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

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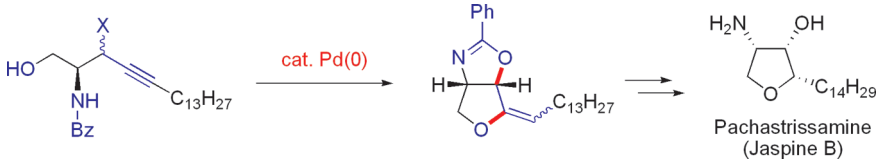

Palladium(0)-catalyzed cyclization of bromoallenes, propargyl chlorides, and carbonates bearing hydroxy and benzamide groups as internal nucleophiles stereoselectively provides functionalized tetrahydrofuran. Cyclization reactivity is dependent on the relative configuration of the benzamide and leaving groups, and on the nature of the leaving groups. This bis-cyclization was used as the key step in a short total synthesis of pachastrissamine, which is a biologically active marine natural product.

Introduction

In recent years, transition-metal-catalyzed cyclization of allenes[1] or alkynes[2] bearing a nucleophilic moiety has been used extensively for construction of cyclic compounds. We investigated the development of cyclization reactions of allenic compounds[3] and found that bromoallenes can function as synthetic equivalents of allyl dication in the presence of a palladium(0) catalyst and alcohol.[4,5] This reactivity is extremely useful for synthesis of medium-sized heterocycles **3** along with their regioisomers **4** from bromoallenes **1** bearing an oxygen, nitrogen, or carbon nucleophile (Scheme 1, eq 1). More recently, we developed an intramolecular domino cyclization of bromoallenes **5** bearing a dual nucleophilic moiety, which produced bicyclic products **7** (Scheme 1, eq 2).[5] Unfortunately, this reaction is limited in that it requires a highly nucleophilic sulfamide group for Nu_A-Nu_B, which might have an appropriate conformation for the 5-*endo*-type second cyclization.

The palladium-catalyzed reaction of propargylic compounds developed by Tsuji et al. has become a useful tool for formation of two carbon−carbon or carbon−heteroatom bonds.[2,6,7] Bromoallenes **11** can be considered as a synthetic equivalent

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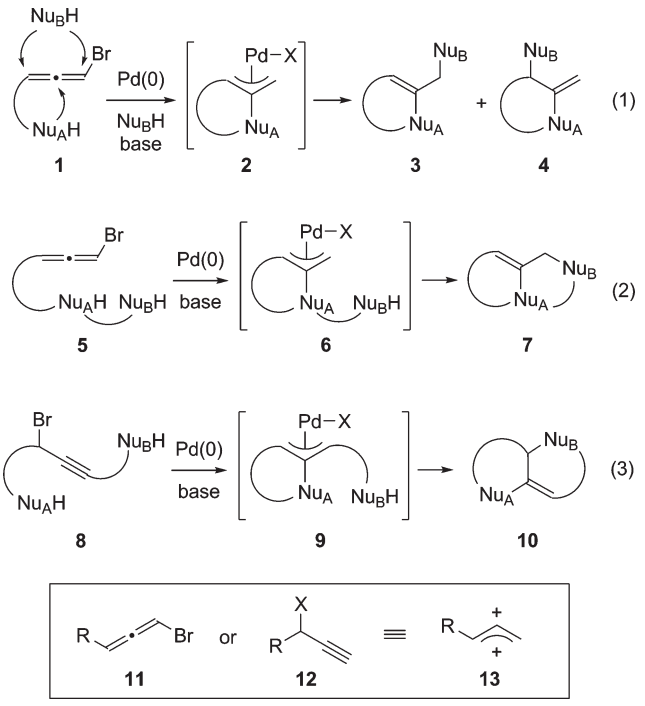
SCHEME 1. Palladium(0)-Catalyzed Cyclization of Bromoallenes and Propargyl Bromides



of propargylic compounds **12**,[8] both of which can work as allyl dication equivalents **13** (Scheme 1). Considerable research in this area has revealed that a combination of nucleophilic attacks by an internal nucleophilic functional group and an appropriate external nucleophile can be an efficient approach to various cyclic compounds, such as carbapenems,[9] furans,[10] indoles,[11] indenes,[12] and cyclic carbonates.[13] Recently, we also developed a palladium(0)-catalyzed domino cyclization of propargyl bromides **8** with two nucleophilic sites, which produced bicyclic products **10** (Scheme 1, eq 3).[14] However, it should be noted that the attempted domino cyclization for bicyclic furan synthesis was unsuccessful, and instead formation of monocyclization products occurred via β-elimination of the type **9** intermediate followed by

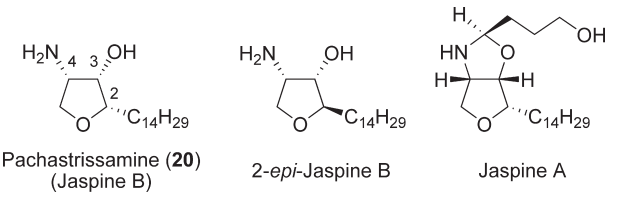
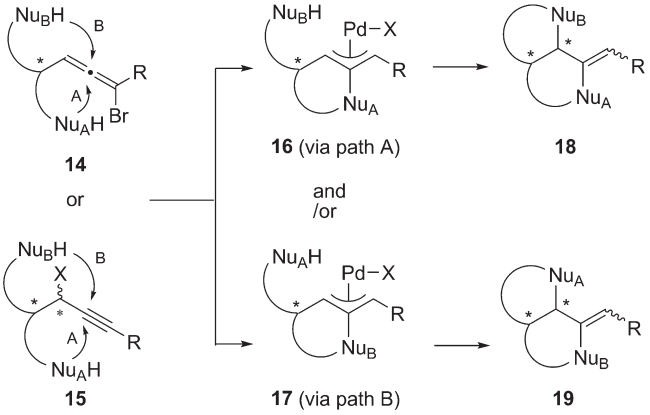


FIGURE 1. Structures of naturally occurring jaspines.

SCHEME 2. Construction of Bicyclic Structures by Palladium(0)-Catalyzed Cascade Cyclization of Bromoallenes 14 and Propargyl Compounds 15



aromatization. The difficulty in the second cyclization is partially due to the *endo*-type reaction.

We turned our attention to domino cyclization of type **14** bromoallenes or type **15** propargyl compounds bearing nucleophilic groups at both ends of a branched alkyl group, which would directly lead to bicyclic products such as **18** or **19** (Scheme 2). This bis-cyclization also enables a cyclization/functionalization cascade, which creates a new chiral center on the *exo*-type second cyclization and utilizes the chiral center at the branched position. The key to success of this domino reaction would be controlled successive nucleophilic attacks by Nu_A and Nu_B in the desired order. First cyclization by Nu_A or Nu_B will produce intermediate **16** or **17**, respectively. These would be converted to the cyclic products **18** or **19**, respectively, by the second intramolecular reaction. We are also interested in the stereochemical course of the domino cyclization, i.e., the effect of the axial or central chirality in the allenic/propargylic moiety of **14**/**15** on the reactivity and selectivity. We chose pachastrissamine **20** (Figure 1), which bears three contiguous stereogenic centers on its tetrahydrofuran core structure, to evaluate this working hypothesis on the ring-construction/stereoselective functionalization cascade.

Pachastrissamine **20** (Figure 1), an anhydrophytosphingosine derivative, was isolated by Higa et al. from Okinawan marine sponge *Pachastrissa* sp. in 2002.[15] Debitus et al. then isolated the same compound from Vanuatuan marine sponge *Jaspis* sp. and named this jaspine B.[16] Other structurally related analogues have also been isolated from the same species,

(8) The reactivities of allenic and propargylic compounds are not necessarily the same. For example, propargyl bromides and carbonates are more reactive than bromoallenes toward S_N2 reactions and alcoholysis, respectively.[4b]

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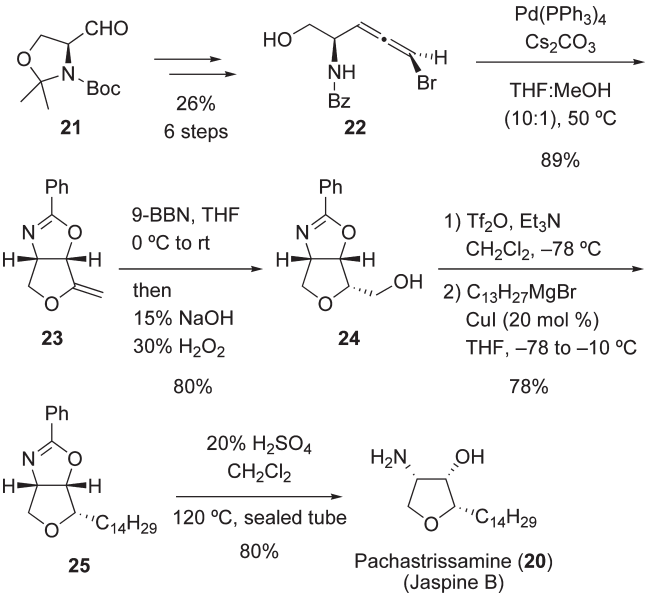
including jaspine A and 2-*epi*-jaspine B. Pachastrissamine **20** displays remarkable cytotoxic activity against several tumor cell lines. In 2009, Delgado et al. reported that dihydroceramides mediated autophagy might be involved in the cytotoxicity.[17] Andrieu-Abadie et al. indicated that pachastrissamine induces apoptotic cell death in melanoma cells by a caspase-dependent pathway.[18] Because of its biological importance, pachastrissamine has attracted considerable interest from the synthetic community. A number of syntheses of pachastrissamine have been reported.[19] More recently, we communicated a pachastrissamine synthesis by palladium-catalyzed bis-cyclization of bromoallene (Scheme 3).[20a] Herein we describe divergent synthesis of various pachastrissamine derivatives through our original synthetic route using bromoallenes and a novel short-step total synthesis of pachastrissamine using several propargyl compounds. We also present a mechanistic consideration based on stereochemical investigations of palladium-catalyzed cyclization of propargylic substrates.

