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Synthesis of (±)-Amathaspiramide F and Discovery of an Unusual Stereocontrolling Element for the [2,3]-Stevens Rearrangement

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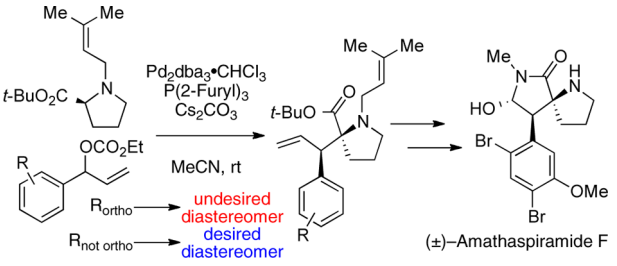
ABSTRACT



A formal total synthesis of (±)-amathaspiramide F through a tandem palladium-catalyzed allylic amination/[2,3]-Stevens rearrangement is reported. The unexpected diastereoselectivity of the [2,3]-Stevens rearrangement was controlled by the substitution patterns of an aromatic ring. This discovery represents a new stereocontrolling element for [2,3]-sigmatropic rearrangements in complex molecular settings.

Since their isolation in 1999, the amathaspiramide alkaloids have garnered attention from the scientific community because of their reported antiviral, cytotoxic, and antimicrobial activities as well as their unique and intricate chemical structures.[1] Synthetic efforts toward these polycyclic alkaloids have unveiled important stereocontrolling elements for the assembly of contiguous stereocenters in complex molecular settings, such as C-1 and C-2 of amathaspiramide F (Scheme 1).[2]

In this context, we were interested in utilizing a diastereoselective [2,3]-Stevens rearrangement to construct the two contiguous stereocenters at C-1 and C-2 of amathaspiramide F. While [3,3]-rearrangements routinely appear as key transformations in the total synthesis of natural products, [2,3]-rearrangements have been relatively underutilized in complex molecular settings.[3] For example, [2,3]-Stevens rearrangements have been employed in the total synthesis of natural products for the generation of one carbon stereocenter.[4] The use of [2,3]-Stevens rearrangements

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(4) (a) Honda, K.; Tabuchi, M.; Inoue, S. *Chem. Lett.* **1996**, 385. (b) Honda, K.; Yoshii, I.; Inoue, S. *Chem. Lett.* **1996**, 671. (c) Honda, K.; Igarashi, D.; Asami, M.; Inoue, S. *Synlett* **1998**, 685. (d) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931. (e) Zhou, C.-Y.; Yu, W.-Y.; Chan, P. W. H.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 7072. (f) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211. (g) Sakaguchi, K.; Ayabe, M.; Watanabe, Y.; Okada, T.; Kawamura, K.; Shiada, T.; Ohfune, Y. *Org. Lett.* **2008**, *10*, 5449. (h) Sun, M.-r.; Lu, H.-t.; Wang, Y.-z.; Yang, H.; Liu, H.-m. *J. Org. Chem.* **2009**, *74*, 2213.

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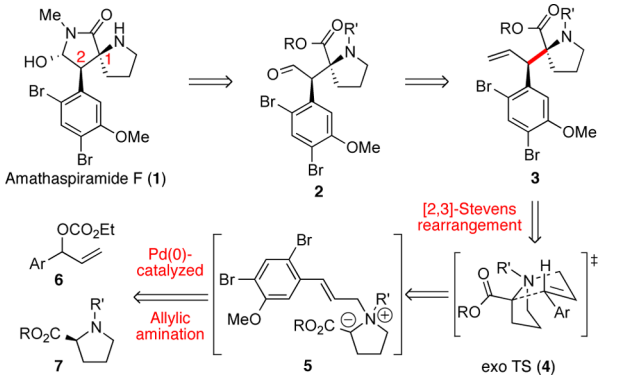
to generate two contiguous stereocenters in the course of a total synthesis often leads to modest and unpredictable diastereoselectivity, with little understanding of the factors that affect the stereochemical outcome.[4e]

