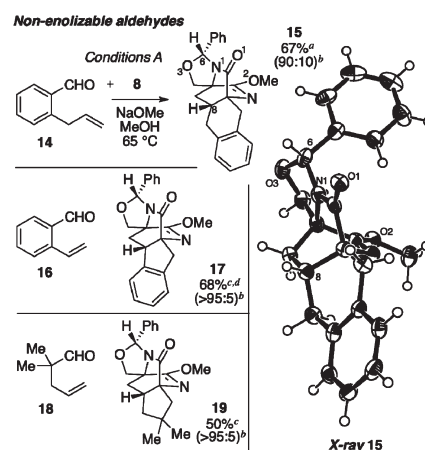
**Scheme 1.** Synthesis of Chiral Nonracemic Diketopiperazines and Initial Discovery of Domino Reaction Sequence



Encouraged by the reactivity and selectivity of this initial result, we explored other substrates (Figures 3 and 4). Aromatic aldehydes such as allyl benzaldehyde **14** and vinyl benzaldehyde **16** proceeded in comparable fashion to give the six- and five-membered carbocyclic ring fused cycloadducts **15** and **17**. Other nonenolizable aldehydes were competent in the domino reaction sequence with methanolic sodium methoxide (reaction conditions A). Aldehyde **18** bearing an  $\alpha$ -quaternary substitution provided product **19** in excellent diastereoselectivity.

Alternate reaction conditions were required to effect the aldol condensation, isomerization, and cycloaddition with enolizable aldehyde dieneophile substrates (Figure 4). For example, the reaction sequence with 5-hexenal (**20**) was realized by first preparing the enolate of DKP **8** (LiHMDS,  $-78$  °C, toluene). Addition of **20** followed by acetic anhydride and warming to ambient temperatures afforded the intermediate  $\beta$ -acetoxy aldol addition product. Acetate elimination to the exocyclic alkene and isomerization to the reactive endocyclic DKP azadiene IMDA precursor was accomplished under mild conditions with DBU. Although elimination and isomerization was rapid at room temperature, the ensuing intramolecular cycloaddition was slow. In practice, the cycloaddition was driven to completion at elevated temperatures (90 °C). In summary,

(19) Williams has adopted *syn/anti* nomenclature for [2.2.2]-diazabicyclic scaffolds that correspond to the diastereomeric relationship found in, for example, stephacidin A (*syn*) and brevianamide B (*anti*) (Figure 1).



**Figure 3.** Reaction sequence with nonenolizable aldehydes. Reaction conditions A: **8** (1 equiv), RCHO (1.2 equiv) at 0.1–0.2 M in MeOH, NaOMe (3 equiv), 65 °C, 16–24 h. <sup>a</sup>Isolated yield of an inseparable 90:10 mixture of diastereomers. <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy on the unpurified product mixture. <sup>c</sup>Isolated yield of single isomer. <sup>d</sup>2 equiv of **16** was used.

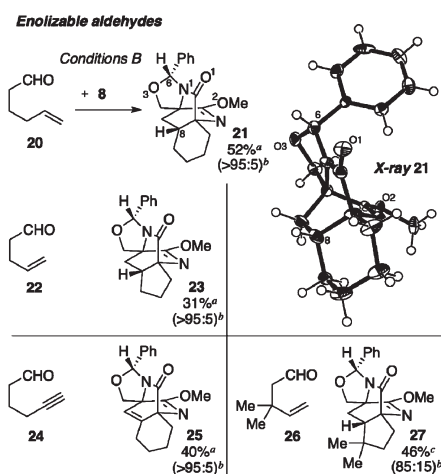
cycloadduct **21** was prepared from hexenal **20** in one reaction vessel and 52% yield over the reaction sequence. The structure of **21** was confirmed by X-ray analysis and the stereochemistry is consistent with cycloadducts derived from nonenolizable aldehydes (e.g., **15**, Figure 3).

Reaction conditions B proved general for nonenolizable aldehydes; **22**, **24**, and **26** delivered products **23**, **25**, and **27**. Hexynal **24** demonstrates that the reaction is competent with alkyne substrates. Overall, reaction conditions B afforded lower product yields (31–51%) than the conditions used for nonenolizable aldehydes (50–86%). All reactions were stereoselective, though an erosion of selectivity was observed with 3,3-dimethylhexenal (**26**). The observed product **27** was produced as an 85:15 mixture of diastereomers.

The chemistry detailed above establishes a clear pathway for the enantioselective synthesis of many members of the [2.2.2]-diazabicyclic natural product family. In this regard, we initiated a synthesis of (+)-malbrancheamide B (**2**), a new calmodulin (CaM) inhibitor, to validate our methodology and demonstrate efficient production of this exceptional alkaloid (Scheme 2).<sup>20,21</sup> Key to the synthesis was the reverse prenylated indole carboxaldehyde **28**, which was prepared largely according to precedent.<sup>21a</sup> Reaction of **28** with DKP **9** under methanolic

(20) (a) Figueroa, M.; Gonzalez, M. D. C.; Mata, R. *Nat. Prod. Res.* **2008**, *22*, 709–714. (b) Martinez-Luis, S.; Rodriguez, R.; Acevedo, L.; Gonzalez, M. C.; Lira-Rocha, A.; Mata, R. *Tetrahedron* **2006**, *62*, 1817–1822.