Results and Discussion

Divergent Synthesis of Various Pachastrissamine Derivatives by Bis-cyclization of Bromoallenes. Our previous study of pachastrissamine synthesis by palladium-catalyzed bis-cyclization of bromoallene is shown in Scheme 3. The requisite bromoallene **22** bearing hydroxy and benzamide groups[21] for palladium-catalyzed reaction was easily accessible from (*S*)-Garner's aldehyde **21**.[22,23] Among the several bases and solvents investigated, we found that reaction of **22** with 5 mol % of $Pd(PPh_3)_4$ and Cs_2CO_3 in THF/MeOH (10:1) at 50 °C successfully produced the desired functionalized tetrahydrofuran **23** in 89% yield. The undesired cyclization initiated by nucleophilic attack of the benzamide group was not promoted. Hydroboration−oxidation of the *exo*-olefin of **23** afforded primary alcohol **24** with the desired configuration as the sole diastereomer.[24] Triflation of the alcohol **24**, followed by copper-catalyzed alkylation with Grignard reagent, gave tetrahydrofuran **25** bearing all the requisite functionalities.[25] Finally, pachastrissamine **20** was obtained by hydrolysis of **25** with 20% aqueous H_2SO_4.[26]

SCHEME 3. Total Synthesis of Pachastrissamine (Jaspine B) through Palladium-Catalyzed Bis-cyclization of Bromoallenes



This synthetic route was characterized by the late-stage introduction of the long alkyl side chain into the tetrahydrofuran ring at the C-2 position by copper-catalyzed reaction. The use of various organocopper reagents derived from Grignard reagents should make it possible to achieve a divergent synthesis of pachastrissamine derivatives. Consequently, we investigated the copper-catalyzed alkylation of the triflate prepared from **24** (Table 1). Reaction with Grignard reagents containing a primary alkyl group such as tridecyl, phenylethyl, and methyl in the presence of a copper salt (20 mol %) afforded the desired alkylation products in good yields (entries 1−3).[25,27] Changing the Grignard reagents to *i*-PrMgCl or $CH_2{=}C(CH_3)MgBr$ gave moderate yields of the corresponding products **26c** or **26d** (entries 4 and 5), respectively, containing a secondary alkyl or alkenyl group.[28] We next examined introduction of an allyl group, which can be readily used for further manipulation (Table 2). However, treatment of the triflate with allylMgBr and catalytic CuBr[27]

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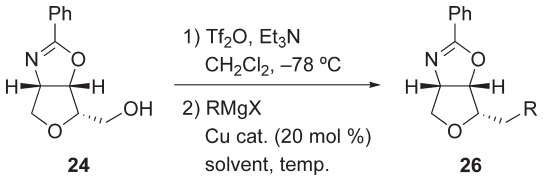
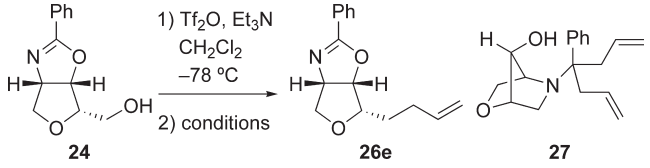
TABLE 1. Copper-Catalyzed Alkylation of Triflates[a]



entry	RMgX	CuX cat.	solvent	temp (°C)	products (% yield)[b]
1	$C_{13}H_{27}MgBr$	CuI	THF	−78 to −10	**25** (78)
2	$Ph(CH_2)_2MgCl$	CuI	THF	−78 °C to rt	**26a** (76)
3	MeMgBr	CuBr	THF/Et_2O (9:1)	−30 °C to rt	**26b** (82)
4	*i*-PrMgCl	CuBr·SMe_2	THF/Me_2S (30:1)	−20 to 0	**26c** (54)
5	CH_2=C(CH_3)MgBr	CuBr·SMe_2	THF/Me_2S (30:1)	−20 to 0	**26d** (66)

[a]Reactions were carried out with RMgX (2.7−7.0 equiv) and CuX (20 mol %) for 1−4.5 h. [b]Isolated yields.

TABLE 2. Copper-Catalyzed Allylation of Triflates and Formation of 2-Oxa-5-azabicyclo[2.2.1]heptane



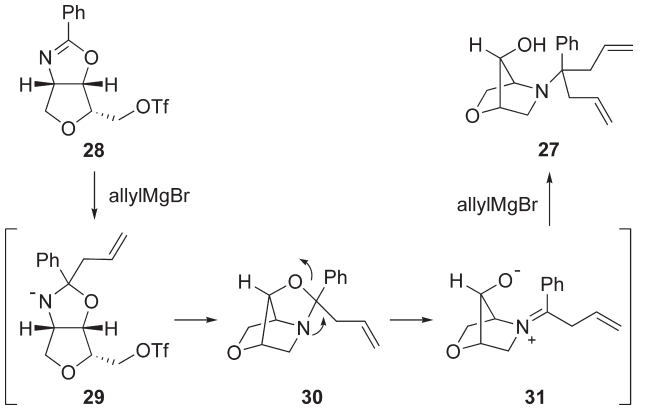
		yield[a,b] (%)	
entry	conditions	**26e**	**27**
1[c]	allylMgBr, CuBr (20 mol %) THF/Et_2O (3:1), −30 °C	ND	90
2[c]	allylMgBr, THF/Et_2O (3:1), −30 °C	ND	91
3[d]	$(allyl)_2Cu(CN)Li_2$, THF, −78 °C	32	ca. 5

[a]Isolated yields. [b]ND = not detected. [c]Reactions were carried out with allylMgBr (5.0 equiv) for 1.5 h. [d]Reactions were carried out with $(allyl)_2Cu(CN)Li_2$ (4.0 equiv) for 30 min.

provided the unanticipated product oxaazabicycloheptane **27** in 90% yield (entry 1).[29] The reaction in the absence of a copper catalyst also afforded **27** in 91% yield (entry 2). In comparison, use of $(allyl)_2Cu(CN)Li_2$[30] resulted in 32% yield of the desired product **26e** along with a small amount of the side product **27** (entry 3).

The rationale for formation of the oxaazabicycloheptane **27** is depicted in Scheme 4. The addition of allylMgBr to imine followed by intramolecular attack of the resulting nitrogen anion to triflate would generate monoallylated intermediate **30**. The second nucleophilic attack of allylMgBr to iminium cation derived from **30** would proceed to give the oxaazabicycloheptane **27**.[31] Servi et al. also reported that 2-phenyloxazolines bearing a tosylate leaving group with allyl Grignard reagent gave bicyclic compounds similar to the intermediate **30**.[32] In contrast, the reaction with the other Grignard reagents did not afford the oxaazabicycloheptane-type products (Table 1). The formation of the oxaazabicycloheptane **27** with allylMgBr would be caused by the first addition step to imine **28** proceeding through six-membered transition state.

SCHEME 4. Formation of 2-Oxa-5-azabicyclo[2.2.1]heptane 27



Novel Strategy for Short-Step Synthesis of Pachastrissamine. Based on the above flexible synthetic route using bromoallenes, we decided to explore a shorter total synthesis of pachastrissamine. This would introduce the alkyl side chain at the beginning. We expected that palladium(0)-catalyzed cyclization of type **33** internal bromoallenes or type **34** propargylic substrates, bearing hydroxy and benzamide groups

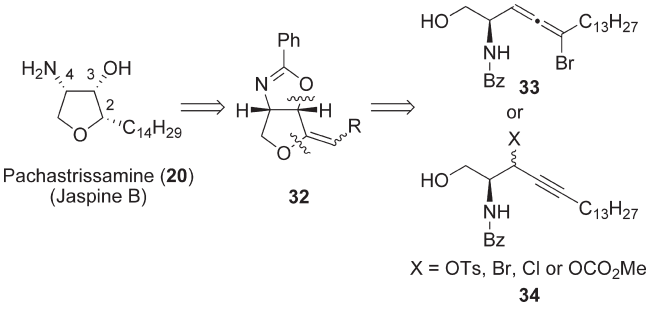
(29) The structure of **27** was confirmed by NMR analysis and comparison with structurally related compounds; see: Hümmer, W.; Dubois, E.; Gracza, T.; Jäger, V. *Synthesis* **1997**, 634–642.

(30) (a) Lipshutz, B. H.; Crow, R.; Dimock, S. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4063–4064. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. K. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404–4410.

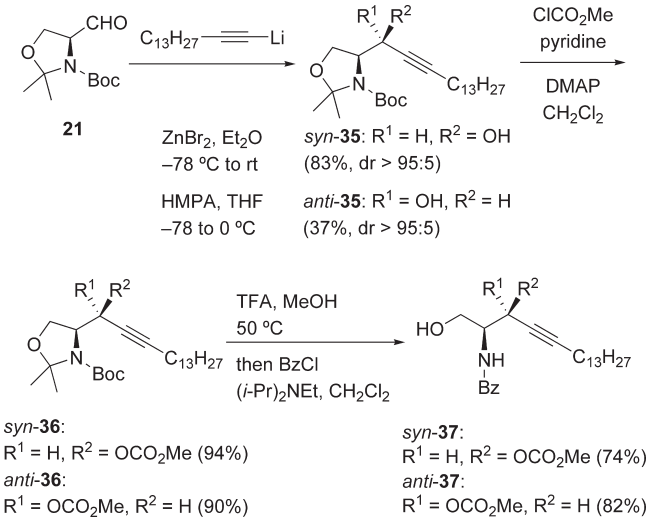
(31) Reaction of triflate **28** with 1.0 equiv of the allyl Grignard reagents gave the oxaazabicycloheptane **27** in 13% yield along with the recovery of the unchanged triflate **28** in 73% yield, without isolation of the intermediate **30**. This is presumably due to a highly strained aminal structure of **30** and facile Grignard reaction to the iminium moiety of **31**.

