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Synthesis of the Asperparaline Core by a Radical Cascade

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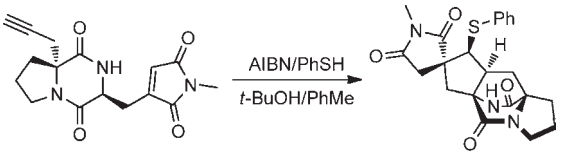
ABSTRACT



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A concise access to the pentacyclic core structure of the asperparalines is described. The key step is a radical cascade sequence comprised of a 1,6-hydrogen atom transfer followed by 6-*exo-trig* and 5-*exo-trig* cyclizations.

The asperparalines (**1**–**3**) are members of the prenylated alkaloid family of fungal-derived natural products, which were isolated from *Aspergillus japonicus* JV-23.[1] Related members of this family include brevianamide (**4**), paraherquamide B (**5**), and malbrancheamide B (**6**) (Figure 1).

These compounds possess a bicyclo[2.2.2]diazaoctane core, present as a keto- or diketopiperazine (DKP), which is usually combined with a fused indole or spiro-oxindole motif. The asperparalines are known to paralyze silkworms, and very recently asperparaline A has been demonstrated to strongly and selectively block insect nicotinic acetylcholine receptors.[2]

The synthetically challenging structures of these alkaloids along with their interesting biological profiles have provoked significant synthetic activity, culminating in the total syntheses of several family members by a number of research groups,[3] most notably that of Williams.[4]

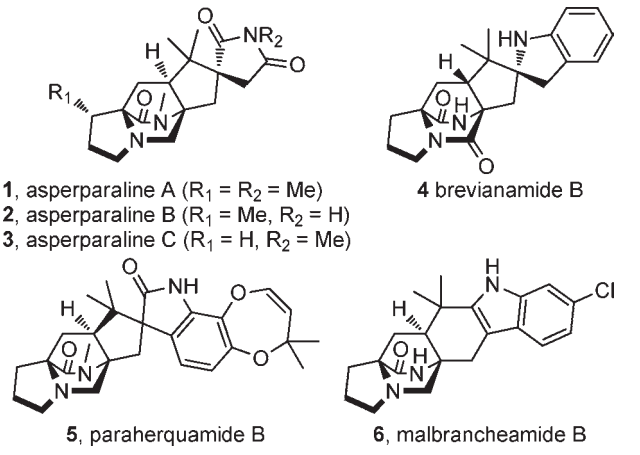

Figure 1

The asperparalines are unique in incorporating a *spiro* succinimide motif, and while Williams[5] and Tanimori[6]

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(1) (a) Hayashi, H.; Nishimoto, Y.; Nozaki, H. *Tetrahedron Lett.* **1997**, *38*, 5655. (b) Banks, R. M.; Blanchflower, S. E.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiot.* **1997**, *50*, 840. (c) Hayashi, H.; Nishimoto, Y.; Akiyama, K.; Nozaki, H. *Biosci., Biotechnol., Biochem.* **2000**, *64*, 111.

(2) Hirata, K.; Kataoka, S.; Furutani, S.; Hayashi, H.; Matsuda, K. *PLoS ONE* **2011**, *6*, doi:10.1371/journal.pone.0018354.

(3) Lead references: (a) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160. (b) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342. (c) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678. (d) Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am. Chem. Soc.* **2007**, *129*, 3086.

(4) Finefield, J. M.; Williams, R. M. *J. Org. Chem.* **2010**, *75*, 2785 and references therein.

(5) (a) Gonzalez, F.; Sanz-Cervera, J. F.; Williams, R. M. *Tetrahedron Lett.* **1999**, *40*, 4519. (b) Adams, L. A.; Gray, C. R.; Williams, R. M. *Tetrahedron Lett.* **2004**, *45*, 4489.

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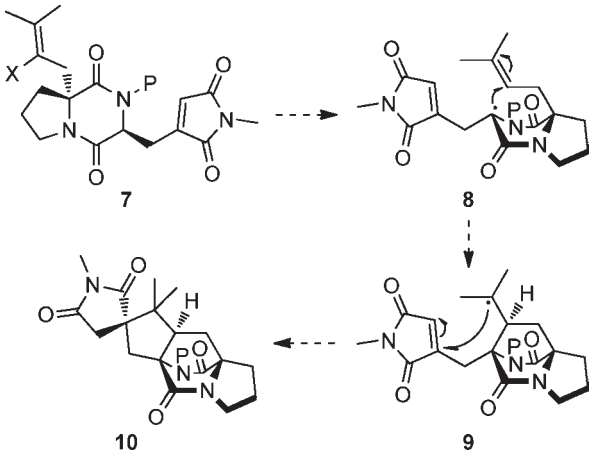
have published approaches to individual components of the asperparalines, no total synthesis has been forthcoming.

We have recently published a concise access to the bicyclo[2.2.2]diazaoctane core structure of these compounds via a cationic cascade, culminating in the total syntheses of (−)-brevianamide B and (−)-malbrancheamide B.[7] Here, we report our initial investigations of a complementary, strategically related, *radical* cascade for the construction of the asperparaline core structure.