Scheme 1. Retrosynthesis of (±)-Amathaspiramide F



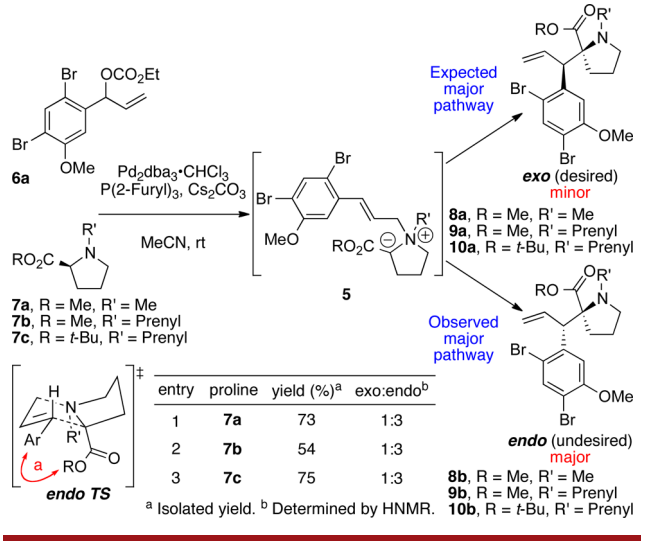
Herein, we describe an efficient formal synthesis of (±)-amathaspiramide F, in which a diastereoselective [2,3]-Stevens rearrangement serves as the key transformation for assembling the core structure of the alkaloid. In the process, we elucidate a novel and synthetically useful stereocontrolling element for this class of sigmatropic rearrangements in a more complex molecular setting, which is based on subtle structural changes in the substrate. We anticipate that an improved understanding of the diastereoselectivity of [2,3]-Stevens rearrangements will lead to the use of these reactions for natural product synthesis in a more predictable manner.

Our retrosynthetic analysis of (±)-amathaspiramide F (**1**) commenced with a disconnection of the aminal ring to furnish aldehyde **2** (Scheme 1). We envisioned that this intermediate could arise from γ,δ-unsaturated aminoester **3**, which possesses the retron for the palladium-catalyzed tandem allylic amination/[2,3]-Stevens rearrangement that was recently reported by our group.[5] Aminoester **3** could be generated from the coupling of carbonate **6** and proline derivative **7**, via the sigmatropic rearrangement of ammonium ylide **5**.[6] Based on our previous studies, as well as the studies of other groups,[3] we expected to obtain the desired diastereomer of **3** through *exo* transition state **4**. This synthetic approach would be applicable to all members of the amathaspiramide family.[1]

We commenced the synthesis of (±)-amathaspiramide F by assembling substrates **6a** and **7a**–**c** for the key [2,3]-Stevens rearrangement step (Scheme 2). Allyl carbonate **6a** was coupled with *N*-substituted proline esters **7a** and **7b** under the palladium-catalyzed [2,3]-Stevens rearrangement conditions, which included catalytic $Pd_2dba_3 \cdot CHCl_3$ and P(2-furyl)$_3$ with Cs_2CO_3 as a stoichiometric base. During this tandem process, aminoesters **7a** and **7b** reacted with the Pd(II)-π-allyl complex generated from carbonate **6a** to yield ammonium ylide **5**, which transformed into the [2,3]-rearrangement products. The expected allylic amination/[2,3]-Stevens rearrangement products were obtained in both reactions as 1:3 mixtures of diastereomers. Interestingly, although proline esters **7a**–**c** were enantiopure, the [2,3]-Stevens rearrangement products **8**–**10** were racemic. We attribute this result to either a nondiastereoselective allylic amination event (the nitrogen in the ammonium ylide is a stereocenter) or a reversible allylic amination event prior to rearrangement (with a loss of the α-carbon stereocenter during ammonium ylide formation). Based on our analysis of the competing pericyclic transition states, we surmised that the desired diastereomers **8a** and **9a** that formed through *exo* transition states would be the major observed products in both cases. The *endo* transition states were expected to be disfavored due to a steric interaction between the methyl ester and the aromatic ring (interaction a, Scheme 2).