(32) Fronza, G.; Mele, A.; Pedrocchi-Fantoni, G.; Pizzi, D.; Servi, S. *J. Org. Chem.* **1990**, *55*, 6216–6219.

SCHEME 5. Retrosynthetic Analysis of Pachastrissamine 20



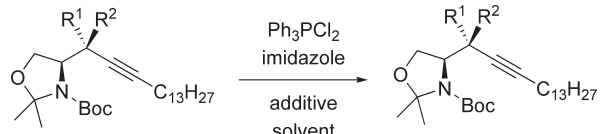
SCHEME 6. Synthesis of Propargyl Carbonates *syn*- and *anti*-37



as nucleophilic functional groups, could regio- and stereoselectively provide the desired bicyclic tetrahydrofuran **32** (Scheme 5). Further hydrogenation of the olefin in **32** from the convex face would allow creation of the C-2 chiral center. Initial examination has revealed that chemoselective preparation of type **33** 1,3-disubstituted bromoallenes and type **34** propargyl tosylates/bromides is difficult.[33,34] Therefore, we chose type **34** propargyl carbonates and chlorides as potential substrates for the palladium(0)-catalyzed bis-cyclization reaction.

Synthesis of Propargyl Carbonates. Initially, we planned to synthesize the diastereomeric propargyl carbonates *syn*- and *anti*-**37** to investigate the difference in reactivity between the diastereoisomers (Scheme 6). Alkynol *syn*-**35** was prepared from (*S*)-Garner's aldehyde **21** following the literature.[23] The alkynol *syn*-**35** was converted into the corresponding carbonate *syn*-**36** by treatment with $ClCO_2Me$, pyridine, and DMAP. Removal of the Boc and acetal groups with TFA and MeOH followed by acylation with BzCl and $(i\text{-Pr})_2NEt$ gave the benzamide *syn*-**37**. The isomeric benzamide *anti*-**37** was obtained in the same manner via the alkynol *anti*-**35**[35] derived from (*S*)-Garner's aldehyde **21**.

TABLE 3. Chlorination of Propargyl Alcohols[a]



entry	substrate	additive	solvent	yield[b] (%)	dr (*syn*/*anti*)[c]
1	*syn*-**35**		DMF	9	> 95:5
2	*syn*-**35**		MeCN	15	93:7
3	*syn*-**35**		THF	22	> 95:5
4	*syn*-**35**		CH_2Cl_2	30	> 95:5
5	*syn*-**35**		toluene	48	55:45
6	*syn*-**35**	LiCl[d]	CH_2Cl_2	8	> 95:5
7	*syn*-**35**	$(n\text{-Bu})_4NCl$[d]	CH_2Cl_2	14	> 95:5
8	*anti*-**35**		CH_2Cl_2	47	5: > 95

[a]Reactions were carried out with Ph_3PCl_2 (4.0 equiv) and imidazole (4.0 equiv) for 2−8 h. [b]Isolated yields. [c]Determined by ^1H NMR analysis. [d]4.0 equiv.

Synthesis of Propargyl Chlorides. We next examined preparation of the required propargyl chloride by chlorination of propargyl alcohol **35** (Table 3).[36] Contrary to our expectations, the reaction of *syn*-**35** with Ph_3PCl_2 and imidazole in DMF afforded propargyl chloride *syn*-**38** in only 9% yield (entry 1). The *syn*-configuration of chloride, determined by cyclization of the corresponding benzamide **41** (vide infra, Scheme 7), demonstrates that the reaction proceeds with net retention of configuration.[37,38] Changing the solvent from DMF to MeCN, THF, or CH_2Cl_2 increased the yields of the desired

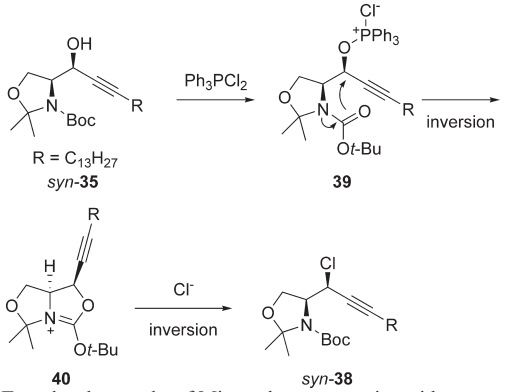
(33) For example, treatment of propargyl mesylates with $CuBr\cdot SMe_2$ in the presence of LiBr gave a mixture of allenyl/propargyl bromides in low yield.

(34) For example, treatment of propargyl tosylates and propargyl bromides with TFA and MeOH followed by acylation with BzCl and DIPEA did not afford the desired benzamide.

(35) According to the literature,[23] *anti*-**35** was produced in 71% yield. However, in our study, the desired product was obtained in low yield (37%) along with unidentified side products, and the optical rotation of alkynol *anti*-**35** was slightly decreased: $[\alpha]^{25}_D$ −33.6 (*c* 1.33, $CHCl_3$) [lit.[23] $[\alpha]^{25}_D$ −40.1 (*c* 1.0, $CHCl_3$)].

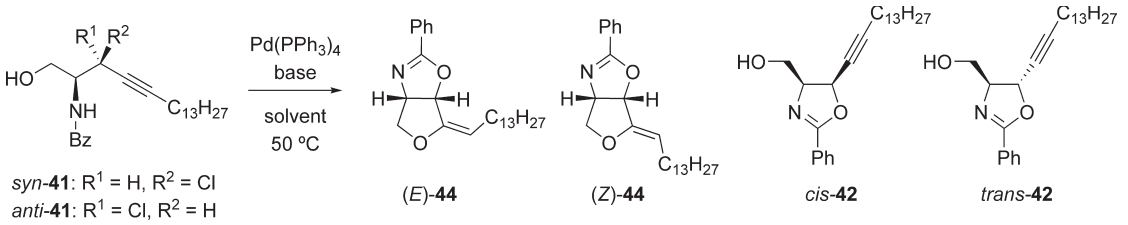
(36) Fluorination reaction of a similar alkynol is known to proceed with inversion of configuration; see: De Jonghe, S.; Van Overmeire, I.; Van Calenbergh, S.; Hendrix, C.; Busson, R.; De Keukeleire, D.; Herdewijn, P. *Eur. J. Org. Chem.* **2000**, 3177–3183.

(37) The observed stereoretention in the chlorination can be rationalized by the double inversion pathway. Activation of *syn*-**35** by Ph_3PCl_2 followed by initial intramolecular nucleophilic attack of a Boc group to the activated propargylic position would form bicyclic intermediate **40** through inversion of configuration. The second intermolecular nucleophilic attack of chloride anion via stereoinversion then gives *syn*-**38**.



(38) For related examples of Mitsunobu-type reaction with net retention of configuration by participation of a vicinal nitorogen functionality, see: (a) Roush, D. M.; Patel, M. M. *Synth. Commun.* **1985**, *15*, 675–679. (b) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670–672. (c) Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1990**, *31*, 5253–5256. (d) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585–4586.

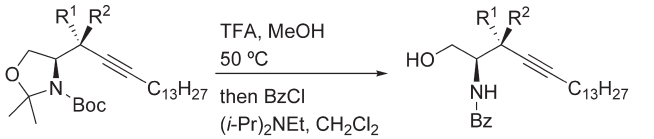
TABLE 4. Palladium-Catalyzed Cascade Cyclization of Propargyl Chlorides[a]



				44		42	
entry	substrate	base (equiv)	solvent	yield[b] (%)	*E*/*Z*[c,d]	yield[b] (%)	*cis*/*trans*[c,d]
1	*syn*-**41**	NaH (2.5)	MeOH	49	92:8	ca. 12	80:20
2	*syn*-**41**	NaH (2.5)	THF	ca. 12	ND	18	>95:5
3	*syn*-**41**	NaH (2.5)	THF/MeOH (10:1)	21	54:46	10	69:31
4[e]	*syn*-**41**	K_2CO_3 (1.2)	THF/MeOH (10:1)	24	>95:5	<18	77:22
5	*syn*-**41**	Cs_2CO_3 (1.2)	THF/MeOH (10:1)	73	95:5	<18	74:26
6[f]	*syn*-**41**	Cs_2CO_3 (1.2)	THF/MeOH (10:1)	89	>95:5	trace	ND
7[f]	*anti*-**41**	Cs_2CO_3 (1.2)	THF/MeOH (10:1)	55	13:87	32	55:45

[a]Reactions were carried out with $Pd(PPh_3)_4$ (5 mol %) at 0.1 M for 1−1.5 h. [b]Isolated yields. [c]Determined by ^1H NMR analysis. [d]ND = not determined. [e]46% of *syn*-**41** was recovered. [f]Reactions were carried out using 10 mol % of $Pd(PPh_3)_4$.

