ORGANIC LETTERS

2009
Vol. 11, No. 19
4478−4481

Ring-Construction/Stereoselective Functionalization Cascade: Total Synthesis of Pachastrissamine (Jaspine B) through Palladium-Catalyzed Bis-cyclization of Bromoallenes

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Received August 17, 2009

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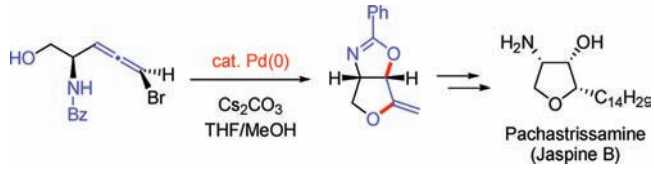
Publication Date (Web): September 9, 2009 | doi: 10.1021/ol901904w

ABSTRACT



Palladium(0)-catalyzed cyclization of bromoallenes bearing hydroxyl and benzamide groups as internal nucleophiles stereoselectively provides functionalized tetrahydrofuran. With this bis-cyclization as the key step, a short total synthesis of pachastrissamine, a biologically active marine natural product, was achieved.

Bromoallenes have attracted much attention due to their interesting chemical properties associated with cumulated double bonds and a bromine atom.[1] Recently, we have developed a novel synthesis of medium-sized heterocycles **3** containing one or two heteroatoms via cyclization of bromoallenes **1** bearing an oxygen, nitrogen, or carbon nucleophile in the presence of a palladium(0) catalyst and alcohol (Scheme 1, eq 1).[2] The first intramolecular nucleophilic attack by Nu_A at the central carbon atom of the allenic moiety of **1**, followed by protonation, gives π-allylpalladium intermediate **2**. Then the second intermolecular reaction with Nu_B proceeds to give the monocyclization products **3** along with their regioisomers **4** in some cases. Namely, bromoallenes **5** can act as allyl dication equivalents **6** (Scheme 1, eq 2). More recently, we expanded this chemistry to cascade cyclization of bromoallenes **7** bearing a dual nucleophilic moiety leading to bicyclic products **9** (Scheme 1, eq 3).[3] Unfortunately, this reaction is limited to highly nucleophilic sulfamides ($Nu_A-Nu_B = NSO_2N$), presumably due to the restricted conformation in the *endo*-type second cyclization. The competing external nucleophilic attack by an alkoxide derived from alcohol, which is a highly effective solvent for this type of transformation, is also problematic.

We turned our attention to cascade cyclization of bromoallenes of type **10** bearing nucleophilic groups at both ends of a branched alkyl group. This would lead to bicyclic products such as **13** (Scheme 2). This reaction could facilitate stereoselective functionalization on the *exo*-type second cyclization, utilizing the chiral center at the branched position. Apparently, the key to success of this cascade

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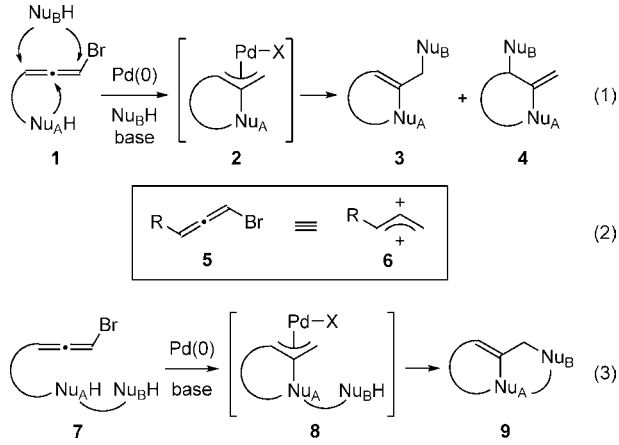
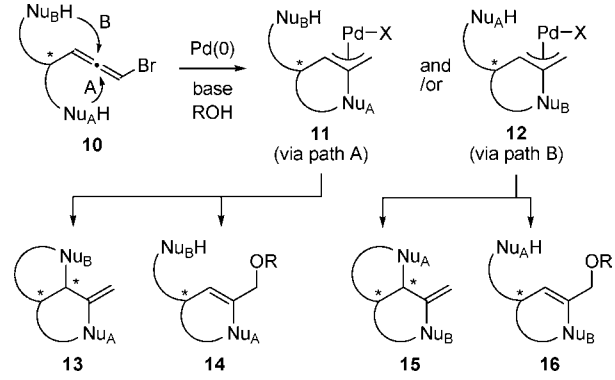
10.1021/ol901904w CCC: $40.75 © 2009 American Chemical Society
Published on Web 09/09/2009