Surprisingly, the major products for the palladium-catalyzed reactions with proline esters **7a** and **7b** were identified as the undesired diastereomers **8b** and **9b**, respectively (Scheme 2, entries 1 and 2). To alter this unexpected diastereoselectivity in the [2,3]-rearrangement, we employed the bulkier *tert*-butyl proline ester **7c**, which was expected to favor the desired *exo* product **10a** because of enhanced steric interactions between the aromatic ring and the ester in the *endo* transition state (interaction a). However, even the *tert*-butyl proline ester **7c** coupled with carbonate **6a** to yield the undesired *endo* product **10b** (entry 3). The stereochemical assignments of rearrangement products

Scheme 2. Unexpected Diastereoselectivity in Palladium-Catalyzed Allylic Amination/[2,3]-Stevens Rearrangement



entry	proline	yield (%)[a]	exo:endo[b]
1	**7a**	73	1:3
2	**7b**	54	1:3
3	**7c**	75	1:3

[a] Isolated yield. [b] Determined by HNMR.

(5) Soheili, A.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 12956.

(6) For other examples of Stevens rearrangements with proline derived ammonium ylides, see: (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420. (b) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565. (c) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31. (d) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236. (e) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3325. (f) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414. (g) Tayama, E.; Nanbara, S.; Nakai, T. *Chem. Lett.* **2006**, *35*, 478. (h) Gawley, R. E.; Moon, K. *Org. Lett.* **2007**, *9*, 3093.

8b, **9b**, and **10b** were confirmed by X-ray crystallographic studies.[7]

Since the structure of the proline derivative did not affect the preference for *endo* diastereomers **8b**, **9b**, and **10b** in [2,3]-Stevens rearrangements, we wondered if the structure of the allyl carbonate may be responsible for this unexpected diastereoselectivity. We examined the effect of the allyl carbonate structure on the diastereoselectivity of [2,3]-Stevens rearrangements with the structurally simpler acyclic *tert*-butyl aminoester **11** (Table 1).

At the outset, we expected that the *exo* product **13** would be favored irrespective of the carbonate structure.[3,5] To our surprise, glycine ester **11** reacted with dibromomethoxyphenyl carbonate **6a** to yield a 1:1 mixture of the two rearrangement diastereomers **13a** and **14a** (entry 1). In contrast, the *para*-bromophenyl carbonate **6b** furnished the expected *exo* diastereomer **13b** in a selective 7:1 dr (entry 2). This observation suggested that the substitution pattern around the aromatic ring might have been responsible for the undesired *endo* diastereoselectivity in our synthetic efforts toward (±)-amathaspiramide F.

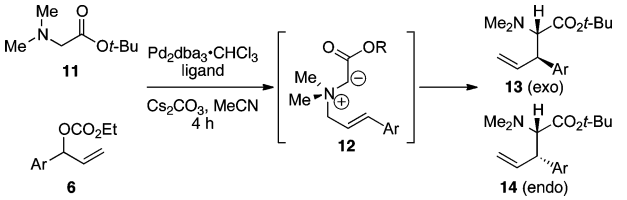
While a *meta*-bromo substituent on the phenyl carbonate (**6c**) did not affect the inherent *exo* selectivity of the [2,3]-rearrangement (6:1 dr, entry 3), an *ortho*-bromo substituent by itself (**6d**) disrupted the diastereoselectivity to a significant extent (2:1 dr, entry 4). The observed dr of 2:1 with the *ortho*-tolyl carbonate suggested that this stereocontrolling effect was steric in origin, not electronic (entry 5). Incorporation of a *meta*-OMOM substituent (**6f**) resulted in the formation of the *exo* diastereomer **13f** as the major product (8:1 dr, entry 6), restoring the high preference for the *exo* transition state. The compatibility of this *meta*-OMOM substituent with the stereoselective formation of the *exo* diastereomer **13f** boded well for the completion of our synthesis of (±)-amathaspiramide F. A similar *meta*-OMOM substituted aromatic ring was converted to the desired dibromo-methoxyphenyl system by Sakaguchi and co-workers in their recent total synthesis of the natural product.[2b]