SCHEME 7. Synthesis of Propargyl Chlorides *syn*- and *anti*-41

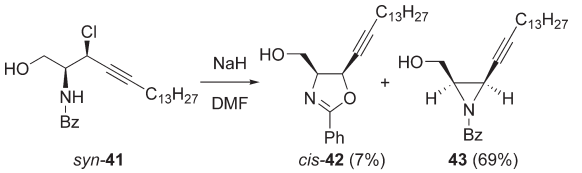


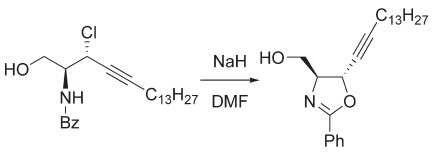
products to some extent with high diastereoselectivities (entries 2−4). It should be noted that the use of toluene as solvent provided the desired propargyl chloride in moderate yield (48%) but with extremely low diastereoselectivity (55:45, entry 5). Further screening of the reaction conditions using the additives LiCl or $(n\text{-Bu})_4NCl$ did not enhance the yield of the desired product. When the alkynol *anti*-**35** was employed, propargyl chloride *anti*-**38** was similarly produced by net retention of configuration in 47% yield.

Next, we prepared benzamides *syn*- and *anti*-**41** by removal of the Boc and acetal groups with TFA and MeOH, followed by acylation with BzCl and $(i\text{-Pr})_2NEt$ (Scheme 7).[39−42]

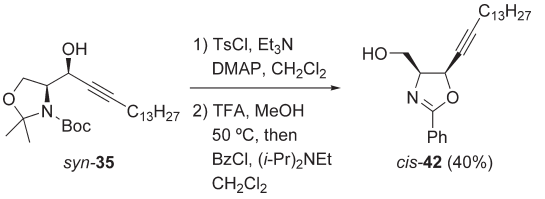
Palladium-Catalyzed Cascade Cyclization of Propargyl Chlorides. We investigated cascade cyclization of propargyl chlorides *syn*-**41** and *anti*-**41** in the presence of palladium(0) (Table 4). Reaction of *syn*-**41** with $Pd(PPh_3)_4$ (5 mol %) and NaH (2.5 equiv) in MeOH at 50 °C (standard conditions for cyclization of propargyl bromide)[14] afforded the desired

(39) The relative configuration of *syn*- and *anti*-**41** was determined by derivatization to the corresponding oxazolines or aziridines. The chloride *syn*-**41** was subjected to NaH in DMF to give the oxazoline *cis*-**42**[40] (7%) and aziridine *cis*-**43**[41] (69%). In contrast, the reaction of *anti*-**41** gave the oxazoline *trans*-**42**[42] in 36% yield.

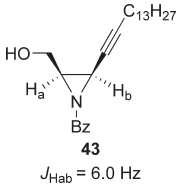




(40) The relative configuration of *cis*-**42** was confirmed by comparison with the authentic sample prepared from the known alkynol *syn*-**35**.[23]



(41) The relative configuration of *cis*-**43** was determined using our J_{Hab}-based configurational analysis: the observed H_a-H_b coupling constant (J_{Hab} = 6.0 Hz) indicates the 2,3-*cis* configuration of the aziridine; see: Ohno, H.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2949–2962.



(42) The relative configuration of *trans*-**42** was confirmed by comparison with the authentic sample prepared from the known alkynol *anti*-**35**.[23]

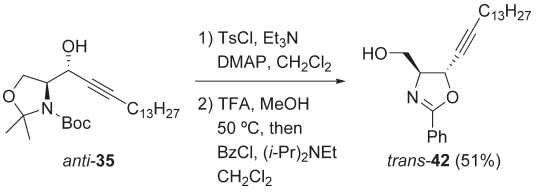
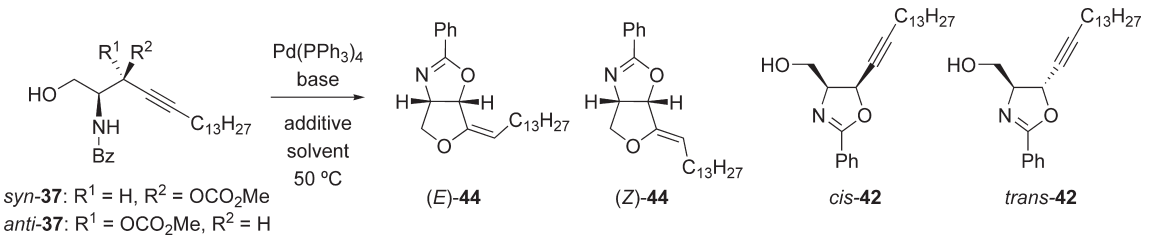


TABLE 5. Palladium-Catalyzed Cascade Cyclization of Propargyl Carbonates [a]



syn-**37**: R^1 = H, R^2 = OCO_2Me
anti-**37**: R^1 = OCO_2Me, R^2 = H

(*E*)-**44** (*Z*)-**44** *cis*-**42** *trans*-**42**

					44		**42**	
entry	substrate	base[b]	additive	solvent	yield[c,d] (%)	*E*/*Z*[e]	yield[c,d] (%)	*cis*/*trans*[e]
1	*syn*-**37**			MeOH	2[f]	>95:5	ND	
2	*syn*-**37**			THF	69	>95:5	ND	
3[g]	*syn*-**37**			THF	60	>95:5	ND	
4	*syn*-**37**			THF:MeOH (10:1)	65	>95:5	ND	
5	*syn*-**37**	Cs_2CO_3		THF	67−78	>95:5	ND	
6[g]	*syn*-**37**	Cs_2CO_3		THF	14	>95:5	ND	
7	*anti*-**37**			THF	<20	>95:5	60	82:18
8	*anti*-**37**		$(n\text{-Bu})_4NCl$[h]	THF	ND		ND	
9	*anti*-**37**		LiCl[i]	THF	ND		ND	
10	*anti*-**37**			THF:MeOH (10:1)	39	13:87	15	>95:5
11	*anti*-**37**	Cs_2CO_3		THF	<26	42:58	39	>95:5
12	*anti*-**37**	Cs_2CO_3		THF:MeOH (10:1)	7	16:84	ND	

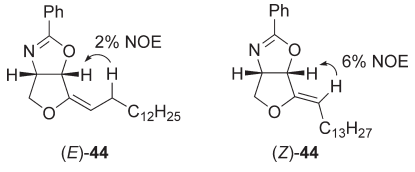
[a]Reactions were carried out with $Pd(PPh_3)_4$ (5 mol %) at 0.1 M for 2−4.5 h. [b]1.2 equiv of a base was used. [c]Isolated yields. [d]ND = not detected. [e]Determined by ^1H NMR analysis. [f]Solvolysis product was obtained. [g]Reactions were carried out on 1 g scale. [h]0.3 equiv. [i]1.0 equiv.

bicyclic tetrahydrofuran **44** in 49% yield with high *E*-selectivity (*E*/*Z*[43] = 92:8, entry 1). Although the undesired monocyclized furan derivatives were not obtained,[14] S_N2-type oxazoline product **42** was observed (ca. 12%, *cis*/*trans* = 80:20).[44] Changing the solvent from MeOH to THF or THF/MeOH (10:1) did not enhance the yield of the desired product (entries 2 and 3). Of the several bases investigated, Cs_2CO_3 was the most effective, yielding 73% of **44** as a 95:5 *E*/*Z* mixture (entries 3−5). Furthermore, increased loading of $Pd(PPh_3)_4$ (10 mol %) improved the yield to 89% and suppressed formation of oxazoline **42** (entry 6). When *anti*-**41** was subjected to the optimized reaction conditions (entry 6), the desired bicyclic tetrahydrofuran **44** was obtained in 55% yield with moderate *Z*-selectivity (*E*/*Z* = 13:87), along with oxazoline **42** (32%, *cis*/*trans* = 55:45, entry 7). These results show utility of propargyl chlorides with *syn*-configuration as a precursor of bicyclic products and a clear difference in reactivity between the diastereomeric substrates.

Palladium-Catalyzed Cascade Cyclization of Propargyl Carbonates. We next investigated the reaction of propargyl carbonates *syn*-**37** and *anti*-**37** in the presence of palladium(0) (Table 5). Treatment of *syn*-**37** with $Pd(PPh_3)_4$ (5 mol %) in MeOH at 50 °C afforded the desired bicyclic tetrahydrofuran **44** in low yield (2%) (entry 1). The main product was the corresponding diol formed by alcoholysis of carbonate **37** (entry 1). When THF was used as the reaction solvent, **44** was obtained with a higher yield (69%) and excellent *E*-selectivity (*E*/*Z* > 95:5, entry 2). Conducting the reaction on a 1 g scale also gave the desired product in satisfactory yield (60%, entry 3). According to our previous reports,[4,5,14] solvents containing alcohol promote the palladium-catalyzed reactions of bromoallenes or propargylic compounds. However, the addition of MeOH did not improve the yield (entry 4). Although the reaction of *syn*-**37** on a 40 mg scale in the presence of Cs_2CO_3 gave **44** in 67−78% yield, this was not reproducible on a 1 g scale (entries 5 and 6). Next, we reacted the diastereomeric carbonates *anti*-**37** under the above optimized conditions (entry 2). This gave the desired product **44** in unexpectedly low yield (<20%) with >95:5 *E*-selectivity and S_N2 product **42** (60%, *cis*/*trans* = 82:18) (entry 7). This result is quite different from the reaction using propargyl chlorides (Table 4, entries 6 and 7). To achieve efficient transformation, further screening was carried out on the basis of the examination of propargyl chlorides (Table 4). Addition of a chloride anion source such as $(n\text{-Bu})_4NCl$ or LiCl did not afford **44** (entries 8 and 9). Among the several reaction conditions investigated (entries 10−12), the use of a mixed solvent THF/MeOH (10:1) under base-free conditions gave the most efficient conversion of *anti*-**37** into the desired product **44** in favor of *Z*-isomer (39%, *E*/*Z* = 13:87, entry 10). These results indicate that an alcoholic solvent plays an important role in stereospecific cyclization of some propargylic systems.