Our approach is outlined in Scheme 1 (for the L-proline series). Initial formation of an alkenyl radical by cleavage of a suitable vinyl halide precursor **7** (e.g., X = Br, I) would be followed by 1,6-hydrogen atom transfer to form the more stabilized captodative DKP radical **8**.[8] Subsequent stereocontrolled 6-*exo*-*trig* and 5-*exo*-*trig* ring closures would furnish 8-oxa-asperparaline **10**.

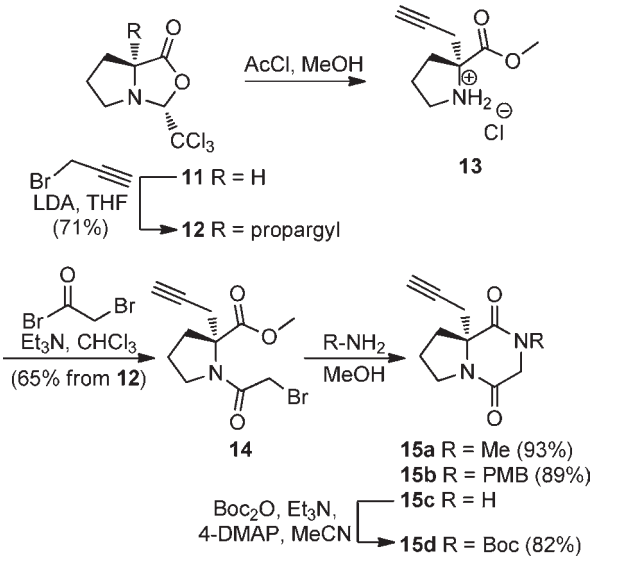
Scheme 1



To test the viability of this type of approach we decided to focus on the initial 1,6-hydrogen atom abstraction in tandem with the first (6-*exo*) cyclization. The use of a simple acetylene to generate the initial alkenyl radical, in place of a vinyl halide, was also preferred so as to facilitate the synthesis of a series of simple model compounds to probe our strategy (*vide infra*).

Starting from L-proline, the enolate of (commercially available) oxazolidinone **11**[9] was treated with propargyl bromide to afford acetylene **12** in 71% yield.[10] Acid-mediated ring opening yielded modified proline *O*-methyl ester **13** as a single enantiomer which could be used in subsequent steps without purification (Scheme 2).[11]

Scheme 2



Next, *N*-acylation by treatment with bromoacetyl bromide in the presence of triethylamine gave bromide **14** in 65% yield. Formation of proline-glycine DKPs **15a**−**c** was then accomplished smoothly by exposure to a methanolic solution of methylamine, *para*-methoxybenzylamine, or ammonia respectively.[12] Secondary amide **15c** was Boc protected under standard conditions to afford carbamate **15d** in 82% yield over two steps.

To generate more complex systems, modified proline **13** was coupled with suitably protected alanine, leucine, or aspartic acid under standard conditions (Scheme 3).[13] Removal of the Boc group by treatment with neat formic acid was followed by thermal ring closure by refluxing in a mixture of toluene and 2-butanol to give the corresponding DKPs which were Boc protected in the presence of 4-DMAP to give **17a**−**c**.[14]

With a variety of acetylene substituted DKPs in hand, the stage was set for our 1,6-hydrogen transfer 6-*exo*-*trig* sequence. Using conditions described by Renaud,[15] we found that slow addition of thiophenol and AIBN to a refluxing solution of DKP in *tert*-butanol afforded the desired bridged system in good to excellent yield (Table 1). Stereocontrol is modest but favors the desired C-6 stereochemistry required for the asperparalines. The nitrogen

(6) (a) Tanimori, S.; Fukubayashi, K.; Kirihata, M. *Biosci., Biotechnol., Biochem.* **2000**, *64*, 1758. (b) Tanimori, S.; Fukubayashi, K.; Kirihata, M. *Tetrahedron Lett.* **2001**, *42*, 4013.

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

(8) For a review of radical translocations, see: Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94.

(9) **11** can be purchased from Sigma Aldrich or synthesized by condensation of chloral with L-proline; see: Amedjkouh, M.; Ahlberg, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2229. Based on Seebach's seminal work on the self-reproduction of chirality:Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(10) Compound **12** has been prepared before in 24% yield; see: Pisaneschi, F.; Cordero, F. M.; Lumini, M.; Brandi, A. *Synlett* **2007**, 2882.

(11) Harris, P. W. R.; Brimble, M. A.; Muir, V. J.; Lai, M. Y. H.; Trotter, N. S.; Callis, D. J. *Tetrahedron* **2005**, *61*, 10018.

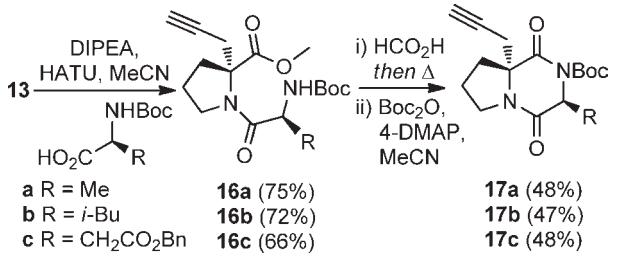
(12) Maw, G. N.; Allerton, C. M. N.; Gbekor, E.; Million, W. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1425.