Scheme 1. Palladium(0)-Catalyzed Cyclization of Bromoallenes



reaction is controlled successive nucleophilic attacks by Nu_A and Nu_B in the desired order, as well as inhibition of the external reaction with alkoxide; first cyclization by Nu_A or Nu_B will produce intermediate **11** or **12**, respectively, which would be converted to the cyclic products **13**/**14** or **15**/**16**, by the intra- or intermolecular reaction. We chose pachastrissamine (jaspine B), which bears three contiguous stereogenic centers on its tetrahydrofuran core structure, for the model study to evaluate this working hypothesis on the ring-construction/stereoselective functionalization cascade.

Scheme 2. Construction of Bicyclic Structures by Palladium(0)-Catalyzed Cascade Cyclization of Bromoallenes **10**



The structure of pachastrissamine **17** (Figure 1), an anhydrophytosphingosine derivative isolated from a marine sponge *Pachastrissa* sp., was reported by Higa and co-workers in 2002.[4] Shortly thereafter, Debitus and co-workers isolated the same compound from a different marine sponge, *Jaspis* sp., and named jaspine B.[5] Other structurally related analogues have also been isolated from the same species, including jaspine A and 2-*epi*-jaspine B. Pachastrissamine (jaspine B) **17** exhibits cytotoxic activity against various tumor cell lines at nanomolar level.[4,5] In 2009, Delgado and co-workers reported that DHCer-mediated autophagy might be involved in the cytotoxicity.[6] Owing to its biological importance, pachastrissamine has been the target of many synthetic studies.[7] Stereoselective construction of the trisubstituted tetrahydrofuran ring is a major issue in the total synthesis.

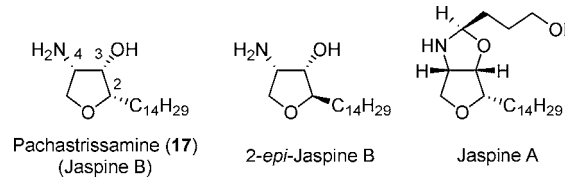


Figure 1. Structures of naturally occurring jaspines.

We expected that palladium(0)-catalyzed cyclization of bromoallenes **19** bearing hydroxy and benzamide groups[8] as internal nucleophiles could regio- and stereoselectively provide appropriately functionalized tetrahydrofuran **18** for synthesis of pachastrissamine **17** (Scheme 3). The bicyclic structure of **18** including the exo-olefin would be useful for stereoselective construction of a C-2 stereogenic center as well as carbon homologation. Herein, we describe an efficient, short, total synthesis of pachastrissamine (jaspine B) utilizing cascade cyclization of a bromoallene of type **19**, which has two internal nucleophiles at both ends of a branched alkyl group.

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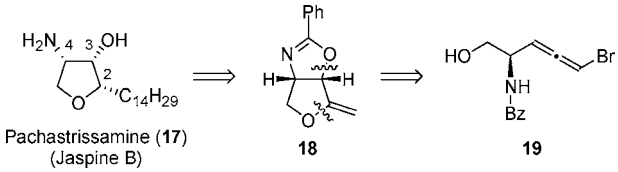
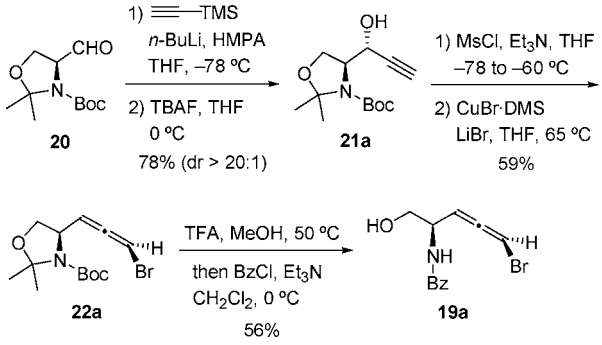
Scheme 3. Retrosynthetic Analysis of Pachastrissamine **17**