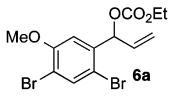
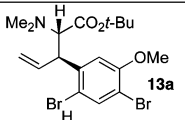
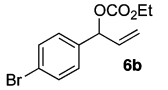
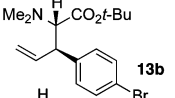
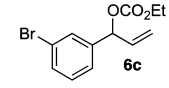
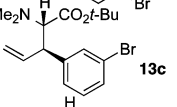
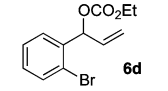
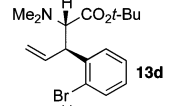
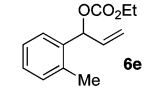
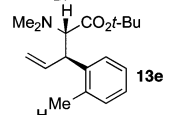
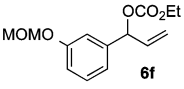
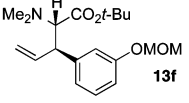
To take advantage of the *exo* selectivity for the [2,3]-Stevens rearrangement with the *meta*-OMOM substituted phenyl carbonate (Table 1, entry 6), we coupled *N*-prenyl proline esters **7b** and **7c** with *meta*-OMOM substituted phenyl carbonate **6f** under our standard palladium-catalyzed reaction conditions (Scheme 3). Methyl ester **7b** furnished the tandem allylic amination/[2,3]-Stevens rearrangement products **16a** and **16b** in 71% yield with an unselective dr of 1:1 (entry 1). However, *tert*-butyl ester **7c** underwent a more stereoselective process, as the rearrangement products **17a** and **17b** were generated in 70% yield with a dr of 3.5:1 (entry 2). Gratifyingly, the *tert*-butyl ester **7c**, in combination with the *meta*-OMOM substituted phenyl carbonate **6f**, favored the formation of the desired diastereomer **17a** as the major product, which was confirmed by X-ray crystallography.[7]

With the desired rearrangement product **17a** in hand, we completed the formal total synthesis of (±)-amathaspiramide F. The *N*-prenyl group of aminoester **17a** was cleaved under olefin isomerization conditions to reveal N−H aminoester **18**.[8] This product was treated with trifluoroacetic acid, which removed the *tert*-butyl and MOM protecting groups. Exposure of the resulting acid to $TMSCHN_2$ furnished phenol **19**, which was an intermediate in Sakaguchi's synthesis of amathaspiramide F.[2b] Our synthetic sequence therefore constituted a formal total synthesis of (±)-amathaspiramide F (**1**) in 10 linear steps from carbonate **6f** and proline ester **7c**.

We hypothesize that this unexpected switch in diastereoselectivity is due to the torsional strain associated with the preference of *ortho*-substituted cinnamyl systems to adopt a nonplanar conformation between the aromatic ring and the allylic system (Scheme 4).[9] When proline derivative **7c** was coupled with *meta*-substituted carbonate **6f**, the *exo* transition state **20a** was favored in the absence of *ortho*-substitution in the aromatic ring because of the well precedented destabilizing interaction between the

Table 1. Effect of the Aryl Substitution Pattern on the Diastereoselectivity of the [2,3]-Stevens Rearrangement[a]



entry	carbonate	major product	yield (%)[b]	exo:endo[c]
1			85	1:1
2			90	7:1
3			80	6:1
4			93	2:1
5			78	2:1
6			87	8:1