(13) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

(14) Pichowicz, M.; Simpkins, N. S.; Blake, A. J.; Wilson, C. *Tetrahedron* **2008**, *64*, 3713.

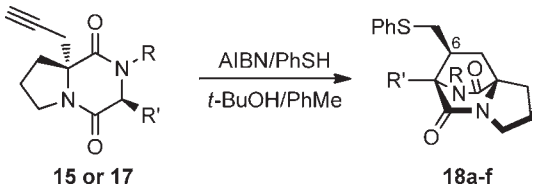
(15) (a) Beaufils, F.; Denes, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563. (b) Denes, F.; Beaufils, F.; Renaud, P. *Org. Lett.* **2007**, *9*, 4375.

Scheme 3



protecting group seems to have only a small effect on the stereochemical outcome of the reaction with the best ratio achieved using PMB protected DKP **15b** (entry 2).

Table 1. Initial Radical Cyclizations[a]



entry	R	R′	% yield	dr
1	Me	H	62	5:4
2	PMB	H	53	2:1
3	Boc	H	55	5:4
4	Boc	Me	98	2:1
5	Boc	*i*-Bu	96	4:1
6	Boc	CH_2CO_2Bn	73	2:1

[a] Reaction conditions: AIBN (2.0 equiv) in toluene and thiophenol (2.0 equiv) in toluene added to a refluxing solution of DKP in *tert*-butanol via syringe pump over 20 h. The major isomer is the C-6 epimer shown.

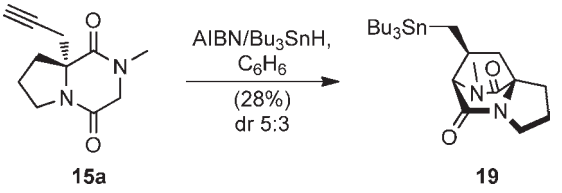
The sequence appears to be more efficient when R′ is not H (Table 1, entries 4−6 vs 1−3). The reason for this is not immediately clear, although conformational and/or radical stabilization effects are presumably responsible.

In principle, heteroatoms other than sulfur can be used for radical addition to a triple bond. For example, treatment of a solution of *N*-methyl DKP **15a** in benzene with AIBN and tributyltin hydride afforded bridged bicyclic stannane **19**, albeit in poor yield (Scheme 4).[16]

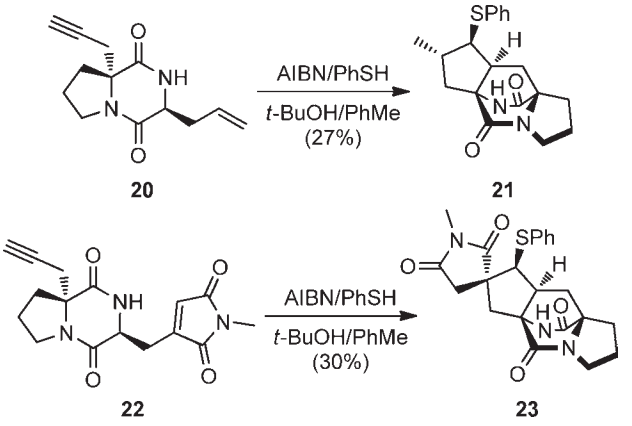
Turning our attention to more faithful mimics of the asperparaline core structure, we synthesized DKPs **20** and **22** incorporating an allyl and maleimide group respectively (Scheme 5; full details in Supporting Information). As we encountered unforeseen difficulties in the introduction of a nitrogen protecting group, we attempted the radical cascade with a free secondary amide.

(16) Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581.

Scheme 4



Scheme 5



Thus, **20** and **22** were treated with thiophenol and AIBN under our established conditions. These cyclizations are considerably more complex than those shown above, as two new carbon−carbon bonds and three stereocenters are formed. Although both examples gave complex mixtures of products, in each case only one major product was formed. Pleasingly, we were able to isolate tetracycle **21** and the asperaparaline core stucture **23**, albeit each in modest yield. In each case the isolated, single diastereomer product has the desired configuration for the majority of known natural products.[17]

In summary, we have developed a novel synthesis of the bridged bicyclic core common to a variety of alkaloids. We have applied this to a radical cascade for the synthesis of the asperparaline core structure **23** in just six steps from commercially available starting materials. Efforts in our laboratory are now focused on completing the total syntheses of the asperparalines, along with probing the activities of readily available *spiro* succinimides such as **23**.

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(17) The stereochemistry was assigned by NOE experiments; see Supporting Information for full details.

World (West Midlands Centre for Advanced Materials Project 2), with support from Advantage West Midlands (AWM) and partial funding by the European Regional Development Fund (ERDF).

Supporting Information Available. Complete experimental details and characterization data for the synthesis of compounds **12**–**23**. This material is available free of charge via the Internet at http://pubs.acs.org.