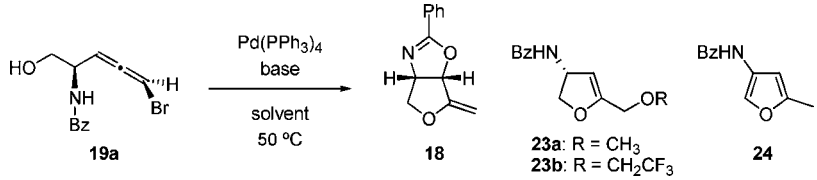
Preparation of the required bromoallene **19a** is outlined in Scheme 4. The *erythro*-alkynol **21a** was easily prepared from (*S*)-Garner's aldehyde **20**[9] following the literature procedure.[10] Treatment of **21a** with MsCl and Et_3N gave the corresponding mesylate, which was then allowed to react with CuBr·DMS/LiBr[11] (DMS = Me_2S) to afford the (*S*,a*R*)-bromoallene **22a**.[12] Removal of the Boc and acetal groups with TFA followed by acylation with BzCl/Et_3N afforded the benzamide **19a**.

Scheme 4. Synthesis of Bromoallene **19a**



We next investigated cascade cyclization of bromoallene **19a** in the presence of palladium(0) (Table 1). Treatment of **19a** with $Pd(PPh_3)_4$ (5 mol %) and NaH (2.0 equiv) in MeOH at 50 °C (standard conditions for cyclization of bromoallenes[2]) successfully produced the desired bicyclic tetrahydrofuran **18** in 50% yield (entry 1). The undesired cyclization initiated by the first cyclization by the benzamide group (Scheme 2) was not promoted. However, the anticipated side products dihydrofuran **23a** (formed by the intermolecular reaction with methoxide) and a small amount of furan **24** were observed. Formation of the furan **24** can be rationalized by β-hydride elimination of the π-allylpalladium intermediate (e.g., **11** or **12**, Scheme 2) followed by aromatization.[13] To suppress the intermolecular reaction with the external alkoxide, the reaction was examined under other conditions, including the use of a mixed solvent. Reaction in THF/MeOH (4:1) decreased yields of both **18** and **23a** (40% and 15%, respectively), while the amount of furan **24** increased (10% yield, entry 2). Of the several bases investigated, Cs_2CO_3 (1.2 equiv) most effectively produced the desired product **18** and suppressed formation of furan **24** (entries 2−5). The best result was obtained using a mixed solvent of THF/MeOH (10:1) in the presence of 1.2 equiv of Cs_2CO_3 (89%, entry 6). It should be noted that the use of solely THF resulted in low yield of **18** (12%, entry 7) and recovery of the starting material, which suggests that an alcoholic solvent plays an important role in this type of transformation. Interestingly, use of CF_3CH_2OH, a more acidic solvent which might facilitate the protonation step, only gave the undesired compound **23b** bearing a trifluoroethoxy group in high yield (93%, entry 8). Moreover, use of *t*-BuOH was not effective (entry 9). These results indicate that pK_a values and bulkiness of the alcohol solvent have significant effects on the reaction, i.e., the intramolecular vs intermolecular reaction in the

Table 1. Palladium-Catalyzed Cascade Cyclization of Bromoallene **19a**[a]



				yield (%)[b]			
entry	base (equiv)	solvent	time (h)	**18**	**23**	**24**	recovery[c] (%)
1	NaH (2.0)	MeOH	2.0	50	45	trace	
2	NaH (2.0)	THF/MeOH (4:1)	1.0	40	15	10	
3	K_2CO_3 (2.0)	THF/MeOH (4:1)	4.0	43			41
4	Cs_2CO_3 (2.0)	THF/MeOH (4:1)	2.5	67	26		
5	Cs_2CO_3 (1.2)	THF/MeOH (4:1)	2.5	78	20		
6	Cs_2CO_3 (1.2)	THF/MeOH (10:1)	2.5	89	trace		
7	Cs_2CO_3 (1.2)	THF	5.5	12			64
8	Cs_2CO_3 (2.0)	THF/TFE (4:1)	2.5		93		
9	Cs_2CO_3 (2.0)	THF/*t*-BuOH (4:1)	2.5	12			60

[a] All reactions were performed with 5 mol % of $Pd(PPh_3)_4$ at 0.1 M in the solvent indicated. [b] Yield of isolated products. [c] Recovery of starting material. TFE = 2,2,2-trifluoroethanol.