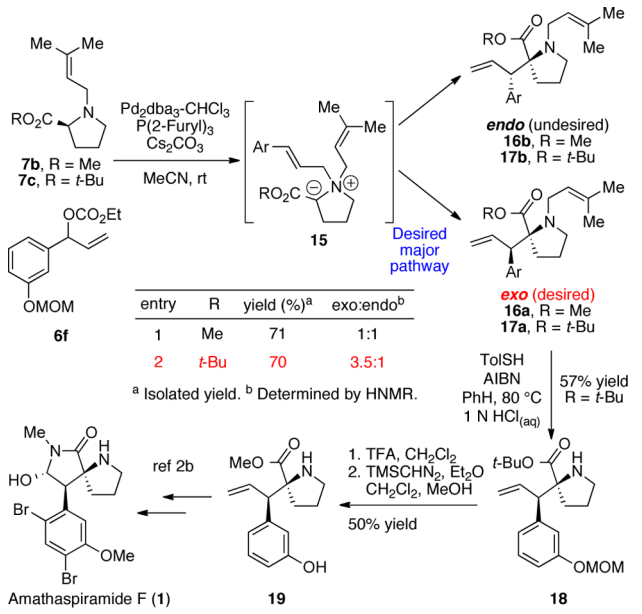
[a] Reaction conditions: 1.5 equiv of aminoester **11**, 1 equiv of allylcarbonate **6**, 1 mol % $Pd_2dba_3 \cdot CHCl_3$, 5 mol % P(2-furyl)$_3$, 3 equiv of Cs_2CO_3, 0.2 M MeCN. [b] Isolated yield. [c] Diastereomeric ratio determined by NMR.

(7) See Supporting Information for details.

(8) Escoubet, S.; Gastaldi, S.; Timokhin, V. I.; Bertrand, M. P.; Siri, D. *J. Am. Chem. Soc.* **2004**, *126*, 12343.

(9) Shen, Q.; Kuhns, J.; Hagen, K.; Richardson, A. D. *J. Mol. Struct.* **2001**, *567–568*, 73 and references therein.

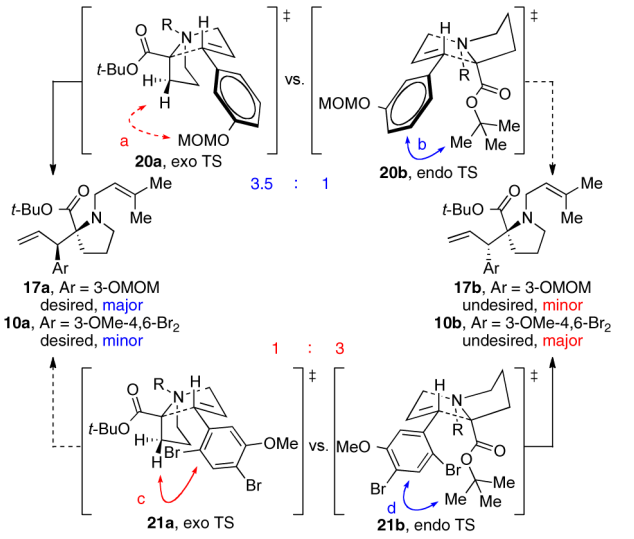
Scheme 3. Switch in Diastereoselectivity for Palladium-Catalyzed Allylic Amination/[2,3]-Rearrangement



aromatic ring and the *tert*-butyl ester in *endo* transition state **20b** (interaction b).[3] While this steric interaction was still present in *endo* transition state **21b** when *ortho*-substituted carbonate **6a** was coupled with aminoester **7c** (interaction d), the *exo* transition state **21a** was destabilized to a greater extent by the proximity of the β-proton of the aminoester and the nonplanar *ortho*-substituted aromatic ring (interaction c). As a result, the diastereomeric ratio switched from to 3.5:1 to 1:3.

In conclusion, we have developed a diastereoselective tandem palladium-catalyzed allylic amination/[2,3]-Stevens rearrangement for the formal total synthesis of (±)-amathaspiramide F. A key component in this approach was the realization that *ortho*-substituted aromatic rings can influence the stereochemical outcome of [2,3]-rearrangements, presumably because of torsional strain caused by their unique conformational preferences. This represents a new stereocontrolling element for [2,3]-sigmatropic

Scheme 4. Rationale for Switch in Diastereoselectivity



rearrangements in complex molecular settings. Computational analysis of this stereochemical switch is currently under investigation. We are also examining this stereocontrolling effect in the synthesis of the remaining amathaspiramides and other complex alkaloids.

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Supporting Information Available. Full experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.