(21) For a previous synthesis of ( $\pm$ )-**2**, see: (a) Miller, K. A.; Welch, T. R.; Greshock, T. J.; Ding, Y. S.; Sherman, D. H.; Williams, R. M. *J. Org. Chem.* **2008**, *73*, 3116–3119. (b) For a synthesis of *ent*-(–)-**2**, see ref 9.



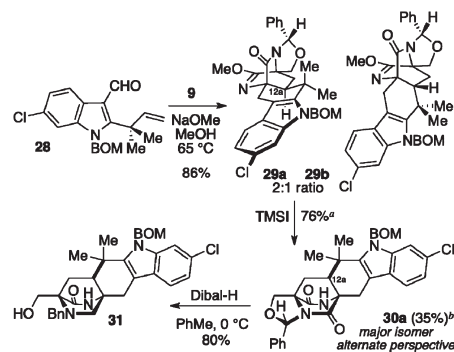
**Figure 4.** Domino reaction sequence with enolizable aldehydes. Reaction conditions B: **8** (1 equiv), LiHMDS (1.1 equiv),  $-78^{\circ}\text{C}$ ; RCHO (1.2 equiv);  $\text{Ac}_2\text{O}$  (1.3 equiv),  $-78$  to rt; DBU (2 equiv) rt to  $90^{\circ}\text{C}$ , 12–16 h. <sup>a</sup>Isolated yield of a single isomer. <sup>b</sup>Determined by  $^1\text{H}$  NMR spectroscopy on the unpurified product mixture. <sup>c</sup>Isolated yield of a mixture of 85:15 mixture of isomers.

sodium methoxide (conditions A) afforded a mixture of diastereomeric cycloadducts **29a** and **29b** (dr 2:1) in 86% combined yield. This reaction outcome demonstrates that the chiral aminal effectively controls the diastereoface of the intramolecular DKP cycloaddition, however, the auxiliary imparts little influence on the diastereoselectivity at C12a relative to related achiral variants.<sup>21a</sup> It is noteworthy that the major product (**29a**) resulting from cycloaddition with the reverse prenyl substituent in **28** is diastereomeric (at C12a) to the observed reaction products illustrated in Figures 3 and 4, a result consistent with previous experimental evidence<sup>22</sup> and theoretical studies.<sup>23</sup>

Although **29a** and **29b** were partially separable by chromatography, it was more convenient to carry the mixture through one additional synthetic operation prior to separation. Correspondingly, the lactim methyl ether in **29** was cleaved with TMSI. After chromatographic separation, the derived major bislactam **30a** was reduced to aminolactam **31** with excess DIBAL at  $0^{\circ}\text{C}$ .<sup>24</sup> This reduction establishes both the requisite oxidation state of the [2.2.2]-diazabicyclic

in malbrancheamide **B** (**2**) and converts the chiral aminal to a benzylamine for subsequent elaboration to the natural product. To complete the synthesis, one final annulation is required to append the pyrrolidine ring. Completion of the synthesis will soon be reported.

**Scheme 2.** Toward Malbrancheamide **B** (**2**): Reaction with Indolecarboxaldehyde, Reductive Cleavage of Aminal Auxiliary



<sup>a</sup> Combined yield of **30a**, **30b** (*epi*-C12a).

<sup>b</sup> Isolated yield **30a** (35%); **30b** (24%); mix fractions (17%).

To summarize, we developed a domino reaction sequence involving aldol condensation, alkene isomerization, and intramolecular DKP Diels–Alder cycloaddition. In one synthetic operation, the reaction sequence rapidly generates molecular complexity (three bonds, two rings) and is compatible with enolizable and nonenolizable aldehyde substrates. Excellent stereoselection is observed and consistent with cycloaddition on the azadiene face opposite the chiral phenyl aminal. Because the aminal auxiliary is somewhat removed from the olefinic components of the cycloaddition, the origin of selectivity may be partly stereoelectronic in nature. The aminal does not appear to notably effect cycloaddition diastereoselectivity with regard to the  $2\pi$  component (dieneophile alkene face) relative to known DKP IMDA examples. Overall, the methods described provide an efficient and diastereoselective method to prepare the [2.2.2]-diazabicyclic skeleton common to many biologically relevant prenylated indole alkaloids.

**Acknowledgment.** This work was supported by the donors of the ACS Petroleum Research Fund and the Research Corporation for Scientific Advancement. A.J.C. was supported in part by funding from a Howard Hughes Medical Institute Undergraduate Science Education Grant to The College of William & Mary.

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

The authors declare no competing financial interest.

(22) In addition to numerous total syntheses (see refs 1 and 4), several model systems also fortify these trends: (a) 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. (b) Adams, L. A.; Gray, C. R.; Williams, R. M. *Tetrahedron Lett.* **2004**, *45*, 4489–4493. (c) Adams, L. A.; Valente, M. W. N.; Williams, R. M. *Tetrahedron* **2006**, *62*, 5195–5200.

(23) (a) Domingo, L. R.; Sanz-Cervera, J. F.; Williams, R. M.; Picher, M. T.; Marco, J. A. *J. Org. Chem.* **1997**, *62*, 1662–1667. (b) Domingo, L. R.; Zaragoza, R. J.; Williams, R. M. *J. Org. Chem.* **2003**, *68*, 2895–2902.

(24) (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.