Proposed Mechanism for the Cascade Reaction. Formation of (*E*)-**44** from the carbonate *syn*-**37** or chloride *syn*-**41** can be explained as follows (Scheme 8). Initially, regio- and

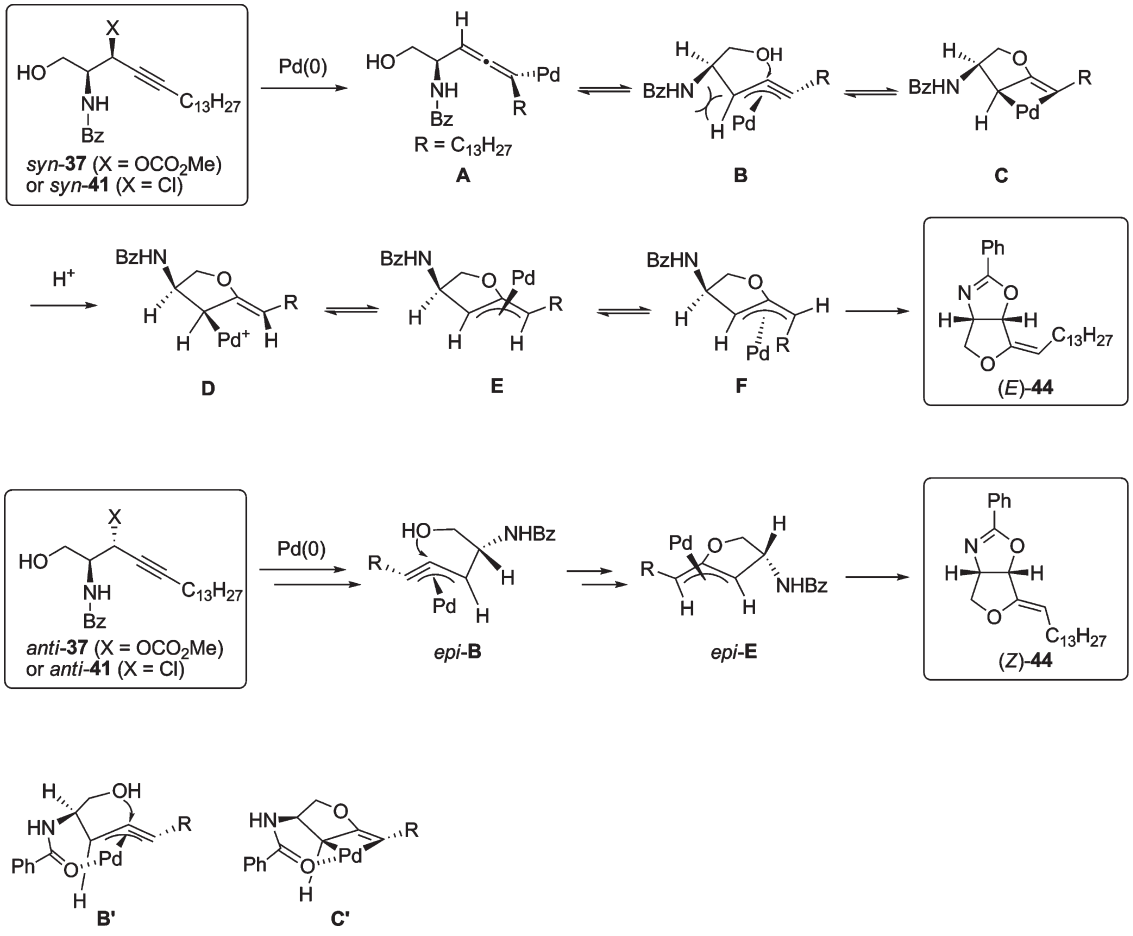
(43) The configuration of the bicyclic tetrahydrofuran **44** was determined by NOE analysis.



(*E*)-**44** (*Z*)-**44**

(44) The minor isomer *trans*-**42** could be produced by double inversion pathway: *anti*-attack of benzamide group to propargyl/allenyl palladium complex, formed by *anti*-attack of palladium(0) to *syn*-**41**, will produce the net retention product *trans*-**42**.

SCHEME 8. Proposed Mechanism for Cascade Reaction



stereoselective S_N2' attack of palladium(0) to propargylic compounds proceeds to yield the allenylpalladium intermediate **A**. First cyclization by the hydroxy group on the central carbon of π-propargylpalladium complex **B**,[45] which is formed by rearrangement of **A**, would generate a fused palladacyclobutene intermediate **C**.[46] This is followed by protonation to form complex **D** without loss of chirality. After formation of the π-allylpalladium intermediate **E**, isomerization to *anti*-type complex **F** is necessary for the next *anti*-cyclization. Therefore, transformation into the intermediate **F** through $\pi-\sigma-\pi$ equilibration followed by the second cyclization by the benzamide group then gives (*E*)-**44**.[47] The carbonate *anti*-**37** or the chloride *anti*-**41** would be converted into π-propargylpalladium complex *epi*-**B** via S_N2' attack of palladium(0). Cyclization by hydroxy group and subsequent protonation will form π-allylpalladium intermediate *epi*-**E**, which gives (*Z*)-**44** by *anti* attack of the benzamide group. It should be noted that the reaction of *syn*-propargylic compounds, which would have unfavorable steric interaction between the palladium and the benzamide group in the first cyclization step, proceeds more efficiently than that of *anti*-compounds (entries 6 vs 7, Table 4; entries 2 vs 7, Table 5). This result suggests that coordination of the benzamide group to palladium would promote the first cyclization by stabilizing the reactive conformer as depicted in **B**' and/or the resulting palladacyclobutene intermediate **C**'. Although the exact reason for the lower *Z*-selectivities in reaction of the *anti*-substrates (Table 5, entries 7 and 10−12) is unclear, it can be attributed to epimerization of allenylpalladium or π-propargylpalladium complex *epi*-**B** due to slower cyclization without assistance of a coordinating effect.[46b,48] Further studies to understand the stereoselectivities and reactivities of these cyclization reactions are currently underway in our laboratory.

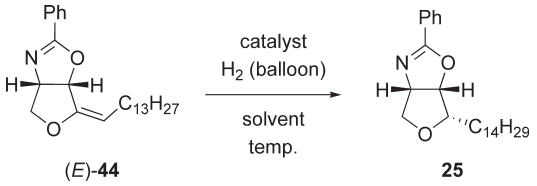
(45) (a) Ogoshi, S.; Tsutsumi, K.; Nishiguchi, S.; Kurosawa, H. *J. Organomet. Chem.* **1995**, *493*, C19–C21. (b) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938–1939. (c) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687–2692.

(46) (a) Casey, C. P.; Nash, J. R.; Yi, C. S.; Selmeczy, A. D.; Chung, S.; Powell, D. R.; Hayashi, R. K. *J. Am. Chem. Soc.* **1998**, *120*, 722–733. (b) Ogoshi, S.; Kurosawa, H. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 14–23. Formation of a palladacyclobutene intermediate in a related reaction has been well rationalized by DFT calculation: (c) Labrosse, J.-R.; Lhoste, P.; Delbecq, F.; Sinou, D. *Eur. J. Org. Chem.* **2003**, 2813–2822.

(47) For related chirality transfer in the reaction of the propargylic compounds via palladacyclobutene intermediates, see: Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325–3327.

(48) (a) Mikami, K.; Yoshida, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 858–860. (b) Ogoshi, S.; Nishida, T.; Shinagawa, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 7164–7165. (c) Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 5573–5575. (d) Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem.* **2006**, *71*, 1563–1568. (e) Yoshida, M.; Hayashi, M.; Shishido, K. *Org. Lett.* **2007**, *9*, 1643–1646. (f) Yoshida, M.; Okada, T.; Shishido, K. *Tetrahedron* **2007**, *63*, 6996–7002. (g) Vaz, B.; Pereira, R.; Pérez, M.; Ávarez, R.; De Lera, A. R. *J. Org. Chem.* **2008**, *73*, 6534–6541.

TABLE 6. Hydrogenation of (*E*)-Olefin 44[a]



(*E*)-**44** **25**

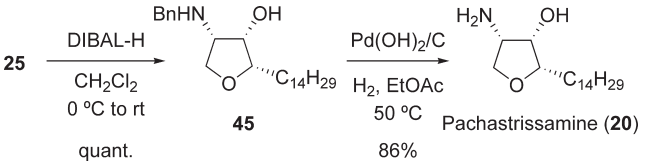
entry	catalyst (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)
1	10% Pd/C (5)	EtOAc	rt	1	45
2	$Pd(OH)_2$/C (5)	EtOAc	rt	16	5
3	PtO_2 (5)	EtOAc	rt	22	ca. 5
4	Ir-black (10)	EtOAc	50	25	28
5	$(Ph_3P)_3RhCl$ (5)	C_6H_6/EtOH	50	27	62
6	$(Ph_3P)_3RhCl$ (10)	C_6H_6/EtOH	50	25	82
7	Crabtree cat. (10)	DCE[c]	70	21	30

[a]Reactions were carried out with pure (*E*)-olefin **44**. [b]Isolated yields. [c]DCE = 1,2-dichloroethane.

Hydrogenation of (*E*)-Olefin 44. We next investigated hydrogenation of (*E*)-olefin **44**, which enabled creation of the C-2 stereogenic center (Table 6). When 10% Pd/C was used, the desired product **25** was obtained in 45% yield as the sole diastereomer. Heterogeneous catalysts ($Pd(OH)_2$/C, PtO_2, and Ir-black entries 2−4) were screened further, but the yield of the desired product decreased with a prolonged reaction time. On examination of the homogeneous catalyst, we found 5 mol % of $(Ph_3P)_3RhCl$ enhanced the yield (62%). When the catalyst loading was increased to 10 mol %, the desired product **25** was isolated in a higher yield (82%, entry 6). In contrast, use of Crabtree catalyst[49] decreased the yield of **25** to 30% (entry 7).