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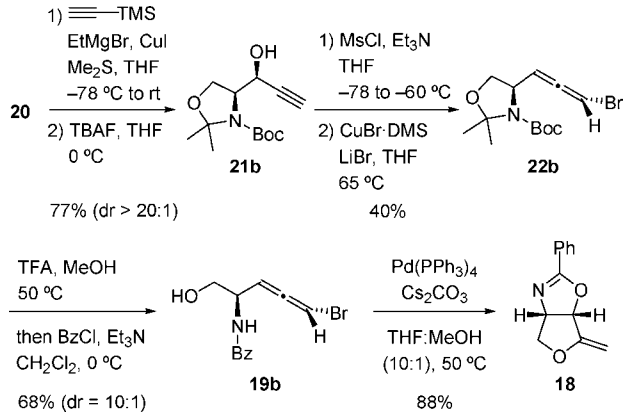
second nucleophilic attack and reactivity of the bromoallene with a palladium catalyst.

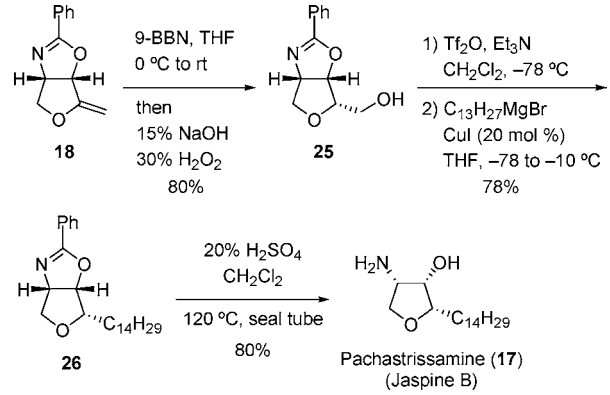
To investigate the difference in reactivity between the diastereomeric bromoallenes **19a** and **19b**, we next synthesized (*S*,a*S*)-bromoallene **19b**, also starting from Garner's aldehyde **20** (Scheme 5). The *threo*-alkynol **21b**, stereoselectively obtained following Taddei's protocol,[12] was converted into the desired bromoallene **19b** in the same manner as described above (Scheme 4). Bromoallene **19b** was then subjected to the optimized reaction conditions shown in entry 6 (Table 1) to give the desired bicyclic product **18** in 88% yield. These results show both bromoallene **19a** and **19b** equally undergo the cascade cyclization to give the same product **18**. This means that a diastereomeric mixture of bromoallenes can be directly employed for preparation of **18**.

Scheme 5. Synthesis and Palladium-Catalyzed Cascade Cyclization of the Epimeric Bromoallene **19b**



With the functionalized tetrahydrofuran **18** prepared, the final stage was to complete the total synthesis of pachastrissamine **17** (Scheme 6). This required introduction of a C-2 side chain with an all-*cis* configuration and hydrolysis of the oxazoline ring. Hydroboration−oxidation of the *exo*-olefin of **18** with 9-BBN provided the primary alcohol **25** with the desired configuration as the sole diastereomer.[14] Treatment of **25** with Tf_2O and Et_3N followed by displacement with a cuprate derived from $C_{13}H_{27}MgBr$/CuI provided the tetrahydrofuran **26** bearing all the requisite functionalities.[15] Finally, pachastrissamine **17** was obtained by hydrolysis of **26** with 20% aqueous H_2SO_4.[16] The spectroscopic data and optical rotation of synthetic pachastrissamine **17** were in agreement with those reported for the natural and synthetic substance [$^1H/^{13}C$ NMR, IR, melting point, $[\alpha]^{25}_D$ 19.7 (EtOH)].[4,5,7]

Scheme 6. Total Synthesis of Pachastrissamine (**17**)



In conclusion, we have developed a novel ring-construction/stereoselective functionalization cascade by palladium(0)-catalyzed bis-cyclization of bromoallenes. Using bromoallenes bearing hydroxy and benzamide groups as internal nucleophiles allows the sequential nucleophilic reactions to selectively proceed in the desired order to form a functionalized tetrahydrofuran ring. This strategy provides an efficient synthetic route to pachastrissamine **17** bearing three contiguous stereogenic centers from Garner's aldehyde as the sole chiral source in 11 steps and 11% overall yield.

Acknowledgment. This work was supported by a Grant-in-Aid for Encouragement of Young Scientists (A) (H.O.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Targeted Proteins Research Program. S.I. is grateful for Research Fellowships from the Japan Society for the Promotion of Science (JSPS) for Young Scientists. Appreciation is expressed to Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO).

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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