Cleavage of Oxazoline Ring. After synthesis of the pachastrissamine derivative **25** bearing the requisite functionalities, we tested cleavage of the oxazoline ring. Previously, we reported the hydrolysis under harsh conditions (20% H_2SO_4, CH_2Cl_2, sealed tube, 120 °C) led to the desired conversion in 80% yield (Scheme 3).[20] We decided to develop an alternative approach for oxazoline group cleavage and used a two-step reduction under mild conditions.[50] Treatment of **25** with DIBAL-H successfully produced the desired benzyl protected pachastrissamine **45** quantitatively.[50c] Finally, removal of the benzyl group with $Pd(OH)_2$/C led to pachastrissamine **20** in 86% yield (Scheme 9).

SCHEME 9. Cleavage of Oxazoline Ring



Conclusion

We have developed a novel ring-construction/stereoselective functionalization cascade by palladium(0)-catalyzed biscyclization of bromoallenes and propargylic carbonates/chlorides. The bromoallene cyclization was expanded to divergent synthesis of various pachastrissamine derivatives with different alkyl groups at the pachastrissamine C-2 position. When using propargylic compounds, a reactivity difference was observed between the diastereomeric *syn*- or *anti*-substrates. Reaction of the *syn*-propargylic isomer proceeded more efficiently than the corresponding *anti*-isomer. We have achieved a short total synthesis of pachastrissamine using propargylic carbonates. This synthetic route furnishes pachastrissamine in 26% overall yield in seven steps (final deprotection by hydrolysis) or 28% overall yield in eight steps (reductive deprotection) starting from Garner's aldehyde as the sole chiral source (Scheme 10).

Experimental Section

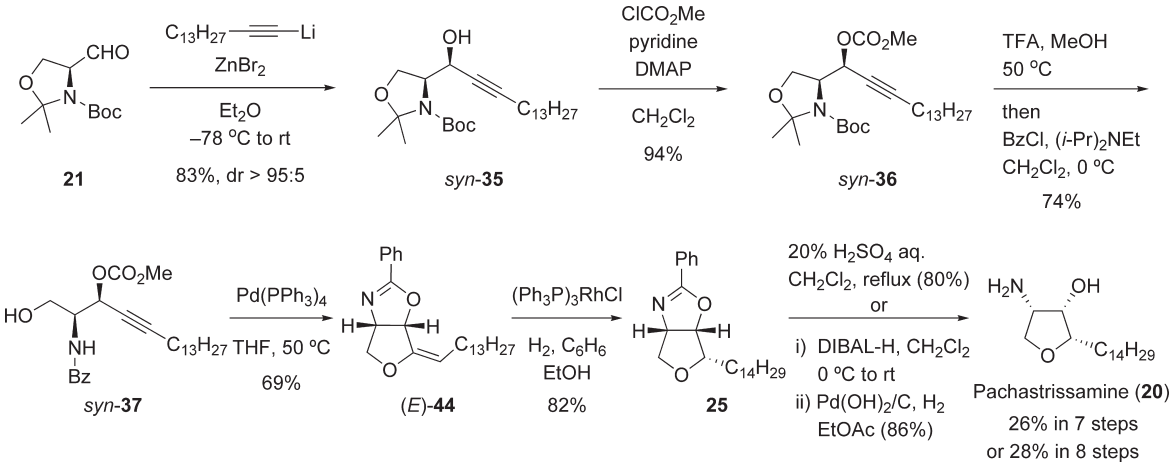
(3a*S*,6*S*,6a*S*)-2-Phenyl-6-(3-phenylpropyl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]oxazole (26a) (Table 1, Entry 2). To a stirred mixture of **24** (40 mg, 0.18 mmol) and Et_3N (0.065 mL, 0.47 mmol) in CH_2Cl_2 (1.8 mL) was added Tf_2O (0.055 mL, 0.32 mmol) at −78 °C, and the mixture was stirred for 30 min at this temperature. The mixture was quenched by addition of saturated NH_4Cl at −78 °C, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O and brine and was dried over Na_2SO_4. Concentration of the filtrate under reduced pressure followed by rapid filtration through a short pad of silica gel with Et_2O−CH_2Cl_2 (1:1) gave a crude triflate, which was used without further purification. To a suspension of CuI (6.9 mg, 0.036 mmol) in THF (0.9 mL) was added dropwise a solution of $Ph(CH_2)_2$-MgCl in THF (1.0 M; 0.90 mL, 0.90 mmol) at −78 °C under argon. The mixture was allowed to warm to 0 °C and was stirred for 10 min at this temperature. To the mixture of the resulting cuprate was added dropwise a solution of the above triflate in THF (1.3 mL) at −78 °C, and the mixture was allowed to warm to room temperature. After being stirred for 1.5 h at this temperature, the mixture was quenched by addition of saturated NH_4Cl and 28% NH_4OH. The whole was extracted with Et_2O, and the extract was washed with H_2O and brine and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane−EtOAc (1:1) and then over Chromatorex with *n*-hexane−AcOEt (2:1) gave **26a** as a colorless oil (42.2 mg, 76% yield): R_f 0.35 (*n*-hexane/EtOAc = 2:3); $[\alpha]^{26}_D$ +97.7 (*c* 1.49, $CHCl_3$); IR (neat) 1650 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77−1.83 (m, 2H), 1.81−1.89 (m, 2H), 2.63−2.70 (m, 1H), 2.71−2.77 (m, 1H), 3.60−3.64 (m, 1H), 3.70 (dd, J = 9.7, 5.4 Hz, 1H), 4.09 (d, J = 9.7 Hz, 1H), 4.81 (dd, J = 7.7, 5.4 Hz, 1H), 4.96 (dd, J = 7.7, 3.7 Hz, 1H), 7.17−7.23 (m, 3H), 7.28 (dd, J = 7.4, 7.4 Hz, 2H), 7.38 (dd, J = 7.7, 7.7 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.85 (d, J = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8, 28.4, 35.9, 72.7, 73.2, 83.5, 83.8, 125.8, 127.2, 128.3 (4C), 128.5 (4C), 131.4, 142.1, 164.3; HRMS (FAB) calcd for $C_{20}H_{22}NO_2$ (MH^+) 308.1651, found 308.1655.

(1*S*,4*S*,7*S*)-5-(4-Phenylhepta-1,6-dien-4-yl)-2-oxa-5-azabicyclo-[2.2.1]heptan-7-ol (27) (Table 2, Entry 2). By a procedure identical with that described for synthesis of **26a** from **24**, the alcohol **24** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification. To a mixture of allylMgBr in Et_2O (1.0 M; 0.90 mL, 0.90 mmol) in THF (1.6 mL) was added dropwise a solution of the above triflate in THF (1.1 mL) at −30 °C under argon. After being stirred for 1.5 h at this temperature, the mixture was quenched

(49) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205–215. (b) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.

(50) (a) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531–532. (b) Wilson, S. R.; Mao, D. T.; Khatri, H. N. *Synth. Commun.* **1980**, *10*, 17–23. (c) Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. *J. Org. Chem.* **1983**, *48*, 4053–4058. (d) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1996**, *118*, 3584–3590. (e) Feldman, K. S.; Cutarelli, T. D; Florio, R. D. *J. Org. Chem.* **2002**, *67*, 8528–8537.

SCHEME 10. Straightforward Total Synthesis of Pachastrissamine (20)



with saturated NH_4Cl. The whole was extracted with Et_2O, and the extract was washed with H_2O and brine and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane−EtOAc (3:2) gave **27** as a colorless oil (46.5 mg, 91% yield): R_f 0.88 (*n*-hexane/EtOAc = 1:2); $[\alpha]^{25}_D$ +35.9 (*c* 1.61, $CHCl_3$); IR (neat) 3445 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (dd, J = 14.6, 8.6 Hz, 2H), 2.85 (dd, J = 14.6, 8.3 Hz, 2H), 2.97 (d, J = 9.5 Hz, 1H), 2.90−2.99 (m, 1H), 3.13 (d, J = 8.0 Hz, 1H), 3.16 (dd, J = 9.5, 2.3 Hz, 1H), 3.38−3.40 (m, 1H), 3.52 (dd, J = 8.0, 1.7 Hz, 1H), 3.96 (dd, J = 2.3, 2.3 Hz, 1H), 4.02−4.04 (m, 1H), 5.09 (d, J = 10.3 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 5.17 (d, J = 16.6 Hz, 2H), 5.68−5.79 (m, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.36 (dd, J = 7.4, 7.4 Hz, 2H), 7.46 (d, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.3, 39.6, 49.0, 59.0, 60.4, 70.5, 73.8, 77.9, 118.3, 118.5, 126.6 (2C), 127.3, 128.5 (2C), 133.8 (2C), 141.7; HRMS (FAB) calcd for $C_{18}H_{24}NO_2$ (MH^+) 286.1807, found 286.1805.

(3a*S*,6*S*,6a*S*)-6-(But-3-enyl)-2-phenyl-3a,4,6,6a-tetrahydrofuro-[3,4-*d*]oxazole (26e) (Table 2, Entry 3). By a procedure identical with that described for synthesis of **26a** from **24**, the alcohol **24** (40 mg, 0.18 mmol) was converted into the corresponding crude triflate, which was used without further purification. To a suspension of CuCN (71.6 mg, 0.72 mmol) in THF (2.0 mL) was added dropwise a solution of MeLi in Et_2O (1.06 M; 1.36 mL, 1.44 mmol) at −78 °C under argon. The mixture was allowed to warm to 0 °C and was stirred for 10 min at this temperature. To the mixture was added dropwise allyltributylstannane (0.45 mL, 1.44 mmol) at −78 °C, and the mixture was allowed to warm to room temperature. The mixture was stirred for 30 min at this temperature. To the mixture of the resulting cuprate was added dropwise a solution of the above triflate in THF (1.1 mL) at −78 °C. After being stirred for 30 min at this temperature, the mixture was quenched with saturated NH_4Cl and 28% NH_4OH. The whole was extracted with Et_2O, and the extract was washed with H_2O and brine and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane−EtOAc (10:1 to 2:3) gave **26e** as a white waxy solid (14.0 mg, 32% yield): R_f 0.70 (*n*-hexane/EtOAc = 3:1); mp 55−56 °C; $[\alpha]^{24}_D$ +91.7 (*c* 0.50, $CHCl_3$); IR (neat) 1651 (C═N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82−1.94 (m, 2H), 2.22−2.35 (m, 2H), 3.65 (ddd, J = 6.9, 6.9, 3.4 Hz, 1H), 3.72 (dd, J = 9.7, 5.4 Hz, 1H), 4.12 (d, J = 9.7 Hz, 1H), 4.84 (dd, J = 7.7, 5.4 Hz, 1H), 5.00 (dd, J = 7.7, 3.4 Hz, 1H), 5.02 (d, J = 10.3 Hz, 1H), 5.10 (d, J = 16.6 Hz, 1H), 5.88 (ddd, J = 16.6, 10.3, 6.8 Hz, 1H), 7.41 (dd, J = 7.7, 7.7 Hz, 2H), 7.48 (t, J = 7.7 Hz, 1H), 7.93 (d, J = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 30.3, 72.8, 73.2, 83.2, 83.5, 115.1, 127.3, 128.3 (4C), 131.4, 138.0, 164.3; HRMS (FAB) calcd for $C_{15}H_{18}NO_2$ (MH^+) 244.1338, found 244.1338.

***tert*-Butyl (*S*)-4-[(*S*)-1-Hydroxyhexadec-2-yn-1-yl]-2,2-dimethyloxazolidine-3-carboxylate (*syn*-35).** To a solution of pentadec-1-yne (562 mg, 2.70 mmol) in Et_2O (5 mL) was added dropwise *n*-BuLi in hexane (1.6 M; 1.64 mL, 2.61 mmol) at −20 °C. After the resulting white suspension was stirred for 1 h at this temperature, a solution of $ZnBr_2$ in Et_2O (ca. 1.0 M; 2.78 mL, 2.78 mmol) was added at 0 °C. After being stirred for 1 h at this temperature and for 1 h at room temperature, a solution of Garner's aldehyde **21** (200 mg, 0.87 mmol) in Et_2O (0.75 mL) was added dropwise at −78 °C. The mixture was allowed to warm to room temperature. After being stirred for 12 h at this temperature, the mixture was quenched by addition of saturated NH_4Cl at −20 °C. After dilution with H_2O, the aqueous layer was separated and extracted with Et_2O. The combined Et_2O extracts were washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (7:1) to give *syn*-**35** as a colorless oil (315 mg, 83% yield, dr > 95:5): R_f 0.48 (*n*-hexane/EtOAc = 4:1); $[\alpha]^{25}_D$ −32.3 (*c* 1.29, $CHCl_3$) [lit.[23] $[\alpha]^{25}_D$ −32.4 (*c* 1.3, $CHCl_3$)]. All of the spectral data were in agreement with those reported by Herold.[23]

***tert*-Butyl (*S*)-4-[(*S*)-1-(Methoxycarbonyloxy)hexadec-2-yn-1-yl]-2,2-dimethyloxazolidine-3-carboxylate (*syn*-36).** To a stirred solution of *syn*-**35** (1.00 g, 2.28 mmol) in CH_2Cl_2 (8.0 mL) were added pyridine (1.11 mL, 13.7 mmol), DMAP (55.7 mg, 0.46 mmol), and $ClCO_2Me$ (1.06 mL, 13.7 mmol) at 0 °C, and the mixture was stirred for 1.5 h at room temperature, followed by quenching with saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (11:1) to give *syn*-**36** as a colorless oil (1.06 g, 94% yield): R_f 0.78 (*n*-hexane/EtOAc = 4:1); $[\alpha]^{25}_D$ −23.4 (*c* 1.10, $CHCl_3$); IR (neat) 2247 (C≡C), 1757 (C═O), 1705 (C═O); ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 0.86 (t, J = 6.9 Hz, 3H), 1.22−1.38 (m, 20H), 1.43 (s, 3H), 1.43 (s, 9H), 1.44−1.47 (m, 2H), 1.52 (s, 3H), 2.20 (td, J = 6.9, 2.3 Hz, 2H), 3.72 (s, 3H), 3.98 (dd, J = 9.2, 3.4 Hz, 1H), 3.99−4.02 (m, 1H), 4.02−4.07 (m, 1H), 5.59 (dt, J = 5.1, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$; as a mixture of amide rotamers) δ 14.1, 18.8, 22.6, 23.4, 24.7, 26.0, 26.8, 28.2, 28.3, 28.8, 29.0, 29.3 (2C), 29.4, 29.6 (3C), 31.8, 54.9, 58.7 (0.5C), 59.3 (0.5C), 64.4 (0.5C), 64.7 (0.5C), 68.0 (0.5C), 68.4 (0.5C), 73.9, 80.5, 88.6 (0.5C), 89.0 (0.5C), 94.3 (0.5C), 94.9 (0.5C), 151.7, 154.5 (0.5C), 154.6 (0.5C). Anal. Calcd for $C_{28}H_{49}NO_6$: C, 67.84; H, 9.96; N, 2.83. Found: C, 67.90; H, 9.68; N, 2.79.

(2*S*,3*S*)-2-Benzamido-1-hydroxyoctadec-4-yn-3-yl Methyl Carbonate (*syn*-37). To a stirred solution of *syn*-**36** (963 mg, 1.94 mmol) in MeOH (6.5 mL) at 0 °C was added trifluoroacetic acid (18 mL), and the mixture was stirred for 1.5 h at 50 °C. The mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (18 mL). The solution was made neutral with (*i*-Pr)$_2$NEt at 0 °C. (*i*-Pr)$_2$NEt (1.18 mL, 6.79 mmol) and BzCl (0.248 mL, 2.13 mmol) were added to the mixture under stirring at 0 °C. The mixture was stirred for 2.5 h at this temperature, followed by addition of H_2O. The whole was extracted with EtOAc. The extract was washed successively with 1 N HCl, H_2O and brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:2) to give *syn*-**37** as a pale yellow oil (664 mg, 74% yield): R_f 0.55 (*n*-hexane/EtOAc = 1:1); $[\alpha]^{25}_D$ +33.3 (*c* 1.43, $CHCl_3$); IR (neat) 3380 (OH), 2237 (C≡C), 1755 (C═O), 1650 (C═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.19−1.35 (m, 20H), 1.47 (tt, *J* = 7.2, 7.2 Hz, 2H), 2.20 (td, *J* = 7.2, 1.7 Hz, 2H), 2.55 (br s, 1H), 3.80 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.81 (s, 3H), 4.02 (dd, *J* = 11.5, 4.6 Hz, 1H), 4.45−4.52 (m, 1H), 5.60−5.66 (m, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.7, 22.7, 28.2, 28.8, 29.1, 29.3, 29.4, 29.6 (3C), 29.7, 31.9, 54.4, 55.2, 61.8, 67.5, 74.3, 89.7, 127.1, 128.6 (2C), 131.8 (2C), 133.9, 154.9, 167.8; HRMS (FAB) calcd for $C_{27}H_{42}NO_5$ (MH^+) 460.3063, found 460.3068.

***tert*-Butyl (*S*)-4-[(*R*)-1-Chlorohexadec-2-yn-1-yl]-2,2-dimethyloxazolidine-3-carboxylate (*syn*-38) (Table 3, Entry 4).** To a stirred solution of *syn*-**35** (2.00 g, 4.57 mmol) and imidazole (1.25 g, 18.3 mmol) in CH_2Cl_2 (8.0 mL) was added a solution of Ph_3PCl_2 (6.09 g, 18.3 mmol) in CH_2Cl_2 (12 mL) at 0 °C. After the solution was stirred for 1.0 h at this temperature, concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (30:1) to give *syn*-**38** as a colorless oil (618 mg, 30% yield); R_f 0.83 (*n*-hexane/EtOAc = 4:1); $[\alpha]^{24}_D$ −96.7 (*c* 1.17, $CHCl_3$); IR (neat): 2246 (C≡C), 1694 (C═O); ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.20−1.38 (m, 20H), 1.43 (s, 3H), 1.44 (s, 9H), 1.45−1.48 (m, 2H), 1.53 (s, 3H), 2.23 (td, *J* = 6.9, 2.3 Hz, 2H), 4.05−4.12 (m, 3H), 5.02−5.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$; as a mixture of amide rotamers) δ 14.1, 18.9, 22.7, 23.5, 24.9, 25.9, 26.5, 28.2, 28.3, 28.4, 28.8, 29.1, 29.3, 29.5, 29.6 (2C), 29.7, 31.9, 48.1 (0.5C), 49.0 (0.5C), 61.9 (0.5C), 62.2 (0.5C), 64.5 (0.5C), 64.9 (0.5C), 75.0 (0.5C), 75.4 (0.5C), 80.6 (0.5C), 80.8 (0.5C), 89.0 (0.5C), 89.5 (0.5C), 94.8 (0.5C), 95.5 (0.5C), 151.5 (0.5C), 152.5 (0.5C); HRMS (FAB) calcd for $C_{26}H_{47}ClNO_3$ (MH^+) 456.3244, found 456.3248.

***N*-[(2*S*,3*R*)-3-Chloro-1-hydroxyoctadec-4-yn-2-yl]benzamide (*syn*-41).** By a procedure identical with that described for the synthesis of the benzamide *syn*-**37** from *syn*-**36**, the carbamate *syn*-**38** (49.1 mg, 0.108 mmol) was converted into *syn*-**41** (31.3 mg, 69% yield): white waxy solid; R_f 0.68 (*n*-hexane/EtOAc = 1:1); mp 60−61 °C; $[\alpha]^{24}_D$ −22.7 (*c* 1.20, $CHCl_3$); IR (neat) 3335 (OH), 2237 (C≡C), 1653 (C═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.19−1.35 (m, 20H), 1.47 (tt, *J* = 7.4, 7.4 Hz, 2H), 2.22 (td, *J* = 7.4, 1.1 Hz, 2H), 3.85 (dd, *J* = 11.7, 5.7 Hz, 1H), 4.16 (dd, *J* = 11.7, 4.3 Hz, 1H), 4.42−4.49 (m, 1H), 5.03−5.07 (m, 1H), 6.72 (d, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.8, 22.7, 28.2, 28.8, 29.1, 29.3, 29.4, 29.6 (3C), 29.7, 31.9, 49.2, 55.8, 61.9, 76.0, 89.9, 127.1, 128.7 (2C), 131.9 (2C), 133.8, 167.8; HRMS (FAB) calcd for $C_{25}H_{39}ClNO_2$ (MH^+) 420.2669, found 420.2671.

General Procedure for Palladium-Catalyzed Cascade Cyclization of Propargyl Chlorides: Synthesis of (3a*S*,6a*S*,*E*)-2-Phenyl-6-tetradecylidene-3a,4,6,6a-tetrahydrofuro[3,4-*d*]oxazole ((*E*)-44) from *syn*-41 (Table 4, Entry 6). To a stirred mixture of *syn*-**41** (40 mg, 0.095 mmol) in THF/MeOH (1.0 mL, 10:1) were added $Pd(PPh_3)_4$ (11.0 mg, 0.0095 mmol) and Cs_2CO_3 (37.1 mg, 0.114 mmol) at room temperature under argon. The mixture was stirred for 1.0 h at 50 °C and filtered through a short pad of SiO_2 with EtOAc. The filtrate was concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) to give (*E*)-**44** as a white solid (32.4 mg, 89% yield): R_f 0.45 (*n*-hexane/EtOAc = 2:1); mp 79−80 °C; $[\alpha]^{24}_D$ +253.32 (*c* 1.38, $CHCl_3$); IR (neat) 1647 (C═N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20−1.47 (m, 22H), 2.13−2.26 (m, 2H), 4.19 (dd, *J* = 9.5, 6.3 Hz, 1H), 4.27 (dd, *J* = 9.5, 1.7 Hz, 1H), 4.91 (ddd, *J* = 8.0, 6.3, 1.7 Hz, 1H), 5.09 (t, *J* = 8.0 Hz, 1H), 5.58 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 27.0, 29.2, 29.4, 29.6, 29.7 (5C), 30.4, 31.9, 70.6, 74.9, 79.0, 105.0, 127.2, 128.3 (2C), 128.5 (2C), 131.6, 154.2, 164.2. Anal. Calcd for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 77.99; H, 9.80; N, 3.67.

General Procedure for Palladium-Catalyzed Cascade Cyclization of Propargyl Carbonates: Synthesis of (3a*S*,6a*S*,*E*)-2-Phenyl-6-tetradecylidene-3a,4,6,6a-tetrahydrofuro[3,4-*d*]oxazole ((*E*)-44) from *syn*-37 (Table 5, Entry 2). To a stirred mixture of *syn*-**37** (40 mg, 0.087 mmol) in THF (0.9 mL) was added $Pd(PPh_3)_4$ (5.03 mg, 0.0044 mmol) at room temperature under argon. After the mixture was stirred for 2.0 h at 50 °C, concentration under reduced pressure gave a yellow oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) to give (*E*)-**44** as a white solid (23.1 mg, 69% yield).

(3a*S*,6a*S*,*Z*)-2-Phenyl-6-tetradecylidene-3a,4,6,6a-tetrahydrofuro-[3,4-*d*]oxazole ((*Z*)-44) (Table 4, Entry 3). To a stirred mixture of *syn*-**41** (40 mg, 0.095 mmol) in THF/MeOH (1.0 mL, 10:1) was added $Pd(PPh_3)_4$ (5.03 mg, 0.0048 mmol) at room temperature under argon. After the mixture was stirred for 1.5 h at 50 °C, concentration under reduced pressure gave a yellow oil, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) to give an isomeric mixture **44** (*E*/*Z* = 54:46) as a white solid (7.7 mg, 21% yield). This mixture was separated by PTLC with hexane−EtOAc (2:1) to give (*Z*)-**44** in a pure form: pale yellow oil; R_f 0.55 (*n*-hexane/EtOAc = 2:1); $[\alpha]^{24}_D$ +143.68 (*c* 0.36, $CHCl_3$); IR (neat) 1646 (C═N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20−1.40 (m, 22H), 2.02−2.20 (m, 2H), 4.25 (dd, *J* = 9.5, 6.3 Hz, 1H), 4.32 (dd, *J* = 9.5, 2.0 Hz, 1H), 4.81 (t, *J* = 7.2 Hz, 1H), 4.89 (ddd, *J* = 8.6, 6.3, 2.0 Hz, 1H), 5.37 (d, *J* = 8.6 Hz, 1H), 7.41 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.4, 29.3, 29.5 (2C), 29.6 (5C), 29.7, 31.9, 70.2, 75.9, 82.3, 106.0, 127.3, 128.3 (2C), 128.5 (2C), 131.5, 153.7, 164.3; HRMS (FAB) calcd for $C_{25}H_{38}NO_2$ (MH^+) 384.2903, found 384.2900.

(3a*S*,6*S*,6a*S*)-2-Phenyl-6-tetradecyl-3a,4,6,6a-tetrahydrofuro-[3,4-*d*]oxazole (25) (Table 6, Entry 6). A mixture of (*E*)-**44** (50.0 mg, 0.13 mmol) and $(Ph_3P)_3RhCl$ (12.1 mg, 0.013 mmol) in C_6H_6/EtOH (1.3 mL, 1:1) was stirred for 25 h at 50 °C under H_2 and then filtered through a short pad of SiO_2 with EtOAc. The filtrate was concentrated under reduced pressure to give a brown solid, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give **25** as a white solid (41.1 mg, 82% yield): R_f 0.40 (*n*-hexane/EtOAc = 1:3); $[\alpha]^{24}_D$ +65.4 (*c* 1.38, $CHCl_3$) [lit.[20a] $[\alpha]^{24}_D$ +60.9 (*c* 1.05, $CHCl_3$)]. All of the spectral data were in agreement with those of our previous report.[20a]

(2*S*,3*S*,4*S*)-4-(Benzylamino)-2-tetradecyltetrahydrofuran-3-ol (*N*-Benzylpachastrissamine) (45). To a stirred solution of **25** (120 mg, 0.31 mmol) in CH_2Cl_2 (6.0 mL) was added DIBAL-H in toluene (1.01 M; 1.24 mL, 1.24 mmol) at 0 °C. After being stirred for 20 min at this temperature, the mixture was allowed to warm to room temperature. The mixture was stirred for 2.0 h at this temperature and quenched with 2 N Rochelle salt. After being stirred for 3.0 h, the

whole was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with $CHCl_3$−MeOH (15:1) gave **45** as a white solid: R_f 0.63 ($CHCl_3$/MeOH = 9:1); mp 72−73 °C; $[\alpha]^{25}_D$ +14.5 (*c* 0.99, $CHCl_3$); IR (neat) 3334 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.22−1.43 (m, 24H), 1.62−1.75 (m, 2H), 2.39−2.90 (m, 2H), 3.44 (ddd, J = 7.4, 7.4, 4.6 Hz, 1H), 3.55 (dd, J = 8.6, 7.4 Hz, 1H), 3.70 (ddd, J = 6.9, 6.9, 2.9 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 3.84 (d, J = 13.2 Hz, 1H), 3.89−3.92 (m, 1H), 3.91−3.94 (m, 1H), 7.26−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.3, 29.3, 29.4, 29.6 (5C), 29.7 (2C), 29.8, 31.9, 52.7, 61.2, 69.7, 70.4, 83.5, 127.5, 128.1 (2C), 128.6 (2C), 139.2; HRMS (FAB) calcd for $C_{25}H_{44}NO_2$ (MH^+) 390.3372, found 390.3372.

(2*S*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (Pachastrissamine) (20). A mixture of **45** (20.0 mg, 0.051 mmol) and 20% w/w $Pd(OH)_2$/C (3.6 mg, 0.0051 mmol) in EtOAc (0.8 mL) was stirred at 50 °C under H_2. After the mixture was stirred for 12 h, further EtOAc (0.4 mL) was added to stirred mixture. The mixture was stirred for 9 h at 50 °C and filtered through a short pad of Celite with EtOAc. The filtrate was concentrated under reduced pressure to give a white solid, which was purified by flash chromatography over silica gel with $CHCl_3$−MeOH−28% NH_4OH (95:4:1) to give **20** as a white solid (13.1 mg, 86% yield): R_f 0.55 (EtOAc/MeOH = 9:1); $[\alpha]^{25}_D$ +18.9 (*c* 0.77, EtOH) [lit.[20a] $[\alpha]^{25}_D$ +19.7 (*c* 0.62, EtOH)]. All of the spectral data were in agreement with those of our previous report.[20a]

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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.